

CLINICAL STUDY

Association of the postoperative white blood cells (WBC) count in peripheral blood after radical surgical treatment of left upper lobe non-small cell lung cancer (NSCLC) with overall survival – single center results

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ABSTRACT

INTRODUCTION: The individual patient prognosis after radical surgery for Non-small cell lung cancer (NSCLC) of left upper lobe remains still unclear. The purpose of this study is to evaluate the predictive value of elevated white blood cell count in peripheral blood as early indicator of postoperative NSCLC prognosis.

METHODS: A retrospective statistical analysis was performed studying patients subject to radical treatment of left upper lobe NSCLC in period of five years with subsequent one to three-year monitoring of morbidity and mortality of the patient population. The statistical ROC (Receiver Operating Characteristic) analysis of the WBC count in peripheral blood third day after the operation was used to evaluate the relationship with overall survival, with respect to patients surviving for at least 24 months.

RESULTS: Based on the results of the ROC analysis with a total area under the curve (AUC) of 0.67, it is possible to confirm that the WBC count established third day after the operation allows us to classify patients into groups according to the 24-month overall survival.

CONCLUSION: Our findings confirm the potential of using WBC count to improve current protocols to establish postoperative prognosis for NSCLC of the upper left lobe (*Tab. 2, Fig. 1, Ref. 11*). Text in PDF www.elis.sk.

KEY WORDS: postoperative white blood cells, peripheral blood, radical surgical treatment, left upper lobe, non-small cell lung cancer, survival-single center results.

Introduction

Non-small cell lung carcinoma (NSCLC) is, despite all the extensive efforts to treat it, one of the most frequent cause of cancer mortality globally. The left upper lobe is characterized by a unique lymph drainage system and early metastases in the lymph nodes in the aortopulmonary region that is arduous to detect pre-operationally. In patients with aortopulmonary area nodal involvement after radical surgery, it is difficult to objectively predict the recurrence of the disease or the prognosis. No marker has yet been found able to indicate the probability of cancer recurrence or to identify risk sub-groups of patients in individual clinical stages. Various molecular genetic markers have been studied, but using such markers is very costly. This is why efforts are made to find a marker that would be a part of the routine perioperative tests and would not add to the costs of medical facilities for treating one patient. The

current trend is to look at tumour-associated immunopathological mechanisms leading to a sterile inflammatory response in order to evaluate the prognosis of solid tumours. These processes cause changes in the inflammatory markers count, specifically WBC (White blood cells) and CRP (C-reactive protein) level in peripheral blood. A few studies have focused on evaluating preoperative WBC and CRP levels as a prognostic marker (1, 2). The results show the comparison of neutrophil and leukocyte ratio to be one of the most promising predictors (3, 4). An analysis of postoperative changes in the concentration of acute-phase serum proteins and WBC count could be influenced by the degree of operative stress. Empirically, WBC counts return to normal 48–72 hours after the operation. A WBC count of $10,000 \times 10^9$ in peripheral blood is generally accepted as the upper limit of the normal range (5). Evaluation of the relationship between WBC count and overall survival after radical surgery of left upper lobe NSCLC has not been published to our knowledge. This study investigates the possibility of using postoperative WBC count on the third day after the operation to predict the recurrence of cancer after radical surgical treatment.

Methods

A retrospective statistical analysis was performed, studying patients who were subject to radical surgical treatment of left upper lobe NSCLC at the First department of surgery in Brno, Czech Republic, in a five-year period (from 2011 to 2015) with subsequent

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Tab. 1. Overall survival of patients after the operation in relation to the WBC count 3 days after the operation.

WBC count 3 days after the operation (10 ⁹ /l)	n	Median OS (95% CI)	1-year survival (95% CI)	2-year survival (95% CI)	3-year survival (95% CI)	p-value Log-rank test
< 10.00	31	N/A	93.1 % (83.9–99.9)	81.5 % (66.8–96.3)	68.5 % (50.0–86.9)	0.012
≥ 10.00	20	19.5 months (10.9–28.1)	72.6 % (51.9–93.3)	46.7 % (19.3–74.0)	37.3 % (10.0–64.7)	

Tab. 2. Comparison of the overall survival of patients and the distribution of the population according to the optimal cut-off value for the WBC count 3 days after the operation.

Distribution according to the optimal cut-off	Overall survival		Total number of patients
	> 24 months	< 24 months	
WBC count 3 days after the operation < 10.00	20	11	31
WBC count 3 days after the operation ≥ 10.00	5	15	20
Total number of patients	25	26	51

Test sensitivity (95% CI) is 80.0 % (59.3–93.2), test specificity (95% CI) is 57.7 % (36.9–76.6), positive predictive value (95% CI) is 64.5 % (45.4–80.8), negative predictive value (95% CI) is 75.0 % (50.9–91.3)

one to three-year monitoring of morbidity and mortality of the patient population. Peripheral WBC counts were obtained for patients on postoperative day 3. The patient population was evaluated according to American Society of Anesthesiologist score (ASA), representing stage ASA II, i.e. patients with various extent of chronic disease lacking functional limitation. Criteria for inclusion were: WBC count under $10,00 \times 10^9$ and CRP level below 5 mg/l as a part of standard pre-operational protocol. Patients with suspected early postoperative infection complications or fever were excluded from the population. A comparative analysis of the relationship between WBC count and overall survival of at least 24 months after the operation was evaluated using statistical methods. Finally, ROC (Receiver Operating Characteristic) analysis was performed in order to estimate the optimal cut-off value for WBC count that would identify patients who will survive for at least 24 months after the operation.

Results

In the five-year period, a total of 51 patients underwent radical surgery. The population included 36 men and 15 women, the average age being 65 years. In order to prevent possible interference of WBC and CRP levels with decompensated chronic co-morbidities, only patients with the maximum of ASA II risk score and stable chronic disease were included. Patients with ASA III or IV were excluded from this study. According to available documentation 31 patients were subject to chronic hypertension treatment in mono- or combined therapeutic setting. 14 patients were diagnosed with diabetes mellitus, 4 out of which were treated with combined therapy and 10 treated with peroral antidiabetics (PAD). 19 patients had chronic obstructive bronchopulmonary disease (COPD) in their history. 6 patients reported long-term use of inhalation corticosteroids discontinued 1 day before the surgery at the latest. The distribution of co-morbidities in the patient population was heterogenous with none being prevalent in any of the groups. None of the patients were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) for longer periods of time that would interfere with WBC and CRP levels. However, occasional use could not be fully excluded. From the aetiology point of view, the most frequent malignancy, as per definitive histology, was adenocarcinoma with 56.6%, followed by squamous-cell carcinoma with 35.7%, while only 7.5% of cases represented another type of malignant tumour. After histopatho-

logical processing, all T sub-groups, defined by the 7th edition of TNM classification were represented in the population (T1 – 32.1 %, T2 – 58.5 %, T3 – 5.7 %, T4 – 3.7 %). According to the evaluation of the degree of spreading to lymph nodes, the population was distributed in the N categories as follows: N0 – 56.6 %, N1 – 13.2 %, N2 – 30.2 %. Based on the above, the patients were divided into groups and the overall survival (OS) was evaluated according to the T and the N categories in one- to three-year intervals (annually). Irrespective of the T and the N categories, the overall survival of the whole population in the given interval was as follows: 1-year survival – 85.7 %, 2-year survival – 70.0 %, 3-year survival – 57.8 %. The median overall survival for individual T categories was 35.9 months for T2 tumours and 6.7 months for T3 and T4 tumours of the left upper lobe. No median OS was established for the T1 category as the patients were alive even after three years, as was also the case of patients who had no lymph node involvement (N0). Thus, the results of these groups were censored. As was expected, the OS results were worse in the N1 category – 25.4 months and the N2 category – 24.3 months. Subsequently, the initial WBC count (drawn on the 3rd day after the operation) of patients surviving at least 24 months after the operation was analysed (Tab. 1). The result of the calculated initial value, $10,00 \times 10^9$ in peripheral blood, correlates with the upper limit of the normal range of WBC count. The ROC analysis has shown a total area under the curve (AUC) of 0.67. Based on these findings, the WBC count established 3 days after the operation allows, with 80 % sensitivity and 57.7 % specificity, to classify patients into groups according to the 24-month overall survival ($p = 0.039$). The positive predictive value is 64.5 % and the negative predictive value is 75.0 % (Tab. 2).

Discussion

Using inflammatory markers as a prognostic indicator of cancer recurrence is based on Rudolf Virchow's initial theories about the relationship between chronic inflammation and the development of malignancy. Recent studies have shown that there is a relationship between preoperative CRP level, the ratio of neutrophils and lymphocytes on the one side, and the overall survival and recurrence risk on the other (1, 11). The interaction of the immune system and malignant cells with developed sterile inflammation may influence angiogenesis and, secondarily, also cell division. Cedres

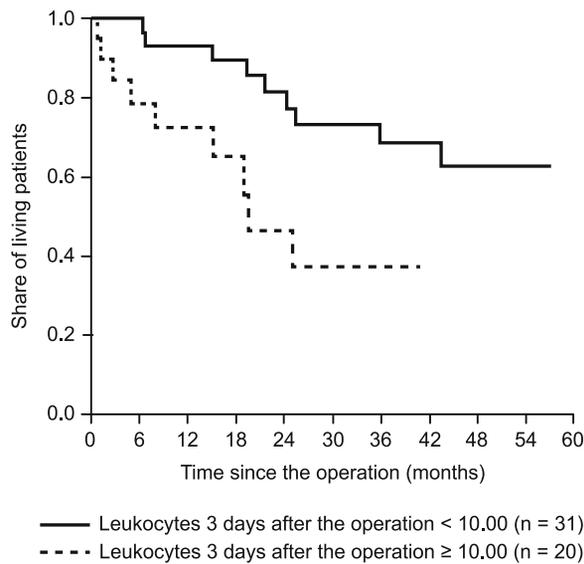


Fig. 1. Overall survival of patients after the operation in relation to the WBC count 3 days after the operation.

et al. and Ramsey et al. have confirmed that changes in the ratio of neutrophils and lymphocytes (NLR) influence the prognosis in patients with advanced and metastatic renal cell carcinoma (2, 8). Tomita et al. and Yao et al. evaluated the ratio of NLR in non-small cell lung carcinoma prior to the operation and its relationship with prognosis and chemotherapy response (9, 10). Hara et al. evaluated the relationship between postoperative CRP level and overall survival. The study has shown that an elevated CRP level has a negative influence on overall survival (6). Hypothetically, elevated values of inflammatory markers could be interpreted as a response of the immune system to varying degrees of “aggressive tumour behaviour”. WBC count may also be influenced by the size of the tumour and the “total tumour mass” (6). A logical consequence of a radical resection of the tumour should be early normalisation of the postoperative WBC count in the peripheral blood due to the lack of interaction between the immune system and the cancer (7). By excluding patients with decompensated co-morbidities and with a long history of NSAID usage, we took effort to exclude most possible interfering factors that might have influenced the WBC and CRP levels. It has been shown that there is a correlation between a WBC count established on the 72 hours after the operation exceeding $10,00 \times 10^9$ in peripheral blood and overall survival for 24 months after the operation. The use of postoperative values of inflammatory markers as a prediction of cancer recurrence could be limited by the influence of operative stress and the subsequent response of the immune system that impacts early postoperative values. However, the values of sensitivity and specificity of the test, as well as the demonstrable statistical significance show that it is possible to predict cancer recurrence. We are aware of the limitations of smaller patient cohorts, however, our findings confirm a significant relationship between WBC and disease recurrence and provide the rationale for performing large-scale prospective cohort studies.

Conclusion

The immunopathogenesis of inflammation in a cancer disease and the evaluation of inflammatory parameters in serum and in peripheral blood appears to be a promising field to search for left upper lobe NSCLC prognostic markers. Our statistical analysis has established a statistically relevant relationship between WBC count in peripheral blood third day after the operation and overall survival for 24 months after the operation where the initial WBC count in peripheral blood exceeded $10,00 \times 10^9$. Our findings confirm the potential of using WBC count to improve current protocols to establish postoperative prognosis for NSCLC of the upper left lobe and highlight the fact that predicting NSCLC recurrence is a multi-field challenge that requires individual approach to each patient.

References

1. Pinato DJ, Shiner RJ, Seckl MJ, Stebbing J, Sharma R, Mauri FA. Prognostic performance of inflammation-based prognostic indices in primary operable non-small cell lung cancer. *BJC* 2014; 110 (8): 1930–1935.
2. Cedres S, Torrejon D, Martinez A et al. Neutrophil to lymphocyte ratio (NLR) as an indicator of poor prognosis in stage IV non-small cell lung cancer. *Clin Transl Oncol* 2012; 14 (11): 864–869.
3. Chua W, Clarke SJ, Charles KA. Systemic inflammation and prediction of chemotherapy outcomes in patients receiving docetaxel for advanced cancer. *Support Care Cancer* 2012; 20 (8): 1869–1874.
4. Forrester LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer. *Br J Cancer* 2004; 90 (9): 1704–1706.
5. Giannousi Z, Gioulbasanis I, Pallis AG et al. Nutritional status, acute phase response and depression in metastatic lung cancer patients: correlations and association prognosis. *Support Care Cancer* 2012; 20 (8): 1823–1829.
6. Hara M, Yonei A, Ayabe T, Tomita M, Nakamura K, Onitsuka T. Postoperative serum C-reactive protein levels in non-small cell lung cancer patients. *Ann Thorac Cardiovasc Surg* 2010; 16 (2): 85–90.
7. Ramsey S, Lamb GW, Aitchison M, Graham J, McMillan DC. Evaluation of an inflammation-based prognostic score in patients with metastatic renal cancer. *Cancer* 2007; 109 (2): 205–212.
8. Tomita M, Shimizu T, Ayabe T, Nakamura K, Onitsuka T. Elevated preoperative inflammatory markers based on neutrophil-to-lymphocyte ratio and C-reactive protein predict poor survival in resected non-small cell lung cancer. *Anticancer Res* 2012; 32 (8): 3535–3538.
9. Yao Y, Yuan D, Liu H, Gu X, Song Y. Pretreatment neutrophil to lymphocyte ratio is associated with response to therapy and prognosis of advanced non-small cell lung cancer patients treated with first-line platinum-based chemotherapy. *Cancer Immunol Immunother* 2012; 62 (3): 471–479.
10. Hung JJ, Wang CY, Huang MH, Huang BS, Hsu WH, Wu YC. Prognostic factors in resected stage I non-small cell lung cancer with a diameter of 3 cm or less: visceral pleural invasion did not influence overall and disease-free survival. *J Thorac Cardiovasc Surg* 2007; 134 (3): 638–643.
11. Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, Clarke SJ. A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. *Br J Cancer* 2012; 107 (4): 695–699.

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