## ORIGINAL ARTICLE

# Atelectasis: positive or negative prognostic factor on outcome of patients with non-small cell lung cancer?

A. Tepavac[1], N. Secen[1], D. Sazdanic Velikic[1], G. Popovic[1], B. Perin[2]

[1]*Department of Chemotherapy,* [2]*Department of Invasive Diagnostics, Institute of Pulmonary Diseases of Vojvodina, Sremska Kamenica, Medical Faculty, University of Novi Sad, Serbia*

## Summary

*Purpose:* The aim of this study was to evaluate the influence of atelectasis (AT) on overall survival of patients with non small cell lung cancer (NSCLC).

*Methods:* The study included patients of both sexes with unresectable stage III and IV NSCLC with good performance status (PS) (ECOG ≤2). Patients were divided into two groups: with AT (AT+) and without AT (AT-): Factors analyzed included sex, age, histologic type, ECOG performance status, stage of disease and treatment modality. Overall survival was estimated according to Kaplan-Meier method, and multivariate analysis was used to identify independent prognostic factors.

*Results:* We evaluated 247 patients (83% males and 17% females); 47/247 (19%) of patients belonged to AT+ group. In this group 21% of patients had stage IIIA, 46% IIIB stage, and 33% IV stage. Overall survival was significantly longer in the AT+ group (15.23 vs. 9.03 months, p=0.001). AT+ patients in stages III and IV had significantly longer overall survival than AT- patients in the same stages (p=0.001, p=0.002, respectively). Multivariate analysis showed that atelectasis (p=0.001), stage of disease (p=0.001), and treatment modality (p=0.005) were independent prognostic factors associated with survival.

*Conclusion:* Atelectasis is favorable prognostic factor concerning overall survival in patients with NSCLC.

Key words: atelectasis, lung cancer, non small cell, overall survival, prognostic factors

## Introduction

Lung cancer represents a major health problem. It is one of the most frequent cancers and ranks first among cancer-related deaths. Most of the patients present with advanced disease. Surgery is the standard curative approach of the early-stage NSCLC but only 20-30% of patients can be candidates for such a treatment [1].

TNM staging system in lung cancer uses tumor size to define T parameter. T definition includes also some non-size-based descriptors, such as visceral pleura invasion, position within the bronchial tree, presence of obstructive pneumonitis or atelectasis (AT), invasion of surrounding structures, pleural or pericardial effusion, and the presence of satellite nodules. The presence of any of these findings is supposed to be associated with a worse prognosis, regardless of the tumor size [2,3].

The present TNM classification includes AT within the negative prognostic factors, if it is associated with hilar or entire-lung AT. However, in early stages, its independent predictive value has not been validated by several reports, and its significance in advanced stages is not well established due to paucity of the published reports on this issue [4].

We hypothesized that NSCLC patients with AT may have a longer survival than those without AT when establishing the disease diagnosis. This study was undertaken to test this hypothesis.

## Methods

This retrospective study was carried out in the Clinic of Pulmonary Oncology of the Institute of Pulmonary Diseases of Vojvodina in Sremska Kamenica.

## Inclusion criteria

Patients of either sex with NSCLC established cytologically and/or histologically in 2003; stages IIIA, IIIB or IV according to the current TNM classification; conservative treatment applied; ECOG PS ≤ 2.

## Treatment administered

### Chemotherapy

Treatment included platinum-based chemotherapy (cisplatin 60 mg/m$^2$, day 1 plus etoposide 120 mg/m$^2$, days 1-3 in 3-week intervals, or cisplatin 50 mg/m$^2$, day 1 plus gemcitabine 1000 mg/m$^2$, days 1 and 8 in 2-week intervals) and irradiation. Four chemotherapy cycles were administered to all patients.

### Radiotherapy

The irradiation field included the primary tumor and the ipsilateral hilar and mediastinal structures. Total dose was 60 Gy (2 Gy/day, 5 days/week), delivered by linear accelerator.

### Chemoradiotherapy

Chemoradiotherapy was administered without dose reduction of the chemotherapeutic drugs.

Depending on their chest X-ray, the patients were classified into two groups: patients with atelectasis (AT+) (n=47), and those without atelectasis (AT-) (n=200). The major criterion to establish the diagnosis of AT was the absence of air on thoracic CT. All of the patients in the AT+ group had complete obstruction of the bronchus confirmed on bronchoscopy as well.

## Statistical analysis

Cumulative survival rates were correlated with the presence/absence of AT, disease stage, histological tumor type, patients' PS and applied treatment modality. Overall survival was calculated from the moment of establishing the diagnosis until death or the last visit/examination.

The relevant data were collected from patients' medical records.

The patient sample size was chosen to confer a margin of error < 3% for the 95% confidence interval. Survival curves were plotted using the Kaplan-Meier method. Multivariate analysis for survival was performed using the stepwise Mantel-Cox proportional hazards model to identify independent prognostic factors. All p-values were estimated by t-test and considered as significant at p<0.05.

SPSS version 11.0 statistical software was used to perform all statistical analyses.

## Results

In the AT+ group there was a statistically significant male sex predominance (85%; p=0.001), whereas females prevailed in the AT- (82%; p=0.001; Table 1).

In the AT+ group, patients aged 51-60 years (17/47; 36%) predominated over other 10-year age increments, and in the AT- group, patients aged 61-70 (80/200; 40%) predominated over other 10-year age increments. No significant difference was established between the AT+ and AT- group regarding the patient age.

According to histological type, squamous cell NSCLC was significantly most frequent in the AT+ group (37/47; 80%) compared to adenocarcinoma (13%; p=0.001) and non-classified NSCLC (7%; p=0.001). Squamous cell NSCLC was also the most common histological type in the AT- group (48.5%), significantly exceeding the frequency of adenocarcinoma (34.5%; p=0.001) and non-classified NSCLC (17%; p=0.001).

In the AT+ group, ECOG PS 0-1 predominated (32/47; 68%) over PS 2 (15/47; 32%; p=0.001). In the AT- group, the corresponding figures were 137/200 (68%) patients for PS 0-1 and 63/200 (31%) for PS 2 (p=0.001).

No significant difference (p=0.98) was established between AT+ and AT- regarding ECOG PS.

Most patients of the AT+ group had stage IIIB disease (22/47; 46%), significantly higher than IIIA (10/47; 21.3%; p=0.001).

Most subjects of the AT- had stage IV disease (98/200; 49%), significantly higher than stage IIIB (66/200; 33%; p=0.001), and stage IIIA (36/200; 18%; p=0.001).

AT+ patients most frequently received combined chemoradiotherapy (15/47; 32%), exceeding irradiation alone (8/47; 17%; p=0.096), best supportive care

**Table 1.** AT$^+$ and AT$^-$ cases according to gender

| Gender | AT (+) | | AT (−) | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Males | 40 | 85 | 164 | 82 | 204 | 83 |
| Females | 7 | 15 | 36 | 18 | 43 | 17 |
| Total | 47 | 100 | 200 | 100 | 247 | 100 |

AT: atelectasis

(6/47; 13%; p=0.028), and chemotherapy alone (4/47; 8%; p=0.006).

AT- patients most frequently received chemotherapy alone (63/200; 32%), significantly exceeding irradiation alone (36/200; 18%; p=0.002), best supportive care (36/200; 18%; p=0.002), as well as other treatment modalities (10/200; 5%; p=0.001).

The mean cumulative survival of the AT+ and AT- patients was 15.23 months (range 2.3-40.2) and 9.03 months (range 1-27), respectively (p=0.001; Figure 1).

Stage III patients (Figure 2) had mean cumulative survival of 14.6 months (range 2-36) and 10.44 months (range 1-27) in the AT+ and AT- groups, respectively (p=0.001).

Stage IV patients (Figure 3) had mean cumulative survival of 13.60 months (range 3-40) and 7.57 months (range 1-26) in the AT+ and AT- group, respectively (p=0.002).

Patients with adenocarcinoma and squamous cell histology had mean cumulative survival of 9.19 (range 1-27) and 10.93 (range 1-40) months, respectively (p = 0.052).

The mean cumulative survival of patients with the ECOG PS 0-1 was 10.47 months (range 2-36), while those with ECOG PS 2 survived for a mean of 9.65 months (range 1-40; p=0.44).

*Multivariate analysis of prognostic factors*

Multivariate analysis (Table 2) identified as independent prognostic factors associated with survival the following: presence vs. absence of atelectasis (p<0.001), stage of disease (p<0.001), and applied treatment modality (p<0.005; radiotherapy attained the
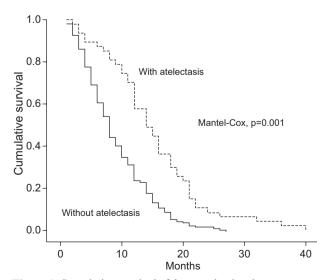
best therapeutic results). Sex, age and histological tumor type were not recognized as independent prognostic factors (p<0.244, p<0.69, p<0.052, respectively).
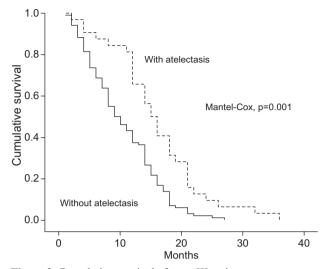


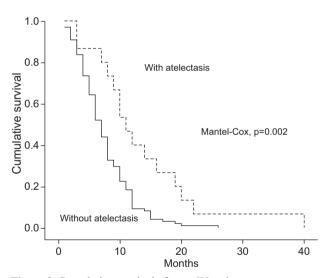**Figure 2.** Cumulative survival of stage III patients.



**Figure 3.** Cumulative survival of stage IV patients.

**Table 2.** Multivariate analysis of potential prognostic factors associated with survival

| Factors | SE | 95% CI | p-value |
|---|---|---|---|
| AT(+)/AT(−) | 0.190 | 0.279-0.588 | 0.001 |
| Male/Female | 0.176 | 0.870-1.733 | 0.244 |
| Adenocarcinoma | 0.198 | 0.724-2.055 | 0.456 |
| Squamous cell | 0.264 | 0.720-2.027 | 0.475 |
| Stage III | 0.193 | 0.244-0.734 | 0.001 |
| Stage IV | 0.157 | 0.507-0.938 | 0.018 |
| Age | 0.007 | 0.983-1.012 | 0.695 |
| Treatment modality | 0.175 | 0.279-0.588 | 0.005 |

AT: atelectasis, SE: standard error, 95% CI: 95% confidence interval



**Figure 1.** Cumulative survival of the examined patients.

## Discussion

Lung cancer represents one of the most important health problems. It is a frequent disease and the leading cause of cancer mortality. Only 25% of NSCLC patients can be candidates for curative surgery. Unfortunately, the prognosis of locally advanced NSCLC is not satisfactory with about only 10% 5-year survival and 20% locoregional control rates [5].

In NSCLC, the TNM staging system includes AT among the negative prognostic factors. Regardless of its geometrical dimension, any tumor is classified as T2 or T3 if it is associated with hilar or entire-lung AT [2]. However, our clinical experience did not support the negative prognostic significance of AT in advanced stages.

Our analysis showed that patients with AT have better survival compared to patients without AT (15.23 vs. 9.03 months, p<0.001).

Median overall survival in stage III patients with AT was significantly longer compared to patients with the same stage but without AT (16.00 vs. 10.44 months, p<0.001). We found the same situation in stage IV: patients with AT had statistical significantly longer overall survival compared to patients without AT (13.6 vs. 7.57 months, p<0.001).

No statistically significant differences in survival were detected concerning different histological types (adenocarcinoma vs. squamous cell carcinoma, p< 0.052), and ECOG PS (0-1 vs. 2, p<0.44).

The incidence of AT in NSCLC is unknown. In early stages, the pathologic examination of the resected material found AT in < 10% of the cases, but in advanced stages its incidence is reported between 23 and 44% [4,6].

In our study the presence of AT was 19%. We need to stress that confirmation of AT was done following bronchoscopic and radiologic assessment. We excluded patients with uncertain confirmation of AT or patients who had false-positive radiologic image like lobar consolidation without complete obstruction, pleural effusion, pleural effusion with subsequent parenchymal collapse, and other non-obstructive atelectatic conditions in which a tumor has infiltrated the entire lobe [7-9].

We consider that the inclusion of AT among the non-size based, negative predictors in NSCLC was not accurately supported by clinical data. Some authors proposing a reliable TNM staging system, analyzed various prognostic factors which were deemed to be independently associated with a worse prognosis. The variables associated with the T factor were size, location, external margin, complication such as AT or obstructive pneumonitis and pleural effusion. Despite the fact that AT and pneumonitis were initially defined as distinct clinical events, the methodology of assessment gathered AT and the obstructive pneumonitis as a single variable, as a negative predictor for survival. However, the final version of the T category characterizes AT and obstructive pneumonitis as separate prognostic factors, both associated with a worse outcome [2].

Obstructive AT induced by lung tumors implies a complete obliteration of the bronchial ostium, with subsequent collapse of the lung parenchyma and absorption of the air trapped distally [9].

The broncho-alveolar space is virtually sterile and therefore the association of an infectious process is not obligatory. Despite the widespread belief that AT is commonly associated with fever and infection, some reports strongly recommend a clear separation between these two conditions, as many clinical studies do not support this association [2,10].

The stage of disease, involved mediastinal lymph nodes, performance status, hypercalcemia and weight loss are well known prognostic factors in lung cancer patients. The negative impact of malignant pleural effusion on the lung cancer patients' survival has been enlightened well, unlike the effects of other tumor-associated conditions. The impact of AT, pulmonary metastases, pleural effusion and other intrathoracic conditions has been reported by several authors. Analyzing each of these conditions separately, only AT has been recognized as significant in terms of survival improvement - the mean survival is significantly longer in patients with AT regardless whether it is segmental, lobar or involving the entire lung. This finding is in contrast with the well-established correlation between the T status and prognosis, as there is a close correlation between a more advanced tumor stage and AT. Although the impact of AT on survival should be additionally investigated, it has been already established that the AT-affected region provides a decreased blood supply to the tumor due to the occurrence of shunt effect. Intratumoral blood flow and angiogenesis are directly associated with tumor growth and progression. Diminished blood flow in the tumor may retard the development of systemic metastases, thus reducing the systemic circulation of the tumor-associated biological and molecular markers such as CYFRA 21-1, chromogranin A and neuron specific enolase, which have been established to correlate with survival. Yilmaz et al. [4] also conclude their paper reporting AT as the most frequent intrathoracic condition identified as a favorable prognostic factor in patients with locally advanced lung cancer.

Identification of the lung cancer prognostic factors is helpful for individual prognosis, treatment modality selection, correlation of patients from diverse studies or centers, definition of inclusion criteria for

clinical trials, and classification of patients into risk subgroups and better understanding of the disease [11].

A number of basic clinical features has been efficiently used to predict the course and outcome of lung cancer, and recently simpler biochemical tests have also been used as a minimal set of prognostic factors. Unfortunately, interpretation, relevance and ranking of certain factors established as prognostic, or potentially prognostic is not simple [11].

The multifactorial analysis has established the following statistically significant prognostic factors: the presence or absence of AT, stage of disease and applied treatment modality.

The results of our study indicate the importance of these prognostic factors for the patients' survival. The stage of disease is obligatorily considered as important factor when selecting the treatment modality in NSCLC cancer patients. The relevance of the disease stage for the patients' survival has been confirmed by many authors [12]. The consensus reached by many studies applying multifactorial analysis, states that the stage of disease represents a significant prognostic factor, together with PS and body weight loss. In many studies patients' age and histological tumor type have shown no effects on survival [11,12].

The results of our study correlate with the consensus regarding the stage of disease (p<0.001).

In our study, the histological tumor type has been shown as statistically irrelevant for the patients' survival, but a slightly better survival was registered in the patients with squamous than those with adeno histological type of lung cancer (10.9 vs. 9.1 months; p<0.052).

PS helps selecting the treatment modality to be applied, having its relevance as a prognostic factor. However, the prognostic value of this parameter has not been confirmed in our study and no statistically significant difference has been registered in our patients' survival depending on their PS score (ECOG 0/1: 10.47 vs. ECOG 2: 9.65 months; p=0.44).

Gender has been investigated in many studies as a potentially relevant factor for the patients' survival, and it may generally been said to have no prognostic value, although there are studies reporting better survival in females [13,14]. In our study gender has not been recognized as a factor associated with better survival (p<0.244).

Age cannot be included in the class of independent prognostic factors, as the consensus of its significance for survival has not been reached yet [13].

Our study also found age to be not significant prognostic factor (p<0.695).

To conclude, it may be said that additional research is required in order to include AT and obstructive pneumonitis in the group of prognostic factors relevant for the treatment outcome and survival. The results of this study have confirmed that patients with AT have a significantly longer survival than those without AT, but inclusion of AT in the group of independent prognostic factors in NSCLC requires further investigation.

## Acknowledgement

## References

1. Cetingoz R, Arican-Alicikus Z, Nur-Demiral A, Durmak-Isman B, Bakis-Altas B, Kinay M. Is re-irradiation effective in symptomatic local recurrence of non small cell lung cancer patients? A single institution experience and review of the literature. J BUON 2009; 14: 33-40.

2. Dediu M, Crisan E, Radut M et al. The favorable prognostic significance of atelectasis in patients with advanced non-small cell lung cancer: results of a prospective observational study. Lung Cancer 2009; 63: 271-276.

3. Ou I, Zell J, Ziogas A, Anton-Culver H. Prognostic significance of the non-size based AJCC T2 descriptors: visceral pleura invasion (VPI), hilar atelectasis or obstructive pneumonitis in stage IB non-small cell lung cancer (NSCLC) is dependent on tumor size. Chest 2008; 133: 662-669.

4. Yilmaz B, Oytuna F, Tobpa M, Ozlu T. Survival analysis of patients with thoracic complications secondary to bronchial carcinoma at the time of diagnosis. Respiration 2005; 72: 388-394.

5. Parkin GM, Pisani P, Ferlay J. Global Cancer Statistics. CA Cancer J Clin 1999; 49: 33-64.

6. Ball D, Fisher R, Burmeister B et al. Stage is not a reliable indicator of tumor volume in non-small cell lung cancer: a preliminary analysis of the trans-Tasman Radiation Oncology Group 99-05 Database. J Thorac Oncol 2006; 1: 667-672.

7. Ashizava K, Hayashi K, Aso N, Minami K. Lobar atelectasis: diagnostic pitfalls on chest radiology. Br J Radiol 2001; 74: 89-97.

8. Peroni DG, Boner AL. Atelectasis: mechanisms, diagnosis and management. Pediatr Respir Rev 2000; 1: 274-278.

9. Sharma S, Mayckes B, Tsuiuki S. Atelectasis. Lobar. http://www.emedicine.com/RADIO/topic64.htm. Last update: January 10, 2007.

10. Engoren M. Lack of association between atelectasis and fever. Chest 1995; 107: 81-84.

11. Maki E, Feld R. Prognostic factors in patients with non-small cell lung cancer. A critique of the world literature. Lung Cancer 1991; 7: 27-34.

12. Perin B. Size and localisation of tumor as factors with influence on outcome among patients with non small cell lung cancer. PhD thesis. University of Novi Sad, Medical Faculty, 1997.

13. Moore DF Jr, Lee JS. Staging and prognostic factors: Non-small cell lung cancer. In: Pass HI, Mitchel JB, Johnson DH, Turrisi AT (Eds): Lung Cancer. Principles and Practice. Lippincott-Raven, Philadelphia, New York, 1996, pp 481-494.

14. Ihde DC. Non-small cell lung cancer. I. Biology, diagnosis and staging. Curr Probl Cancer 1991; 15: 65.