ABSTRACT

**Aim** To investigate the impact of some parameters of lung function (forced expiratory volume in 1 second - FEV₁, forced vital capacity - FVC and ratio FEV₁/FVC%) on survival in patients with advanced non-small cell lung cancer (NSCLC).

**Methods** It retrospectively analyzed data of 155 patients with NSCLC receiving second-line treatment in the Clinic for Lung Diseases, Clinical Center Niš, Serbia, from October 2009 to December 2012. Fifteen potential prognostic variables were subjected to univariate and multivariate analysis to investigate prognostic impact to survival.

**Results** Among the total of 155 patients, 124 (80%) were males. The most frequent was squamous carcinoma, 86 (55.5%). Mean FEV₁ was 1.89 ± 0.71 L (61.8%), mean FVC 2.95 ± 0.8 L (77.2%) and mean FEV₁/FVC% was 63.6%. In a multivariate analysis using Cox regression hazard model (hazard ratio, HR), independent prognostic factors for overall survival (OS) were: FEV₁ <50% of predicted HR= 4.513, 95% confidence interval (CI): 1.433-14.216 (p=0.010), performance status 2 (HR= 0.090, CI= 0.035-0.230 (p=0.000) and weight loss ≥5 % (HR= 0.162, CI= 0.068-0.382 (p=0.000).

**Conclusion** FEV₁ in patients with advanced NSCLC receiving chemotherapy is an important independent factor that can predict survival. There was close relationship between impaired lung function and lung cancer patients survival.

**Key words:** lung neoplasms, spirometry, forced expiratory volume, survival
INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide (1). Approximately 80% of these cases represent non–small-cell lung cancer (NSCLC) (2). The low cure rate for NSCLC can be attributed to the high rate of metastasis at diagnosis and inability of chemotherapy to cure metastatic disease (3). However, randomized trials and meta-analyses demonstrated that platinum-based chemotherapy increases survival, palliates symptoms, improves quality of life (QOL), and is cost effective (4).

Prediction of survival in case of advanced non–small cell lung cancer (NSCLC), when patients have already received first line treatment, is critical to the decision of subsequent treatments. Defining prognostic determinants of NSCLC may help physicians to improve their decision-making for both clinical trials and routine practice (5). Many studies have reported predictive models for survival in metastatic cancers (6). These models integrated a combination of clinical and biological factors (7). Biological characteristics such as lactate dehydrogenase (LDH) level or interleukin 6 level have been correlated with poor outcome in metastatic cancer (8,9).

Patients with advanced NSCLC eventually experience disease progression and require second-line therapy. Very little knowledge is available about the prognostic factors in patients receiving second-line chemotherapy (11). There is close relationship between obstructive lung disease and lung cancer. Smokers with reduced forced expiratory volume in 1 second (FEV₁) carry as much as five to six-fold risk of lung cancer compared with smokers with normal lung function (12). In particular, spirometry might play a very useful role in improving patient selection for targeted lung cancer screening or to predict response to therapy and survival (12). In a large prospective cohort of heavy smokers, it was demonstrated that even a relatively small reduction in FEV₁% (predicted) is a significant predictor of increased lung cancer risk (13). In series of non-screened lung cancer cases, 80% had FEV₁ <90% predicted (13). Surgical resection remains the treatment of choice for early stage NSCLC, offering the best prospect of longterm survival (14). Nevertheless, many patients have coexisted chronic airflow limitation and/or diffusion impairment, which is associated with an increased risk during surgery (15). In patients with advanced NSCLC, factors essential to decision making are the extent of disease, weight loss, and performance status (PS), as these are the most predictive indicators of median patient survival time after undergoing systemic chemotherapy (16). Good performance status, female sex, age ≤70 years, and cisplatin-based chemotherapy have been known to be predictive of favorable survival rates overall (17).

Approximately 40%–50% of patients in recent first-line trials received second-line treatment (18). Patients who appear more likely to receive second-line therapy are those with a good PS, female patients, and those with nonsquamous histology (19). Many patients who maintain a good PS and tolerate therapy without significant toxicities will receive third-line therapy (20). Almost 50% of the patients received chemotherapy in the last month of life, and 20% received systemic treatment in the last two weeks of the life (21). Recognition of prognostic factors in patients with advanced NSCLC candidates to receive chemotherapy, mainly second and third lines treatment, is fundamental to avoid futility of therapies (22).

The aim of this study is to investigate the impact of some parameters of lung function (FEV₁, FVC and FEV₁/FVC%) on survival in patients with advanced NSCLC and to compare importance of potential prognostic factors of survival.

PATIENTS AND METHODS

This study has shown a retrospective chart review of patients who had undergone chemotherapy for NSCLC and collected data from patients with NSCLC of stage IIIB or IV and available spirometry at diagnosis of lung cancer. Retrospectively, 155 patients receiving second-line treatments were reviewed from October 2009 to December 2012 at the Clinic for lung Diseases of the Clinical Center Niš. The staging was decided according to the seventh edition of Tumor Nodus Metastasis (TNM) classification of NSCLC (23). Lung function was measured at baseline in all study participants by using a flow MasterLab, Yaeger, softver 2006 according to the American Thoracic Society/European Respiratory Society recommendations (24). The following values were evaluated: FEV₁, forced vital capacity (FVC), and the ratio of FEV₁ to FVC (FEV₁/FVC).

Fourteen potential prognostic variables were chosen on the basis of previously published clinical trials.
The variables were divided to the following categories: age (<65 or ≥65 years), sex (male, female), performance status (PS) (ECOG 0-1, 2) (25), smoking (ever, never), weight loss ≥5% (yes, no), comorbidities (yes, no), number of meta localization (1, 2-4), histology (adenocarcinoma, non-adenocarcinoma), stage (IIIB, IV), first line chemotherapy regimen (gemcitabin/cisplatin (GC), etoposide/cisplatin (EP)), first line chemotherapy response (responders: complete response + partial response, non-responders: stable disease + progression of disease), second line chemotherapy regimen (gemcitabin/cisplatin (GC), etoposide/cisplatin (EP), gemcitabin mono, paclitaxel/carboplatin, docetaxel mono, erlotinib), FEV₁ (FEV₁ ≥50% predicted, FEV₁ <50% predicted), FVC (FVC ≥80% predicted, FVC <80% predicted), FEV₁/FVC ratio (FEV₁/FVC ≥70%, FEV₁/FVC <70%).

Descriptive data are expressed as mean ± SD, and frequencies are expressed as numbers (%). Differences between two groups were tested using the Student’s t test. Categorical variables were analyzed using χ² test. Overall survival (OS) was calculated from the start of the first cycle of chemotherapy to death from any cause or the date of the last follow-up. Progression free survival (PFS) was defined as the time between the first day of chemotherapy and progression or death. Cumulative survival was analyzed by the Kaplan-Meier method and compared by log-rank test. A multivariate Cox proportional hazard model was used to identify prognostic factors. Statistical significance was accepted at the “p” values of less than 0.05 level. All patients signed informed consents before the treatment regarding the purpose and intent of the treatment and the need for information about the treatment to be used in professional and scientific purposes. Using and publication of the data from this study were approved by the Ethics Committee of the Clinical Center of Nis.

RESULTS

Second line treatment at the time of progression after the first line cisplatin-based chemotherapy was received by 155 patients. The median age of patients was 58.61 ± 7.860 with 124 (80%) males and 31 (20%) females. Among 155 patients, 57 (36.8%) died and their mean age was 56.7 ± 9.022 years; 48 (84.2%) were males. Survivors did not have significantly better performance status than non-survivors (p=0.273). Never smokers were not more common in survivors (8.2% vs 8.8%) (p=0.456) (Table 1), but weight loss ≥5% was frequently in survivors, 50 vs. 18 (51% vs. 31.6%). Squamous carcinoma was the most common histologic type, 55% (86 pts). There were 35 at stage IIIB and 120 at stage IV. (Table 2). Between survivors and non-survivors not significant differences were found in the number of meta localization, frequently used chemotherapy regimen for first or second line and response to the therapy. Mean FEV₁ was 1.89 ± 0.71 L (61.8 ± 18.6%), but there was no significant difference between survivors and non-survivors. Significant differences were not found among observed patients for FVC and FEV₁/FVC ratio (Table 1).

The results of univariate analysis for PFS are summarized in Table 3. Among fifteen variables eight had prognostic significance: PS (p=0.000), weight loss ≥5% (p= 0.000), comorbidities (p= 0.000), number of meta localization (p=0.005), first-line chemotherapy regimen (p=0.026), first-line therapy...
response (p=0.000), FEV1% predicted (p=0.000), and FEV1/FVC%, (p=0.000). In multivariate analysis using Cox regression hazard model, independent prognostic factors for PFS were performance status (mean 11.4 months for PS2 vs. 5.8 months for PS 0 or 1, HR: 0.317), weight loss ≥5% (12.6 m for yes vs. 6.7 m for no, HR: 0.152), comorbidities (11.7 m for yes vs. 7.5 m for no, HR: 0.449) and first-line chemotherapy regimen (10.1 m for Gem/Cis vs. 8.5 m for E/Cis, HR: 0.021) (Table 4).

Univariate analysis for overall survival showed that eight variables had prognostic significance (Table 3): PS (p=0.000), weight loss ≥5% (p=0.000), comorbidities (p=0.000), number of meta localization (p=0.002), first-line chemotherapy regimen (p=0.026), first-line therapy response (p=0.029) FEV1, predicted (p=0.000), FVC% predicted (p=0.000) and FEV1/FVC%, (p=0.025).

Multivariate analysis established three independent factors for overall survival (Table 4).

### Table 2. Disease-related characteristic

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Survivor</th>
<th>Non-survivor</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.505</td>
<td>0.477</td>
<td>0.269</td>
<td>0.604</td>
</tr>
<tr>
<td>Sex</td>
<td>0.606</td>
<td>0.436</td>
<td>2.164</td>
<td>0.141</td>
</tr>
<tr>
<td>Performance status</td>
<td>85.736</td>
<td>0.000</td>
<td>72.506</td>
<td>0.269</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.764</td>
<td>0.382</td>
<td>1.204</td>
<td>0.273</td>
</tr>
<tr>
<td>Weight loss &gt;5%</td>
<td>71.706</td>
<td>0.000</td>
<td>42.158</td>
<td>0.000</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>47.641</td>
<td>0.000</td>
<td>42.409</td>
<td>0.000</td>
</tr>
<tr>
<td>Histology</td>
<td>44.129</td>
<td>0.000</td>
<td>26.149</td>
<td>0.000</td>
</tr>
<tr>
<td>Stage</td>
<td>39.527</td>
<td>0.000</td>
<td>17.37</td>
<td>0.000</td>
</tr>
<tr>
<td>No of meta localisation</td>
<td>0.955</td>
<td>0.000</td>
<td>1.014</td>
<td>0.327</td>
</tr>
<tr>
<td>First-line HT regimen</td>
<td>0.220</td>
<td>1.090</td>
<td>1.003</td>
<td>0.902</td>
</tr>
<tr>
<td>FEV1/FVC% predicted</td>
<td>13.691</td>
<td>0.000</td>
<td>5.009</td>
<td>0.025</td>
</tr>
</tbody>
</table>

### Table 3 Univariate analysis by categorical variable

<table>
<thead>
<tr>
<th>Variables</th>
<th>Progression Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Log rank</td>
<td>Log rank</td>
</tr>
<tr>
<td>Sex</td>
<td>0.505</td>
<td>0.477</td>
</tr>
<tr>
<td>Performance status</td>
<td>85.736</td>
<td>0.000</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.764</td>
<td>0.382</td>
</tr>
<tr>
<td>Weight loss &gt;5%</td>
<td>71.706</td>
<td>0.000</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>47.641</td>
<td>0.000</td>
</tr>
<tr>
<td>Histology</td>
<td>44.129</td>
<td>0.000</td>
</tr>
<tr>
<td>Stage</td>
<td>39.527</td>
<td>0.000</td>
</tr>
<tr>
<td>No of meta localisation</td>
<td>0.955</td>
<td>0.000</td>
</tr>
<tr>
<td>First-line HT regimen</td>
<td>0.220</td>
<td>1.090</td>
</tr>
<tr>
<td>FEV1/FVC% predicted</td>
<td>13.691</td>
<td>0.000</td>
</tr>
</tbody>
</table>

### Table 4. Prognostic factors by Cox regression model

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>0.317</td>
<td>0.161 - 0.623</td>
</tr>
<tr>
<td>Weight loss &gt;5%</td>
<td>0.152</td>
<td>0.076 - 0.303</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>0.449</td>
<td>0.249 - 0.808</td>
</tr>
<tr>
<td>No meta localisation</td>
<td>0.449</td>
<td>0.249 - 0.808</td>
</tr>
<tr>
<td>First-line HT regimen</td>
<td>0.179</td>
<td>0.706 - 1.173</td>
</tr>
<tr>
<td>FEV1% predicted</td>
<td>0.279</td>
<td>1.442 - 2.798</td>
</tr>
<tr>
<td>FVC% predicted</td>
<td>0.481</td>
<td>1.246 - 2.297</td>
</tr>
</tbody>
</table>

HR: Hazard ratio; CI: Confidence interval.

Patients with FEV1 less than 50% predicted showed shorter median survival than those with FEV1 ≥50% predicted (7.9 months versus 18.6 months, p=0.010, HR= 4.513, CI= 1.433-14.216). (Figure 1). The median survival for pa-
tients with performance status 0 or 1 was 20.4 months compared with 7.9 months for patients who had performance status 2 (p=0.000, HR=0.090, CI=0.035-0.230). Finally, patients with weight loss ≥5% had shorter median survival compared with those without weight loss ≥5% (9.4 months versus 24.8 months, p=0.000, HR=0.162, CI=0.068-0.382).

**DISCUSSION**

FEV₁ less than 50% predicted is well known as a criterion of severe airway obstruction according to the Global initiative for Obstructive Lung Disease guideline (26) and a predictor of mortality in patients with chronic obstructive pulmonary disease (27). In our study we likewise chose FEV₁ of less than 50% predicted as a criterion of lung function decline. The effects of FEV₁% predicted and FEV₁/FVC% have been identified as prognostic values for PFS, but Cox regression analysis did not confirm these parameters as independent factors for PFS. All three observed parameters of lung function had a prognostic value for overall survival, but only FEV₁% predicted independent impact on overall survival. This result confirms the importance of lung function parameters, not only in assessing the functional status of the patients, but also in the assessment of survival.

The significance reduction of pulmonary function on survival in advanced NSCLC has not been properly appreciated. In general population, reduced FEV₁ has been reported to be a predictor of mortality (28). It was second in importance to cigarette smoking as a predictor of subsequent all cause mortality. FEV₁ to be a surrogate marker of exposure to carcinogens from smoking. Although smoking exposure is an important pre-requisite for most lung cancer, the contribution of smoking dose to the variance in FEV₁ is modest and much less than that from genetic factors (29). Calabro et al. have shown that between 50 and 80% of patients diagnosed with lung cancer had pre-existing chronic obstructive pulmonary disease (COPD) (30). Lung function is well known to be an important prognostic factor for patients with NSCLC to consider surgery (31). However, 90% of lung cancer patients, are current or past smokers and frequently have varying degrees of concomitant chronic obstructive pulmonary disease (COPD) and/ischaemic heart disease (32). In the study population, the majority of patients were smokers or former smokers (142 – 91.6%) and therefore at high risk of COPD. The mean value of FEV₁ of the entire population was 1.89 L (6.8 ± 18.6%), with a mean value (63.6 ± 13.4%) FEV₁/FVC% <70%, which indirectly indicates a probable high incidence COPD among subjects. In patients with a FEV₁ was less than 50% predicted, reduction in lung function had a direct impact on the survival of lung cancer. In study Lee JH et al. FEV₁ less than 50% predicted was an independent predictor of mortality for advanced NSCLC in both univariate and multivariate analyses (33).

Few data are available about the prognostic factors in patients who receive second-line treatments (34). Prognostic factors are not sufficiently predictive of second-line treatment efficacy, while it may be concluded help that the choice of a treatment should be based according to prognostic factors (35). Multivariate analysis of factors influencing survival in the current study showed that response to therapy was an important prognostic factor for OS. Using a methodology of non-inferiority, in the study of Hanna N et al. pemetrexed showed identical clinical efficacy as docetaxel in second-line treatment (36). Typical favorable prognostic factors were identified by a Cox proportional multiple regression analysis and noted to include favorable performance status (PS= 0-1), lower stage of disease (III vs IV), and time since the first-line chemotherapy (> 3 months).

The current study demonstrated that PS not only negatively affected OS, but also affected PFS negatively. A poor PS confirmed negative prognostic factors in advanced NSCLC patients who received second-line treatment (37). Study of prognostic factors in elderly patients with NSCLC (Kefeli et al.) identified performance status significantly affected OS, but was not an independent prognostic factor (38). The combination of poor PS and anemia is an effective strategy to predict survival in the case of patients with metastatic NSCLC receiving further treatment after the first line. From a prospective study by Belbaraka R. et al. both PS and anemia were found as independent determinants of survival (39).
Series of 14 South Western Oncology Group (SWOG) trials, where 2531 patients with inoperable lung cancer were recruited during 1974-1988 in order to investigate the impact that 50 prognostic factors had on survival, revealed that performance status, extent of the disease, and weight loss were among the most important ones (40). The association between low BMI and lung cancer is unexplained and requires further investigation but, low body mass index (BMI) has been associated with an increased risk of lung cancer particularly in males and smokers (41). Nevertheless, BMI and FEV₁ reflect nutritional status and respiratory function, respectively, both of which comprise a large portion of the performance status. Lee JH et al found in a retrospective study of 156 patients with NSCLC that BMI had significant independent prognostic impact on overall survival (33).

The association between body mass index (BMI) and lung cancer is still disputed because of possible residual confounding by smoking and preclinical weight loss in case-control studies. Recent multicenter ICARE study in France discovered an inverse dose-dependent association between lung cancer risk and BMI two years prior to interviews in current smokers. (42). In our study weight loss ≥5% in 87 (56.1%) of patients was a significant independent prognostic factor for both PFS and OS. Given that there was close relationship between obstructive lung disease and lung cancer, spirometry might play a very useful role in improving patient selection for targeted lung cancer screening or treatment. Pretreatment spirometry may assist in determining the optimal management plan not only in resectable NSCLC but in advanced NSCLC and allows for a more accurate prediction of prognosis. Besides the known prognostic factors such as weight loss and performance status, the study found that the reduced FEV₁ is an important prognostic factor in patients with advanced NSCLC who were treated with second-line chemotherapy.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

Parametri plućne funkcije kao važni prognostički faktori kod uznapredovalog nemikrocelularnog karcinoma pluća

Milan Rančić, Lidija Ristić, Snežana Rančić, Milan Radović, Zorica Ćirić
Odeljenje za plućnu onkologiju, Klinika za plućne bolesti, Klinički centar Niš, Srbija

SAŽETAK

Cilj Utvrditi uticaj pojedinih parametara plućne funkcije (forsiranog ekspiratornog volumena u prvoj sekundi – FEV1; forsiranog vitalnog kapaciteta – FVC; te odnosa FEV1/FVC%) na preživljavanje pacijenata s nemikrocelularnim karcinomom pluća.

Metode Retrospektivno su analizirani podaci 155 pacijenata s nemikrocelularnim karcinomom pluća (NSCLC) koji su primali sekundarnu liniju hemioterapije u Klinici za plućne bolesti Knez Selo, u Srbiji, u periodu od oktobra 2009. do decembra 2012. godine. Petnaest potencijalnih prognostičkih varijabli podvrgnuto je univarijantnoj i multivarijantnoj analizi s ciljem utvrđivanja prognostičkog značaja za preživljavanje.

Rezultati Od ukupno 155 pacijenata, 124 (80%) bili su muškarci. Najučestaliji je bio skvamozni karcinom, 86 (55,5%). Srednja vrednost FEV1 bila je 1.89 ± 0.71 L (61.8%), srednja vrednost FVC-a bila je 2.95 ± 0.8 L (77.2%), a srednja vrednost FEV1/FVC% 63.6%. Multivarijantnom analizom, koristeći Coxov regresionalni hazardni model (hazard ratio, HR), utvrđeni su nezavisni prognostički faktori za preživljavanje: FEV1 <50% norme (HR= 4.513, 95% confidence interval [CI] 1.433-14.216 (p=0.010), performans status 2 (HR= 0.090, CI= 0.035-0.230 (p=0.000) i gubitak težine više od 5% (HR= 0.162, CI= 0.068-0.382 (p=0.000).

Zaključak FEV1 je važan nezavisni prognostički faktor preživljavanja kod pacijenata s uznapredovalim nemikrocelularnim karcinomom pluća koji su lečeni hemioterapijom. Utvrđena je uska povezanost između oštećene plućne funkcije i preživljavanja pacijenata s karcinomom pluća.

Ključne reči: plućne neoplazme, spirometrija, forsirani ekspiratorni volumen, preživljavanje