Review article

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PREOPERATIVE ASSESSMENT FOR NON-SMALL-CELL LUNG CANCER SURGERY

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Lung cancer is the most common malignant tumor and globally the leading cause of death from malignant diseases in the general population, accounting for approximately 25% of all cancer deaths. According to current data, approximately 7,000 people are diagnosed with lung cancer in Serbia annually, and about 5,000 die from the disease. Treatment for lung cancer is complex and multidisciplinary, with surgery playing a central role in stages I to III-A. Despite numerous studies confirming that surgical resection offers the best chance of recovery, only 20–30% of patients are eligible for surgery at the time of diagnosis. There are many reasons for this, including advanced disease, comorbidities, weakened respiratory function, and poor performance status. Considering that surgical lung resections are often accompanied by peri- and postoperative complications, a detailed preoperative risk assessment is crucial for determining the outcome of treatment. The remainder of this text will outline the currently valid guidelines and protocols for preoperative risk assessment, with a particular focus on high-risk patients (elderly, smokers, chronic obstructive pulmonary disease—COPD—patients, and obese individuals). It will also delve into the role of spirometric-diffusion parameters and stress tests in this assessment.

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Key words: *lung cancer, surgery, spirometry, diffusion, stress tests*

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Introduction

Lung cancer is the most common malignant tumor and the leading cause of death from malignant diseases in men. In women, it is the third most common malignant tumor and the second most common cause of death (1). In Serbia, according to the data of the "Dr. Milan Jovanović Batut" Institute of Public Health, 6,863 people were diagnosed and 5,242 people died from lung cancer in 2019 (2).

Treatment for lung cancer can be surgical or conservative (chemotherapy, radiation therapy, targeted molecular therapy, and immunotherapy). Depending on their overall health status, non-small-cell lung cancer (NSCLC) patients with stage I, II, and III-A may be candidates for surgical treatment (3). Radical surgical intervention offers the best chance of cure. This is supported by the fact that the median survival of NSCLC patients who were not surgically treated and were diagnosed with stage I disease was only 13 months or 25 months (if detected by screening versus symptomatic disease) (4). Unfortunately, at the time of diagnosis, as much as 70–80% of patients are not eligible for surgery, mainly due to advanced disease, comorbidities, and, consequently, poor general health. According to some authors, the percentage of patients with anatomically resectable NSCLC who are not suitable for surgical treatment solely due to poor respiratory function is as high as 37% (5–7). Moreover, 50–70% of NSCLC patients have COPD, arterial hypertension, diabetes mellitus, peripheral vascular disease, and/or other significant comorbidities, which can further complicate potential surgical treatment (8, 9).

Considering the above, it is clear that a properly conducted preoperative evaluation is central to preventing complications, which are otherwise relatively frequent following NSCLC resection (5, 10). Therefore, addressing this issue necessitates a team effort (involving thoracic surgeons, cardiologists, pulmonologists, and anesthesiologists) and an extremely responsible approach.

Preoperative Assessment of Cardiorespiratory Function

The most common cardiorespiratory complications following NSCLC resection include: prolonged mechanical ventilation, reintubation, acute respiratory distress syndrome, pneumonia, atelectasis requiring bronchoscopy, pulmonary embolism, unstable angina pectoris, myocardial infarction, heart failure, and arrhythmias (11). According to Motono et al., the main predisposing factors associated with the development of the aforementioned conditions include male gender, age over 65 years, COPD, upper lobectomy, surgery duration > 2.5 h, lymphovascular invasion, and body mass index (BMI) of less than 21.68 (10). Petrella et al. came to similar conclusions, claiming that malnutrition (BMI < 18.5), obesity (BMI > 30), active smoking, obstructive sleep apnea, COPD, and asthma are the primary triggers for the development of postoperative complications (11).

The basic parameters to be considered when determining the functional operability of an NSCLC patient include age, general health condition, performance status, cardiorespiratory function, physical fitness, and extent of lung resection (8). The latter is significantly correlated with the rate of postoperative mortality, which, according to the results of Powell et al., reaches 2.3% after lobectomy and 7% after pneumonectomy (13).

Regarding the patient's age, today, most authors believe it is not a contraindication for surgical treatment of NSCLC (more than 30% of patients are over 70 years old) (6, 14). However, the risk of postoperative mortality increases with age, primarily due to comorbidities and impaired cardiorespiratory function. In patients over 70 years of age, it reaches 7% after lobectomy and 14% after pneumonectomy (14). Despite this, current recommendations are that elderly patients should be evaluated using the same algorithms as younger people (14).

European Respiratory Society (ERS) and European Society of Thoracic Surgeons (ESTS) experts recommend that all candidates for NSCLC resection should undergo spirometry and diffusing capacity for carbon monoxide (DLco) measurement (14, 15). Forced expiratory volume in 1 s (FEV_1), as the most critical spirometric parameter, provides insight into the state of pulmonary ventilation, while DLco indicates the integrity and function of the alveolar-capillary membrane (16). Following tumor resection, and due to the loss of the surrounding healthy lung parenchyma, the values of both parameters decrease, with the decrease being proportional to the extent of the resection itself. Numerous researchers have addressed this issue. Table 1 shows the average (%) postoperative values of FEV_1 and DLco expressed relative to the preoperative values obtained by some of the authors in their studies (17–19).

Table 1. Average postoperative (%) values of FEV_1 and DLco compared to preoperative values (17–19)

	Lobectomy			
	After one month	After 3 months	After 6 months	After 12 months
FEV_1	71.4%	75.6%	84.3%	84.2%
DLco	64.5%	70.1%	91.3%	96.5%
	Pneumonectomy			
	After one month	After 3 months	After 6 months	After 12 months
FEV_1	48.1%	50.7%	65%	75%
DLco	50.6%	55.9%	80%	85%

The table shows that the most significant recovery of respiratory function occurs in the period 3 to 6 months post-surgery, while the recovery is insignificant later.

ERS and ESTS experts believe that patients with FEV_1 and DLco ≥ 80% can safely undergo surgical resection up to pneumonectomy, without the need for additional analyses (15). Candidates with FEV_1 > 1.5 L can undergo lobectomy, while segmentectomy or wedge resection may be considered if FEV_1 is > 0.6 L (15, 20). Otherwise, patients should not be lightly excluded from consideration for surgical treatment, but should instead be further investigated. In such circumstances, it is suggested that stress tests (described below) be performed to determine maximal oxygen consumption (VO_2max). A VO2max > 20 mL/kg/min indicates that resection up to pneumonectomy can be safely performed. In contrast, a VO_2max < 10 mL/kg/min suggests that surgical treatment should be abandoned due to the high risk of postoperative complications and death (15). Patients with a reduced aerobic capacity (VO_2max between 10 and 20 mL/kg/min) fall into a potentially operable category. In these cases, alternative treatment methods such as wedge resection, stereotaxic radiotherapy, or radiofrequency ablation should be considered in addition to radical surgical resection (21, 22).

If one still opts for radical surgical intervention, it must be kept in mind that reduced aerobic capacity indicates impaired cardiopulmonary function. Accordingly, the scope of potential resection should be adjusted to the predicted postoperative pulmonary reserve, i.e., predicted postoperative value (ppo) FEV1 and ppoDLco. The two formulas most commonly used to calculate these values are as follows (14):

1) $ppoFEV_1$ = preoperative FEV_1 × (1—fraction of total perfusion for the resected lung)

2) $ppoFEV_1$ = preoperative FEV_1 × (19 segments—the number of segments to be removed—the number of non-functional segments/19—the number of non-functional segments)

The term non-functional segment refers to those bronchovascular segments with no adequate gas exchange taking place due to broncho-obstruction, atelectasis, emphysema, etc. The expert consensus is that the first formula should be used when planning a pneumonectomy (the perfusion fraction of the right and left lung is normally 55% and 45%, respectively), and the second formula should be applied when planning a lobectomy or segmentectomy (8, 14). If both parameters are > 30%, resection up to lobectomy can be performed. If one of the parameters is < 30%, $ppoVO_2$max should also be calculated. A $ppoVO_2$max > 10 mL/kg/min is sufficient for resection up to lobectomy. Otherwise, due to the high risk of peri- and postoperative mortality, surgery is contraindicated, and preference should be given to another option (21, 22). High postoperative mortality (29% and 100%) in patients with $ppoVO_2$max < 10 mL/kg/min was confirmed by the results of two studies independently conducted by Bechard et al. and Bolliger et al. (23, 24). As far as $ppoFEV_1$ is concerned, if its value is < 30%, the percentage of postoperative complications reaches as much as 41% (19).

There has been a debate among authors concerning the VO_2max value that would rule out the risk of postoperative complications. Most agree that a VO_2max > 20 mL/kg/min (23, 25, 26) is sufficient for pneumonectomy, and a VO_2max > 15 mL/kg/min for lobectomy (25, 27, 28). A VO_2max of 10 mL/kg/min is often considered the safe lower limit of resection. However, some argue that a VO_2max < 15 mL/kg/min already indicates functional inoperability (23, 29).

Stress Tests

Stress tests are diagnostic procedures used to assess the function of the cardiorespiratory system during exertion. They are designed to assess the body's maximum oxygen intake and consumption capacity during intense exercise. The most important parameters measured in these tests include: heart rate, stroke volume and cardiac output, pulmonary ventilation, VO_2max, and saturation of peripheral oxygen (SpO_2) (30).

The most common stress tests include the bicycle and treadmill stress tests (30). Regarding the latter, in addition to treadmill grade, the speed of ascent also shows a linear correlation with VO_2max. A speed of ascent of 15 m/min approximates VO_2max = 20 mL/kg/min (sufficient for pneumonectomy), and a speed of 12 m/min approximates VO_2max = 15 mL/kg/min (sufficient for lobectomy) (8, 31, 32).

In the absence of demanding and expensive tests, we can perform the 6-minute walk test (6-MWT), stair climbing test, or shuttle walk test. Although ERS and ESTS experts do not recommend the 6-MWT in the routine evaluation of NSCLC operability, Pierce et al. claim it is the best predictor of postoperative respiratory failure (33). At the same time, Holden et al. believe that completing > 1,000 steps indicates a low risk of postoperative complications and mortality (34).

The stair climbing test can be used as a first-line evaluation of candidates for surgical resection of NSCLC, to detect the patients who require more precise evaluation using more sophisticated methods (15, 35). Patients who can climb five floors without pausing (equivalent to FEV_1 > 2 L or VO_2max > 20 mL/kg/min) can undergo pneumonectomy safely, while patients who climb three floors (equivalent to FEV_1 > 1.7 L) can undergo lobectomy (32, 36, 37). Specifically, a 22 m ascent is the limit for safe pneumonectomy, while a 14 m ascent is the limit for safe lobectomy (35). The patient's climbing pace should also be considered. Bernasconi et al. argue that a speed of ascent > 15 m/min indicates safe resection of NSCLC up to pneumonectomy. Otherwise, physicians should not rush to decide to perform surgical treatment but should instead evaluate VO_2max using more precise tests (38).

When performing the shuttle walk test, the subject walks along a ten-meter-long path in two directions, gradually speeding up (usually 12 minutes) (39). Tsubochi et al. report that > 400 m traveling indicates a low risk of postoperative complications and death (5). Although the shuttle walk test is the least used for diagnostic purposes, its application is significant in the period of postoperative rehabilitation of patients.

Gas Analyses and Saturation

The gas analysis involves measuring O_2 and CO_2 concentrations in arterial blood to assess respiratory function, metabolism, and acid-base balance.

SpO_2 measures the percentage of hemoglobin in arterial blood that is bound to O2 molecules. It is measured using the non-invasive pulse oximetry procedure.

According to some authors, hypoxemia (partial pressure of oxygen < 60 mmHg), hypercapnia (partial pressure of carbon dioxide > 45 mmHg), and SpO_2 < 90% (or desaturation > 4% during the stress test) are relative contraindications for NSCLC surgery (20, 40, 41).

American College of Chest Physicians (ACCP) Guidelines

According to the current 2013 ACCP guidelines, the two key assessment parameters for postoperative risk following surgical resection of NSCLC are ppoFEV1 and ppoDLco. If the values of both parameters are > 60%, the postoperative risk is low. If at least one of them is between 30–60%, ACCP experts suggest performing one of the two tests listed above—the stair climbing test or the shuttle walk test—to grasp the risks involved more comprehensively. If the patient achieves a result > 22 m in the first test or > 400 m in the second, they are considered a suitable candidate for lung resection up to pneumonectomy. Cardiorespiratory function and VO_2max should be assessed using more sophisticated tests if either or both are < 30%. In that case, and based on the obtained results, the categories of low-risk and high-risk patients include those with $ppoVO_2max$ > 20 mL/kg/min and $ppoVO_2max$ < 10 mL/kg/min, respectively (42).

Conclusion

Given that surgical resections of NSCLC are among the most complex procedures (technically challenging, accompanied by numerous comorbidities and relatively frequent peri- and postoperative complications), a detailed preoperative risk assessment is crucial for the treatment outcome and disease prognosis. For this reason, spirometry, lung diffusion, and stress tests in high-risk patients are now considered standard and imperative.

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PREOPERATIVNA PROCENA KANDIDATA ZA HIRURŠKO LEČENJE NEMIKROCELULARNOG KARCINOMA PLUĆA

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Karcinom pluća je najčešći maligni tumor i vodeći uzrok smrti od malignih bolesti u opštoj populaciji, sa udelom od otprilike 25%. Prema aktuelnim podacima, od ove bolesti u Srbiji na godišnjem nivou oboli skoro sedam hiljada ljudi, a umre oko pet hiljada. Lečenje je kompleksno i multidisciplinarno. Hirurgija ima centralnu ulogu u lečenju tumora od I do III-A stadijuma. Mada su brojne studije potvrdile da hirurška resekcija tumora pruža najveće šanse za izlečenje bolesnika, u vreme postavljanja dijagnoze može se operisati samo između 20% i 30% bolesnika. Razlozi za to su brojni, a kao najčešći se izdvajaju odmakla bolest, komorbiditeti, oslabljena disajna funkcija i loše opšte funkcionalno stanje. S obzirom na to da su hirurške resekcije pluća relativno često praćene perioperativnim i postoperativnim komplikacijama, treba istaći da je detaljna preoperativna procena rizika izuzetno važna za ishod lečenja. U radu su predstavljene trenutno važeće smernice i protokoli za preoperativnu procenu rizika, sa posebnim osvrtom na bolesnike kod kojih postoji povišen rizik od razvoja ove bolesti (stare osobe, pušači, osobe sa hroničnom opstruktivnom bolesti pluća i gojazne osobe) i na ulogu spirometrijsko-difuzijskih parametara i testova opterećenja.

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***Ključne reči**: karcinom pluća, hirurško lečenje, spirometrija, difuzija, testovi opterećenja*