Comorbidities with non-small cell lung cancer: Is there an interdisciplinary consensus needed to qualify patients for surgical treatment?

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Abstract:

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Submission: 13-08-2017 Accepted: 04-11-2017 **INTRODUCTION:** Radical surgical treatment is the preferred action for patients with early-stage non-small cell lung cancer (NSCLC). Qualification for surgical treatment should consider a risk associated with the effect of comorbidities on the general condition of the patient. The aim of this article was an attempt to identify the risk factors for postoperative complications in patients treated for NSCLC, with a special focus on the coexisting diseases.

METHODS: A total of 400 patients with NSCLC were included in this retrospective study. The incidence of postoperative complications (including major complications according to the European Society of Thoracic Surgeons [ESTS]) was analyzed. Factors associated with high risk of postoperative complications were identified.

RESULTS: Postoperative complications occurred in 151 patients (39% operated patients), including severe complications according to ESTS in 75 patients (19%). From univariate analysis, risk factors for postoperative complications were arrhythmias, pneumonectomy, and open thoracotomy. According to ESTS, for major complications, the risk factors included age \geq 65 years, the presence of comorbidities, hypertension, and arrhythmias. From multivariate analysis, the risk of complications was higher in patients undergoing pneumonectomy and with cardiac arrhythmias, whereas the risk of serious complications according to ESTS was found in people \geq 65 years of age and suffering from comorbidities.

CONCLUSIONS: The risk of postoperative complications is affected by both surgical factors and the general health of the patient. Elderly patients with chronic disease history, hypertension, and arrhythmias have an increased risk of postoperative complications. Knowledge of these factors will identify a group of patients requiring internal consultation and optimization of preoperative treatment and postoperative follow-up.

Keywords:

Comorbidity, nonsmall cell lung cancer, postoperative complication



Despite advances in oncological treatment, lung cancer is currently the leading cause of death from malignant neoplasia.^[1,2] The disease is most often related to the elderly and long-term smokers, which causes a sizable proportion of patients with coexisting illnesses.^[3] Radical surgical treatment is the preferred

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treatment for patients with early-stage nonsmall cell lung cancer (NSCLC).^[4] Qualification for surgical treatment should consider a risk associated with the impact of comorbidities on the general condition of the patient. According to commonly accepted recommendations, the basic parameters considered for the qualification

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of patients for surgical treatment are the stage of the cancer, patient's performance, and the functional parameters of the lungs.^[5,6] The effect of comorbidities with lung cancer on oncological treatment and prognosis has been discussed for several years. In patients in early stages of cancer who are candidates for radical surgical treatment, coexisting illnesses may have significant importance.^[7,8] In this retrospective study, postoperative complications were identified in patients with surgically treated NSCLC. We made an attempt to identify the risk factors for postoperative complications, with a special focus on the coexisting diseases.

Methods

Patients

A total of 400 patients (280 men and 120 women) diagnosed with NSCLC, who have been qualified for surgical treatment and operated on in the selected period (from January 2012 to September 2013), were included in this retrospective study. To assure a real-life character of the study, no other specific inclusion/exclusion criteria have been applied. For all patients, data about histopathological diagnosis (squamous cell carcinoma, adenocarcinoma, and other histological types) and stage of the disease (tumor-node-metastasis [TNM] classification at the time of surgical eligibility – the 7th edition^[9]) were collected. Medical records have provided data on the incidence of comorbidities (including coronary artery disease, hypertension, history of myocardial infarction, atrial fibrillation, and other arrhythmias - newly diagnosed and recurrent arrhythmias, peripheral arterial disease, chronic obstructive pulmonary disease (COPD), tuberculosis, diabetes, stroke, thyroid disease, other cancers, and chronic kidney disease). In all patients, the extent of surgery (segmentectomy, lobectomy, bilobectomy, and pneumonectomy), type of surgical access (video-assisted thoracoscopic surgery [VATS] and thoracotomy), and postoperative hospitalization were determined.

The occurrence of complications during the postoperative period, up to the date of discharge from the hospital, was analyzed. Any complications were considered, regardless of severity and major pulmonary and cardiovascular complications according to the European Society of Thoracic Surgeons (ESTS), including pneumonia, atelectasis requiring bronchoscopy, adult respiratory distress syndrome, mechanical ventilation lasting >24 h, pulmonary edema, pulmonary embolism, myocardial ischemia, heart failure, arrhythmias, stroke, and acute kidney failure.^[10]

In the study group, comorbidities of lung cancer were analyzed. Postoperative complications and severe pulmonary and cardiovascular complications according to ESTS were investigated. The incidence of postoperative complications was analyzed according to the age of the patients (≤ 65 and >65 years), the type of surgical procedure performed, surgical access applied, and the presence of particular comorbidities. The factors affecting the hospitalization time after surgery were also determined.

Quantitative variables are represented by the following descriptive statistics - mean (range, standard deviation [SD]) – and – qualitative variables as number (*n*) and percentage (%). For quantitative variables, compliance with the Gaussian distribution was verified using the Shapiro-Wilk test. The homogeneity of variance was verified by the Kolmogorov-Smirnov test. The Student's t-test was used to examine the differences between groups, for Gaussian distribution variables and homogeneous variance. The Mann-Whitney U-test was used for variables with non-Gaussian distribution or nonhomogeneous variance. Pearson's test was used to examine the relationship between variables of Gaussian distribution. In case one of the variables did not show Gaussian distribution, the Spearman's test was used. Pearson's Chi-squared test was used to investigate the differences between groups for qualitative variables. Statistical significance level of P = 0.05was assumed. Univariate analysis and multivariate logistic regression (stepwise progressive model) were performed to identify the risk factors for postoperative complications. Factors identified as significant for postoperative complications from univariate analysis were included in multivariate analysis model. Statistical analyses were performed using Statistica 10.0 software (StatSoft, Inc., Tulsa, Oklahoma, USA).

Ethics

For this type of study (retrospective), formal consent is not required.

Results

A group of 400 patients treated for NSCLC (280 men and 120 women) were analyzed. The mean age of the patients was 64 years (34–84; SD = 7.47). The characteristics of the study group are shown in Tables 1 and 2. Data on surgical operations are presented in Table 3.

The occurrence of postoperative complications

Postoperative complications were observed in 151 patients (39% operated), including severe pulmonary and cardiovascular complications according to ESTS in 75 patients (19%). In the study group, 10 deaths occurred (2%). The description of postoperative complications is presented in Tables 4 and 5 and in Figures 1 and 2.

Table 1: 0	Characteristics o	f the study	y group
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Table 1. Characteristics of the study g	
Characteristics of the study group	n (%)
Study group	400 (100)
Women	120 (30)
Men	280 (70)
Histopathological diagnosis	
Squamous cell carcinoma	192 (48)
Adenocarcinoma	186 (47)
Other histological types	22 (6)
Stage of disease (TNM, 7th edition)	398 (99)
IA	63 (16)
IB	90 (23)
IIA	104 (26)
IIB	42 (11)
IIIA	84 (21)
IIIB, IV	15 (4)
History of tobacco smoking	
Current or former smokers	386 (96)
Nonsmokers	14 (4)
Age	
<65 years old	186 (47)
≥65 years old	214 (53)
TNM = Tumor-node-metastasis	

Table 2: Diseases coexisting with non-small cell lung cancer in the study group

Diseases coexisting with NSCLC in the study group	n (%)
Comorbidities	278 (70)
Hypertension	167 (42)
COPD	86 (22)
Ischemic heart disease	69 (17)
Diabetes	44 (11)
A history of myocardial infarction	37 (9)
Peripheral arterial disease	33 (8)
Cancers	29 (7)
Thyroid disease (hyperthyroidism or hypothyroidism)	24 (6)
Atrial fibrillation and other arrhythmias	21 (5)
Tuberculosis	6 (2)
Stroke	6 (2)
Chronic kidney disease	2 (0.5)
NSCLC = Non-small cell lung cancer, COPD = Chronic obstructive	e pulmonary

disease

Table 3: Number of operations performed with regard to operational access

	Thoracotomy, n (%)	VATS, <i>n</i> (%)	Total, <i>n</i> (%)
Pneumonectomy	66 (16.5)	5 (1.25)	71 (17.75)
Bilobectomy	22 (5.5)	2 (0.5)	24 (6)
Lobectomy	180 (45)	92 (23)	272 (68)
Segmentectomy	16 (4)	17 (4.25)	33 (8.25)
Total	284 (71)	116 (29)	400 (100)

VATS = Video-assisted thoracoscopic surgery

The influence of comorbidities on the occurrence of postoperative complications

There was a significantly higher incidence of postoperative complications in patients with cardiac arrhythmias (P = 0.02). For COPD (P = 0.08) and

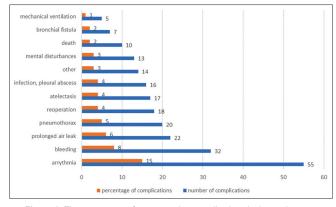


Figure 1: The occurrence of postoperative complications in the study group

diabetes (P = 0.09), the correlation with the occurrence of complications was close to statistically significant. There was no relationship between the incidence of postoperative complications and thyroid disease, stroke, peripheral arterial disease, ischemic heart disease and myocardial infarction, and pulmonary tuberculosis. Statistical analyses did not include chronic kidney disease due to the small number of patients with this coexisting disease (n = 2, 0.5% of the study group).

The occurrence of serious complications according to ESTS was found more often in patients >65 years of age with coexisting illnesses, especially hypertension (P < 0.05).

Postoperative complications were significantly less often in patients with a history of cancer other than lung cancer (P = 0.03), which was associated with lower stages of NSCLC (stage Ia and Ib, according to TNM classification, P < 0.05) and less extensive surgical procedures (segmentectomy, P < 0.003) in this group.

The influence of the extent of surgery and the type of surgical access on postoperative complications Most complications were found in patients undergoing pneumonectomy (P < 0.05). The rate of complications after lobectomy and bilobectomy was similar. The least complications occurred after the segmentectomy. Data on the occurrence of postoperative complications depending on the extent of surgery are presented in Table 3.

There was a significantly lower incidence of postoperative complications and serious pulmonary and cardiovascular complications according to ESTS in patients operated by the VATS compared to thoracotomy (P < 0.05). Data on the occurrence of postoperative complications depending on operational access are presented in Table 4.

Univariate analysis of risk factors for postoperative complications

Univariate analysis included variables that were significantly associated with the occurrence of

complications. The following risk factors for postoperative complications were identified: pneumonectomy (odds ratio [OR] 2.84, 95% confidence interval [CI]: 1.77–4.57, P = 0.00), atrial fibrillation and other arrhythmias (OR 1.63, 95% CI: 1.04–2.57, P = 0.03), and thoracotomy (OR 1.4, 95% CI: 1.10–1.77, P = 0.0055).

COPD diagnosis was associated with a higher risk of complications – close to statistical significance (OR 1.23, 95% CI: 0.97–1.57, P = 0.09) and similarly diabetes (OR 1.32, 95% CI: 0.95–1.82, P = 0.09).

Segmentectomy was associated with a significantly lower risk of postoperative complications (OR 0.45, 95% CI: 0.23–0.89, P = 0.02). Patients with a history of neoplasm also had a lower risk of complications (OR 0.62, 95% CI: 0.39–0.98, P = 0.04).

Significant risk of major pulmonary and cardiovascular complications according to ESTS was associated with total comorbidity (OR 1.67, 95% CI: 1.14–2.44, P = 0.008), in particular arterial hypertension (OR 1.52, 95% CI: 1.10–2.11, P = 0.01) and atrial fibrillation and other arrhythmias (OR 1.93, 95% CI: 0.99–3.77, P = 0.05) and age ≥ 65 years (OR 1.52, 95% CI: 1.10–2.10, P = 0.01).

Table 4: Occurrence of postoperative complications depending on the extent of surgery

	Number of postoperative complications (<i>n</i>)	Percentage of treatments	Significant difference (<i>P</i>)
Pneumonectomy	44	63	< 0.05
Bilobectomy	8	33	
Lobectomy	92	35	
Segmentectomy	7	21	

Patients who underwent pneumonectomy had significantly higher incidence of postoperative complications than patients with smaller extent of surgery

Multivariate analysis of risk factors for postoperative complications

Risk factors identified as significant for postoperative complications and severe pulmonary and cardiovascular complications from univariate analysis were included in multivariate analysis models (stepwise progressive model). An important risk factor for postoperative complications was pneumonectomy (P = 0.000, OR 2.844, 95% CI: 1.756–4.582) and cardiac arrhythmia (P = 0.04, OR 1.610, 95% CI: 1.011–2.565). The risk factors for major pulmonary and cardiovascular complications according to ESTS included age ≥ 65 years (P = 0.028, OR 1.452, 95% CI: 1.040–2.026) and the presence of coexisting diseases (P = 0.018, OR 1.593, 95% CI: 1.083–2.344).

The influence of postoperative complications and the time of hospitalization

The mean hospitalization time after surgery was 9.8 days (4–87; SD 8.59). Data on hospitalization time are presented in Table 6. The extent of surgery

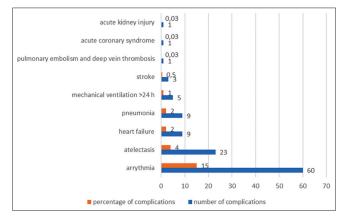


Figure 2: The occurrence of severe pulmonary and cardiovascular complications according to the European Society of Thoracic Surgeons in the study group

Table 5: Occurrence of postoperative complications depending on the operational access applied

	Number of complications (<i>n</i>)	Percentage of treatments	Number of serious complications according to ESTS	Percentage of treatments	Statistical significance (P)
VATS	32	28	14	12	<0.05
Thoracotomy	119	43	61	21	

Patients operated by VATS had significantly lower incidence of postoperative complications than patients after open thoracotomy. VATS = Video-assisted thoracoscopic surgery, ESTS = European Society of Thoracic Surgeons

Table 6: Time of hospitalization following surgery, depending on the extent of surgery and surgical access

	Ti	Significant differences (P)			
	Average	Minimum	Maximum	SD	
Total	9.8	4	87	8.6	
Pneumonectomy	14.6	4	87	13.67	<0.05
Bilobectomy	9.62	5	22	4.84	
Lobectomy	8.92	4	82	7.04	
Segmentectomy	6.48	4	13	2.32	
Thoracotomy	9.96	4	48	6.48	<0.05
VATS	9.46	4	87	12.34	

Patients who underwent pneumonectomy and open thoracotomy required longer hospitalizations than patients operated in VATS and with smaller extent of surgery. VATS = Video-assisted thoracoscopic surgery, SD = Standard deviation has had a significant impact on hospitalization. The hospitalization time of pneumonectomized patients was significantly longer than after lobectomy and segmentectomy (P < 0.05) but did not significantly differ from hospital admission to bilobectomy. Patients undergoing VATS required shorter hospitalizations than patients operated by open method (P = 0.000). The occurrence of postoperative complications was associated with longer hospitalization time (P < 0.05).

Discussion

For several years, the oncological literature is a discussion on the importance of the diseases coexisting with lung cancer for the course of treatment and prognosis. Opinion on the importance of coexisting diseases in this group of patients is divided. There are opinions that the diseases coexisting with lung cancer are important for the course of oncological treatment, the occurrence of complications, and long-term prognosis of patients. Thereby, they should be considered for qualification for oncological treatment.^[11] This applies particularly to patients in early stages of disease eligible for radical (including surgical) treatment.^[7,8,12] In patients with advanced lung cancer, the effect of the tumor itself on the prognosis is predominant, and the significance of coexisting diseases is lower.^[13,14]

Radical surgical treatment is the method of choice in patients with NSCLC in early stages of disease and provides chance for cure.^[4] However, patients with lung cancer are usually elderly people with multiple comorbidities, especially tobacco-related diseases. The presence of comorbidities often affects the decisions of physicians that qualify patients for treatment, who prefer less aggressive treatment due to concern of possible complications.^[15] This is a significant clinical problem for an internist or pulmonologist who refers the patient for surgical treatment. The main aim of the article was to determine the effect of comorbidities of lung cancer on the course of surgical treatment, in order to qualify patients for surgery, avoiding on the one hand excessive operational risk and on the other hand, too cautious approach, reducing the chances of a cure.

In this article, we attempted to identify the risk factors for postoperative complications in the Polish population of patients with lung cancer, with particular emphasis on the role of coexisting diseases. We have analyzed a large group of patients (n = 400) operated on because of NSCLC, representative of gender, age, and history of smoking.^[3] High prevalence of comorbidities, most commonly hypertension (42%) and COPD (22%), was observed in the study group. These diseases were more frequent in the study group than those described for the Polish population,^[16-18] which can be attributed to the prevalence of tobacco smokers in the study group (94% of current or former smokers).

In the present study, the overall complication rate was 39%, and severe pulmonary and cardiovascular complications according to ESTS database were 19%. In the available literature, both reports describing a similar incidence of complications^[19-20] and also reports of significantly lower postoperative complications can be found.^[21,22] Differences in the reported incidence of complications are due to the complicated reporting criteria. This is caused by the detailed recording of clinical events such as the recurrence of previously diagnosed arrhythmia in the postoperative period or the necessity of transfusion of blood products, which are not considered by many authors but are important for the assessment of the postoperative period.

In the available literature, there is an agreement that the severity of disease according to TNM and the extent of surgery has an effect on the course of the postoperative period,^[22-24] which is also confirmed by our results, although there are reports that undermine the importance of progression as a risk factor of complications.^[21]

As for the importance of other factors, including coexisting illnesses, researchers' opinions are more divided. Many studies have demonstrated the significant effects of chronic pulmonary disease and poor lung function on complications and mortality in postoperative patients.^[19,25,26] An article has also been published that undermines the importance of spirometry parameters for the incidence of postoperative complications.^[27] Our study did not show statistically significant effects of COPD on the incidence of postoperative complications, although the results were close to statistical significance. This could have resulted from lower COPD severity in the study group compared to other studies on this subject.[28] Kim et al. have shown that the effect of COPD on the incidence of postoperative complications is relatively small in the early stages of the disease and increases with the deterioration of spirometric parameters, hence the absence of statistically significant differences in the study group.^[19]

Researchers' opinions on the importance of cardiovascular diseases in the postoperative course are divided. In many studies, there is a significantly higher risk of postoperative complications in cardiologically ill patients,^[29,30] although some authors present different data.^[21] In our study, we did not observe the relationship between the occurrence of complications and the diagnosis of ischemic heart disease or myocardial infarction, but we showed a significantly higher incidence of complications in patients with hypertension and arrhythmias. Atrial fibrillation is a particularly common complication in patients operated

on for lung cancer.^[22] The high incidence of arrhythmias in patients treated for lung cancer is thought to be associated with mediastinal lymph node dissection.^[31] In the study group, cardiac arrhythmias accounted for 80% of the observed complications and related to 15% of patients treated, which is higher than reported by other authors.^[22,31] It is probably related to the inclusion of recurrence of previously diagnosed arrhythmias in our study.

There were significantly fewer postoperative complications in patients with a prior history of oncological treatment. These patients at the same time were characterized by relatively low NSCLC stage and a higher proportion of saving treatments, which can be explained by earlier diagnosis of lung cancer in patients with a history of other cancer disease under constant oncological control.

There was also a relationship between the occurrence of postoperative complications and surgical access (thoracotomy vs. VATS). Patients undergoing VATS had significantly fewer postoperative complications and serious pulmonary and cardiovascular complications than patients operated by open method. These observations correspond to previous reports.^[32]

The extent of the surgery had a significant effect on the duration of hospitalization after the procedure (the longest hospital stay after pneumonectomy and bilobectomy) and applied surgical access (after open surgery). Furthermore, postoperative complications were associated with prolonged hospitalization.

Conclusion

We have identified a number of factors that affect the increased risk of postoperative complications in patients treated for NSCLC. Significant for the occurrence of complications are both surgical-related factors (extent of surgery and type of surgical access) and factors related to the general state of health of the patient. Elderly patients, with chronic disease history and hypertension, and especially patients with heart rhythm disorders, have an increased risk of postoperative complications. Knowledge of these risk factors will identify a group of patients requiring internal consultation and optimization of preoperative treatment and postoperative follow-up. This will also allow to avoid higher hospital costs associated with the occurrence of complications. In the age of progressive specialization of particular fields of medicine, it is particularly important to assess the overall clinical condition of the patient by an interdisciplinary team.

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Conflicts of interest

There are no conflicts of interest.

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