Introduction

Lung cancer is a leading cause of mortality owing to malignancies in the population of smokers older than 60 years. The median age for primary lung cancer is 70 years old (1) and most papers refer to early lung cancer onset (ELCO) as lung cancer diagnosed before the age of 50 (2). There are conflicting data concerning survival and prognosis in the younger and older lung cancer populations (2-4). Undoubtedly patients with ELCO are a distinct population in comparison with late lung cancer onset (LLCO) patients. There is lower smoking exposure in the ELCO group and the influence of genetic factors has more impact than in LLCO. Carcinoids more commonly occur in the ELCO population compared to more common squamous cell histology in LLCO. Molecular patterns of mutations characterize these groups of patients differently and there are data suggesting a more aggressive course of lung cancer treated at earlier age (3). On the other hand, the younger population is not affected by the number...
of significant, tobacco-related comorbidities that may influence the overall survival (OS). There are few papers in this field that focus on surgical treatment of early-stage lung cancer solely. The purpose of this study was to compare the differences in survival and prognosis in young and old patients with surgically treated lung cancer.

Methods
Study methods
This is a retrospectively analyzed study made of prospectively collected data of 1,518 patients with lung cancer treated in a Thoracic Surgery Department in the years 2007–2015.

All patients in the study underwent routine preoperative pulmonary evaluation consisting of baseline spirometry. DLCO, predicted postoperative (ppo) spirometry, and ppoDLCO were assessed in selected patients with FEV1% lower than 80%. At that time positron emission tomography (PET) CT was performed in patients with clinical stages cII or higher. Brain CT was undertaken in symptomatic patients and mediastinal staging was performed if indicated by enlarged mediastinal lymph nodes in the mediastinum or if suggested by PET CT.

All patients with coronary heart disease, heart failure or other significant cardiovascular comorbidities were consulted by a cardiologist. Oncological and surgical therapeutic decisions were made during multidisciplinary tumor board meetings. A multidisciplinary team consisting of thoracic surgeons, oncologists, pathologists and radiologists decided treatment options for each patient. A further adjuvant treatment in patients with pathological stages IIA or higher occurred postoperatively, but this data was not collected.

Stage I patients not scheduled for surgical treatment owing to significant comorbidities were accepted to stereotactic radiotherapy program. After the surgery, the patients were surveilled according to routine protocol (follow up every third months during first two years and every six months thereafter). The data were analyzed retrospectively and thus disease-free survival and cancer-specific survival was not registered. The patients in stages higher than IIB were consulted by medical oncologist and considered for adjuvant systemic therapy in cisplatin-based regimen. These data were not recorded and did not enter the analysis.

The operative specimens were not routinely tested for most oncogene mutations like ALK, ROS1, EGFR or others.

The last follow-up visit was recorded in January 2017. The median follow-up was 54 months. Two hundred seventy-five patients died during the study period. No patient data was lost due to incomplete data sampling (i.e., death, withdrawn data consent). The reason of death was not recognized as this data is not accessible from the used national sources.

The death of the patient was obtained using the national registry lead by the Ministry of Internal Affairs and Administration.

Statistical analysis
Including the tumors with histology typical for an age like carcinoids may blur ELCO and LLCO populations comparison. These tumors are characterized by very good long-term prognosis that may a bias in the ELCO group. In order to avoid this, we have performed three different analyses which are listed below.

Comparison 1—direct comparison of 86 patients with ELCO were compared to 1,432 patients with LLCO.

Comparison 2—65 patients with ELCO were matched with 453 patients with LLCO in a propensity-score matched analysis (based on exact matching—by sex, pTNM, type of operation, pathological diagnosis and Charlson Comorbidity Index). This study included patients with carcinoid tumors, salivary gland tumors, mucoepidermoid carcinoma, and patients post neoadjuvant treatment and stages IIIB and IV. In each of three comparisons the proportion of males was higher. In this comparison this difference reached the level of statistical significance. We do not find that this incidentally proved trend is discriminating for making conclusions.

Comparison 3—426 patients with LLCO were matched with 50 patients with ELCO in a propensity-score matched analysis (based on exact matching—by sex, pTNM, type of operation, pathological diagnosis and Charlson Comorbidity Index). In this study patients with carcinoid tumors, salivary gland tumors, mucoepidermoid carcinoma, and patients post neoadjuvant treatment and stages IIIB and IV were excluded.

Unpaired data characterized by normal distribution were compared with the unpaired \( t \)-test. In the case of non-normal distribution, the Mann-Whitney U-test was applied for comparing two unmatched samples. Categorical variables were assessed by the chi-square test. The accepted
level of significance was P<0.05, and hazard ratios (HR) were calculated with 95% confidence interval (CI). In univariable analysis, data were split into two groups: alive or deceased after the end of the study. Those two groups were then compared.

Owing to the nature of this study: a retrospective analysis of prospectively gathered data and the lack of experimental intervention in the study group, university institutional review board accepted the study and decided to waive informed consent (NKBBN/88/2016). Factors which achieved a P value of <0.05 in the univariable analysis entered further assessment via Cox multivariable models of proportional hazards, a multivariable analysis model that makes use of logistic stepwise regression. All variables had P value >0.05 in Schoenfeld Residuals Test meaning the slope of scaled residuals on time is not statistically different from zero, thus, not violating the proportionality assumption.

**Results**

Comparison 1—in the unmatched population, no differences in gender, pTNM, and type of surgery performed were found. Younger patients were more likely to have typical carcinoid (23.1% vs. 2.6%, P<0.05, OR 11.06, 95% CI, 5.695–21.360) and mucoepidermoid tumours (2.6% vs. 0.3%, P<0.05, OR 7.547, 95% CI, 0.997–44.708), whereas the older patients were more likely to have squamous cell lung carcinoma (39.7% vs. 23.1%, P<0.05, OR 0.455, 95% CI, 0.256–0.799). Younger patients were less likely to be current smokers (18% vs. 41%, P<0.05, OR 0.316, 95% CI, 0.192–0.519). Median Charlson Comorbidity Index in the younger population was 0 and in the older population was 1 (P<0.05). The characteristics of operated patients are presented in Table 1. Five-year survival in patients with ELCO was 71.9% comparing to 58.7% in LLCO patients (log-rank P=0.008) (Figure 1).

Comparison 2—the propensity score-matched analysis (PSMA) with the exact method including carcinoid tumors, salivary gland tumors, mucoepidermoid carcinoma, and patients post neoadjuvant treatment and stages IIIB and IV; comparing sex, pTNM, type of operation, pathological diagnosis and Charlson Comorbidity Index), excluding carcinoid tumors, salivary gland tumors, mucoepidermoid carcinoma and patients post neoadjuvant treatment and stages IIIB and IV, showed no significant difference in survival rates comparing ELCO patients with LLCO patients, although there was still a trend towards better survival in ELCO patients (P=0.085, HR =0.607, 95% CI, 0.343–1.073) (Figure 3).

The detailed list of comorbidities is listed in Table 2. Early mortality as well as complications following the surgery are presented in Table 3.

**Discussion**

ELCO population is characterized by different histopathological lung cancer characteristics comparing with LLCO. A high occurrence of neoplasms with relatively low aggressiveness impedes direct analysis of this cohort of patients. The main finding of this study is supporting the thesis that patients with ELCO have better prognosis comparing to LOLC. This trend was observed in the general population of patients operated due to lung cancer.

To reduce potential biases we decided to perform two PSMA analyzes.

There are conflicting data concerning the prognosis of patients with ELCO compared to patients with LLCO. While some studies have shown that there is a significantly worse prognosis in the younger population (3) other studies have shown that the prognosis is significantly worse in older patients (2). On the basis of the results of our study, patients with ELCO have higher five-year survival after surgical treatment compared to patients with LLCO.

Bryant and colleagues state in their article that younger patients with surgically resected lung cancer have a significantly worse prognosis compared to older patients (3), which differs greatly from our results. They matched 254 younger patients with 508 older patients. The selection of patients was based on symptoms reported at referral. This study protocol raises selection biases what impairs the ability to conclude rather than relatively small study population. Designing study protocol on vague and often misreported symptoms in the population of patients treated operatively due to early stages of lung cancer may result in a skewed interpretation of obtained data. Our study does not confirm results reported in the mentioned publication. On the other hand, Dell’Amore and colleague presented another paper in 2015 that also compared outcomes in NSCLC in younger and older patients (2). They compared 113 young patients
Table 1 Study characteristics. ELCO early lung cancer onset

| Variable                      | Subtype                  | Comparison 1 | Comparison 2 | Comparison 3 |
|-------------------------------|--------------------------|--------------|--------------|--------------|
|                               |                          | >50 ELCO     | >50 ELCO     | >50 ELCO     |
|                               |                          | P value      | P value      | P value      |
| N                             |                          | 1,432 [86]   | 453 [65]     | 426 [50]     |
| Age                           | Median                   | 64 [46]      | 63 [47]      | 63 [47]      |
|                               | Range                    | 49–86 [18–49]| 50–85 [18–49]| 50–85 [18–49]|
| Sex, n [%]                    | Female                   | 535 [37]     | 158 [35]     | 142 [33]     |
|                               | Male                     | 897 [63]     | 295 [65]     | 284 [67]     |
| Pack-years                    | Median                   | 30 [15]      | 30 [20]      | 30 [20]      |
|                               | Range                    | 0–120 [0–120]| 0–120 [0–120]| 0–120 [0–120]|
| Years of smoking              | Median                   | 30 [15]      | 30 [20]      | 30 [20]      |
|                               | Range                    | 0–300 [0–40]| 0–250 [0–40]| 0–250 [0–40]|
| Cigarettes a day              | Median                   | 20 [20]      | 20 [20]      | 20 [20]      |
|                               | Range                    | 0–60 [0–60]| 0–60 [0–60]| 0–60 [0–60]|
| Video thoracoscopic           |                         | 237 [17]     | 82 [18]      | 77 [18]      |
| approach, n [%]               |                          |              | 12 [18]      | 9 [18]       |
| Type of resection, n [%]      | Pneumonectomy            | 169 [12]     | 58 [13]      | 58 [14]      |
|                               | Lobectomy                | 1,187 [83]   | 395 [87]     | 368 [86]     |
|                               | Bronchial sleeve resection| 1 [0.1]    | 395 [87]     | 368 [86]     |
|                               | Wedge resection          | 28 [2]       | 28 [2]       | 28 [2]       |
|                               | Segmentectomy            | 47 [3]       | 47 [3]       | 47 [3]       |
| Pathology report, n [%]       | Adenocarcinoma           | 589 [41]     | 225 [50]     | 225 [53]     |
|                               | Carcinoid                | 54 [4]       | 24 [5]       | 0 [0]        |
|                               | Squamous cell carcinoma  | 571 [40]     | 190 [42]     | 190 [45]     |
|                               | Other                    | 218 [15]     | 14 [3]       | 11 [3]       |
| pTNM, n [%]                   | IA                       | 364 [25]     | 120 [26]     | 102 [24]     |
|                               | IB                       | 375 [26]     | 112 [25]     | 106 [25]     |
|                               | II A                     | 253 [18]     | 75 [17]      | 73 [17]      |
|                               | II B                     | 177 [12]     | 90 [20]      | 89 [21]      |
|                               | III A                    | 238 [17]     | 56 [12]      | 56 [13]      |
|                               | III B                    | 6 [6]        | 0 [0]        | 0 [0]        |
|                               | IV                       | 4 [0]        | 0 [0]        | 0 [0]        |
|                               | NA                       | 15 [1]       | 0 [0]        | 0 [0]        |

Table 1 (Continued)
with 347 older patients. They concluded that the OS in young patients is better than in older patients, similar to our data. It was also confirmed by findings of Radzikowska et al. (5) and Tian et al. (6). The above-mentioned reports represent the situation in early stages of lung cancer. The data concerning advanced stages is also conflicting. The results of the analysis of big datasets prove the beneficial effect of younger age in a population of patients with dominating adenocarcinoma in stage III and IV (7,8). Other reports of smaller datasets inform of advanced stage suggest a more aggressive course in younger adults (6,8). In summary, according to most convincing studies young age is a beneficial prognostic factor in both early and advanced stages of lung cancer.

It is difficult to assess what age limit should define the ELCO as there is no definition. Most of the papers define ELCO between 40 and 50 years of age (2-6,9). The advantage of arbitral choice of 50 years of age is supported by relatively high proportion of non-carcinoid tumors in this study group what increases the strengths of the analysis. Age is not a uniform prognostic factor in different malignancies. What is more, age may be an opposite prognosticator in early and advanced disease. In most subtypes of most common neoplasm in women—breast cancer young age is widely recognized as adverse disease prognosticator (10). Other cancers have similar biology

### Table 1 (Continued)

| Variable                  | Subtype | Comparison 1 |                  |                  |                  | Comparison 2 |                  |                  |                  | Comparison 3 |                  |                  |
|---------------------------|---------|--------------|-----------------|-----------------|-----------------|--------------|-----------------|-----------------|-----------------|--------------|-----------------|-----------------|
|                           |         | >50          | ELCO            | P value         | >50             | ELCO         | P value         | >50             | ELCO            | P value       | >50             | ELCO            | P value         |
| Diameter (mm)             | Mean    | 34.8         | 33.8            | 0.06            | 36.4            | 35.2         | 0.15            | 37.2            | 38.9            | 0.55          |                  |                  |                  |
|                           | Median  | 30.0         | 25.5            |                  | 32              | 27           |                  | 32              | 30             |              |                  |                  |                  |
|                           | Range   | 0–190        | 7–190           |                  | 1–110           | 9–190        |                  | 1–110           | 9–190          |              |                  |                  |                  |
| Charlson Comorbidity Index| Mean    | 0.99         | 0.49            | <0.001          | 0.22            | 0.31         | 0.18            | 0.21            | 0.26            | 0.5          |                  |                  |                  |
|                           | Median  | 1            | 0               |                  | 0               | 0           |                  | 0               | 0              |              |                  |                  |                  |
|                           | Range   | 0–8          | 0–6             |                  | 0–3             | 0–3         |                  | 0–2             | 0–2            |              |                  |                  |                  |

ELCO, early lung cancer onset.

**Figure 1** Survival analysis of patients in comparison 1.
to lung cancer and published studies confirm the results obtained by us. Colorectal cancer is a disease mostly affecting the older population. Wang and colleagues (11) mention that young patients with colorectal cancer had higher stage presentation and more aggressive pathological features, but better survival. This trend in survival was also discovered in the present study. Similarly, in another highly discussed cancer type such as ovarian cancer, Chan and colleagues (12) found that younger patients have better survival compared to their older cohort. Even after adjusting for clinicopathologic prognostic factors the younger patients still had a more favorable outcome and prognosis.

The effect of age on survival is not a result of perioperative risk. Not surprisingly younger patients had less comorbidities (Table 2). It reflects the situation of a pleiotropic effect of tobacco. Many years of cigarette smoking leads not only to increased risk of lung cancer
but also chronic obturatory pulmonary disease and arterial hypertension. The population of LLCO has definitely more comorbidities and the postoperative period is characterized by higher level of complications (Table 3). Despite the higher number of both pulmonary and cardiovascular complications they did not affect the 30- and 90-mortality in our study group. It is possible that the trend would be confirmed in an analysis of bigger population. However, on the basis of the analysis we postulate that in general, surgical treatment in EOLC is as safe as in the LOLC. The effect on the survival should not be interpreted as obviously riskier surgical procedure by itself. It should rather be advocated to the biological character of the tumor.

The main obstacle in the interpretation of data obtained directly from the study is the blurring effect of favorable pathology of carcinoids. In order to avoid that

| Study groups characteristics—detailed information about complications. The numbers do not sum up to 100% | ELCO (n=86) | LLCO (n=1,432) | P value | OR (95% CI) |
|---|---|---|---|---|
| Uncomplicated | 56 (65.1%) | 600 (41.8%) | <0.001 | 2.157 (1.401–3.321) |
| Mortality 30-day | 0 (0%) | 23 (1.6%) | 0.236 | N/A |
| Mortality 90-day | 1 (1.1%) | 49 (3.4%) | 0.254 | 0.332 (0.045–2.434) |
| Cardiovascular complications | 4 (4.6%) | 251 (17.5%) | 0.002 | 0.230 (0.083–0.632) |
| Atrial arrhythmia | 3 (3.4%) | 224 (15.6%) | 0.002 | 0.195 (0.061–0.622) |
| Heart infarct | 0 (0%) | 5 (0.3%) | 0.583 | N/A |
| Pulmonary emboli | 0 (0%) | 6 (0.4%) | 0.548 | N/A |
| Cerebral infarct | 0 (0%) | 12 (0.8%) | 0.394 | N/A |
| Pulmonary complications | 25 (29.0%) | 650 (45.4%) | 0.003 | 0.493 (0.306–0.794) |
| Atelectasis requiring aspiration | 7 (8.1%) | 135 (9.4%) | 0.690 | 0.851 (0.385–1.881) |
| Prolonged air leak | 5 (5.8%) | 108 (7.5%) | 0.676 | 0.757 (0.300–1.907) |
| Redrainage | 3 (3.4%) | 88 (6.1%) | 0.313 | 0.552 (0.171–1.782) |
| Persistent pneumothorax | 3 (3.4%) | 70 (4.8%) | 0.795 | 0.703 (0.217–2.281) |
| Adult respiratory distress syndrome | 1 (1.1%) | 10 (0.6%) | 0.622 | 1.673 (2.212–13.221) |
| Pneumonia | 0 (0%) | 49 (3.4%) | 0.081 | N/A |

ELCO, early lung cancer onset; LLCO, late lung cancer onset; N/A, non-applicable.
weigh of scientific proof in most of the cases. Nevertheless, we deem to present the present study basing on OS being the objective measure of outcome of oncological treatment. The cut-off value of 50 years of age was not confirmed by a mathematical definition that poses another weak point of the study. This cut-off line, however, enables a comparison of a distinct population of roughly 5% of patients with lung cancer with a rare characteristic.

The clear clinical message of this study is that the clinical aggressiveness of early stage NSCLC in adults younger than 50 years seems to be lower than in older individuals. This should encourage to wider involvement of this patients in the radical treatment. Local treatment should be considered in higher risk patients like stage III patients or selected population of individuals with oligometastatic disease. This statement is not clearly supported by the evidence gathered, but it may guide the directions for the future studies.

Conclusions

Our study has shown that younger patients may have better OS compared to older patients. In the future, studies should take into consideration that including neuroendocrine tumors such as typical and atypical carcinoid tumors might skew the result as these tumors behave differently compared to the more prominent lung cancers.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd.2020.04.55). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. A retrospective analysis of prospectively gathered data and the lack of experimental intervention in the study group, university institutional review board accepted the study and decided to waive informed consent (NKBBN/88/2016).

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