Original Article

Emphysema and lung cancer risk

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Background: With increasing significance of lung cancer screening programs, it is essential to determine the group of participants, who would benefit the most from screening. In our study, we aimed to establish the correlation between lung emphysema and lung cancer risk.

Methods: The study design was cross-sectional. Low-dose computed tomography (LDCT) scans of 896 subjects from MOLTEST-BIS lung cancer screening program, including 100 subjects with detected lung cancer, were visually evaluated for the presence, type and severity of emphysema. Quantitative emphysema evaluation was performed with Siemens syngo.via Pulmo 3D application.

Results: Visually detected presence of centrilobular emphysema (CLE) correlated with male gender (P=0.02), age (P<0.001) and pack-years of smoking (P=0.004), as well as with quantitative assessment of Emphysema Index (EI) (P=0.008), and with emphysema clusters of given size (Clas 1–4) Clas 1, Clas 3 and Clas 4 (P<0.001). Visually assessed severity grade of emphysema correlated with age (P<0.001), pack-years of smoking history (P=0.002) and EI (P<0.001). There was a correlation between lung cancer occurrence and pack-years (P<0.001), age (P<0.001), and presence of CLE (P<0.001) but no correlation with gender (P=0.88) and EI (P=0.32) was found. In the logistic regression model pack-years, age, qualitative severity of CLE and Clas 1 were significant factors correlated with lung cancer occurrence (P<0.001).

Conclusions: Qualitative and quantitative emphysema evaluation correlate with each other. Both, presence and severity of CLE correlate with higher incidence of lung cancer. Severity of visually assessed emphysema, age and pack-years of smoking are significant predictors of lung cancer occurrence.

Keywords: Emphysema; chronic obstructive pulmonary disease (COPD); lung cancer screening; low-dose computed tomography (LDCT)

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Introduction

Background

Lung cancer is the leading cause of cancer-related mortality worldwide according to World Health Organization (WHO), being responsible for an estimated 18.4% of all cancer deaths (1). Due to frequent diagnosis in advanced stage and high malignancy of some histological types of lung cancer, the prognosis is poor and the 5-year overall survival rate is 10–20% (2).

It legitimates efforts to implement an effective lung cancer screening program for high-risk individuals, which would reduce overall mortality from lung cancer. Several low-dose computed tomography (LDCT) lung cancer screening programs proved effective in saving lives in high-risk cohorts (3-7).

Rationale and knowledge gap

Identification of individuals at the highest risk of developing lung cancer is essential due to radiation exposure and potential costs of LDCT examinations. Age and smoking history were established the main criteria for the determination of the screening cohort. However, it has been indicated, that additional criteria such as airway obstruction, emphysema, family history of lung cancer, and exposure to air pollution, asbestos or other toxic substances, may help construct a better risk assessment model to more effectively determine, who would benefit the most from participation in the screening programs (8-11).

Highlight box

Key findings

- Qualitative and quantitative assessment of emphysema correlate with each other.
- Presence and severity of visually recognized centrilobular emphysema correlate with higher incidence of lung cancer.

What is known and what is new?

- Chronic lung diseases, like chronic obstructive pulmonary disease are also associated with lung cancer morbidity.
- The most significant lung cancer predictors are severity of visually assessed emphysema, age and pack-years of smoking.

What is the implication, and what should change now?

- Lung emphysema should be reported in lung cancer screening low-dose computed tomography and considered in prediction, who would benefit most from screening.

To our knowledge, there was previously only one study evaluating the impact of emphysema subtype on lung cancer incidence (12). Furthermore, we found only one study on correlation between lung cancer and emphysema occurrence, in which emphysema was assessed both quantitatively and qualitatively (13). We found no studies in which fractal dimension of low attenuation areas (LAA) clusters were used for automated emphysema evaluation. Optimalization of selection of lung cancer screening candidates requires specific information about correlation between lung cancer risk and emphysema subtypes, as well as determination of the best method for emphysema evaluation.

Objective

In our study, we aimed to establish the correlation between lung emphysema in quantitative and qualitative evaluation and lung cancer risk in MOLTEST-BIS lung cancer screening program participants. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-197/rc).

Methods

MOLTEST-BIS lung cancer screening program

Participants and examination protocol

The MOLTEST-BIS lung cancer screening program was conducted in 2016–2018 at the Medical University of Gdańsk. It was the second lung cancer screening programme in this institution after the Pilot Pomeranian Lung Cancer Screening Programme performed between 2009–2011. Participants were a group of 6,643 volunteers aged 50–79 years, with at least 30 pack-years of smoking history and no clinical lung cancer symptoms. No additional lung cancer risk model was applied in patient selection.

Each volunteer was interviewed by a trained staff member from the Department of Thoracic Surgery. Clinical data such as age, gender and smoking history were recorded for each patient. The blood samples were collected for molecular studies. LDCT scan of the chest was performed once in each participant and in 1,472 participants with indeterminate nodules second computed tomography (CT) scan was performed after 6 months. Each scan was evaluated concurrently by computed aided diagnosis (CAD) and visually by a trained thoracic radiologist. Protocol for nodule assessment is presented in *Figure 1*.

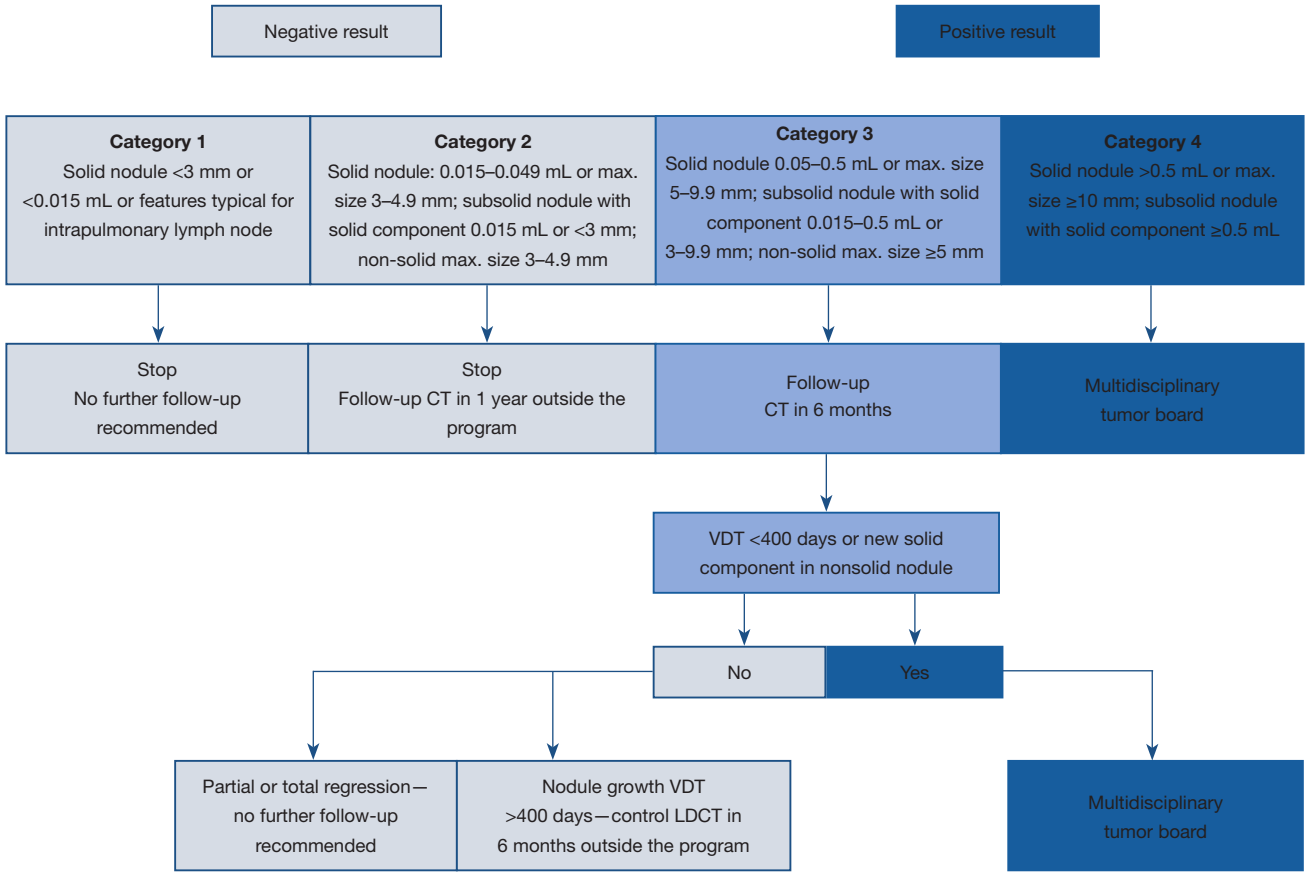

Figure 1 Nodule assessment protocol used in the MOLTEST-BIS study. CT, computed tomography; VDT, volume doubling time; LDCT, low-dose computed tomography.

Patients with positive LDCT results were referred to a multidisciplinary tumor board. The further diagnostic process included fine-needle- or core-aspiration biopsy of the lesion and bronchofiberoscopy, according to the tumor location. Patients were assigned into lung cancer positive (LCP) and lung cancer negative (LCN) group. The LCP group was further divided according to lung cancer type into the group with squamous cell cancer, adenocarcinoma and other types of cancer.

The study design was cross-sectional. Nine hundred fourteen individuals were included in the emphysema evaluation group. Eighteen participants were excluded, due to failure in automatic lung segmentation. The remaining group of 896 individuals included 729 individuals randomly chosen from all the MOLTEST-BIS screening program participants and 167 individuals randomly chosen from the group that underwent diagnostic work-up of indeterminate lung nodule inside the programme. The group consisted of 315 patients with negative scan regarding the nodules, 581 individuals with nodules and 100 participants with detected lung cancer. This semi-random group selection was expected to increase the number of LCP patients.

The study was approved by Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk (No. 126/2016). Informed consent was taken from all MOLTEST-BIS screening program participants. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

LDCT

LDCT was performed with 64 rows CT scanner GE Light Speed VCT (Boston, USA). The exposition conditions were 20 mAs and 120 kV. The reconstruction kernel was "lung" from GE Light Speed VCT. Slice thickness was 1.25 mm with reconstruction at 0.625. Pixel spacing was 0.98. All scans were acquired at University Clinical Centre in Gdańsk.

Emphysema evaluation

Qualitative

Baseline LDCT scans were evaluated for emphysema presence, type and severity by a radiology residents trained in thoracic radiology. Clinical data were not available to the researchers at the time. Pulmonary emphysema was classified according to Fleischner Society classification into centrilobular (CLE), paraseptal (PSE) and panlobular emphysema (PLE) subtypes.

CLE severity classification:

(I) Trace—centrilobular lucencies involving <0.5% of lung zone;
(II) Mild—sparse centrilobular lucencies, usually separated by large areas of normal lung, involving 0.5–5% of lung zone;
(III) Moderate—multiple well-defined centrilobular lucencies, involving >5% of any lung zone;
(IV) Confluent—convergent centrilobular or lobular lucencies, in multiple regions, involving several secondary pulmonary lobules, but without extensive hyperexpansion of secondary pulmonary lobules or distortion of pulmonary architecture;
(V) Advanced destructive emphysema—panlobular lucencies, with hyperexpansion of secondary pulmonary lobules and distortion of pulmonary architecture.

PSE was scored into two categories:

(I) Mild—small (≤1 cm), well-defined, rounded, juxtapleural lucencies, aligned adjacent to the pleural margin or along the interlobar fissure, sometimes including a few small rounded lucencies immediately central to the juxtapleural lucencies;
(II) Substantial—mainly large (>1 cm) juxtapleural, cyst-like lucencies or bullae, involving more than the lung apices, aligned adjacent to the pleural margin (14).

No studies in the analyzed group of participants were classified as PLE due to lack of clinical and radiological data consistent with this diagnosis.

In agreement with Fleischner Society recommendations, participant was considered as having CLE, when over 0.5% of lung zone was involved. Trace CLE was considered clinically insignificant (14).

Quantitative

Automated emphysema evaluation was conducted by Siemens Syngo.via Pulmo 3D application (Munich, Germany). We used two evaluation methods:

(I) Lung densitometry—all voxels representing lung tissue with attenuation value <–950 Hounsfield unit (HU) were recognized as LAA. Based on the extent of the LAA the Emphysema Index (EI) representing the proportion of LAA in the lung zones was calculated.
(II) Fractal dimension of LAA clusters—quantitative identification of neighboring LAA voxels as a cluster, measured as volume in mm^3. Size and distribution of these LAA clusters has the fractal characteristic, which is characterized by the fractal dimension (15). In this method, the clusters were divided according to size: Clas 1 (up to 2 mm), Clas 2 (up to 8 mm), Clas 3 (up to 65 mm), and Clas 4 (up to 167 mm).

Statistical analysis

Eight hundred and ninety-six subjects were included in the analysis.

The statistical tests included Welsch *t*-test, analysis of variance (ANOVA) with *post-hoc* honestly significant difference (HSD) Turkey test and Chi^2 test. The Quasi-Newton estimation logistic regression model was used to determine, which variables were significant for lung cancer risk.

Welsch *t*-test was used to determine the correlation between visually recognized emphysema >0.5% of lung zone and gender, age, number of pack-years of smoking history and EI.

ANOVA with *post-hoc* HSD Turkey test was used to determine a correlation between CLE severity grade and age, number of pack-years and EI. Severity grades 4 and 5 were considered in conjunction, due to the small number of participants involved.

Welsch *t*-test was used to determine a correlation between lung cancer occurrence and age, smoking history, gender and quantitative emphysema assessment parameters.

Chi^2 tests were used to determine the correlation between visually determined centrilobular and paraseptal emphysema and lung cancer occurrence.

Wilks lambda discriminant function analysis was performed for prognosis of visually determined emphysema occurrence based on automatic emphysema evaluation. In this model EI and Clas 1 was determined insignificant, and Clas 2–4 were significant (P<0.001).

Logistic regression model was used to determine, which variables are the most significant predictors of lung cancer

Table 1 Participants demographics

Demographic variable	N
Number of subjects	896
Sex	
Male	499
Female	397
Age, years, mean (SD)	63.6 (6.5)
Male	64 (6.5)
Female	63 (6.5)
Pack-years of smoking, mean (SD)	44 (16.6)
Male	48 (16.6)
Female	40 (16.6)
Lung cancer occurrence	100
Squamous cell carcinoma	24
Adenocarcinoma	52
Other	24

SD, standard deviation.

risk. The potential significant variables were EI, Clas 1–4, visually recognized presence of CLE >0.5%, the severity of CLE, the severity of paraseptal emphysema, pack-years of smoking history, patient age and patient gender. Pack-years, age, qualitative severity of CLE and Clas 1 were determined as significant in the model. Variables determined as statistically insignificant were: EI, Clas 2–4, visually recognized presence of CLE >0.5%, severity of paraseptal emphysema and patient gender. New logistic regression model was created for the significant results (P<0.001).

Results

Participants demographic data is presented in *Table 1*.

The results showing correlation with gender, age, pack-years, EI and Clas 1, 3 and 4 are presented in *Tables 2,3*.

Results showing correlation between emphysema severity grade and age, number of pack-years and EI are presented in *Figures 2-4*.

Discriminant function model results for significant variables are presented in *Table 4*.

Table 2 Correlation between visually recognized CLE and sex

Sex	No emphysema, N (%)	Emphysema, N (%)	P
All	591 (100.00)	305 (100.00)	–
Male	313 (52.96)	186 (60.98)	0.02
Female	278 (47.04)	119 (39.02)	

CLE, centrilobular emphysema.

Table 3 Correlation between visually recognized CLE and age, pack-years, EI and clusters

Variables	Emphysema (N=305)	No emphysema (N=591)	P
Age, years	65.07 (6.61)	62.95 (6.31)	<0.001
Pack-years	46.72 (17.17)	43.26 (16.04)	0.004
EI	4.19 (4.21)	3.49 (2.57)	0.008
Clas			
Clas 1 (2 mm^3)	1.16 (0.78)	1.43 (0.90)	<0.001
Clas 2 (8 mm^3)	0.93 (0.78)	0.99 (0.90)	0.26
Clas 3 (65 mm^3)	0.20 (0.22)	0.14 (0.20)	<0.001
Clas 4 (167 mm^3)	1.43 (3.19)	0.33 (0.89)	<0.001

Data are presented as mean (SD). Clas represent emphysema clusters of given size. CLE, centrilobular emphysema; EI, Emphysema Index; SD, standard deviation.

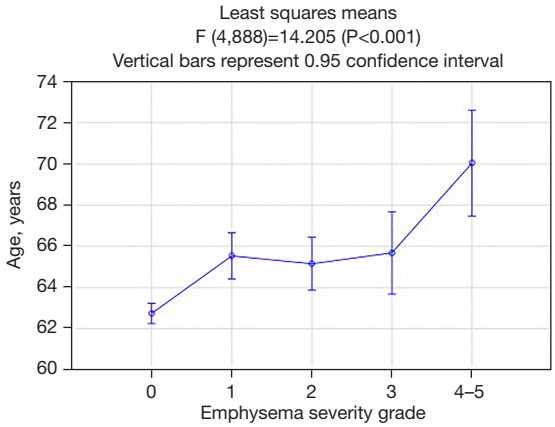

Figure 2 Correlation between emphysema severity grade and age. *Post-hoc* HSD Turkey test showed significant differences between mean age in groups 4–5 and 0 (P<0.001), 4–5 and 1 (P=0.01), 4–5 and 2 (P=0.008), 3 and 0 (P=0.04), 2 and 0 (P=0.005), 1 and 0 (P<0.001). HSD, honestly significant difference.

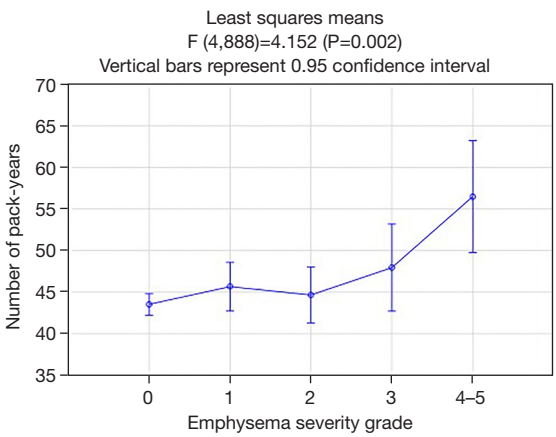

Figure 3 Correlation between emphysema severity grade and number of pack-years. *Post-hoc* HSD Turkey test showed significant differences between mean number of pack-years in groups 4–5 and 0 (P=0.002), 4–5 and 1 (P=0.03), 4–5 and 2 (P=0.02). HSD, honestly significant difference.

Results of the analysis of correlation between lung cancer incidence and age, smoking history, gender and quantitative emphysema assessment parameters are presented in *Tables 5*-7. A significant correlation was found for age and pack-years. No significant correlation was found for sex. In quantitative emphysema assessment there was only a correlation between lung cancer incidence and small emphysema clusters (Clas 1).

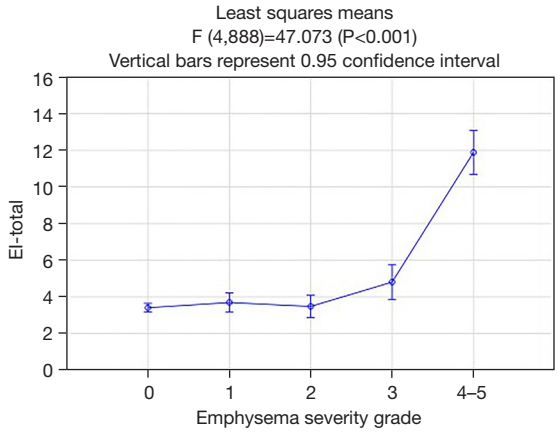

Figure 4 Correlation between emphysema severity grade and EI. *Post-hoc* HSD Turkey test showed significant differences between mean EI in groups 4–5 and 0 (P<0.001), 4–5 and 1 (P<0.001), 4–5 and 2 (P<0.001), 4–5 and 3 (P<0.001), 3 and 0 (P=0.04). EI, Emphysema Index; HSD, honestly significant difference.

Results presented in *Tables 8-10* show significant correlation between CLE and/or PSE and lung cancer incidence. However, there is a high coexistence between CLE and PSE—80.52% participants with significant CLE were also recognized with PSE. We found no correlation with lung cancer incidence if we included patients with PSE, who did not have coexisting significant CLE in the analysis.

The most common lung cancer type was adenocarcinoma (52%); 24% of lung cancer were squamous cell carcinoma and 24% comprised other types. No significant correlation between lung cancer type and gender (P=0.53), age (P=0.38), pack-years (P=0.11), EI (P=0.51) and severity of visually assessed CLE (P=0.77) was found.

The results of logistic regression model for variables determined significant for lung cancer risk are presented in *Table 11*.

Discussion

Key findings

In our study, we evaluated lung emphysema both, qualitatively and quantitatively. We found, that presence of CLE was significantly more common in males and increased with age and pack-years of smoking history. Presence of CLE in qualitative assessment responded to higher EI and the presence of emphysema clusters up to 2 mm and over

Table 4 Discriminant function analysis—prognosis of visually determined emphysema occurrence based on automatic emphysema evaluation

Clas	Discriminant function analysis results[†]					
	Wilks lambda	Partial lambda	F to remove	P	Tolerance	1-tolerance (R-square)
Clas 4	0.874	0.989	9.517	0.002	0.637	0.363
Clas 3	0.903	0.957	39.817	<0.001	0.104	0.896
Clas 2	0.884	0.978	20.231	<0.001	0.061	0.939

[†], Wilks lambda: 0.86433, F (4.891)=34.964, P<0.001. Effectiveness of discriminant model is significant, but weak—overall accuracy equals 71.54% (NPV 97.12%, PPV 21.97%). Clas represent emphysema clusters of given size. NPV, negative predictive value; PPV, positive predictive value.

Table 5 Correlation between lung cancer occurrence and age and pack-years

Variables	Cancer		No cancer		P
	N	Mean (SD)	N	Mean (SD)	
Age, years	100	66.95 (6.18)	796	63.26 (6.41)	<0.001
Pack-years	100	51.33 (21.11)	796	43.58 (15.64)	<0.001

SD, standard deviation.

Table 6 Correlation between lung cancer occurrence and sex

Sex	Cancer, N (%)	No cancer, N (%)	P
Male	55 (55.00)	444 (55.78)	0.88
Female	45 (45.00)	352 (44.22)	

Table 7 Correlation between lung cancer occurrence and quantitative emphysema parameters

Quantitative emphysema parameters	Cancer		No cancer		P
	N	Mean (SD)	N	Mean (SD)	
EI	100	4.10 (3.95)	796	3.68 (3.14)	0.32
Clas					
Clas 1 (2 mm^3)	100	1.13 (0.80)	796	1.36 (0.88)	0.008
Clas 2 (8 mm^3)	100	0.96 (0.88)	796	0.97 (0.86)	0.90
Clas 3 (65 mm^3)	100	0.20 (0.25)	796	0.15 (0.20)	0.10
Clas 4 (167 mm^3)	100	1.20 (2.83)	796	0.64 (1.94)	0.055

Clas represents emphysema clusters of given size. EI, Emphysema Index; SD, standard deviation.

8 mm (Clas 1, Clas 3 and Clas 4) in quantitative assessment. CLE severity grade correlated with age, number of pack-years and EI. Quantity of emphysema clusters bigger than 8 mm in automatic evaluation is in concordance with presence of emphysema in visual evaluation, however the relationship is weak.

In the logistic regression model the most significant lung cancer predictors are the severity of visually assessed emphysema, age and pack-years of smoking history.

Results of our study suggest, that presence of lung emphysema, when assessed visually, is an independent risk factor of lung cancer occurrence. However, we found

Table 8 Correlation between visually determined presence of CLE >0.5% of lung area and lung cancer occurrence

Presence of CLE >0.5%	N (%)		
	No cancer	Cancer	All
No CLE >0.5%	681 (76.00)	61 (6.81)	742 (82.81)
CLE >0.5%	115 (12.83)	39 (4.35)	154 (17.19)
All	796 (88.84)	100 (11.16)	896 (100.00)

Chi^2=37.63 (P<0.001). CLE, centrilobular emphysema.

Table 9 Correlation between visually determined PSE and lung cancer occurrence

Presence of PSE	N (%)		
	No cancer	Cancer	All
No PSE	569 (63.50)	44 (4.91)	613 (68.42)
PSE	227 (25.33)	56 (6.25)	283 (31.58)
All	796 (88.84)	100 (11.16)	896 (100.00)

Chi^2=31.05 (P<0.001). PSE, paraseptal emphysema.

Table 10 Correlation between visually determined PSE without coexistence of CLE and lung cancer occurrence

Emphysema—qualitative assessment	N (%)		
	No cancer	Cancer	All
No PSE without CLE	660 (73.66)	77 (8.59)	737 (82.25)
PSE without CLE	136 (15.18)	23 (2.57)	159 (17.75)
All	796 (88.84)	100 (11.16)	896 (100.00)

Chi^2=2.13 (P=0.15). PSE, paraseptal emphysema; CLE, centrilobular emphysema.

Table 11 Logistic regression model—relationship between lung cancer risk and significant variables

Statistical parameters	Dependent variable: cancer diagnosis			
	Clas 1	CLE severity grade	Pack-years	Age
P value	0.001	<0.001	0.001	<0.001
−95% CI	−0.804	0.217	0.008	0.04
+95% CI	−0.195	0.559	0.032	0.113
OR unit	0.607	1.474	1.021	1.08
−95% CI	0.448	1.242	1.008	1.04
+95% CI	0.823	1.749	1.033	1.12
OR range	0.087	6.958	11.108	10.738
−95% CI	0.019	2.96	2.692	3.421
+95% CI	0.385	16.352	45.839	33.7

The whole model was statistically significant [Chi^2(4)=76.667, P<0.001] as were individual dependent variables: Clas 1 (P=0.001), CLE severity grade (P<0.001), pack-years (P=0.001) and age (P<0.001). Clas represents emphysema clusters of given size. CLE, centrilobular emphysema; CI, confidence interval; OR, odds ratio.

no correlation between lung cancer and quantitative emphysema evaluation with EI and clusters over 2 mm.

Strengths and limitations

The main strength of our study is relatively large number of subjects, including patients with lung cancer detected within a lung cancer screening program, as well as application of several methods of evaluation of emphysema.

In our opinion, the main factor limiting quantitative evaluation of emphysema are artifacts related to low-dose CT imaging technique, which alter the evaluation of emphysema with dedicated software. We consider this is the main reason for weak correlation between visual and automatic emphysema evaluation, and the correlation between small emphysema clusters up to 2 mm and decreased lung cancer risk.

Another limitation of our study is existence of several previous studies on correlation between emphysema and lung cancer risk. However, due to significant progress in lung cancer screening, it is essential to optimalize the selection of the patients for screening. In our opinion, additional studies on this topic, including follow-up and validation against lung cancer risk prediction models, are needed.

Comparison with similar researches

Several studies have demonstrated, that chronic lung diseases, like chronic obstructive pulmonary disease (COPD) are also associated with lung cancer morbidity (16-18). There is evidence, that features of COPD like airway obstruction, presence of emphysema and its exacerbation increase risk of lung cancer development (19). However, study by Wilson *et al.* showed, that in patients with COPD, lung emphysema is the main factor related to lung cancer risk, and the airway obstruction is not responsible for increased lung cancer risk if adjusted for the presence of emphysema (20).

Our results are in line with several prior studies, which found a correlation between lung emphysema and lung cancer when emphysema was evaluated visually (12,16,21-23), but when emphysema was assessed automatically, no correlation was found (19,24,25). Wilson *et al.* evaluated emphysema in Pittsburgh Lung Screening Study (PLuSS) group visually, and found significant correlation with lung cancer occurrence (20). He also evaluated a matched group of patients in case-control study, and found significant correlation for visual evaluation for emphysema, but none for automated evaluation (13).

CLE shows the significant relationship with tobacco smoking. That is not the case for PSE. We observed that CLE is a risk factor for developing lung cancer, which is similar to results reported by González *et al.* (12). However, we found correlation between PSE and lung cancer risk, which was not present in the study mentioned above. However in our group, there was a high coincidence of PSE in patients with CLE. No significant correlation between lung cancer incidence and PSE in logistic regression lung cancer risk model, and when we analyzed patients who had PSE but no CLE was observed. Correlation between lung cancer and PSE is mainly due to the high coincidence of PSE in patients with CLE.

We found that the severity of visually assessed emphysema is one of the most significant lung cancer predictors, which differs from Wilson *et al.* results, who found no association between emphysema severity and lung cancer risk (20).

Implications and actions needed

Due to the poor outcome of the treatment of advanced lung cancer, it is essential to establish a screening program to detect lung cancer in early stage, when the treatment prognosis is better. Because of potential costs and radiation exposure, it is essential to determine which group of patients would most benefit from lung cancer screening. We found a correlation between lung cancer occurrence and age and pack-years of smoking history and no correlation with gender, which corresponds to recognized inclusion criteria for lung cancer screening programs (3,26). However, Sanchez-Salcedo *et al.* in their study showed, that if the criteria applied in National Lung Screening Trial (NLST) were supplemented with radiographic emphysema, lung cancer detection rates in annual lung cancer screening rounds would improve, with fewer cancers undetected (21). Furthermore, if NLST criteria and/or evidence of emphysema on baseline LDCT were used as inclusion criteria in the Pamplona International Early Lung Cancer Detection Program (P-IELCAP) and the PLuSS, the screening cohort would be reduced by 48% and 27% respectively, with 88% and 95% of incident lung cancers

detected nonetheless (21).

Conclusions

There is a correlation of qualitative and quantitative emphysema evaluation results. Presence and severity of CLE correlate with higher lung cancer occurrence. The most important lung cancer predictors in our study are the severity of visually assessed emphysema, age and pack-years of smoking history.

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Footnote

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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. The study was approved by Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk (No. 126/2016). Informed consent was taken from all MOLTEST-BIS screening program participants. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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