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Original Article

Emphysema or Bronchiectasis with Pulmonary Nodules: Impact on The Risk of Malignancy

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ABSTRACT

OBJECTIVE: The increasing use of computed tomography (CT) has led to a significant rise in the detection of pulmonary nodules. This has resulted in more studies aimed at identifying risk factors associated with increased detection of early-stage lung cancer. The aim of this study is to investigate the effect of coexisting emphysema or bronchiectasis on the incidence of malignancy in pulmonary nodules.

MATERIAL AND METHODS: The study included 212 patients with pulmonary nodules detected on CT images. They were divided into three groups based on the presence of emphysema or bronchiectasis. The effects of demographic factors and pulmonary nodule characteristics on malignancy were evaluated in these groups.

RESULTS: Comparison of the incidence of malignancy in pulmonary nodules across groups showed no significant difference in the emphysema or bronchiectasis groups compared with the control group ($P > 0.05$).

CONCLUSION: Contrary to what is frequently reported in the literature, the presence of emphysema was not found to be a risk factor for lung cancer in this study. The presence of bronchiectasis was also found not to be a risk factor; however, there are insufficient data in the literature on this point.

KEYWORDS: Pulmonary nodule with emphysema, pulmonary nodule with bronchiectasis, lung cancer risk factors, lung cancer screening

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INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide. As a result of studies conducted to enable early diagnosis, lung cancer screening programs have been developed.[1] Risk-based lung cancer screening programs evaluate patient characteristics such as age, smoking history, gender, ethnic origin, personal and family history of cancer, and presence of emphysema.[2] Risk models based on characteristics of pulmonary nodules detected on computed tomography (CT) scans have also been developed to predict malignancy.[3] The criteria in these models include large nodule size, upper lobe location, and irregular margins.[4]

More than 85% of patients diagnosed with lung cancer are smokers.[5] A history of smoking is also the most common cause of emphysema. Lung cancer and emphysema share this common primary risk factor.[6] Despite this common risk factor, studies investigating the relationship between these two diseases have reported conflicting results. While some studies have shown that the detection of emphysema on CT scans is a risk factor for lung cancer,[7,8] another study failed to find this correlation.[9]

Chronic inflammation and infection play important roles in the pathophysiology of lung cancer.[10] Bronchiectasis is one of the pulmonary diseases associated with chronic infection and systemic inflammation; few studies have evaluated whether it is a risk factor for lung cancer.[11]

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Conflicting data exist regarding the effect of pulmonary emphysema on the incidence of malignancy among patients with pulmonary nodules. The aim of this study is to investigate the effects of emphysema or bronchiectasis coexisting with pulmonary nodules, and of nodule characteristics, on the incidence of malignancy in the nodules.

MATERIAL AND METHODS

Study Design and Setting

The study was designed as a retrospective study. The study included patients who presented to the pulmonary diseases outpatient clinic between March 1, 2018, and March 1, 2022; had a pulmonary nodule detected on chest X-ray; underwent thoracic CT that showed a pulmonary nodule measuring 8–30 mm; and had persistent nodules despite non-specific antibiotic therapy. Patients with pulmonary nodules were grouped into three categories: those with emphysema (emphysema group), those with bronchiectasis (bronchiectasis group), and those in a control group. Patients with concurrent emphysema and bronchiectasis were excluded from the study because the number of such cases was small.

This study was approved by the İstanbul University-Cerrahpaşa Clinical Research Ethics Committee on May 16, 2022 (no: E83045809-604.01.01-381251).

Participants

Inclusion criteria:

- Between March 1, 2018, and March 1, 2022, a non-calcified solid pulmonary nodule was detected on a chest CT scan performed at the outpatient chest diseases clinic after a nodule was identified on a chest X-ray. The nodule persisted on a follow-up CT scan performed two months after non-specific antibiotic therapy
- Pulmonary nodule measuring 8–30 mm in size with further investigations performed to assess malignancy
- Aged between 30 and 90
- Detection of a pulmonary nodule measuring 8–30 mm on the initial CT scan
- Completion of a 2-year CT follow-up program from the date of nodule detection or diagnosis of malignancy during follow-up

Main Points

- In this study, contrary to reports in the literature, it was found that the presence of emphysema with pulmonary nodules had no significant effect on the incidence of malignancy and was not a risk factor for lung cancer.
- Bronchiectasis has not been identified as a risk factor with this study.
- The incidence of malignancy in pulmonary nodules of 8 mm or larger in the emphysema group was not different from that in the control group.

Exclusion criteria:

- Presence of emphysema and bronchiectasis
- Presence of regression after non-specific antibiotics
- Failure to complete 2 years of follow-up during nodule monitoring
- History of lung cancer or any other malignancy
- Presence of active lung infection
- Diagnosis or suspicion of interstitial lung disease
- Pulmonary vascular disease
- Pleural diseases, pleural effusion
- Alveolar hemorrhage
- Pregnancy
- Chronic diseases such as heart failure, kidney failure
- History of known rheumatological diseases

Variables and Data Collection

Demographic data(age, gender), family history, and smoking status (pack-years) were recorded from the patients' files. Pulmonary nodule characteristics and the presence of coexisting emphysema or bronchiectasis were recorded from chest CT scans.

Thorax CT Scans

Data on the single largest pulmonary nodule detected on the initial and follow-up lung parenchymal-window CT scans were included in the study. Each nodule that was regularly monitored according to the Fleischner guidelines and remained unchanged for at least 2 years was considered benign and included in the dataset. Data on patients who received a histopathological diagnosis of malignancy during follow-up were added. The presence of emphysema or bronchiectasis was recorded. Patients with emphysema were included in the emphysema group, those with bronchiectasis were included in the bronchiectasis group, and those with both conditions were excluded from the study. Patients without emphysema or bronchiectasis were included in the control group.

The size, location, and margin characteristics of pulmonary nodules were recorded. Nodules diagnosed as malignant during the 2-year follow-up period are included, along with their size at the time of diagnosis. Location data were recorded as peripheral or central. Nodules defined as central were located in the segmental bronchi or in more proximal airways, whereas peripheral nodules were located distally in the subsegmental bronchi.[12]

Diagnosis of Malignancy

Patients diagnosed with lung cancer by histopathological examination of biopsy samples were classified according to the World Health Organization classification of lung neoplasms.[13]

Study Size

All patients who met the eligibility criteria and provided informed consent were included in the study.

Statistical Analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) v22 (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation or median (minimum-maximum) for continuous variables and frequency (percentage) for categorical variables, depending on the normality of the distribution, and descriptive statistics were used in the analysis of the data. The chi-square test was used to compare categorical data. For normally distributed data, one-way analysis of variance was used; for non-normally distributed data, the Kruskal-Wallis test and the Mann-Whitney U test were used. Two-tailed *P* values less than 0.05 were considered statistically significant.

RESULTS

Of the 212 patients included in the study, 36.8% (n = 78) had emphysema, 24.5% (n = 52) had bronchiectasis, and 38.7% (n = 82) were in the control group. The mean age of the patients was 67.39±10.90, and the mean number of cigarettes smoked was 48.33±30.60 pack-years. 75.5% of the patients were male, 84.9% had a history of smoking, 80.7% had a family history of cancer, 0.5% had asbestos exposure, and 14.6% had a history of tuberculosis.

When comparing the variables of gender, smoking history, and tuberculosis history in patients with emphysema, bronchiectasis, and the control group, there were significant differences between the three groups (*P* = 0.000, *P* = 0.000, *P* = 0.005, respectively); 45.6% of male patients, 52.1% of active smokers, and 48.4% of patients with a history of tuberculosis were in the emphysema group. In addition, the average number of pack-years smoked by patients in the emphysema group was significantly higher (*P* = 0.000) (Table 1).

The characteristics of all pulmonary nodules, benign and malignant, were evaluated with respect to the presence of bronchiectasis, and no significant differences were found between the bronchiectasis and control groups (*P* > 0.05; Table 2).

The relationship between the size of all pulmonary nodules (benign and malignant) and the presence of emphysema was evaluated; no significant difference was found between nodules with and without emphysema (*P* > 0.05) (Table 3). When the relationship between the presence of emphysema and the edge characteristics and location of pulmonary nodules was evaluated, differences were observed between the two groups (*P* = 0.007 and *P* = 0.042, respectively). While nodules with smooth margins were frequently observed in the group without emphysema, nodules with irregular margins were more frequent in the emphysema group (odds ratio: 2.462; 95% confidence interval: 1.270–4.772). The likelihood of pulmonary nodules with irregular margins was 2.46 times higher in the emphysema group than in the non-emphysema group. 66.7% of centrally located pulmonary nodules were found in the emphysema group (odds ratio: 2.433; 95% confidence interval: 1.019–5.808). The likelihood of a pulmonary nodule being centrally located was 2.43 times higher in the presence of emphysema than in its absence (*P* = 0.041; Table 3).

Malignant pulmonary nodules are summarized in Table 4; no statistically significant differences were found between the emphysema, bronchiectasis, and control groups with respect to nodule size, margin characteristics, location, and histopathological type (*P* > 0.05). It was determined that 45.6% of malignant pulmonary nodules were >31 mm in size, 87.7% had irregular margins, and 63.2% were peripherally

Table 1. Demographic characteristics of patients (n = 212)

Demographic characteristics	Emphysema group (n = 78) Mean ± SD	Bronchiectasis group (n = 52) Mean ± SD	Control group (c) (n = 82) Mean ± SD	Total Mean ± SD	*P*
Age	69.44±8.44	67.00±11.58	65.69±12.25	67.39±10.90	*P* = 0.131
Amount of cigarettes smoked (pack-year) (pack-years) (n = 180)	57.42±28.21	47.23±31.75	37.80±29.58	48.33±30.60	***P* = 0.000*** a>c†
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Gender					
Female	5 (9.6)	11 (21.2)	36 (69.2)	52 (24.5)	***P* = 0.000***
Male	73 (45.6)	41 (25.6)	46 (28.8)	160 (75.5)	
Smoking status					
Never smoked	2 (6.3)	9 (28.1)	21 (65.6)	32 (15.1)	
Ex-smoker	27 (31.4)	26 (30.2)	33 (38.4)	86 (40.6)	***P* = 0.000***
Smoker	49 (52.1)	17 (18.1)	28 (29.8)	94 (44.3)	
Family history of cancer	10 (24.4)	9 (22.0)	22 (53.7)	41 (19.3)	*P* = 0.074
Asbestos exposure	0 (0)	0 (0)	1 (100.0)	1 (0.5)	*P* = 0.451
Tuberculosis history	15 (48.4)	12 (38.7)	4 (12.9)	31 (14.6)	***P* = 0.005***

*$P < 0.05$, †The *P* value obtained after Bonferroni correction was $P < 0.0167$. The chi-square test was used for categorical variables. Since numerical variables did not show a normal distribution, the Kruskal-Wallis test was used. Note: Row percentage (row percent) and column percentage (column percent) are given for groups
SD: standard deviation

located. Comparison of the margin characteristics of malignant pulmonary nodules between the emphysema and control groups revealed a significant difference (P = 0.039). 60% of pulmonary nodules with irregular margins occurred in the emphysema group (odds ratio: 9.000; 95% confidence interval: 1.006–80.522). The likelihood of a malignant pulmonary nodule with irregular margins was 9 times higher in the presence of emphysema than in its absence.

DISCUSSION

This study aimed to determine the incidence of malignancy among pulmonary nodules in patients with emphysema or bronchiectasis. We found that the frequency of malignancy in pulmonary nodules in the presence of emphysema did not differ from that in the control group; emphysema, often identified in the literature as a risk factor for lung cancer, was not found to be a risk factor in this study. Similarly, bronchiectasis was not identified as a risk factor for lung cancer.

The literature reports conflicting results regarding whether the association between emphysema and pulmonary nodules contributes to nodule malignancy risk. Wachuła et al.[14] showed that pulmonary nodules were more frequently associated with active smoking among patients with emphysema, but they did not find that malignant pulmonary nodules were more common among patients with emphysema. While the results of this study support our data, other studies have reported that, among pulmonary nodules in patients with emphysema, malignant nodules are more common than benign nodules.[15,16] Hohberger

Table 2. Comparison of pulmonary nodule characteristics according to the presence of emphysema (n = 160)

Nodule characteristics	Emphysema		Total	*P*
	Presence (n = 78) Mean ± SD	Absence (n = 82) Mean ± SD	Mean ± SD	
Pulmonary nodule size	25.48±21.30	20.84±14.65	23.10±18.29	*P* = 0.470
	n (%)	n (%)	n (%)	
Margin characteristics				
Smooth	21 (35.0)	39 (65.0)	60 (37.5)	***P* = 0.007***
Irregular	57 (57.0)	43 (43.0)	100 (62.5)	
Location				
Peripheral	60 (45.1)	73 (54.9)	133 (83.1)	***P* = 0.041***
Near the hilum	18 (66.7)	9 (33.3)	27 (16.9)	
Malignancy status				
Benign	47 (45.6)	56 (54.4)	103 (64.4)	*P* = 0.289
Malignant	31 (54.4)	26 (45.6)	57 (35.6)	

P < 0.05, the chi-square test was used for categorical variables. Since numerical variables did not show a normal distribution, the Mann-Whitney U test was used.
Note: Row percentages were given for groups, and column percentages were given for the total
SD: standard deviation

Table 3. Comparison of pulmonary nodule characteristics according to the presence of bronchiectasis (n = 134)

Nodule characteristics	Bronchiectasis		Total	*P*
	Presence (n = 52) Mean ± SD	Absence (n = 82) Mean ± SD	Mean ± SD	
Pulmonary nodule size	19.27±14.75	20.84±14.65	20.23±14.65	*P* = 0.545
	n (%)	n (%)	n (%)	
Margin characteristics				
Smooth	22 (36.1)	39 (63.9)	61 (45.5)	*P* = 0.552
Irregular	30 (41.1)	43 (58.9)	73 (54.5)	
Location				
Peripheral	48 (39.7)	73 (60.3)	121 (90.3)	*P* = 0.531
Near the hilum	4 (30.8)	9 (69.2)	13 (9.7)	
Malignancy status				
Benign	42 (42.9)	56 (57.1)	98 (73.1)	*P* = 0.112
Malignant	10 (27.8)	26 (72.2)	36 (26.9)	

P < 0.05, the chi-square test was used for categorical variables. Since numerical variables did not show a normal distribution, the Mann-Whitney U test was used.
Note: Row percentages were given for groups, and column percentages were given for the total
SD: standard deviation

Table 4. Comparison of malignant pulmonary nodule characteristics between groups (n = 67)

Malignant nodule characteristics	Emphysema group (a) (n = 78) n (%)	Bronchiectasis group (b) (n = 52) n (%)	Control group (n=82) n (%)	Total n (%)	*P*
Margin characteristics					
Smooth	1 (11.1)	2 (22.2)	6 (66.7)	9 (13.4)	*P* = 0.073
Irregular	30 (51.7)	8 (13.8)	20 (34.5)	58 (86.6)	
Location					
Peripheral	17 (38.6)	8 (18.2)	19 (43.2)	44 (65.7)	*P* = 0.206
Near the hilum	14 (60.9)	2 (8.7)	7 (30.4)	23 (34.3)	
Histopathological type					
Adenocarcinoma	12 (40.0)	6 (20.0)	12 (40.0)	30 (44.8)	*P* = 0.843
Squamous cell carcinoma	11 (55.0)	2 (10.0)	7 (35.0)	20 (29.9)	
Small cell carcinoma	3 (50.0)	0 (0)	3 (50.0)	6 (9.0)	
Metastasis	5 (45.5)	2 (18.2)	4 (36.4)	11 (16.4)	

P < 0.05, the chi-square test was used for categorical variables. Since numerical variables did not show a normal distribution, the Mann-Whitney U test was used. Note: Row percentages were given for groups, and column percentages were given for the total

et al.[15] evaluated the relationship between emphysema severity and tumors in patients with lung cancer, and found that primary lung cancer developed more frequently in lung areas with severe emphysema.

The National Lung Screening Trial is one of the studies that have examined the relationship between pulmonary nodules and emphysema severity. Groups of patients with benign and malignant pulmonary nodules, mostly comprising individuals with emphysema who had similar smoking histories, were compared based on emphysema severity. Only severe emphysema was significantly associated with malignant pulmonary nodules; however, this association was not compared with a control group. The data also showed that the malignant pulmonary nodule group had a significantly higher incidence of diagnosed chronic obstructive pulmonary disease.[16] In our study, however, a comparison was made with a control group without emphysema, and the smoking amount in this control group was significantly lower than that in the emphysema group. In this respect, it is consistent with the data of Wachuła et al.[14]

Sanchez-Salcedo et al.[17] investigated the presence of emphysema in patients diagnosed with malignancy and demonstrated a association with lung cancer incidence; however, this association was not examined in relation to pulmonary nodules. A similar study by Henschke et al.[18] reported a significantly higher incidence of emphysema among patients diagnosed with lung cancer. However, the contribution of emphysema to the risk of malignancy in a pulmonary nodule was not evaluated in these studies. In our study, the relationship between emphysema and malignancy was evaluated based on pulmonary nodules.

Despite these studies, other studies did not find emphysema to be a significant risk factor for lung cancer. Maldonado et al.[19] found no significant association between severe emphysema and lung cancer. In our study, patients diagnosed with lung cancer were not evaluated for emphysema. Patients with pulmonary nodules were evaluated for emphysema, and the frequency of malignancy in pulmonary nodules associated with emphysema did not differ from that in the control group.

These conflicting results may be explained by interindividual variation in the biological damage caused by smoking; only a proportion of smokers develop emphysema, and the effect of pulmonary nodules on malignancy risk also varies.[20]

Worldwide, there are still more than one billion smokers, the vast majority of whom are men.[21,22] Chronic smoking, the primary cause of lung cancer and emphysema, is a common risk factor for these diseases and is more prevalent among men.[23-26] In line with these findings, the majority of our patients who smoked, as well as those with emphysema, were men. Tuberculosis has been identified as a risk factor for both bronchiectasis and emphysema.[27] We also found that patients with a history of tuberculosis frequently had emphysema.

Marginal characteristics of pulmonary nodules are among the parameters examined as risk factors for malignancy.[4,28] Upper-lobe localization is considered a predictor of lung cancer.[4,29] In this study, the incidence of irregular-edged pulmonary nodules in emphysematous lung parenchyma was 2.46 times higher, while the incidence of central localization of nodules was 2.43 times higher.

In the final model of their study evaluating the risk of malignancy associated with irregular margins in pulmonary nodules, McWilliams et al.[4] found no association between margin characteristics and risk of malignancy. The Dutch-Belgian randomized lung cancer screening trial (NELSON) reported similar findings: among pulmonary nodules with irregular margins, only the initial volume predicted malignancy, whereas morphology did not.[28] In our study, pulmonary nodules with irregular margins were more common in patients with emphysema; however, their effect on malignancy risk was assessed independently of emphysema.

Conflicting data exist on whether emphysema is a risk factor for lung cancer; however, our study did not identify emphysema as a risk factor.[14-19] However, irregularly shaped pulmonary

nodules were more common in the emphysema group. Data on the relationship between pulmonary nodule margin characteristics and malignancy risk are also variable.[4,28] We have not found any studies that evaluate the risk of malignancy in pulmonary nodules with irregular margins in patients with emphysema.

In a study by Sanchez-Carpintero Abad et al.[30] examining the role of bronchiectasis in lung cancer screening programs, the presence of bronchiectasis was associated with increased numbers of nodules and false-positive results. It has been emphasized that, although bronchiectasis is more common in smokers and therefore more common among patients included in lung cancer screening programs than in the general population, it has no effect on cancer incidence.[30] Similar findings were reported in the study by Cai et al.[31] In our study, we also found that the coexistence of bronchiectasis and pulmonary nodules did not increase the incidence of malignancy.

Study Limitations

The limitations of this study include that it was not prospective. Although a sample size appropriate for power analysis was obtained, a larger number of patients could have been included to allow for evaluation based on the severity of emphysema. Additionally, this suggests that an increased number of cases is associated with a higher risk of malignancy in emphysema cases and a lower risk of malignancy in nodules in bronchiectasis cases. The gender and smoking-status variables of the control and emphysema groups could have been made more similar. Since routine follow-up is not required for patients with pulmonary nodules smaller than 6 mm who do not have lung cancer risk factors, the absence of these patients in the control group may have introduced bias. The inclusion of metastatic nodules in the study was another limitation.

Strengths of the study include comparison of the emphysema group with the bronchiectasis group and with a control group. It investigated the effect of nodule-related characteristics on malignancy in the emphysema group. This study adds a contrary perspective to studies reporting emphysema as a risk factor for lung cancer and highlights the need for further research from a new perspective. It was a unique study in that it investigated the frequency of malignancy in pulmonary nodules in patients with bronchiectasis.

CONCLUSION

In conclusion, contrary to frequent reports in the literature, emphysema has not been identified as a risk factor for lung cancer among patients with pulmonary nodules. Bronchiectasis, which has not previously been investigated in this context, was also not identified as a risk factor in our study.

Ethics

Ethics Committee Approval: This study was approved by the İstanbul University-Cerrahpaşa Clinical Research Ethics Committee on May 16, 2022 (no: E83045809-604.01.01-381251).

Informed Consent: All patients who met the eligibility criteria and provided informed consent were included in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.G., B.Ç.Ö., Concept: A.G., B.Ç.Ö., Design: A.G., B.Ç.Ö., Data Collection or Processing: A.G., B.Ç.Ö., Analysis or Interpretation: A.G., E.A., B.G., Ş.B., B.Ç.Ö., Literature Search: A.G., Writing: A.G.

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