Simultaneous pathological findings in biopsy specimens of patients with surgically resected lung carcinoids and their role in survival

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Abstract. Pulmonary carcinoid tumors are rare, low-grade malignant tumors that constitute 1-2% of all lung tumors. The present study aimed to describe the simultaneous pathological findings in biopsy specimens of patients with surgically resected lung carcinoids and determine their association with survival rates. For this purpose, 108 patients with resected carcinoid lung tumors were followed-up for 96 months and analyzed for simultaneous pathological findings in biopsy specimens. Among these, simultaneous pathological findings were found in 82 patients. The association between these findings and patient survival rates was evaluated. Atelectasis was a simultaneous finding in 52.4% of the patients, desquamative interstitial pneumonia (DIP) in 13.4%, emphysema in 24.4% and bronchiectasis in 9.8%. The survival rate was 100% for the patients with atelectasis, 81.8% for the patients with DIP, 90% for the patients with emphysema and 75% for the patients with bronchiectasis ($P<0.05$). According to the univariate analysis, the type of carcinoid was associated with patient survival with better survival rates for patients with typical carcinoids, while age, sex, stage and simultaneous pathological findings were not associated with patient survival. On the whole, there was a statistically significant difference in the survival rates of patients with resected lung carcinoids with different simultaneous pathological findings. However, further studies are warranted to assess the role of these findings in the survival of these patients.

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Introduction

Carcinoid tumors are low-grade malignant tumors that are most frequently located in the gastrointestinal system. The respiratory tract is the second most frequent site and carcinoids account for 1-2% of all lung tumors (1). Lung carcinoids are categorized into typical carcinoids (TCs) and atypical carcinoids (ACs). This division is dependent on the mitotic rate and necrosis. TC is defined as <2 mitoses per 2 mm^2 without necrosis. AC is defined as ≥2 mitoses, but <10 mitoses per 2 mm^2 or necrosis, or both (2).

Bronchopulmonary carcinoids are mostly found as an incidental radiographic finding (3). They are usually observed as well-defined pulmonary nodules, and TCs and ACs cannot be distinguished radiographically (4).

Carcinoid tumors are macroscopically well demarcated, tan to yellow lesions (5,6). They consist of uniform polygonal cells with granular chromatin, unobtrusive nucleoli and an eosinophilic cytoplasm (6). The most frequent growth patterns are the organoid and trabecular; with an arrangement of the

tumor cells in nests or cords, respectively, with less common patterns comprising spindle cell, pseudoglandular, papillary, rosette formation and follicular (5,7,8). There may also be neuroendocrine cell hyperplasia in the adjacent airway epithelium (9,10). A recent study described the co-existence of pulmonary carcinoid tumorlets, which are confined neuroendocrine tumors, with chronic pulmonary inflammatory entities, such as bronchiectasis, atelectasis and recurrent pulmonary infections in lung tissue specimens (11).

Numerous prognostic factors for carcinoid tumors have been described, including age, sex, tumor size, stage, type, the type of surgical procedure performed, chemotherapy and radiation (12-14). In addition, vascular invasion, nuclear pleomorphism and aerogenous spread, a Ki-67 index ≥5%, infiltrative growth and the absence of orthopedia homeobox protein expression are considered unfavorable prognostic factors, whereas palisading, papillary formation and pseudoglandular patterns are favorable prognostic features (9,15,16).

However, the simultaneous pathological findings in lung specimens of surgically resected pulmonary carcinoids and their prognostic role have not been described to date, at least to the best of our knowledge. The identification of prognostic factors in lung carcinoids, which are relatively rare tumors, is significant for a variety of reasons, such as understanding which characteristics are predictive of outcomes, acquiring knowledge into the biology and natural history of the disease, treatment optimization, the inclusion of these factors in clinical trial designs and the awareness of the possibility of recurrence or death (17). The present study aimed to describe the simultaneous pathological findings and determine their association with the survival rates of patients with surgically resected pulmonary carcinoids.

Table I. Histopathological characteristics of the patients.

Variable	TC	AC	All
Stage			
I	62	16	78
II	14	4	18
III	4	8	12
Recurrent tumors	4	4	8
Stage I	4	0	4
Stage II	0	2	2
Stage III	0	2	2
Deaths	4	4	8
Stage I	4	0	4
Stage II	0	2	2
Stage III	0	2	2

AC, atypical carcinoid; TC, typical carcinoid.

Table II. Concurrent pathological findings of pulmonary carcinoid tumors.

Pathological findings	TC	AC	All
DIP	4	7	11 (13.4%)
Emphysema	13	7	20 (24.4%)
Bronchiectasis	8	0	8 (9.8%)
Atelectasis	31	12	43 (52.4%)

AC, atypical carcinoid; TC, typical carcinoid; DIP, desquamative interstitial pneumonia.

Patients and methods

Study design. From March, 2005 to March, 2019, the present study retrospectively evaluated patients with a histological diagnosis of a lung carcinoid who had undergone thoracic surgery. The assessment was made with a medical history, clinical examination, chest X-ray and computed tomography (CT) scan of the chest, brain and upper abdomen, while a bone scintigraphy was also performed. All patients had a pre-operative examination with a fiberoptic bronchoscope, and in some patients, endoscopic biopsy was conducted while CT-guided fine-needle aspiration biopsy was performed for tumors in the lung periphery. All samples that were resected during surgery, including the mediastinal and hilar lymph nodes, were assessed by a pathological examination. The categorization of the tumors into TCs and ACs was performed as stated by the World Health Organization (WHO) (18). The estimation of carcinoid stage was made in accordance with the 8th tumors, nodes and metastases (TNM) staging system for lung cancer (19). Age, sex, type of carcinoid, stage and simultaneous pathological findings were noted, and the association with the patient survival rates was recorded. The present study enrolled 108 patients. AC was diagnosed in 28 patients and TC was diagnosed in 80 patients (13). Ethical approval for the present study was obtained from the Research Ethics Committee of Athens medical Group with file accession no. 4234. The study was in line with the declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Written informed consent was obtained from the patients for publication of this research and accompanying images.

Histological examination. Immunohistochemistry (IHC) was performed to confirm the diagnosis of lung carcinoids and was broadly positive for chromogranin and synaptophysin. For histochemistry, the tissue specimens from the patients were formalin-fixed and paraffin-embedded, as per the standard histopathology laboratory routine (FFPE). The fixative used was 10% formalin solution, neutral buffered, for 24 h at room temperature. The thickness of the sections used was 2 μm. Histochemical staining with hematoxylin and eosin (supplied by Dako; Agilent Technologies, Inc.) was performed using a Dako CoverStainer (Dako; Agilent Technologies, Inc.) for ~1 h and 15 min at room temperature.

As regards immunohistochemistry, formalin-fixed paraffin sections (2-μm-thick) were used. The staining of the slides was performed on an AutoStainer Link 48 Dako instrument (Dako; Agilent Technologies, Inc.). The sections were deparaffinized and antigen retrieval was performed using Envision Flex Target Tetrieval Solution High pH (Dako; Agilent Technologies, Inc.)

Table III. Kaplan Meier survival analysis based on concurrent pathological findings.

Characteristic	Survival time (months)	95% CI	No. of deaths	%	No. of survivors	%	Log-rank test P-value
Pathological findings							0.001
Atelectasis	72.2	59.6-84.8	0	0	44	100.0	
DIP	46.6	28.7-64.5	2	18.2	8	81.8	
Emphysema	100.5	83.9-117.1	2	10	18	90.0	
Bronchiectasis	91.0	55.8-126.1	2	25	6	75.0	

DIP, desquamative interstitial pneumonia.

at 90˚C for 20 min. The sections were then immunostained for synaptophysin using Leica mouse anti-human synaptophysin monoclonal antibody (Clone 27G12; Leica Biosystems, cat; NCL-SYNAP-29) at a 1:50 dilution with a 30-min incubation time at room temperature and for chromogranin using monoclonal chromogranin A monoclonal antibody (clone LK2H10; Thermo Fisher Scientific, Inc, cat; MA5-13096) at a 1:400 dilution with a 25-min incubation time at room temperature. Immunoreactions were detected using EnVision Detection Systems (Dako; Agilent Technologies, Inc.), which includes secondary antibody ready-to-use EnVisionTM FLEX/HRP (Code No. K8000/K8002/K8023) solution. For the secondary antibody, the incubation time was 20 min, at room temperature. All slides were counterstained with Mayer's hematoxylin (Dako; Agilent Technologies, Inc.) for 10 min at room temperature.

The categorization of the tumors into TCs and ACs was performed by an experienced pathologist, and was based on the evaluation of hematoxylin- and eosin-stained (histochemical) sections. Namely, beyond the fact that all tumors had the characteristic neuroendocrine morphology, TC had a mitotic count of <2 mitoses/2 mm^2 and lacked necrosis, whereas ACs had 2-10 mitoses/2 mm^2 and/or had focal and punctuated necrosis. The presence of simultaneous pathological findings was noted.

Statistical analysis. The Statistical Package for Social Sciences software (SPSS) version 13.0 (SPSS, Inc.) was used for statistical analyses. The assessment of survival was made using Kaplan-Meier statistics, and the comparison of the survival curves was made using the log-rank test. Survival was estimated in units of months from surgery. The Cox hazard-regression model was also used, including relative risk, probability and 95% confidence intervals for univariate analysis of the prognostic factors, while 5% was selected as the level of statistical significance. The censoring was random and as far as possible non-informative. In addition, the proportionality of the hazards was tested, by examining the scaled Schoenfeld residuals. A value of $P<0.05$ was considered to indicate a statistically significant difference.

Results

Surgical resection was the only treatment that patients received. In total, 78, 18 and 12 patients were categorized into stages I, II and III respectively (Table I).

Simultaneous pathological findings were noted in the biopsy specimens of 82 patients (56 patients with TC, 26 patients with AC). These findings were atelectasis, emphysema, bronchiectasis and desquamative interstitial pneumonia (DIP) (Table II).

The observation of the patients ended after a mean follow-up time of 96 months. All the patients had a good attendance at the follow-up appointments. Of the 82 patients that had simultaneous pathological findings, 6 patients did not survive. All the deaths were related to disease progression. In total, 4 patients were in stage II and 2 patients were in stage III, while 4 patients had AC and 2 patients had TC. There was a statistically significant difference in survival between patients with different simultaneous pathological findings (P=0.001). The most deaths were observed among patients with bronchiectasis (Table III). The survival rates based on simultaneous pathological findings are presented in Fig. 1 and Table III.

As regards all the patients, there was a total of eight deaths. According to the Cox regression univariate analysis for all the patients, the type of carcinoid was associated with patient survival, with improved survival rates in patients with TCs, while age, sex, stage and simultaneous pathological findings were not associated with patient survival (Table IV). The results of the comparison between the overall survival of patients with TCs and ACs is presented in Table SI. The simultaneous pathological findings in the biopsy specimens of patients with surgically resected lung carcinoids are illustrated in Figs. 2-5.

Discussion

According to the results of the present study, atelectasis was related to the most favorable outcome among patients with simultaneous pathological findings, with a survival rate of 100%. Atelectasis is a term describing the loss of lung volume as a result of the collapse of lung tissue. According to the underlying pathophysiological mechanisms, atelectasis is classified as obstructive atelectasis, which is the consequence of a blockage of the airways, and non-obstructive atelectasis. It is also classified according to the amount of lung involved (lobar, segmental, subsegmental atelectasis), or the location involved (specific lobe or segment) (20). Non-obstructive atelectasis is caused by the loss of contact between the visceral and parietal pleural membranes, the compression of lung parenchyma, surfactant dysfunction, the scarring or infiltration of lung tissue, and strong vertical acceleration forces; it is thus divided

Table IV. Univariate analysis of prognostic factors analyzed by Cox's hazard-regression model.

Variable	Exp(B)	P-value	95% CI for Exp(B)
Pathological findings		0.064	
Atelectasis vs. DIP	0.114	0.043	0.014-0.029
Atelectasis vs. emphysema	0.000	0.954	0.000-1, 281E+188
Atelectasis vs. bronchiectasis	1.270	0.813	0.176-9.177
Pathological findings (presence vs. absence)	1.120	0.976	0.269-3.873
Age at surgery (>45 vs. <45 years)	2.767	0.244	0.499-15.35
Sex (Male vs. female)	1.237	0.743	0.346-4.424
Histological type (typical vs. atypical)	0.191	0.001	0.053-0.687
Stage		0.131	
I vs. II	0.491	0.886	0.087-2.787
I vs. III	2.157	0.867	0.394-11.81

Exp(B), relative risk between groups; DIP, desquamative interstitial pneumonia.

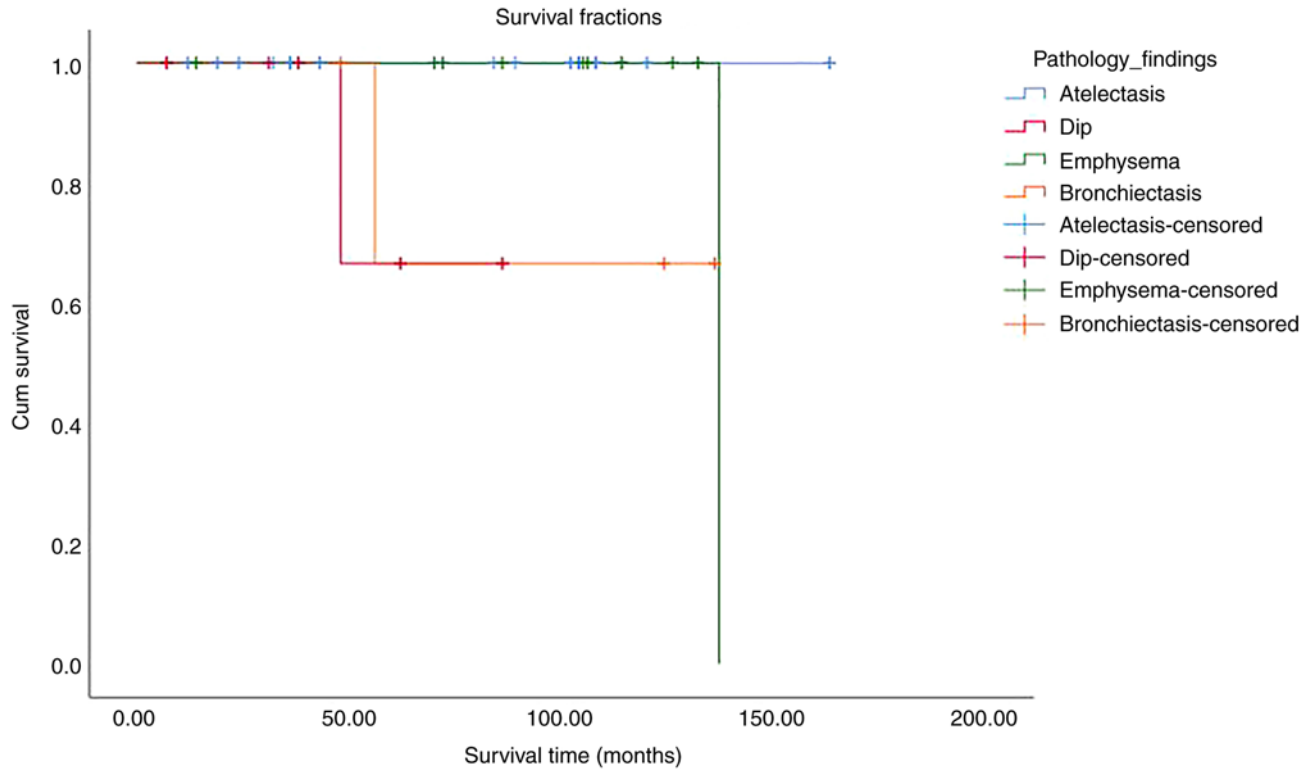

Figure 1. Survival rates based on simultaneous pathology findings. The x-axis represents months from surgery, and the y-axis represents the proportion of surviving patients. (Survival among patients with different pathological findings: atelectasis, emphysema, bronchiectasis and desquamative interstitial pneumonia; P=0.001). dip, desquamative interstitial pneumonia.

into passive, compressive, adhesive, cicatricial, replacement, acceleration, rounded and plate-like atelectasis (21).

To the best of our knowledge, the present study is the first to describe atelectasis as a prognostic factor of survival in lung neuroendocrine tumors. Atelectasis has been reported as a prognostic factor in other types of lung cancer. More specifically, atelectasis has been shown to be associated with the prolonged survival of patients with non-small cell lung carcinoma (NSCLC) (22-25) even at advanced stages (26). In lung cancer, atelectasis traditionally develops due to endobronchial obstruction and rarely due to the compression of a mass or pleural effusion (25). It has been hypothesized that the prolonged survival of patients with atelectasis may be associated with decreased intratumoral blood flow and nutrition due to vascular shunts in the adjacent atelectatic region, leading to the decreased release of inflammatory cytokines from malignant cells. Other hypotheses are the susceptibility of infection and the alteration of immunity in atelectasis and

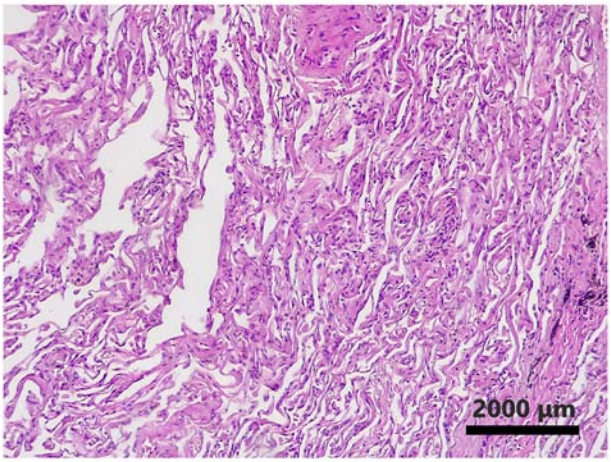

Figure 2. Hematoxylin and eosin staining; original magnification, x100. Simultaneous pathological finding in surgically resected typical carcinoid indicating atelectasis with markedly compressed alveoli.

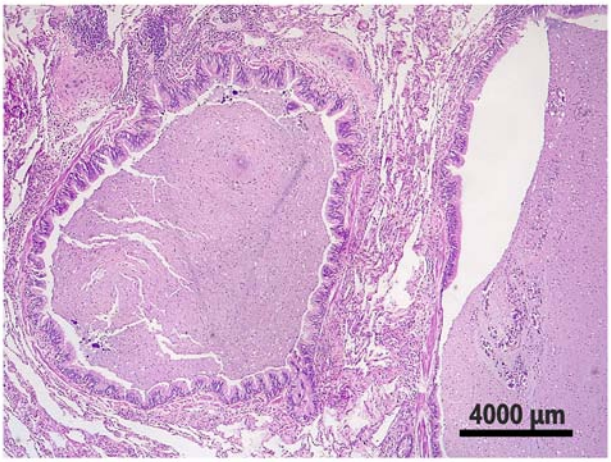

Figure 4. Hematoxylin and eosin staining; original magnification, x40. Simultaneous pathological finding in surgically resected typical carcinoid indicating bronchiectasis with dilated bronchi.

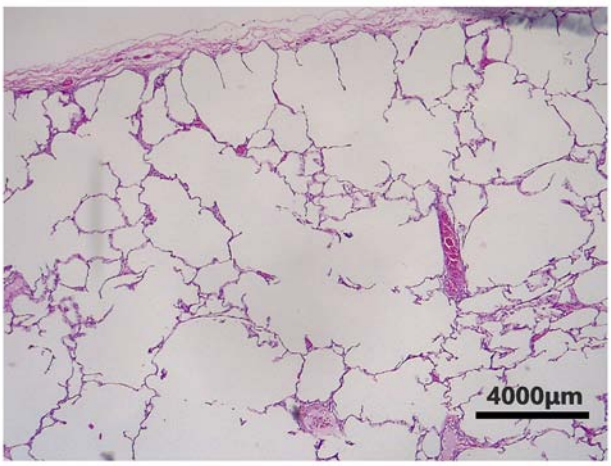

Figure 3. Hematoxylin and eosin staining; original magnification, x40. Simultaneous pathological finding in surgically resected typical carcinoid indicating emphysematous lung, with enlarged air-spaces, and fragmented and 'free-floating' alveolar septa.

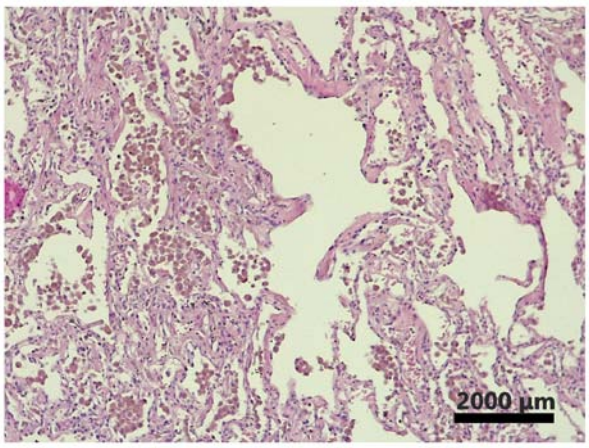

Figure 5. Hematoxylin and eosin staining; original magnification, x100. Simultaneous pathological finding in surgically resected typical carcinoid: Desquamative interstitial pneumonia-like pattern. Alveolar spaces filled with abundant macrophages were also observed, which contain cytoplasmic finely granular brown pigment.

the concentric growth of the tumor, resulting in early presentation and diagnosis (25). These mechanisms may explain the protective effect of atelectasis in patients with lung carcinoids. However, according to another study, preoperative obstructive pneumonitis and atelectasis can predict poor survival independently in patients with NSCLC (27).

In the present study, patients with emphysema and pulmonary carcinoids presented with a survival rate of 90%. Pulmonary emphysema is a pathological definition. It demonstrates the abnormal permanent enlargement of the airspaces distal to the terminal bronchioles. This enlargement coexists with the destruction of their walls without conspicuous fibrosis (28). In addition, emphysema has not been studied as a prognostic factor for patients with lung carcinoids. Emphysema can develop in patients with pulmonary carcinoids through the check-valve effect of an endobronchial tumor and the compensatory effect of the residual lung (29). Emphysema, as estimated with imaging methods, has been reported as a prognostic factor in other types of lung cancer. The severity of lung emphysema has been found to be associated with a decreased survival rate, the development of post-operative complications in early-stage cancer and the recurrence of resected lung cancer in patients with NSCLC (30-32), as well as with a poor prognosis of patients with small cell lung carcinoma (33).

Bronchiectasis is a lung disorder that is mostly caused by bronchial inflammation and characterized by the permanent dilation of the airways due to bronchial wall destruction (34). According to the results of the present study, patients with bronchiectasis had a worse outcome compared to patients with other simultaneous pathological findings. Bronchiectasis have, in some cases, been described as the first finding before a diagnosis of a pulmonary carcinoid. Bronchiectasis develop due to recurrent pneumonia in cases that a lung carcinoid leads to bronchial obstruction. The persistence of inflammation is a major factor in the pathogenesis of bronchiectasis (35-38). In addition, it has been reported that the presence of bronchiectasis is a predisposing factor for the genesis of pulmonary neuroendocrine tumors (39-41). To date, bronchiectasis has

not been studied as a prognostic factor in lung carcinoids or in other types of lung cancer, at least to the best of our knowledge.

DIP is an interstitial lung disease associated with smoking. The accumulation of macrophages in alveoli is the underlying mechanism of its pathogenesis, leading to interstitial inflammation and fibrosis. However, DIP has been mentioned as a result of other exposures and disease conditions, such as occupational exposures, medications and autoimmune diseases (42). Moreover, it has been reported that DIP is a pattern of pulmonary reaction that accompanies other pulmonary lesions, such as eosinophilic granulomas and rheumatoid nodules (42). To the best of our knowledge, the present study is the first to report the co-existence of DIP with lung carcinoids and the impact of DIP on the survival of patients with lung carcinoids that underwent thoracic surgery. Patients with DIP and pulmonary carcinoids had a survival rate of 81.8%.

Of note, there was not a statistically significant difference in survival rates between patients with and without simultaneous pathological findings. It has been reported that monocyte-derived myeloid cells in lung carcinoid tissues have equal to slightly lower expression scores of numerous gene profiles associated with inflammation and the immune response when compared to normal tissues, indicating that the lung carcinoid immune microenvironment is predominated by non-inflammatory monocyte-derived myeloid cells, without mentioning if this finding is associated with better outcomes (43). However, it remains to be determined whether this finding is associated with improved outcomes.

The present study has some limitations. The present study was one of the largest on lung carcinoids in Greece. The data rely on a large number of patients with an accurate follow-up period. However, this was a single-center study and only a limited number of disease-specific deaths were recorded. Therefore, a multivariate analysis could not be performed. Another limitation of the present study is the absence of control group which could be patients with other types of lung cancer. Thus, further larger multi-center, prospective studies are required to evaluate the role of these pathological findings in the outcomes of patients with surgically resected lung carcinoids.

In conclusion, to the best of our knowledge, the present study is the first to examine the impact of the simultaneous pathological findings of resected lung tissue specimens on the survival of patients with pulmonary carcinoids. There was a statistically significant difference in the survival rates of patients with resected lung carcinoids with different simultaneous pathological findings. However, further studies are required to assess the role of these findings in the survival of these patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JD, JJ and EZ conceptualized the study. AP performed the immunohistochemical examination and prepared the tables. VEG, KM, CD, SC, PP, AAF and AG advised on patient treatment, and wrote and prepared the draft of the manuscript. JD and DAS analyzed the data and provided critical revisions. NT and PS performed the statistical analysis. VEG and EZ confirm the authenticity of all the data. All authors contributed to manuscript revision and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Ethical approval for the present study was obtained from the Research Ethics Committee of Athens medical Group with file accession no. 4234. The study was in line with the declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Written informed consent was obtained from the patients for publication of this research and accompanying images.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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