Original Article

Indeterminate pulmonary nodules and prior malignancy: survival and recurrence after surgery in newly diagnosed stage I non-small cell lung cancer

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Background: Surgical excision biopsy remains the only reliable option in most cases of indeterminate pulmonary nodules, particularly in cancer survivors for whom surgery provides local control of pulmonary metastasis and the best chance of cure for early-stage lung cancer. Nevertheless, unnecessary surgeries remain a concern and the prognosis of newly diagnosed lung cancer might be influenced by the history of previous malignancy. We aimed to analyze the outcomes of resected indeterminate pulmonary nodules in patients with and without previous malignancy, and the impact of prior cancer history on survival and recurrence in stage I non-small cell lung cancer (NSCLC) patients.

Methods: We retrospectively studied 176 resected indeterminate pulmonary nodules from 169 patients (58% with and 42% without previous cancer). Recurrence and overall survival (OS) were analyzed in newly diagnosed stage I NSCLC using the Kaplan-Meier method and Cox proportional hazard models.

Results: The rate of benign lesions was 15.3% (9.6% in the previous cancer group and 23.6% in the no previous cancer group). In stage I NSCLC patients (n=86), previous malignancy was associated with recurrence (P<0.001) but not OS (P=0.23). Chronic obstructive pulmonary disease and visceral pleural invasion were associated with impaired OS and recurrence. Mediastinal lymph node removal was associated with better OS.

Conclusions: The rate of benign resections among indeterminate pulmonary nodules in the no-previous cancer group more than doubled that of the previous cancer group and, in newly diagnosed stage I NSCLC patients, recurrence was independently associated with prior cancer. Therefore, in this setting, a history of previous malignancy should be taken into consideration when identifying patients at risk of tumor recurrence.

Keywords: Indeterminate pulmonary nodules; cancer survivors; early-stage lung cancer; recurrence; overall survival (OS)

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Introduction

Background

Lung cancer is the leading cause of cancer-related mortality worldwide (1). The majority of lung cancer patients are diagnosed with regional or distant advanced disease with a poor five-year survival rate of 34.8% and 8.2% respectively. Conversely, for localized disease survival comes to 62.8% at five years, but early-stage lung cancer accounts for only 21% of total cases (2). With the increasingly widespread use of imaging studies, particularly computed tomographic (CT) scans, the number of pulmonary nodules detected incidentally is growing continuously and represents an invaluable opportunity for early detection of lung cancer. As overall survival (OS) of oncological patients continues to increase, they represent a growing body who frequently undergo imaging for staging investigations or follow-up (3).

Rationale and knowledge gap

The final option in most cases of indeterminate pulmonary nodules is surgical excision biopsy, particularly in patients with a history of previous cancer, in whom surgery offers local control in metastatic disease and a curative option in the case of early-stage lung cancer (4). Nevertheless, unnecessary surgeries remain a concern and the prognosis of early-stage lung cancer might be influenced by the history of prior malignancy. Available retrospective data from studies focused generally on OS suggest a variable impact of prior cancer history on the prognosis of lung cancer patients. While for later stages a previous history of malignancy appears to be associated with improved OS, for early stages different studies have found either no effect (5) or impaired OS (6-8). Furthermore, studies evaluating the impact of prior cancer on recurrence following resection of stage I non-small cell lung cancer (NSCLC) yield conflicting results (7,9).

Objective

The aim of this study was to analyze the outcomes of resected indeterminate pulmonary nodules in patients with and without previous malignancy, and the impact of prior cancer history on survival and recurrence in newly diagnosed stage I NSCLC patients. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1834/rc).

Highlight box

Key findings

- The rate of benign resections was lower in patients with previous cancer.
- Recurrence in stage I non-small cell lung cancer (NSCLC) was independently associated with prior cancer.

What is known and what is new?

- In patients with prior cancer history, resection of indeterminate pulmonary nodules provides local control of pulmonary metastasis and the best chance of cure for early-stage lung cancer.
- This study analyzes the outcomes of resected indeterminate pulmonary nodules in patients with and without previous malignancy, and the impact of prior cancer history on survival and recurrence in newly diagnosed stage I NSCLC.

What is the implication, and what should change now?

- For indeterminate pulmonary nodules being considered for surgery, the proportion of benign outcomes can be smaller in patients with prior cancer.
- For newly diagnosed stage I NSCLC, the history of previous malignancy should be taken into consideration when identifying patients at risk of recurrence.

Methods

Study design and patient selection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by our institutional review board (Research Ethics Committee of Hospital Clínico Universitario INCLIVA, No. 2022/156), which waived the need for patient consent. We retrospectively reviewed data from patients with resected indeterminate pulmonary nodules from January 2015 to June 2020. For suspicious malignant nodules, preoperative diagnostic attempts by bronchoscopy or transthoracic needle biopsy were made depending on nodule size and location. Indeterminate pulmonary nodules, without a histological diagnosis, were evaluated by a multidisciplinary team (MDT) including specialists in thoracic surgery, pulmonary medicine, medical and radiation oncology, thoracic and interventional radiology, and pathology.

In patients selected for surgery, video-assisted thoracoscopic surgery (VATS) was the preferred surgical approach. Whenever possible, a wedge resection with intraoperative frozen-section examination was performed. The extent of resection and eventual mediastinal lymph node

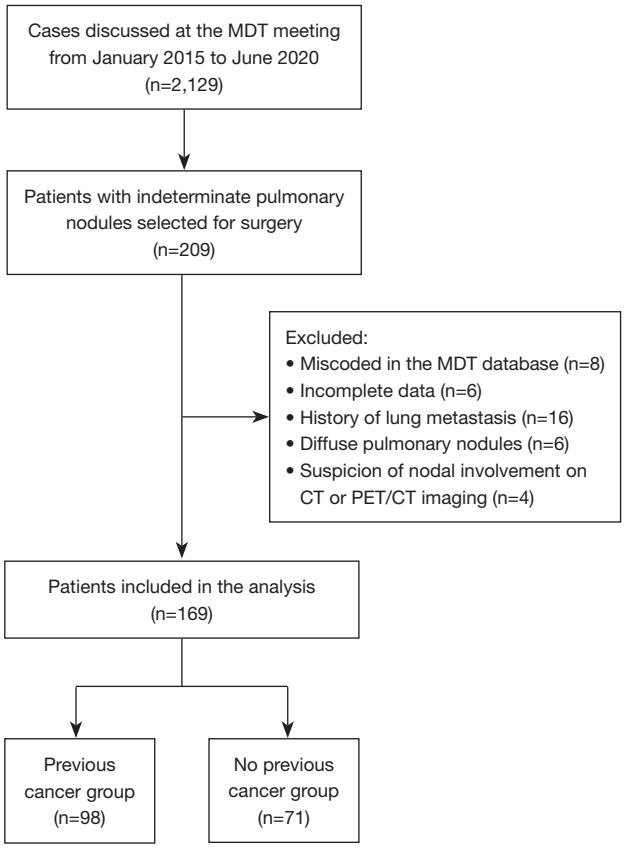

Figure 1 Study flow chart. MDT, multidisciplinary team; CT, computed tomography; PET/CT, positron emission tomography/computed tomography.

removal was decided by the operating surgeon based on the intraoperative frozen section analysis, patient functional status, nodule characteristics, and technical feasibility. In the case of benign or metastatic lesions, the main objective was to achieve a complete resection while preserving as much lung parenchyma as possible. Patients with peripheral tumors smaller than 2 cm or comorbidities were candidates for sublobar resections as long as adequate parenchymal margins could be obtained. Wedge resection was considered for frail patients or those with limited lung function. The decision not to remove the lymph nodes was usually made in order to minimize surgical intervention.

Patients with a history of lung metastasis, diffuse pulmonary nodules, or findings suggestive of nodal involvement on CT or positron emission tomography/computed tomography (PET/CT) imaging were excluded from the analysis. Cases miscoded in the MDT database or with incomplete data were also not included (*Figure 1*).

Indeterminate pulmonary nodules

Data were collected on patient sex, age, previous history of malignancy (type and time since last cancer diagnosis, excluding non-melanoma skin cancer), smoking history, pulmonary function test parameters, diagnosis of chronic obstructive pulmonary disease (COPD), CT nodule characteristics, fluorine-18-fluorodeoxyglucose (FDG) uptake on PET/CT, surgical characteristics, and histology of the resection specimen. Patients were separated into two groups according to whether they had a history of previous cancer. Between-group comparisons were performed using χ^2 test or Fisher exact test for categorical variables and Student's *t*-test for continuous variables. As more than one nodule was resected in some patients, both nodule- and patient-level data were reported.

Recurrence and survival analysis in stage I NSCLC patients

All patients newly diagnosed with lung cancer were followed up in a dedicated oncology clinic. CT scan was obtained 3 months after surgery, then repeated every 3–6 months for up to a year, and thereafter on a yearly basis. Patient survival status was recorded until December 2021, and the primary outcome variables were freedom from recurrence (FFR) and OS. FFR was defined as the time from surgery to first diagnosis of local, regional, or distant recurrence, and was censored at the last follow-up or death without recurrence. OS was calculated from the date of surgery to date of death from any cause; for surviving patients, it was censored at the last contact date.

Statistical analysis

Between-group comparisons were performed using χ^2 test or Fisher exact test for categorical variables and Student's *t*-test for continuous variables. As more than one nodule was resected in some patients, both nodule- and patient-level data were reported.

In stage I NSCLC patients, FFR and OS curves were estimated using the Kaplan-Meier method, and comparisons were made with the log-rank test. Univariable and multivariable Cox proportional hazard models were used to identify variables associated with survival and recurrence outcomes. The variables considered included patient demographics and clinical characteristics, tumor characteristics, and surgical variables. To produce the final

Table 1 Patient demographics and clinical characteristics (n=169)

Characteristics	Previous cancer history		P value
	Yes (n=98)	No (n=71)	
Age (years), mean (SD)	66.8 (10.0)	66.2 (9.7)	0.70
Sex, n (%)			0.88
Male	66 (67.3)	47 (66.2)	
Female	32 (32.7)	24 (33.8)	
Smoking status, n (%)			0.12
Never	22 (22.4)	14 (19.7)	
Former	48 (49.0)	26 (36.6)	
Current	28 (28.6)	31 (43.7)	
Pack-years, mean (SD)	48.1 (26.1)	45.5 (23.9)	0.56
COPD, n (%)			0.81
No	72 (73.5)	51 (71.8)	
Yes	26 (26.5)	20 (28.2)	
Preoperative lung function testing, mean (SD)			
FEV1 % predicted	90.7 (20.7)	91.6 (19.6)	0.79
DLCO % predicted	70.2 (18.4)	77.3 (20.2)	0.02

SD, standard deviation; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in the first second; DLCO, diffusion capacity of the lung for carbon monoxide.

model, we used a backward elimination process, with 0.05 as the significance level of the Wald chi-squared test for a variable to remain in the model. All data were analyzed using IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY, USA) except for Kaplan-Meier plots which were conducted using R version 4.0.0 (R Core, 2021). The cut-off for statistical significance was set at 0.05.

Results

Indeterminate pulmonary nodules

The analysis included 176 indeterminate pulmonary nodules from 169 patients: 58% (98/169) with a history of at least one previous cancer and 42% (71/169) with no previous malignancy. The most common sites of prior malignancy were colorectal in 29/98 patients (29.6%), lung in 25/98 (25.5%) and breast in 20/98 (20.4%), followed by bladder in 10/98 (10.2%), head and neck in 10/98 (10.2%), prostate in 6/98 (6.1%) and malignant melanoma in 6/98 (6.1%). Other malignancies were seen in 14/98 patients (14.3%).

Demographics, patient clinical characteristics and between-group comparisons are shown in *Table 1*. The percentage of patients with two or more nodules detected on CT images was not significantly different (P=0.46) between the two groups: 27.6% (27/98) for patients with previous cancer and 22.5% (16/71) for patients with no previous cancer. VATS was the preferred surgical approach (79.6% in patients with previous cancer and 85.9% in the no-previous cancer group). Nodule characteristics and between-group comparisons are shown in *Table 2*. A single nodule was resected in 162 patients, and two nodules were resected in each of the other seven patients. The metastatic nodule in the no previous cancer group was a metastatic leiomyosarcoma of unknown primary origin. The rate of benign outcomes among the total of resected nodules was 15.3% (27/176).

Variables associated with malignancy at patient-level were increasing age (P=0.002) and previous cancer history (P=0.005). At the nodule-level, significant variables associated with malignancy were growth (P=0.002), size over 10 mm (P=0.043), and higher maximum standardized uptake values (SUVmax) (P=0.001).

Within the previous cancer group, pathological results did not differ significantly (P>0.05) by patient history of pulmonary versus extrapulmonary cancer, single or multiple primary cancers or cancer diagnosis within the last 5 years (*Table 3*). There were also no significant differences by cancer type in the subgroup of patients with a history of a single extrapulmonary cancer, although primary lung cancer was the most common pathological diagnosis for head and neck, bladder, and other cancers. Additionally, no significant differences were found (P=0.67) between patients with single or multiple pulmonary nodules on CT images: benign 8.5% (6/71) and 7.4% (2/27) respectively, primary lung cancer 49.3% (35/71) and 59.3% (16/27) respectively, and metastasis 42.2% (30/71) and 33.3% (9/27) respectively.

Newly diagnosed lung cancers

A total of 104 patients were finally diagnosed with primary lung cancer, including two patients with synchronous primary tumors, of which only the highest stage tumor (both adenocarcinoma pT1bN0M0) was included in the analysis. Surgical variables, tumor characteristics and between-group comparisons are shown in *Table 4*. Most patients in both groups underwent anatomic resection, with lobectomy as the commonest approach used in 22/51 (43.1%) of patients with, and 31/53 (58.5%) without previous malignancy.

Table 2 Characteristics of resected nodules (n=176)

Characteristics	Previous cancer history		P value
	Yes (n=104)	No (n=72)	
Size (mm), mean (SD)	13.6 (5.8)	14.8 (5.2)	0.18
Type, n (%)			0.37
Solid	87 (83.7)	55 (76.4)	
Subsolid	12 (11.5)	10 (13.9)	
GGO	5 (4.8)	7 (9.7)	
Spiculated margins, n (%)			0.14
No	72 (69.2)	42 (58.3)	
Yes	32 (30.8)	30 (41.7)	
Growth, n (%)			0.06
No	43 (41.3)	40 (55.6)	
Yes	61 (58.7)	32 (44.4)	
Location, n (%)			0.18
Right upper lobe	31 (29.8)	26 (36.1)	
Right lower lobe	6 (5.8)	3 (4.2)	
Right middle lobe	21 (20.2)	13 (18.1)	
Left upper lobe			
Upper division	19 (18.3)	21 (29.2)	
Lingula	3 (2.9)	–	
Left lower lobe	24 (23.1)	9 (12.5)	
SUVmax, mean (SD)	2.83 (2.9)	2.32 (2.6)	0.26
Type of resection, n (%)			0.02
Lobectomy	29 (27.9)	34 (47.2)	
Segmentectomy	19 (18.3)	13 (18.1)	
Wedge	56 (53.8)	25 (34.7)	
Pathological results, n (%)			<0.001
Benign	10 (9.6)	17 (23.6)	
Primary lung cancer	52 (50.0)	54 (75.0)	
Metastasis	42 (40.4)	1 (1.4)	

SD, standard deviation; GGO, ground glass opacity; SUVmax, maximum standardized uptake value.

Recurrence and survival in stage I NSCLC patients

Recurrence and survival were analyzed in the subset of stage I NSCLC patients (n=86) made up of 27 (31.4%) stage IA1, 34 (39.5%) stage IA2, 12 (14.0%) IA3, and 13 (15.1%) IB. Median follow-up time until death or censoring was 36 months. FFR and OS Kaplan-Meier curves according to previous cancer history are displayed in *Figures 2*,*3*, respectively. Previous malignancy was associated with impaired FFR (log-rank test, P<0.001) but no significant differences were found in OS (log-rank test, P=0.23). There were no significant differences in FFR or OS (log-rank test, P=0.76 and 0.99, respectively) between segmentectomy (16/86; 18.6%) and lobectomy (45/86; 52.3%). Within the previous cancer group, no significant differences (log-rank test, P>0.05) were found in FFR or OS among patients with history of pulmonary versus extrapulmonary cancer, more than one previous cancer, or last cancer diagnosed in the 5 years prior to lung cancer diagnosis. Kaplan-Meier FFR estimates at 5 years were 64% [95% confidence interval (CI): 50–81%] in the previous cancer group and 98% (95% CI: 93–100%) in the no previous cancer group (P<0.001). There were no significant between-group differences (P=0.24) in 5-year OS: 73% (95% CI: 57–94%) and 86% (95% CI: 75–98%) respectively. Univariable and multivariable Cox regression analyses for FFR and OS are shown in *Table 5*. Previous cancer, COPD, and visceral pleural invasion were independent factors associated with impaired FFR,

Table 3 Pathological results of resected nodules according to cancer history in the previous cancer group (n=104)

Variables	Benign	Primary lung cancer	Metastasis	P value
Location of prior cancer (n=104)				0.77
Pulmonary† (n=27)	2 (7.4)	15 (55.6)	10 (37.0)	
Extrapulmonary (n=77)	8 (10.4)	37 (48.0)	32 (41.6)	
History of multiple cancers (n=104)				0.58
Yes (n=24)	1 (4.2)	13 (54.1)	10 (41.7)	
No (n=80)	9 (11.2)	39 (48.8)	32 (40.0)	
Date of last cancer (n=104)				0.36
≥5 years ago (n=27)	1 (3.7)	16 (59.3)	10 (37.0)	
<5 years ago (n=77)	9 (11.7)	36 (46.7)	32 (41.6)	
Type of neoplasm‡ (n=63)				0.54
Colon (n=23)	3 (13.0)	8 (34.8)	12 (52.2)	
Breast (n=14)	1 (7.1)	6 (42.9)	7 (50.0)	
Head and neck (n=8)	1 (12.5)	6 (75.0)	1 (12.5)	
Bladder (n=7)	–	4 (57.1)	3 (42.9)	
Others (n=11)	2 (18.2)	6 (54.5)	3 (27.3)	

Data are presented as n (%). †, irrespective of other cancers; ‡, subgroup of patients with history of single extrapulmonary cancer.

Table 4 Surgical variables and tumor characteristics of newly diagnosed primary lung cancers (n=104)

Variables	Previous cancer history		P value
	Yes (n=51)	No (n=53)	
Resection, n (%)			0.16
Anatomical	33 (64.7)	41 (77.4)	
Wedge	18 (35.3)	12 (22.6)	
Nodal dissection or sampling, n (%)			0.08
No	15 (29.4)	8 (15.1)	
Yes	36 (70.6)	45 (84.9)	
Number of resected lymph nodes, mean (SD)	3.63 (4.4)	3.85 (3.3)	0.77
Surgical margins, n (%)			0.63
Negative	48 (94.1)	50 (96.2)	
Positive	5 (5.9)	2 (3.8)	
Angiolymphatic invasion, n (%)			0.66
No	38 (86.4)	42 (89.4)	
Yes	6 (13.6)	5 (10.6)	
Visceral pleural invasion, n (%)			0.96
No	39 (76.5)	40 (76.9)	
Yes	12 (23.5)	12 (23.1)	
Histology, n (%)			0.63
Adenocarcinoma	40 (78.4)	41 (77.4)	
Squamous-cell carcinoma	8 (15.6)	5 (9.4)	
Large-cell carcinoma	1 (2.0)	1 (1.9)	
Large-cell neuroendocrine carcinoma	1 (2.0)	1 (1.9)	
Typical carcinoid	1 (2.0)	4 (7.5)	
Small-cell carcinoma	–	1 (1.9)	
Pathological stage†, n (%)			0.67
In situ	3 (5.9)	7 (13.2)	
IA	39 (76.4)	34 (64.1)	
IB	6 (11.8)	8 (15.1)	
IIB	2 (3.9)	2 (3.8)	
IIIA	1 (2.0)	1 (1.9)	
IVA	–	1 (1.9)	

†, eighth edition TNM staging system. SD, standard deviation. TNM, tumor, node, metastasis.

whereas COPD, visceral pleural invasion, and absence of lymph node dissection or sampling were independently associated with impaired OS.

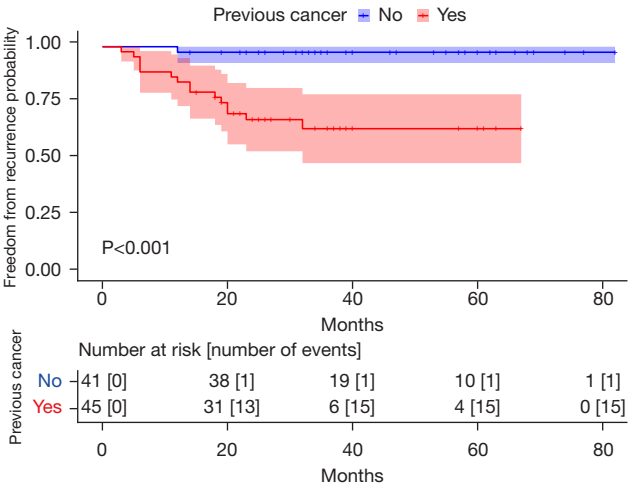

Figure 2 Kaplan-Meier curves of freedom from recurrence for pathological stage I non-small cell lung cancer patients according to previous cancer history.

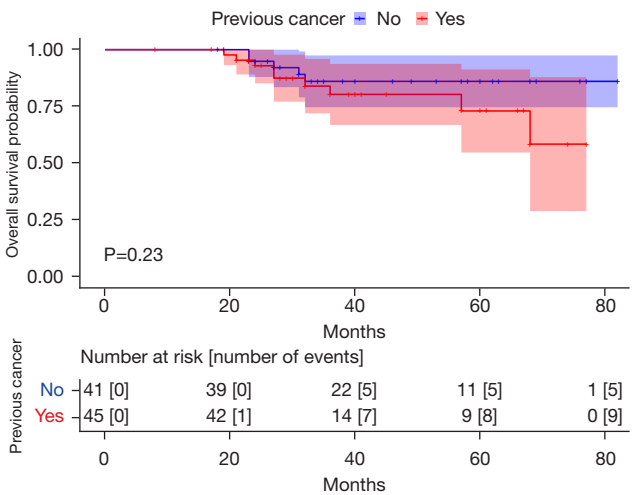

Figure 3 Kaplan-Meier curves of overall survival for pathological stage I non-small cell lung cancer patients according to previous cancer history.

Discussion

Indeterminate pulmonary nodules

In our study, after a multidisciplinary selection process, 15.3% of resected pulmonary nodules turned out to be benign. The percentage of benign diagnoses among surgically resected nodules has been proposed as a quality indicator (10), but the acceptable rate has not been established and a wide range of benign resections (12–86%)

Table 5 Univariable and multivariable Cox regression analyses for freedom from recurrence and overall survival of stage I non-small cell lung cancer patients (n=86)

Variables	Freedom from recurrence						Overall survival					
	Univariable			Multivariable			Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Demographic and clinical characteristics												
Age, years	1.04	0.97–1.10	0.27				1.04	0.98–1.11	0.22			
Sex												
Female	Reference						Reference					
Male	1.54	0.60–4.78	0.46				2.89	0.65–12.93	0.17			
COPD												
No	Reference						Reference					
Yes	4.14	1.54–11.14	0.005*	7.52	1.73–32.56	0.007*	3.76	1.30–10.89	0.02*	5.94	1.42–24.79	0.01*
Smoking history, pack-years	1.01	0.99–1.03	0.29				1.01	0.98–1.03	0.66			
Previous cancer												
No	Reference						Reference					
Yes	16.45	2.17–124.7	0.007*	12.80	1.48–110.9	0.021*	1.92	0.64–5.75	0.24			
Tumor characteristics												
SUVmax	1.12	0.97–1.29	0.13				1.13	0.99–1.30	0.08			
Size												
<20 mm	Reference											
≥20 mm	0.50	0.11–2.20	0.36				0.61	0.14–2.75	0.52			
Histology												
Adenocarcinoma	Reference						Reference					
Others†	1.05	0.83–1.33	0.71				1.19	0.40–3.57	0.75			
Angiolymphatic invasion												
No	Reference						Reference					
Yes	2.45	0.54–11.18	0.25				0.04	0.00–295.3	0.48			
Visceral pleura invasion												
No	Reference						Reference					
Yes	2.33	0.80–6.73	0.12	8.26	1.88–36.27	0.005*	2.10	0.65–6.76	0.21	4.76	1.13–19.95	0.03*
Surgical variables												
Resection												
Anatomical	Reference						Reference					
Wedge	4.69	1.70–12.92	0.003*				2.42	0.85–6.93	0.10			
Nodal dissection/sampling												
No	Reference						Reference					
Yes	0.20	0.07–0.54	0.001*				0.24	0.08–0.69	0.008*	0.25	0.07–0.95	0.042*
Resected lymph nodes	0.80	0.66–0.98	0.03*				0.84	0.69–1.03	0.09			
Surgical margins												
Negative	Reference						Reference					
Positive	2.53	0.57–11.17	0.22				3.09	0.68–14.05	0.14			

*, significant P values (<0.05). †, excluding carcinoid tumors. HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; SUVmax, maximum standardized uptake value.

have been reported in the literature (11). We found a lower rate of benign resections in patients with previous cancer (9.6%) than in those without a previous cancer diagnosis (23.6%). Other authors have also found a lower percentage of benign resections among patients with a history of prior malignancy. In a large series of patients undergoing excisional biopsy for solitary pulmonary nodules the probability of being benign was 37% in patients with no history of cancer whereas this percentage was cut in half if there was a history of cancer (12). Rena *et al.* (4) found 10.2% of benign diagnoses (5 out of 49 nodules without pre-operative diagnosis) in patients with a history of previous malignancy.

Fifty percent of the nodules in our previous cancer group were diagnosed as primary lung cancer, and no association was found between the final diagnosis (metastasis, primary lung cancer or benign) and a past history of pulmonary versus extrapulmonary cancer, single versus multiple cancers or cancer diagnosis within the last 5 years. In the series of Mery *et al.* (12), there were also no differences between patients with a history of a single extrapulmonary cancer and those with a history of several tumors. A 5-year period after a diagnosis of cancer has been arbitrarily considered as 'at risk for metastases' (3); however, 74% of patients in our series with a history of malignancy had the previous cancer diagnosed within the last 5 years, and there was no association with a final diagnosis of metastasis.

For indeterminate pulmonary nodules in patients with history of extrapulmonary cancer, previous studies have demonstrated that the probability of metastasis depends on the histology of the previous tumor (12,13). In our subgroup of patients with prior single extrapulmonary malignancy, colon cancer accounted for the highest percentage of metastasis, while the lowest was for head and neck cancer. Conversely, previous head and neck cancer was associated with the highest percentage of primary lung cancer. Nevertheless, the differences were not significant probably due to small sample size after stratification by type of cancer.

Prior malignancy and lung cancer prognosis

Although there is currently insufficient data on the relationship between lung cancer and other malignancies (3), a prior cancer history seemingly has a heterogeneous impact on the prognosis of lung cancer patients. Survival analysis using large datasets found non-inferior (14) or slightly better (6,15) survival in advanced-stage lung cancer patients with prior cancer. However, the impact of previous cancer on the survival of early-stage lung cancer patients appears to be different. Pruitt *et al.* reported improved lung cancer-specific survival and no difference in all-cause OS among early-stage (defined as stage I and II) patients >65 years of age with prior cancer, although all-cause OS was slightly worse in the subset of these patients who had undergone surgical resection (5). In the study of Liu *et al.* (14), a history of prior cancer was associated with adverse OS in both stage I and II lung cancer patients under 65 years old. In a comprehensive study including a more complete range of adult patient ages, Monsalve *et al.* (6) reported worse survival across all treatment modalities in patients with stage I NSCLC with prior cancer history, with the strongest association among surgically managed patients. Likewise, a recent meta-analysis (8) found that surgically treated stage-I lung cancer patients with previous extrapulmonary malignancies had an inferior OS than those without.

Although in stage I NSCLC we did not find differences in OS between patients with or without previous malignancy, FFR was significantly impaired in the previous cancer group and prior cancer history was an independent factor associated with worse FFR. Lung cancer postoperative recurrences generally occur within the first 2 years (16); in our study, 87.5% (14 out of 16) of recurrences presented within 20 months following surgery. In a study on recurrence risk factors for stage I NSCLC patients who underwent lung resection, Wu *et al.* (9) found that a history of previous malignancy was independently associated with recurrence. In contrast, Schuchert *et al.* did not find previous malignancy to be a statistically significant predictor of recurrence following anatomic lung resection for clinical stage I NSCLC (17). The meta-analysis of Peng *et al.* (8) included only extrapulmonary malignancies, and two further studies that predominantly (7) or exclusively (18) included patients with a history of gastrointestinal cancer also found no association with recurrence.

In our multivariable analysis, we found other factors independently associated with survival or recurrence. COPD and visceral pleural invasion were independent factors associated with both, impaired OS and FFR. Conversely, mediastinal lymph node dissection or sampling was related with better OS. Mediastinal lymph node evaluation is an important predictor of prognosis when performing lobar or sublobar resection. In a study on patients with early-stage NSCLC, examination of at least one lymph node was associated with a survival benefit regardless of the extent of the sublobar resection (19). Although in our univariable

analysis non-anatomical resection and a lower number of resected lymph nodes were associated with tumor recurrence, none of them turned out to be an independent predictor of poor prognosis in the multivariable analysis.

Limitations

Limitations of our study include the single-institution and retrospective nature of its design. In addition, the sample size and the small numbers after stratification precluded finding an association between previous cancer site and primary lung cancer or metastatic outcome. Furthermore, the survival analysis has an inherent selection bias since all newly diagnosed lung cancers derive from a specific cohort of resected indeterminate pulmonary nodules. Therefore, our results may not be generalizable to all patients with surgically treated stage I NSCLC.

Conclusions

In conclusion, 15.3% of the resected nodules in our study turned out to be benign, but the rate of benign resections in the no-previous cancer group more than doubled that of the previous cancer group. For newly diagnosed stage I NSCLC, a history of prior cancer was independently associated with recurrence. Therefore, in this setting, a history of previous malignancy should be taken into consideration when identifying patients at risk of tumor recurrence, particularly in the first two years after surgery. Large prospective studies are still needed to address the impact of previous cancer on the prognosis of surgically treated early-stage lung cancer.

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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 conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by our institutional review board (Research Ethics Committee of Hospital Clínico Universitario INCLIVA, No. 2022/156), which waived the need for patient consent.

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