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Diagnostic value of surgical lung biopsy: comparison with clinical and radiological diagnosis☆

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Abstract

Objective: To determine overall and disease-related accuracy of the clinical/imagiological evaluation for pulmonary infiltrates of unknown aetiology, compared with the pathological result of the surgical lung biopsy (SLB) and to evaluate the need for the latter in this setting. **Methods**: We conducted a retrospective review of the experiences of SLB in 366 consecutive patients during the past 5 years. The presumptive diagnosis was based on clinical, imagiological and non-invasive or minimally invasive diagnostic procedures and compared with the gold standard of histological diagnosis by SLB. We considered five major pathological groups: diffuse parenchymal lung disease (DPLD), primitive neoplasms, metastases, infectious disease and other lesions. Patients with previous histological diagnosis were excluded. **Results**: In 56.0% of patients (n = 205) clinical evaluation reached a correct diagnosis, in 42.6% a new diagnosis was established (n = 156) by the SLB, which was inconclusive in 1.4% (n = 5). The pre-test probability for each disease was 85% for DPLD, 75% for infectious disease, 64% for primitive neoplasms and 60% for metastases. Overall sensitivity, specificity, positive and negative predictive values for the clinical/radiological diagnosis were 70%, 90%, 62% and 92%, respectively. For DPLD: 67%, 90%, 76% and 85%; primitive neoplasms: 47%, 90%, 46% and 90%; metastases: 99%, 79%, 60% and 99%; infectious disease 38%, 98%, 53% and 96%. **Conclusions**: Despite a high sensitivity and specificity of the clinical and imagiological diagnosis, the positive predictive value was low, particularly in the malignancy group. SLB should be performed in pulmonary infiltrates of unknown aetiology because the clinical/imagiological assessment missed and/or misdiagnosed an important number of patients.

Keywords: Lung biopsy; Clinical diagnosis; Diffuse parenchymal lung disease; Solitary nodules

1. Introduction

Surgical lung biopsy (SLB) is often considered essential for the definitive diagnosis of patients with undiagnosed or incompletely diagnosed pulmonary lesions. The decision to perform a biopsy or a wedge resection of a specific lesion is based on the likelihood that the pathologic examination of the tissue obtained will yield specific information about the nature of the disease and that this information can be used to modulate the treatment or to simply treat by complete resection *ab initio*.

However, the development and refinement of more sophisticated and accurate imaging and diagnostic methods, such as positron emission tomography (PET), high resolution computer tomography (HRCT) and bronchoscopic techniques [1], complemented by minimally invasive diagnostic procedures (image-directed biopsy or fine-needle aspiration), may challenge the usefulness of SLB. Consequently, the value of the biopsy on the diagnosis, treatment and outcome of these patients has become even more controversial [2—5].

The purpose of the present study was: (1) to determine the overall and disease-related accuracy of clinical and imagiological diagnosis; (2) to compare the presumptive clinical/imagiological diagnosis with the histological result of SLB for indeterminate pulmonary lesions/infiltrates; and (3) to evaluate the need and value of the SLB in this setting.

2. Material and methods

2.1. Patients

In the period from January 2000 through December 2005, a total of 366 patients with undiagnosed or incompletely diagnosed nodular or interstitial lung disease underwent surgical lung biopsy or wedge resection, for diagnostic and/or treatment purpose. Patients with solitary pulmonary nodules

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(SPN-defined as a single spherical lesion, 3 cm or less in diameter, completely surrounded by normal lung, without associated atelectasis or adenopathy [6,7]), or other focal pulmonary processes were included in the study. Patients who had an established diagnosis on accepted histological criteria prior to referral, or had a transbronchial (TBB) or transthoracic (TTB) diagnostic biopsy were excluded.

Data were retrospectively retrieved from the patients' records and included: demographic material (age, sex, smoking status); clinical assessment (detailed medical, family, occupational, immunological status and drug use history); physiologic results (pulmonary function tests, including spirometry, lung volumes and diffusing capacity of carbon monoxide); imagiological data (standard chest X-ray and CT and HRCT scans); bronchoscopic examination and related procedures (bronchial lavage or transbronchial biopsy); and microbiology culture results.

The ages of the patients ranged from 5 to 84 (mean, 54) years and there was a slight male predominance. Other clinical data are shown in Table 1.

The patients were classified according to their immunocompetence status, resulting from (1) primary diagnosis of malignancy for which the patient received chemotherapy, radiation or surgical intervention; (2) organ transplantation with immunosuppressive therapy; (3) collagen vascular disease or other autoimmune diseases requiring corticosteroid or immunosuppressive therapy; (4) AIDS; and (5) chronic renal failure. One hundred and twenty-four (33.8%) patients were immunocompromised.

Surgical biopsy was performed under general anaesthesia, by video-assisted thoracoscopic surgery (VATS) or a limited open thoracotomy. The site and number of lung biopsy specimens were determined by the findings on the chest X-rays or the CT scans. If there was suspicion of diffuse parenchymal lung disease (DPLD), specimens were obtained in a triangular fashion, 2–3 cm in each margin, whenever possible from two different lobes, including the transition zone between macroscopically normal-appearing parenchyma and macroscopic diseased lung. Areas of obvious severe fibrotic reaction (honeycomb pattern on HRCT scan) were avoided.

For VATS biopsy, 1 or 2 EndoGIA staples (Auto Suture Company Division, U.S. Surgical, Norwalk, Conn) were used to secure the pulmonary margins. For mini-thoracotomy, the lung specimen was excised after clamping proximally, and tissue was secured by a double running suture of 3-0 vicryl. Conversion to lobectomy and local lymphadenectomy was performed in 13 patients after obtaining extemporaneous histopathological results.

Operative morbidity and mortality were recorded.

2.2. *Analysis*

The presumed diagnosis based on clinical and imagiological findings, made preoperatively, was compared to the histological diagnosis obtained by lung biopsy and categorized as: correct diagnosis (CD), new (incorrect) diagnosis (ND), and inconclusive (INC).

For the final analysis, five major pathological groups were considered: DPLD (occupational, granulomatous disorders, idiopathic interstitial pneumonias and others); primitive neoplasm; metastases; infectious disease; and other lesions.

The validity and accuracy of the clinical diagnosis were investigated. Sensitivity (proportion of individuals with the disease who have a positive test) and specificity (proportion of individuals without the disease who have a negative test) were determined as measures of validity. The predictive value (positive and negative) was also determined to ascertain whether or not an individual has the disease, based on a positive test [8]. The pre-test probability was defined as the probability of the target disease (pathological groups designated) known before the result of the lung biopsy. It was calculated as the proportion of patients with the target disease out of all the patients with that specific presumptive diagnosis (clinical/imagiological), both those with and without the disease [9]. The probability of the target disorder was calculated by the formula: $P(D+) = D+/(D+ + D-)$, where $D+$ indicates the number of patients with the target disorder and $D-$ indicates the number of patients without the target disorder.

3. Results

There was no operative mortality. Postoperative complications were rare, seven patients (1.9%) having experienced prolonged (more than 5 days) air leakage. Chest tube drainage was required for a median of 3 days (range, 1–10 days). The median hospital stay was 4 days (range, 1–12 days).

For the analysis specific to this work, we considered six patterns of imagiological presentation (based on chest X-ray/CT/HRCT) and related them to the histological diagnosis (Table 2). The DPLD group had a more heterogeneous imagiological pattern and the honeycombing and ground glass were almost specific features of this disease. In the malignancy groups (metastases and primitive neoplasms), the nodular pattern was overwhelming, but in 8 patients with primitive neoplasms the radiological features were mainly reticular/micronodular and associated to undifferentiated or bronchioloalveolar carcinomas. The classical pleural inden-

Table 1
Patient characteristics

Characteristics	DPLD[a] (n = 120)	Lung metastasis (n = 87)	Primitive neoplasm (n = 57)	Other lesions (n = 46)	Inconclusive (n = 5)
Mean age (years)[b]	55.8 ± 14.0 (17–77)	52.9 ± 17.7 (12–79)	61.2 ± 12.1 (24–84)	53.8 ± 14.2 (15–79)	62.4 ± 4.2 (55–66)
Male (%)	50.0	59.8	59.7	45.7	60.0
Smoking status (%)	37.5	26.4	49.1	32.6	20.0
Immunosuppressed (%)	30.8	97.7	14.0	19.6	20.0
Symptomatic (%)	67.5	12.6	26.3	32.6	60.0

[a] Diffuse parenchymal lung disease.
[b] Values given as mean ± SD (range).

Table 2
Radiological patterns

	DPLD[a]		Lung metastases		Primitive neoplasm		Infectious disease		Other lesions	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Nodular[b]	18	15.0	81	93.1	44	77.1	13	54.2	27	58.7
Reticular/micronodular	46	38.3	1	1.2	8	14.0	7	29.2	8	17.4
Ground glass	37	30.8	—	—	—	—	3	12.5	1	2.2
Honeycombing	7	5.8	—	—	—	—	—	—	1	2.2
Condensation	10	8.3	3	3.5	3	5.3	1	4.2	3	65
Others	2	1.6	2	2.3	2	3.5	—	—	6	13.0

[a] Diffuse parenchymal lung disease.
[b] Pleural indentation was a specific finding of this radiological pattern and almost exclusive of the primitive neoplasm group.

tation associated with nodular lesions was also almost exclusively present in the malignancy group, especially in primary lung cancer, but was present in only one third of these patients (*n* = 16).

The correlation between the clinical/imagiological and the histopathological diagnosis is shown in Fig. 1. In 205 patients (56.0%) clinical/imagiological evaluation reached a correct diagnosis (CD) and in 156 (42.6%) a new diagnosis was obtained unexpectedly (new diagnosis — ND). Biopsy was inconclusive (INC) in five patients (1.4%).

These results varied among different pathologies: For DPLD: CD —76% (*n* = 80), ND —21% (*n* = 22) and INC —3% (*n* = 3); primitive neoplasms: CD —46% (*n* = 27), ND —21% (*n* = 32); metastases: CD —60% (*n* = 86), ND —40% (*n* = 57) and INC —3% (*n* = 1); infectious disease: CD —53% (*n* = 9), ND —47% (*n* = 8); other lesions: CD —50% (*n* = 3), ND —50% (*n* = 3); solitary pulmonary nodules: CD —59% (*n* = 36), ND —41% (*n* = 25). SLB was also able to discriminate the various subtypes of lung tumours encountered (Table 3), with consequent different prognosis.

Overall sensitivity, specificity, positive and negative predictive values for the clinical/imagiological diagnosis were 70% (95% confidence interval, 65—75), 90% (CI, 88—91), 62.3% (CI, 57—68) and 93% (CI, 91—94), respectively (Table 4). The values for each disease are also shown in Table 4.

The pre-test probability was 85% for DPLD, 75% for infectious disease, 64% for primitive neoplasms and 60% for metastases, meaning that there was a good correlation between the predicted probability and the observed frequency in the case of the DPLD, less good in the malignancy group.

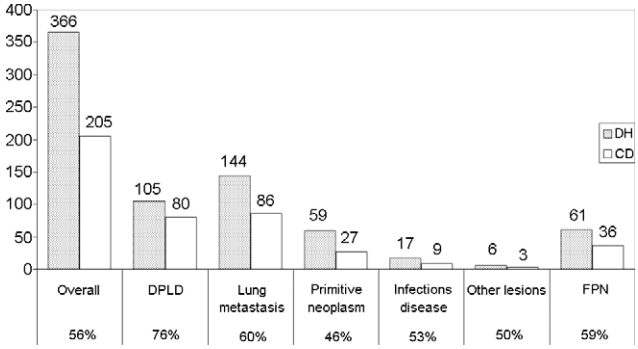

Fig. 1. Relationship between the clinical/imagiological and the pathological diagnosis, globally and for each disease. DPLD — diffuse parenchymal lung disease; SPN — solitary pulmonary nodules; DH — diagnostic hypothesis; CD — correct diagnosis. Figures in the bottom indicate the percentage of correct diagnosis made by the clinical evaluation.

SLB was able to define and characterise the most prevalent diseases, such as pulmonary malignancies and DPLD; it reached a definitive diagnosis in 94.8% of patients; 42.6% of the pathological findings were different from the initially proposed diagnosis; 52.6% of the primary lung cancers were detected unexpectedly; in 40.3% of patients with an initial diagnosis of lung metastases, this was excluded; and in 37% of patients with suspicion of DPLD a specific diagnosis could only be made after SLB.

4. Discussion

The decision of whether or not to perform a SLB is not straightforward. The procedure is clearly indicated in cases in which clinical or imagiological findings are atypical or when the presumptive diagnosis has a low degree of certainty. The predictive value of the clinical criteria largely depends on the experience of the clinician and of the radiologist, but considerable interobserver variability exists, even when evaluations are performed by experts in the field [10]. These

Table 3
Histopathological findings of malignant lung biopsies

Origin	Histology	*N*	(%)
Primary lung cancer (*n* = 57)	Adenocarcinoma	25	43.9
	Squamous cell carcinoma	6	10.5
	Mixed[a]	5	8.8
	Small-cell carcinoma	3	5.3
	Undifferentiated carcinoma	3	5.3
	Adenosquamous carcinoma	2	3.5
	Large-cell carcinoma	2	3.5
	Sarcoma	2	3.5
	Carcinoid	2	3.5
	Others	7	12.3
Secondary lung cancer (*n* = 87)	Colorectal	22	25.3
	Sarcoma (osseous and others)	38	43.7
	Breast	9	10.3
	Thyroid	4	4.6
	Renal	4	4.6
	Stomach	3	3.4
	Larynx	3	3.4
	Skin	2	2.3
	Others	2	2.3

[a] In five cases the pathologist could not differentiate between adenocarcinoma and squamous cell carcinoma.

Table 4
Clinical/imagiological diagnosis disease-related accuracy

	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
DPLD[a]	67 (57—75)	90 (85—93)	76 (67—84)	85 (80—89)
Lung metastases	90 (93—99)	79 (74—84)	60 (51—68)	99 (97—100)
Primitive neoplasms	47 (34—61)	90 (86—93)	46 (33—59)	90 (86—93)
Infectious disease	38 (20—59)	98 (95—100)	53 (29—76)	96 (93—97)
Overall	70 (65—75)	90 (88—91)	62 (57—68)	92 (91—94)

[a] Diffuse parenchymal lung disease.

criteria led to misdiagnosis in about 40% of our cases. Interobserver variability is reduced and diagnostic accuracy is improved in cases in which a diagnosis is made with a high degree of confidence [11,12].

In the daily practice, there are two different scenarios presented to the thoracic surgeon. First, there are the patients with diffuse pulmonary infiltrates. Usually referred by chest physicians with a presumed diagnosis of interstitial lung disorder, but where the clinical/radiological evaluation cannot precise the diagnosis, without which the physician is usually reluctant to initiate medical treatment (corticoids or immunosuppressive medication) or alter the treatment instituted. In this case, SLB is merely a diagnostic procedure. Second, are those patients with a SPN or other focal pulmonary lesions and the possibility of malignancy is the main concern. Observation for growth, biopsy and resection are the available options, simultaneously aiming at avoiding delay in the diagnosis and treatment of lung cancer, false negative results, and unnecessary resection of benign lesions. In this situation, SLB is simultaneously a diagnostic and therapeutic procedure.

On the other hand, despite the recent advances in imaging techniques (contrast-enhanced CT, PET, CT + PET) and in the refinement of minimally invasive diagnostic procedures (TTB, TBB), these techniques still have limitations. Although CT scanning is a sensitive imaging technique, it cannot prove malignancy. In multiple series, 25—40% of malignant nodules (SPN) were misclassified as benign [13]. In our study, a correct diagnosis was achieved in only 59% of the SPN. Even in fine-needle aspiration cytology, the sensitivity varies from 71% to 97% and the specificity from 97% to 100% and inadequate samples are obtained in 4—18% of the cases [14]. Despite the already proven applicability of PET (sensitivity and specificity for malignancy were 89—100% and 79—100%, respectively, and diagnostic accuracy ranging from 89% to 100%), false-negatives can occur, most notably in association with bronchioloalveolar carcinoma, carcinoids and in tumours less than 10 mm in diameter. Furthermore, false positives have been reported in active lung diseases such as granulomas, aspergillomas, active tuberculosis and abscesses [15].

Despite the high specificity of the clinical diagnosis, the sensitivity was quite low in our study (except for the metastases group), as was the positive predictive value, meaning that there were a significant number of patients in whom a correct diagnosis would be missed if a lung biopsy was not performed. The high sensitivity for the lung metastases is misleading, because it was a diagnostic hypothesis usually considered in patients with a known history of malignant tumours, hence the probability to miss the diagnosis was minimal. But when we evaluated the probability that a patient had the disease based on a positive test (PPV), the clinical diagnosis was not satisfactory (low PPV), reflecting an important number of false-positives in this group. Conversely, the negative predictive value was very high (99%), reflecting a very small number of false-negatives and resulting in that almost all metastases (except one from a tumour of unknown origin) confirmed by pathological examination were previously presumed by the clinical/radiological evaluation.

Regarding the DPLD group, the result of the positive predictive value (76%) can be deceiving, because this is a heterogeneous group with more than 100 entities and several diagnostic hypotheses were present under the cover of this broad term. In a considerable number of patients ($n = 57$) with suspicion of having DPLD, a specific diagnosis could only be made after SLB (Fig. 2). SLB was also able to distinguish the several clinicopathological entities of idiopathic interstitial pneumonias, in accordance with the definition of the American Thoracic Society and European Respiratory Society [20], discriminating different prognosis (Fig. 3).

There are several reports in the literature analysing the accuracy of a clinical and radiological diagnosis of idiopathic pulmonary fibrosis (IPF) and other subsets of DPLD [10,16—19]. Although Hunninghake et al. [10] reported that a clinical diagnosis of IPF made by experts in DPLD has a high sensitivity and specificity, they emphasised that lung biopsy should be undertaken when the clinical picture is unclear or when patients are thought to have conditions other than IPF. Raghu and colleagues [16] found that clinical assessment combined with HRCT scanning has a specificity of over 90% for the diagnosis of IPF. However, the sensitivity was lower, suggesting that if they relied solely on clinical/radiological assessment they would have missed an important number (nearly one third) of IPF.

We had a high specificity in this group, probably related to the inclusion of focal pulmonary lesions that would

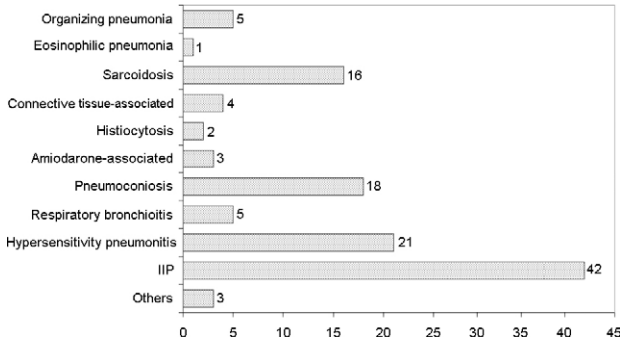

Fig. 2. Specific interstitial lung diseases detected by lung biopsy.

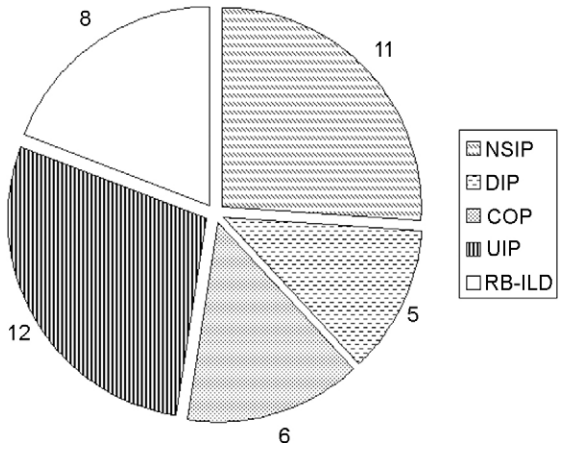

Fig. 3. Differential diagnosis of the several clinical—pathological entities of idiopathic interstitial pneumonias. NSIP — non-specific interstitial pneumonia; DIP — desquamative interstitial pneumonia; COP — cryptogenic organizing pneumonia; UIP — usual interstitial pneumonia; RB-ILD — respiratory bronchiolitis-associated interstitial lung disease.

practically exclude the diagnosis of DPLD, and a reasonable sensitivity of the clinical evaluation, consistent with other studies. Our experience shows that SLB almost uniformly results in a precise diagnosis. As the classification schemes for DPLD become more complex [20], diagnostic accuracy becomes a more pressing issue.

With regards to focal lesions or SPN, 55% of the nodules excised were malignant, comparable to the incidence reported in the literature [21,22]. Eighteen patients (22%) had primary and 20 (34%) had secondary lung cancer. We were probably overzealous in the approach to these patients, because nearly 45% of the nodules excised were benign, meaning that an observational strategy could have been carried out in some cases.

Finally, there was not a sufficient size sample for the infectious group to draw conclusions about the accuracy of the clinical diagnosis, even though it is important to refer that 15 unexpected diagnoses were made after SLB, mostly from infection with BK, which is still endemic in our country.

Our study has several limitations that deserve further discussion. Firstly, we have coupled two distinct groups of patients (diffuse infiltrates vs focal infiltrates), which could have altered the overall accuracy, especially in respect of the specificity and NPV (high in our study). Secondly, this is a retrospective analysis. All the patients included were referred for SLB and it is difficult to know the real accuracy of the clinical/imagiological evaluation because there surely were patients treated conservatively and others with a correct pathological diagnosis obtained by less invasive diagnostic procedures (TBB, TTB), not included in our study. Thirdly, not all patients originated from inside our institution. Many were referred from other primary and secondary centres and from isolated chest physicians, meaning that the clinical and imagiological observation was not uniform for all patients, with probable impact on accuracy.

In conclusion, SLB is a safe and accurate diagnostic tool for pulmonary infiltrates of unknown aetiology, and, in our opinion, remains the gold standard for undiagnosed or incompletely diagnosed diffuse pulmonary disease.

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