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Original Article / Özgün Makale

Surgical lung biopsy for differential diagnosis of interstitial lung disease

İnterstisyel akciğer hastalığının ayırıcı tanısında cerrahi akciğer biyopsisi

Tülin Sevim,[1] Fatma Tokgöz Akyıl,[1] Hakan Kıral,[2] Emine Aksoy,[1] Mustafa Akyıl,[2] Mustafa Vayvada,[2] Ayçim Şen,[3] Çağatay Tezel,[2] Volkan Baysungur[2]

Departments of [1]Chest Diseases, [2]Thoracic Surgery, [3]Pathology,
Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Background: This study aims to investigate the diagnostic yield of surgical lung biopsy for the differential diagnosis of interstitial lung disease and the factors affecting diagnosis.

Methods: We retrospectively reviewed medical records of 202 patients (91 males, 111 females; mean age 49±12 years; range 18 to 78 years) who underwent surgical lung biopsy in our hospital between May 2008 and December 2014. We recorded patients' demographic characteristics, surgery type, number and localization of biopsies, and final diagnoses established in light of histopathological findings. According to the final diagnoses, we divided patients into two groups as patients with an established specific diagnosis (group 1) and patients without an established specific diagnosis (group 2). We investigated the effect of surgical procedure on final diagnosis.

Results: Left lung was more frequently sampled (72%) and 75% of the procedures ended up with a single biopsy. Total number of biopsies was 255. Of all samples, 44% were taken from the middle lobe or lingula. Rate of patients with a histopathologically established and clinically and radiologically verified final diagnosis was 80% (group 1). Gender (p=0.161), number of samples (p=0.541), lung side (p=0.954), or lung segment (p=0.592) did not affect the rate of establishing a diagnosis. Of the patients, mortality was observed in 2%, major complications in 1.5%, and minor complications in 9.5%. No relationship was detected between localization or number of biopsies and development of complications (p>0.05).

Conclusion: Albeit with low probability, surgical lung biopsies are correlated with morbidity and mortality. Not all procedures result in a specific diagnosis. Localization, type or number of biopsies do not affect the diagnosis rate significantly.

Keywords: Idiopathic interstitial pneumonia; idiopathic pulmonary fibrosis; non-specific interstitial pneumonia.

ÖZ

Amaç: Bu çalışmada, interstisyel akciğer hastalığının ayırıcı tanısı için cerrahi akciğer biyopsisinin tanısal değeri ve tanıyı etkileyen faktörler araştırıldı.

Çalışma planı: Hastanemizde May 2008 - Aralık 2014 tarihleri arasında cerrahi akciğer biyopsisi uygulanan 202 hastanın (91 erkek, 111 kadın; ort. yaş 49±12 yıl; dağılım 18-78 yıl) tıbbi kayıtları retrospektif olarak incelendi. Hastaların demografik özellikleri, cerrahi tipi, biyopsi sayısı ve yeri ve histopatolojik bulgular ışığında ulaşılan son tanıları kaydedildi. Son tanılara göre, hastalar spesifik tanıya ulaşılanlar (grup 1) ve spesifik tanıya ulaşılamayanlar (grup 2) olarak iki gruba ayrıldı. Cerrahi işlemin son tanıya olan etkisi araştırıldı.

Bulgular: Sol akciğer daha sık örneklenmiş (%72) ve işlemlerin %75'i tek bir biyopsi ile sonlanmış idi. Toplam biyopsi sayısı 255 idi. Tüm örneklerin %44'ü orta lob veya linguladan alınmış idi. Histopatolojik olarak son tanıya ulaşılan ve klinik ve radyolojik olarak doğrulanan hasta oranı %80 idi (grup 1). Cinsiyet, (p=0.161), örnek sayısı (p=0.541), akciğer tarafı (p=0.954) ve akciğer segmenti (p=0.592) tanıya ulaşma oranını etkilememiş idi. Hastaların %2'sinde mortalite, %1.5'inde majör ve %9.5'inde minör komplikasyon gözlemlendi. Biyopsi yeri ve sayısı ile komplikasyon gelişmesi arasında ilişki saptanmadı (p>0.05).

Sonuç: Cerrahi akciğer biyopsileri, düşük olasılıkla da olsa, morbidite ve mortalite ile ilişkilidir. Tüm işlemlerde spesifik tanıya ulaşılamamaktadır. Cerrahi biyopsinin yeri, tipi ve sayısı tanı oranını anlamlı olarak etkilememektedir.

Anahtar sözcükler: İdyopatik interstisyel pnömoni; idyopatik pulmoner fibrozis; nonspesifik interstisyel pnömoni.

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Correspondence: Fatma Tokgöz Akyıl, MD. Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, 34854 Maltepe, İstanbul, Turkey.
Tel: +90 541 - 887 34 07 e-mail: fatmatokgoz86@gmail.com

Diffuse interstitial lung disease (ILD) constitutes a heterogeneous group of diseases comprising similar clinical, radiologic, and lung function presentations, in which the interstitial alveolar structures are affected principally. The etiology of ILD is extremely varied. Currently, more than 150 different causes are known to exist.[1]

Specific diagnosis of ILD is important for prognostic purposes and determining the patient treatment regimen. The most important issue here is to differentiate idiopathic pulmonary fibrosis (IPF) since the clinical prognosis is poor and corticosteroids are not used in the treatment.[2,3]

Despite all diagnostic methods, surgical lung biopsy (SLB) is required in one third of ILD patients. Surgical lung biopsy is often discussed in terms of its diagnostic value, mortality and morbidity.[4-6] Even though there has been continuous practice of SLB for decades, there is still no consensus on the site and number of the surgical biopsies. Lingula and middle lobe have been reported to be common sites of inflammatory, fibrotic and vascular changes so that segments other than lingula and middle lobe are suggested to be sampled. However, lingula and middle lobe are more frequently preferred by the surgeon since the tissue is delivered easily.[7,8] There are reports concluding that the site of the biopsy, whether lingula, middle lobe or other segments, do not affect the diagnosis rate.[9,10] Furthermore, both positive and negative results have been reported on the effect of the number of biopsies on the diagnosis rate.[6,9] Therefore, in this study, we aimed to investigate the diagnostic yield of SLB for the differential diagnosis of ILD and the factors affecting diagnosis.

PATIENTS AND METHODS

We retrospectively reviewed the records of 202 patients (91 males, 111 females; mean age 49±12 years; range 18 to 78 years) who had undergone a mini-thoracotomy or video-assisted thoracoscopic surgery (VATS) for differential diagnosis of ILD between May 2008 and December 2014 at Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital.

Patients with interstitial involvement are evaluated for surgery when specific diagnoses cannot be made upon medical history, clinical laboratory, and radiological findings.[1] Biopsy is avoided when radiological findings are suggestive of a definite usual interstitial pneumonia (UIP) pattern.[3] Surgery decision is made by the consultation of a pulmonologist and thoracic surgeon, taking the consent of the patient.

Site of biopsy was decided according to high resolution computed tomography findings. In patients with widespread involvement, either lingula or middle lobe was sampled. Otherwise, the involved segment was sampled. The number of biopsy was decided by the surgeon during the procedure, based on the intraoperative exploration findings. Mini-thoracotomy was performed more often until 2010, while later on, most biopsies were obtained by VATS.

We obtained the medical files of the patients from the archive of the hospital. We recorded patients' demographic characteristics and examinations prior to surgery. Also, we recorded the side, site, and number of biopsies from the operation notes.

We coded biopsy sites as *(i)* segments of the upper lobes except lingula, *(ii)* lingula or middle lobe, and *(iii)* segments of the lower lobe. We investigated postoperative duration of hospital stay (day) and procedure-related complications. We accepted death within the first 30 days of the procedure as postoperative mortality. We considered prolonged air leak (>96 hours) and wound infection as minor complications. We accepted respiratory failure and rethoracotomy requirement as major complications.[11] Then, we compared patients with complications (minor/major complications and death) to patients without complications.

We recorded the final diagnosis based on histopathological findings along with radiological findings and clinical follow-up. We grouped patients with a definitive diagnosis as group 1 and patients with no definitive diagnosis as group 2. We compared the diagnostic yield of the procedure between the two groups. The study was approved by the local Ethics Committee of the Institution (Dr. Lufti Kırdar Training and Research Hospital, Reference Number: 89513307/1009/410) and it proceeded in accordance with the ethical principles stated in the Declaration of Helsinki.

Statistical analysis

Categorical variables were compared using the Fisher's exact test. Continuous variables are presented as the mean ± standard deviation and were analyzed with the Student's t-test. All tests were two-tailed, and a p value of <0.05 was accepted as significant. All analyses were performed using SPSS version 16.0 statistical software package (SPSS Inc., Chicago, IL, USA).

RESULTS

Prior to SLB, 75% of patients (n=151) had undergone fiberoptic bronchoscopy. Transbronchial biopsy (TBB)

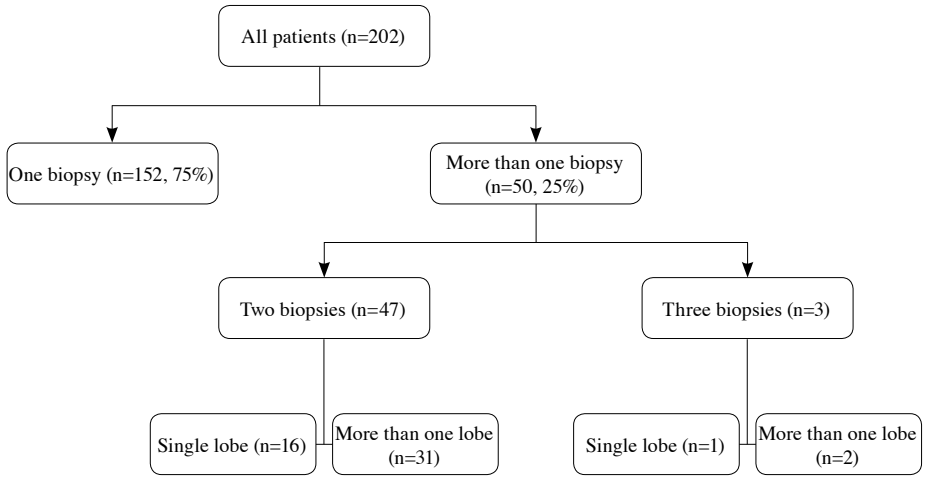

Figure 1. Number of biopsies performed.

and broncholaveolar lavage (BAL) were both performed in 44 patients (22%). Only TBB was performed in 29 (14%) and only BAL in 37 (18%) patients. Bronchial lavage was conducted in the other 41 procedures.

Mini-thoracotomy was carried out in 72 (36%) and VATS in 130 (64%) patients. The left lung was more frequently sampled (72%, n=145). Biopsy was performed from one site in 152 patients (75%) and multiple times in 50 patients (25%) (Figure 1). Number of samples totally was 255. Thirty-one samples (12%) were from the upper lobes except lingula, while 111 (44%) were from middle lobe or lingula (Figure 2). Median duration of postoperative hospital stay was two days (range, 1 to 18 days). In total, 162 of 202 patients (80%) had a specific diagnosis (group 1) whereas 40 patients (20%) were not specifically diagnosed (group 2).

The most frequent diagnosis was UIP (26.7%), followed by sarcoidosis, hypersensitivity pneumonia, and non-specific interstitial pneumonia (NSIP). Ten patients were diagnosed as cancer (nine had adenocancer and one had thyroid anaplastic carcinoma metastasis) (Table 1).

We detected no gender difference between the two groups (p=0.161). Of 152 patients with single biopsy, 120 (79%) were specifically diagnosed. Number of biopsies did not influence the diagnosis rate (p=0.541).

An analysis of the impact of biopsy segments on the diagnosis rate revealed that 74% of the samples taken from the upper lobes, 79% of the lingula or middle lobe samples, and 78% of the lower lobe samples resulted in a specific diagnosis. The site of the biopsy did not have significant effect on diagnosis (p=0.592). Also, sampling from either right or left lung did not make any difference (p=0.954) (Table 2).

Postoperative mortality (within 30 days) was recorded in four patients (2%). Major complications developed in three (1.5%) and minor complications in 19 (9.5%) patients. Non-complicated patient rate was 87% (n=176). Major complications were respiratory failure (n=1), respiratory failure and cerebrovascular attack (n=1), and bleeding and re-thoracotomy (n=1). Minor complications were prolonged air-leak (n=18) and wound infection (n=1).

Duration of hospital stay of patients with complications was significantly longer (6.2 days vs. 2.3 days, respectively) (p<0.001). Mean age was similar between the complicated and non-complicated patients (50 vs. 49) (p=0.751). There

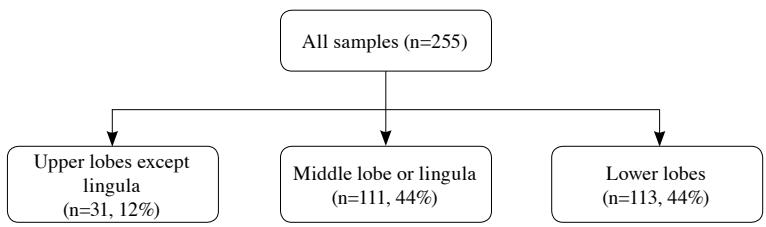

Figure 2. Selected site according to number of biopsies.

Table 1. Final diagnoses

	n	%
Nonspecific interstitial changes	40	19.8
Usual interstitial pneumonia	54	26.7
Sarcoidosis	25	12.4
Hypersensitivity pneumonitis	11	5.3
Nonspecific interstitial pneumonia	11	5.3
Malignancy	10	5
Organizing pneumonia	8	4
Tuberculosis	8	4
Bronchiectasis	7	3.5
Desquamative interstitial pneumonia	7	3.5
Pulmonary alveolar proteinosis	6	3
Langerhans cell histiocytosis	4	2
Bronchiolitis	3	1.5
Lymphocytic interstitial pneumonia	2	1
Respiratory bronchiolitis-ILD	2	1
Silicosis	2	1
Asbestosis	1	0.5
Granulomatous reaction-vasculitis	1	0.5

ILD: Interstitial lung disease.

was no significant difference in gender, type of surgery, lung side, the number of biopsies, and diagnosis rate between the complicated and non-complicated patients (Table 3).

DISCUSSION

Specific diagnosis of ILD is important for patient management and predicting the prognosis. When the clinical and radiological findings are inadequate, SLB is considered as the optimal method for correct diagnosis.[3,12]

Some patients cannot be clearly classified as ILD.[12] The main reasons for this are: inadequate clinical-radiological-pathological findings, discordance between clinical-radiological-pathological findings, and coexistence of multiple radiological and/or histological patterns.[12,13] More than one pattern in the same patient's biopsy is mostly reported for NSIP and UIP. Additionally, there may be multiple patterns in smokers. In this situation, multidisciplinary discussion is necessary for final diagnosis and adequate approach to patient management.[14-17]

Sarcoidosis, tuberculosis, and malignancy can also be diagnosed in patients with a preliminary diagnosis of ILD. Lee et al.[18] identified infectious etiology in 31% in a series of 196 patients. Sigurdsson et al.[19] obtained non-interstitial diagnoses in 10% of patients. Granulomatous diseases have been reported in 5 to 16% and malignancy in 5 to 13.3% of patients.[5-7,18,20,21] In the published series, the diagnostic yield of SLB ranged between 34 to 98% and the most common diagnosis was reported as IPF.[19,20] In the current study, final diagnosis was reached in 80% and the most common diagnosis was UIP, which complies with the existing literature. Also, diagnoses of sarcoidosis and tuberculosis were reached in 12.4% and 4%, respectively, while malignancy was diagnosed in 5% of the patients.

Table 2. Comparison between groups

	Group 1 (n=162)		Group 2 (n=40)		
	n	%	n	%	*p*
Gender					0.161
Male	77	48	14	35	
Female	85	52	26	65	
Surgery type					0.464
Video-assisted thoracoscopic surgery	102	63	28	70	
Thoracotomy	60	37	12	30	
Biopsy side					0.954
Right	46	28	11	27	
Left	116	72	29	73	
Biopsy number					0.541
Single	120	74	32	80	
More than one	42	26	8	20	
Biopsy lobe*					0.592
Upper lobe**	23	12	8	14	
Middle lobe/lingula	88	44	23	41	
Lower lobe	88	44	25	45	

* Biopsy lobes are given according to the number of biopsies (total: 255); ** Except lingula.

Table 3. Comparison of patients with and without complication

	Any complication		No complication		
	n	%	n	%	*p*
Gender					0.835
Male	11	42	80	45	
Female	15	58	96	55	
Operation type					0.274
Video-assisted thoracoscopic surgery	14	53	116	66	
Thoracotomy	12	46	60	34	
Biopsy side					0,354
Right	5	19	49	29	
Lung	21	81	119	71	
Biopsy number					0.797
Single	20	77	132	75	
More than one	6	23	44	25	
Diagnosis rate					0.999
Diagnosis	21	81	141	80	
No diagnosis	5	19	35	20	

Various results have been reported on how many biopsies should be taken. The main reasons in preference of a single biopsy by the surgeon are to prevent extension of operation duration and decrease costs and complications. However, taking multiple biopsies have been suggested in the first published reports and in current guidelines.[3,4,22] In 2013, Blackhall et al.[6] reported that a median of two biopsies significantly increases the probability of reaching a definitive diagnosis. On the other hand, sampling from either a single biopsy or multiple biopsies have not made a significant difference in providing a diagnosis in other reports.[19,21] Chechani et al.[9] indicated that single biopsy would be enough when a radiologically convenient segment is sampled. In the last few years, two studies consisting 224 and 194 patients concluded that the number of biopsies has no effect on reaching a specific diagnosis and taking less biopsies was defended since less inflammation and less injury would be provided in lung parenchyma.[20,23] In the present study, the number of biopsies was mostly decided during the procedure and the number of biopsies did not make a significant difference on diagnostic yield.

Another issue regarding the number of biopsies is the possibility of a misdiagnosis. It is suggested that interstitial involvement may vary among lobes, especially in the distinction of NSIP and UIP. When more than one biopsy preparations of the same patients were evaluated discretely, UIP and NSIP discord was reported as 12% and 26%, respectively.[14,24] However, with similar methods, Flint et al.[25] did not find a statistically significant difference in diagnosis.In the current study, we did not evaluate the specimens in this regard. Since the most discussed issue is misdiagnosed NSIP, we reevaluated patients with NSIP. Among 11 patients, single biopsy was taken in nine (collagen vascular disease-associated NSIP diagnosis was established in three and corticosteroid treatment was effective in six patients). In the other two patients, two biopsies were taken. One patient died with an acute exacerbation in the fourth year of the diagnosis. The other patient underwent lung transplantation in the third year of the diagnosis. The results of the present study is not sufficient to comment on the possibility of misdiagnosis. Prospective studies with larger series may shed further light on this issue. In our opinion, it may be reasonable to take more than one biopsy in patients with a high probability of NISP or UIP.

Biopsy localization is another subject under discussion. Sampling radiologically less-involved segments without 'honeycomb' pattern has been proposed.[7,24,26] Lingula and middle lobe biopsies are more frequently preferred by the surgeon but those segments are suggested to be avoided since inflammatory, vascular, and fibrotic changes are seen more often.[7,8,25,27] In recent studies, the site of biopsy has been reported to have no influence on the diagnosis rate (Table 4).[9,10,19,21,28] Similarly, in this study, we found that the site of biopsy does not affect the diagnosis rate. We believe that it is important to evaluate radiological involvement in the selection of the appropriate segment.

Table 4. Comparison of the reported series

	n	Biopsy number	Biopsy site	Result
Klassen et al.[22]	270	-	-	Taking multiple biopsy is suggested
Gaensler et al.[7]	502	-	-	Sampling either lingula or middle lobe should be avoided
Rena et al.[5]	58	Single in 95% of the patients	59% right lung, 27% left upper lobe	-
Qureshi et al.[21]	100	>1 in 32% of the patients	52% right lung, 34% left upper lobe	Biopsy site and number do not effect diagnosis rate
Lee et al.[18]	196	>1 in 17% of the patients	-	-
Sigurdsson et al.[19]	73	>1 in 30% of the patients	30% lingula	Biopsy site and number do not effect diagnosis rate
Fibla et al.[23]	224	>1 in 80% of the patients	34% left upper lobe	Biopsy site and number do not effect diagnosis rate
Blackhall et al.[6]	103	Median 2 biopsy in patients with specifically diagnosed	-	Taking at least 2 biopsy is suggested
Kayatta et al.[20]	194	>1 in 100% of the patients	-	Biopsy site and number do not effect diagnosis rate

Compatible with the literature, diagnostic yield of thoracotomy and VATS was found to be similar.[21] In the literature, median postoperative duration of hospital stay were reported as four days, with a range of 2 to 10 days.[23,29] In line with the literature, the median duration of hospital stay was two days in the present study.

Perioperative morbidity has been reported to be between 3.8 to 16%, while 30-day mortality have been reported to be 0 to 6.7%.[5,19,20] The most frequent complication has been described as prolonged air leak.[6,19] In our study, mortality rate was 2%, and rates of major and minor complications were 1.5% and 9.5%, respectively. The most common minor complication was prolonged air leak. No significant risk factors were identified for mortality.

The present study has some limitations. Firstly, this is a retrospective and single-center study. Secondly, the histopathologic specimens were not evaluated separately in terms of misdiagnosis.

In conclusion, surgical lung biopsy may cause morbidity and mortality, albeit with a low probability. Although non-interstitial diagnosis can be established, specific diagnosis cannot be achieved in some patients. With respect to radiological involvement, the site and number of biopsies do not seem to affect the diagnosis rate. Nevertheless, we believe that patients should be approached from a multidisciplinary perspective in this regard.

Declaration of conflicting interests

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