Original Article

Shifted focus of bronchoalveolar lavage in patients with suspected thoracic malignancy: an analysis of 224 patients

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Background: Bronchoscopies are extensively adopted for diagnosing and staging thoracic malignancies, but studies are missing as how to keep the process streamlined and more efficient. To evaluate current role of bronchoalveolar lavage (BAL) for cancer and possible infection diagnosis when practicing comprehensive bronchoscopy for patients suspected with thoracic malignancy, and provide foundation for possible practice modification.

Methods: We retrospectively analyzed a prospectively kept database of immunocompetent patients undergoing bronchoscopy for suspected non-hematologic malignancies. Clinical, radiographic data, bronchoscopic sampling techniques and diagnostic results were recorded. Initially undiagnostic patients were followed up for 2 years for a definitive diagnosis.

Results: Of 224 patients included, 179 (79.9%) were confirmed with active thoracic malignancies. BAL diagnostic yield of cancer based on different radiographic characters of target lesion are as follow: isolated lymphadenopathies 0%, central lesions 45.5%, peripheral masses (diameter ≥3 cm) 21.4%, peripheral large nodules (2≤ diameter <3 cm) 15.8%, and peripheral small nodules (diameter <2 cm) 7.1%, while composite bronchoscopy achieved diagnostic yield of 93.3%, 95.5%, 91.7%, 76.9%, and 66.7% in corresponding lesion types. No cancer was diagnosed solely by BAL-cytology. Proportions of patients with positive BAL culture did not differ significantly between patients with and without pre-test suspicion for infections (P=0.199). In multivariable analysis, infections were associated with age ≥75 (OR 3.0; 95% CI: 1.29–7.06), chronic obstructive pulmonary disease (COPD) (OR 2.7; 95% CI: 1.14–6.26) and diabetes mellitus (DM) (OR 4.5; 95% CI: 1.90–10.44).

Conclusions: Omitting BAL cytology in settings of comprehensive bronchoscopy may not compromise cancer diagnosis. For patients primarily suspected with thoracic malignancy, performing BAL culture only based on clinical suspicion could miss important infectious etiology.

Keywords: Thoracic malignancies; bronchoalveolar lavage (BAL); bronchoscopy; lower respiratory tract infections (LRTIs); peripheral lung lesion

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Introduction

Bronchoscopy has been an integral part of diagnosis and staging for patients suspected with thoracic malignancies. Interventional pulmonologists have the options of combining different techniques to obtain tissue samples and to maximize diagnostic yields. However, keeping bronchoscopic evaluation streamlined, which involves reducing redundancy and having each approach serving the best purpose, will have great implications in terms of efficiency and cost.

Bronchoalveolar lavage (BAL) cytology constitutes a standard part in bronchoscopic evaluation for thoracic malignancies, which is primarily supported by earlier studies before introduction of image-guided navigation, showing 28% to 65% diagnostic yield for malignant peripheral lung lesions with BAL (1-3). However, major lung cancer guidelines currently recommend determination of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) status for all non-squamous cell types in non-small cell lung cancer (NSCLC) (4,5), and shifting treatment paradigm of lung cancer and other malignancies relies heavily on a growing list of predictive and prognostic biomarkers (6-10). Subtyping and genotyping tests would require sufficient tumor tissues which are usually more than that could be obtained from BAL. But whether omitting BAL cytology would compromise cancer diagnosis remains unknown and further evidence is needed if we had to modify our practice.

Co-infection in patients with thoracic malignancies is common. For infectious disease, BAL has the advantage of a larger sampling volume. However, when BAL culture would be indicated for patients primarily suspected with malignancy remains to be determined. We aim to assess the role of BAL in patients with suspected thoracic malignancies. We hypothesize that in context of comprehensive sampling with transbronchial brushings (TBB), transbronchial lung biopsies (TBLBx) and transbronchial needle aspirations (TBNA), BAL might not be additive to cancer diagnosis, while how to set threshold for BAL culture in this population remains to be explored.

Methods

Patient inclusion

We retrospectively analyzed a prospectively kept bronchoscopy database for patients with suspected thoracic malignancies at the Johns Hopkins Hospital. Patients were excluded if they had previous hematological malignancies, or were immunocompromised (received bone marrow/solid organ transplantation, with hereditary/acquired/iatrogenic immunodeficiency). The Institutional Review Board at the Johns Hopkins Medical Institute approved this study (JHMI IRB NA_00026855). Consents were obtained from all patients.

For included patients, clinical characteristics, characteristics of thoracic imaging [thoracic computer-tomographic (CT) or whole-body positron emission tomography (PET) scan], results of index bronchoscopy and BAL cytology/culture were recorded. Patients were followed up if the index bronchoscopy failed to establish a definitive diagnosis of cancer. A definitive benign etiology was confirmed by specific pathology or by radiographically stable lesion over 2 years or by spontaneous lesion shrinkage without anti-tumor therapy.

The pre-test suspicion for underlying or coexisting pulmonary infection was independently evaluated by two pulmonologists (Xin Zhang and Rex C. Yung) for each case. Disparities were referred to a third physician (Yuan Zhang) for final judgement. Clinical suspicion for lower respiratory tract infection (LRTI) is based on one or more of following symptoms/signs: Body temperature >37.5 ℃ within 48 h of inclusion, leukocytosis (>10×10^9/L), newly developed or worsening cough, sputum purulence, dyspnea (11).

BAL culture for infectious pathogens was classified into three categories (primary infection, colonization/possible infection, negative) based on established criteria for each pathogen group (12). Primary infection was diagnosed with positive bacteriology results in BAL (i.e., culture yielding a single pathogenic bacterial microorganism at the minimum concentration of 10^3 cfu/mL or any microorganism excluding mouth flora above the minimum concentration of 10^4 cfu/mL; or the identification of *Legionella* spp., *Nocardia* spp., *Chlamydia* spp., Mycoplasmas, Mycobacteria, *Aspergillus* spp., *Cryptococcus* spp., *Pneumocystis jirovecii* regardless of colony counts). Bacterial cultures fewer than 10^3 cfu/mL were considered as colonization/possible infection.

Bronchoscopy sampling strategy

Flexible bronchoscopy was performed with the patient under conscious sedation using fentanyl and midazolam according to the British Thoracic Society guidelines (13). BAL was routinely performed in all patients undergoing diagnostic bronchoscopy for suspected thoracic malignancy,

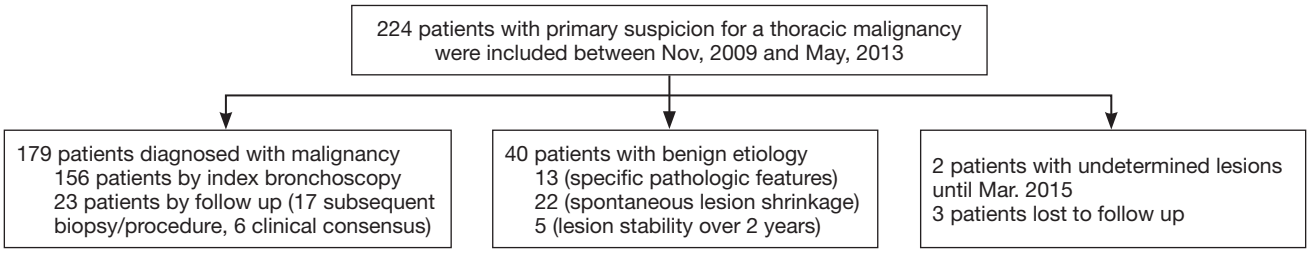

Figure 1 Consort diagram of patient flow.

Table 1 Demographic and clinical features of included patients

Variables	Median [range] or n (%) (N=224)
Age (years)	63 [19–94]
Gender	
Male	124 (55.4)
Race	
White	148 (66.1)
Black	50 (22.3)
Others	26 (11.6)
Smoking history	
Current smoker	53 (23.7)
Former smoker	119 (53.1)
Never smoker	52 (23.2)
Cancer history	
Documented cancer activity within previous 5 years	117 (52.2)
Documented cancer activity 5 years before	25 (11.2)
No previous cancer history	82 (36.6)
Reasons for bronchoscopy referral	
Routine image follow-up (asymptomatic)	93 (41.5)
Fever	2 (0.9)
Other pulmonary symptoms	129 (57.6)

and was performed by three installations of 50 mL sterile saline over the working channel of the bronchoscope and was recovered by suction according to standard guidelines and as described earlier (14-16). In patients with diffuse pulmonary infiltrates or with solely mediastinal/hilar lymphadenopathy (BAL indicated to rule out endotracheal spread of disease and infection), BAL was performed either in the right middle lobe or the lingula. For patients with focal lesions, BAL was performed in corresponding pulmonary segment. The choice of further sampling techniques, combinations of endobronchial/transbronchial forceps biopsies, TBNA with or without endobronchial ultrasound (EBUS), and endobronchial/TBB was at the pulmonologist's discretion. Often multiple sites were sampled and multiple techniques used to obtain sufficient sample for subtyping, genotyping and staging when indicated. BAL was universally sent for bacteria culture, while evaluation for mycobacterium, fungus, and virus was performed when clinically indicated.

Statistical analysis

Statistical analyses were done with Stata version 12 (StataCorp LP, College Station, TX, USA). Group differences were examined using Chi-square test. We investigated possible demographic, clinical and radiographic predictive factors for BAL to detect primary LRTI in patients primarily suspected for lung malignancy. Univariate associations for the outcome (positive or negative primary infection) were investigated with logistic regression, adjusted for age. We included variables with $P \leq 0.20$ in multivariable analysis using backward elimination process. Variables with $P \leq 0.05$ (two tails) in multivariable analysis were retained in the final model.

Results

Demographics of included patients

From November 2009 to May 2013, 224 patients were included. *Figure 1* details the patient flow and diagnosis information.

Clinical characteristics of included patients are summarized in *Table 1*. Median age was 63 years (range, 19–94 years); 55.4% were male; 23.7% were current and

Table 2 Diagnosis information of malignant cases

Radiographic features of target lesions	Number of patients	Diagnostic yield of bronchoscopy for malignant cases[a]	Diagnostic yield of BAL for malignant cases[b]	Number of approaches adopted during bronchoscopy[c], mean ± SD (range)	Number of diagnostic procedural approaches[d], mean ± SD (range)	Percentage of diagnostic procedure[e]
Mediastinal and hilar lymphadenopathy only	26	93.30% (14/15)	0 (0/19)	2.2±0.8 [1–3]	0.9±0.3 (0–1)	0.5±0.3
Endobronchially visible central lesions	67	95.50% (63/66)	45.50% (25/55)	2.9±1.1 [1–6]	2.7±1.4 (0–6)	0.7±0.3
Peripheral consolidation	10	100% (6/6)	50.00% (3/6)	4.2±0.8 [3–5]	2.0±1.4 [1–4]	0.5±0.3
Peripheral mass (d ≥3 cm)	40	91.70% (33/36)	21.40% (6/28)	4.1±1.1 [2–6]	2.1±1.2 (0–5)	0.5±0.3
Peripheral nodule (2 cm ≤ d <3 cm)	27	76.90% (20/26)	15.80% (3/19)	3.6±1.4 [1–6]	1.4±1.1 (0–4)	0.5±0.3
Peripheral nodule (d <2 cm)	54	66.70% (20/30)	7.10% (2/28)	3.5±1.0 [1–5]	0.9±0.9 (0–4)	0.3±0.3
Total number count	224	87.15% (156/179)	25.16% (39/155)	3.5±1.3 [1–6]	1.6±1.2 (0–6)	0.5±0.3

[a], number of malignant cases diagnosed by index bronchoscopy divided by number of malignant cases diagnosed by index bronchoscopy and follow up; [b], number of malignant cases diagnosed by BAL cytology divided by number of malignant cases in which BAL cytology was undertaken; [c], adopted approaches indicate the following six sampling methods: BAL, endobronchial or transbronchial brushing, endobronchial forceps biopsy, transbronchial forcep biopsy, transbronchial needle aspirations of primary tumor, lymph node transbronchial needle aspirations; [d], number of procedural approaches that provided a positive cancer diagnosis; [e], percentage of diagnostic procedure: number of diagnostic procedural approaches divided by number of approaches adopted during bronchoscopy). Lower percentage shows relatively more approaches are needed to secure a positive diagnosis in corresponding lesion type. BAL, bronchoalveolar lavage; SD, standard deviation; d, diameter.

53.1% were former smokers. 63.4% had history of solid malignancy, and correspondingly 41.5% were referred for bronchoscopy because of positive follow-up imaging while remained asymptomatic.

Yield by BAL compared to overall bronchoscopy for diagnosis of malignancies

Among 224 patients, 156 were diagnosed as malignant on index bronchoscopy (*Table 1*), of which 85 were with NSCLC [51 adenocarcinomas, 29 squamous cell carcinomas, 5 non-small cell lung cancer-not otherwise specified (NSCLC-NOS)]; 13 were with small cell lung cancer (SCLC); 4 were with carcinoid; 50 were with metastasis from extra-thoracic cancers and 4 were with primary parenchymal lung lymphomas. Of the remaining 68 patients, 23 were diagnosed with malignancy on follow-up, giving an 87.2% (156/179) initial diagnostic yield for malignancy. 40 cases were confirmed as benign (*Figure 1*).

Patients were categorized into six groups based on chest radiographic features (*Table 2*). By BAL alone the diagnostic yields were 50% for peripheral consolidations, and were lower with smaller and more peripheral lesions, being 21.4% for masses >3 cm, and 7.1% for small peripheral nodules <2 cm. No cancer was diagnosed solely by BAL cytology. Combining all techniques, overall diagnostic yield for malignant lesions ranged from 66.7% (small nodules <2 cm) to 100% (peripheral consolidations). *Table 2* outlines the comprehensive tissue sampling strategy adopted.

BAL in the diagnosis of underlying or coexisting LRTI

All 224 patients had BAL for bacteria culture, of which 30 had primary LRTIs. One hundred seventy-three patients had BAL for mycobacteria culture, of which 5 were positive. Two hundred and five patients had BAL for fungal culture, of which 12 were primary infections. Seventy two patients had BAL for viral cultures or PCR test, none of which reported positive. Overall, 41 cases were classified as primary LRTIs, of which 33 were also diagnosed with a thoracic malignancy, 1 with concurrent sarcoidosis. *Table 3* lists the pathogens detected in LRTI patients.

Table 4 details the breakdown of patients by pre-test suspicion for infections and BAL culture results. Twenty patients (48.8% in the primary infection group) were proved with LRTI by BAL even without clinical indication

for infections. Proportions of patients with different infectious status do not differ significantly between patients with and without pre-test suspicion for infections (P=0.199), suggesting common practice to perform BAL culture in selected patients based on clinical suspicion could lead to underdiagnoses of infection.

Table 3 Pathogens in cases with BAL proved primary infections

Category, pathogen	Cases, n [%]
Bacterial infection (n=30)	
Pseudomonas aeruginosa	6 [20]
Moraxella catarrhalis	4 [13]
Escherichia coli	4 [13]
Haemophilus influenza	3 [10]
MRSA	3 [10]
Staphylococcus aureus	2 [7]
Streptococcus anginosus	2 [7]
Group C Streptococcus	1 [3]
Group G Streptococcus	1 [3]
Streptococcus pneumonia	1 [3]
Enterobacter cloacae	1 [3]
Nocardia Farcinica	1 [3]
Nocardia Nova	1 [3]
Mycobacterial infection (n=5)	
Mycobacterium avium intracellulare complex	3 [60]
Mycobacterium gordonae	1 [20]
Mycobacterium abscessus	1 [20]
Fungal infection (n=12)	
Aspergillus species	10 [83]
Cryptococcus neoformans	2 [17]

BAL, bronchoalveolar lavage; MRSA, methicillin-resistant Staphylococcus aureus.

Patients' risk factors for BAL to detect primary LRTI

We studied 23 demographic, clinical and radiographic variables as potential predictors for BAL to detect primary LRTI in this population with primary concern for thoracic malignancy. Age ≥75 years, coexisting chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM) and white blood cell count <4,000/mL were significantly associated with BAL proved primary LRTI by univariate analysis (*Table 5*). Since blood counts were missing in 39 patients during peri-procedure period, we couldn't include this parameter in multivariate model. Variables with P≤0.2 were retained for multivariable logistic regression, which indicated age ≥75 years, coexisting COPD or DM significantly increased the likelihood of BAL detected LRTI by 3.0 fold (OR 3.0; 95% CI: 1.29–7.06), 2.7 fold (adjusted OR 2.7; 95% CI: 1.14–6.26), and 4.5 fold (adjusted OR 4.5; 95% CI: 1.90–10.44), respectively. There was no significant association between primary infection and pulmonary symptoms, radiographic infiltration, concurrent systemic steroids/immunosuppressant therapy or recent chemotherapy in our study population.

Discussion

This study reevaluated a routinely adopted bronchoscopic approach in the context of comprehensive diagnostic strategy. We have shown that diagnostic yield of BAL for malignancy was highest at 50% (3/6) with cases presenting as peripheral consolidations, and decreased to the lowest 7.1% (2/28) in patients with small peripheral nodules (diameter <2 cm). Overall, diagnostic yields of BAL comprise only 10.6% (small peripheral nodules) to 50% (peripheral consolidations) of the cumulative bronchoscopy yields in our cohort, and no cancer was diagnosed solely

Table 4 Proportions of different Infection status in patients with or without pre-test suspicion of infection

Patient categorization based on BAL culture results	With pre-test suspicion for infection, n (%)	Without pretest suspicion for infection, n (%)	Pearson chi square test
Primary infection	21 (24.1)	20 (14.6)	P*=0.199
Possible infection/colonization	23 (26.4)	44 (32.1)	
Culture negative	44 (50.6)	72 (52.6)	
Total	88	136	

*, Pearson chi square test was applied to all three groups simultaneously. P>0.05 (we cannot reject the null hypothesis that there is no difference between the distribution among the three groups). BAL, bronchoalveolar lavage.

Table 5 Univariate and multivariate analysis of factors associated with BAL detected lower air tract infections

Parameters included in univariate regression	Primary infection by BAL (n=41), n (%)	Without primary infection by BAL (n=183), n (%)	Univariate regression			Multivariate regression		
			Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Age								
≥75 years old	15 (36.6)	25 (13.75)	3.7	1.70–7.82	0.001*	3.0	1.29–7.06	0.011*
Gender								
Male	21 (51.2)	103 (56.3)	0.8	0.42–1.68	0.62			
Smoking status								
Current	9 (22.0)	44 (24.0)	0.9	0.35–2.05	0.710			
Former	21 (51.2)	98 (53.6)	1.4	0.50–3.75	0.534			
Comorbidities								
COPD	13 (31.7)	27 (14.8)	2.5	1.12–5.56	0.025*	2.7	1.14–6.26	0.023*
DM	15 (36.6)	22 (12.0)	4.1	1.84–9.20	0.001*	4.5	1.90–10.44	0.001*
CHF	2 (4.9)	5 (2.7)	1.2	0.22–6.81	0.220			
CKD	3 (7.3)	6 (3.3)	2.4	0.54–10.25	0.255			
Neural deficit	3 (7.3)	4 (2.2)	2.8	0.58–13.86	0.198			
Active cancer in previous 5 years	22 (53.7)	95 (51.9)	1.2	0.22–6.81	1.826			
Pneumonia in recent 3 months	4 (9.8)	11 (6.0)	1.3	0.39–4.60	0.645			
Medication/treatment								
Systemic steroids	5 (12.2)	17 (9.3)	1.2	0.41–3.61	0.724			
Immunosuppressant	4 (9.8)	8 (4.4)	2.2	0.60–7.92	0.235			
Chemotherapy[§]	13 (31.7)	46 (25.1)	1.4	0.67–3.02	0.363			
Radiation therapy[§]	7 (17.1)	12 (6.6)	2.7	0.97–7.62	0.058			
Pulmonary infiltration/consolidation	21 (51.2)	74 (40.4)	1.6	0.78–3.14	0.206			
Pulmonary symptoms								
Cough	19 (46.3)	81 (44.3)	1.1	0.52–2.11	0.887			
Purulent secretion	3 (7.3)	13 ((7.1)	1.0	0.27–3.92	0.961			
Hemoptysis	6 (14.6)	15 (8.2)	1.7	0.60–4.87	1.010			
Dyspnea	4 (9.8)	40 (21.9)	0.4	0.14–1.32	0.144			
Chest pain	7 (17.1)	15 (8.2)	2.0	0.74–5.48	0.168			
Lab results[†]								
WBC <4,000/mL	5 (15.2)	7 (4.6)	4.1	1.06–15.55	0.041*			
WBC >10,000/mL	10 (30.3)	41 (27.0)	1.1	0.44–2.76	0.827			
Lymphocyte <1,000/mL	8 (25.0)	40 (28.2)	1.0	0.39–2.36	0.917			
Hemoglobin <10g/L	6 (18.2)	12 (7.9)	2.9	0.88–9.24	0.081			

*, risk factors show significant association; [†], WBC and hemoglobin counts were available in 185 patients; lymphocyte counts were available in 174 patients. Because of missing data, blood counts couldn't be included in the multiple regression analysis; [§], chemotherapy and radiation therapy in previous one year. For inclusion of univariate variables, the author panel made decision based on common understanding of pulmonary infection, clinical experience and previous publications regarding risk factors for lower airway track infection (12-14). BAL, bronchoalveolar lavage; CHF, chronic heart failure; CKD, chronic kidney disease; WBC, white blood cell.

by BAL cytology. We also showed that BAL identified potentially dangerous yet treatable infections in patients primarily suspected for thoracic malignancy (18.3% in our cohort), and 48.8% of those would have been missed if BAL culture had only been performed based on clinical suspicion for infections. Taken together, our results advocate not depending on BAL cytology for cancer diagnosis while lowering the threshold for BAL culture in patients primarily suspected for thoracic malignancy. Considering the large number of patients that would require bronchoscopies for cancer evaluation, this modification could have significant practical implications in terms of diagnostic accuracy, cost and efficiency.

BAL is currently a routine practice in bronchoscopic evaluation for patients with suspected thoracic malignancies largely because previous studies proved it as a useful tool in diagnosing peripheral lesions (17). However, three ongoing changes prompted us to make a new evaluation. Firstly, smaller and more peripheral lesions are more often presented for bronchoscopic evaluation, for which our study showed BAL is the least helpful. With major organizations recommending screening with yearly low-dose CT for selected high-risk current and former smokers (18-22), more positive screening would need diagnostic assessment. Also, routine image follow-up for an enlarging cancer survivor population would pick up more asymptomatic, hence much smaller lesions. 41.5% of our included patients were referred due to positive image results reflected this trend. Secondly, shifting therapeutic paradigm for lung cancer and other malignancies would require adequate tissue samples to support cancer subtyping, genotyping and staging. A positive cytology from BAL alone would fall short on these requirements, making personalized targeted treatment impossible. Thirdly, the above challenges are coupled with advances in bronchoscopy instruments and image-guiding interventions. Planar and CT-fluoroscopy (23), EBUS (24-26) and virtual bronchoscopic navigation (27-29) have improved targeting for endoscopically non-visible lesions. Current NCCN guideline recommends radial EBUS or navigational bronchoscopy as the preferred biopsy approach for peripheral lesions (5,30). Once directed to a target lesion, TBLBx and TBNA are expected to play a more important role since they would garner larger amount of tissue. BAL is generally safe but is not without risks. BAL has a reported complication rate of 0–49%, depending on how the complications were defined, and deaths associated with BAL have been reported (31-34). The main complications associated with BAL are desaturation, a drop in FEV_1 and hemorrhage.

The diagnostic yield of BAL in our study appears lower than that in previous reports. Poletti *et al.* reported a 76% diagnostic yield of BAL for overall malignant cases (35). However, previous studies tend to include patients with more diffuse lesions and more advanced diseases (27.2% with bronchoalveolar carcinoma type, 42.6% with carcinomatous lymphangitis and 13.6% with hematogenous metastatic disease). Our diagnostic yields of the overall bronchoscopies are comparable with studies adopting guided bronchoscopies (66.7–94.7% for peripheral lesions >2 cm, and 18.2–77.8% for lesions ≤2 cm) (29,36-39), and contrasted with those from non-guided bronchoscopies (Baaklini *et al.* reported diagnostic yields of 14% and 31% for lesions ≤2 cm when located in the peripheral one third *vs.* the inner two thirds of the lung) (40). Hence our results remain representative of current practice of guided bronchoscopy.

In our study, the percentage of NSCLC-NOS among NSCLC is 5.9%, which is much lower compared to around 20% reported in recent series (41,42). Overall survival for NSCLC-NOS patients was lowest among patients with NSCLC, and it has been shown that relying on cytology alone were associated with higher risk for a diagnosis of NSCLC-NOS (41). We attribute our low NSCLC-NOS proportion to the consistent adoption of comprehensive sampling strategy.

Co-infection in patients with bronchogenic carcinoma are common (43-46), yet there is no consensus as to where to set the threshold for BAL culture. Practice varies between institutions and physicians and is largely based on clinical suspicion. We found 18.3% patients had BAL proved LRTI even the primary suspicion were malignancy. Notably clinical suspicion doesn't effectively separate patients with and without primary LRTI. Further investigation of the pathogens suggests these would cause severe outcomes if untreated, especially for patients who would be immunosuppressed from cancer treatment. It's not safe to restrain BAL culture only in patients with clinical suspicion for infections, which is unfortunately a common practice.

We showed that age ≥75, coexisting COPD or DM were associated with significantly increased BAL proven LRTI. Reasoning would suggest factors like recent chemotherapy, consolidation on image should be risk factors for pulmonary infection. The fact that those variables didn't show significant association reflects our selection of study population, which excluded patients whose primary

concerns were infectious etiology only.

Our study had several limitations. Bronchoscopies in this study were performed by experienced interventional pulmonologists with assistance of appropriate imaging guiding; this could represent a higher standard of performance than average bronchoscopy services. However, the fact that the diagnostic yield could be achieved consistently and falls in the previously reported range indicate that the comprehensive sampling approach could be repeated and would do patients great benefit by avoiding repetitive procedures and reducing risks of being labelled as NSCLC-NOS. We did not study how the BAL cultures have influenced clinical care for included patients, since the majority of which were treated on outpatient basis by different physicians. Whether BAL-directed anti-microbial therapy would be beneficial remains to be explored.

When new techniques are increasingly integrated into routine diagnostic workup, the decision to discard or modify the traditional technique should be based on solid evidence to avoid any loss of marginal benefit while keeping the biopsy process in streamline. Based on our analysis, we conclude that BAL cytology do not have additional diagnostic benefit for malignancy when adopting a comprehensive bronchoscopy approach. Excluding infection is a more important application for BAL in patients with suspected thoracic malignancy, and it's not safe to restrain BAL culture only in patients with pre-test suspicion for infection. We recommend lowering the threshold for BAL culture while integrating risk factors such as age, coexisting COPD and DM.

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Footnote

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