International Journal of Medical Arts 2020; 2 [3]: 631-638

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main subject [Medicine [Pulmonology]] *

Original article

Diagnosis of Peripherally Located Bronchogenic Carcinoma: Utility of Non-Guided Flexible Bronchoscopy

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Received at: April 27, 2020; Revised at: June 08, 2020; Accepted at: June 08, 2020; Available online at: June 08, 2020

DOI: 10.21608/ijma.2020.28841.1120

ABSTRACT

Background: The role of flexible bronchoscopy in diagnosis of peripheral pulmonary neoplasia remains controversial.

Aim of the work: To assess the diagnostic yield of non-guided flexible bronchoscopy biopsy techniques in diagnosis of peripherally located bronchogenic carcinoma.

Patients and Methods: This cross-sectional study was conducted on 49 out of 85 patients with confirmed bronchogenic carcinoma; they were subjected to flexible bronchoscopy forceps biopsy [FB], bronchoalveolar lavage [BAL], transbronchial needle aspiration [TBNA], and bronchial brushing [BB].

Results: Diagnostic yield of bronchoscopy was positive in 40.8%. The procedures were; BAL in 26.5% of patients with positive yield in 15.0%, FB in 18.4% of patients with positive yield in 70.0%, TBNA in 26.5% of patients with no positive yield [0.0%] and BB in 18.4% of patients with positive yield in 15.0%. More than ≥6 Biopsy were taken in 79.6% and < 6 biopsies was taken in 20.4%. Lesions in the lower lobes had a high diagnostic yield [60.0%] [P0.007]. Lesions > 3cm had a diagnostic yield of 70% compared to 30 % in lesions ≤ 3 cm [P 0.001]. Cases with CT-Bronchus sign had a higher diagnostic yield [85.0%] [p 0.003]. Also, ≥ 6 Biopsy had higher diagnostic yield than those with lesions < 3cm [100.0% and 34.5% respectively] [P 0.003]. The presence of bronchial lesions and its lobar locations had higher diagnostic yield.

Conclusion: The diagnostic yield of bronchoscopy in peripherally locating bronchogenic carcinoma depends on a several factors, including lower lobe location, lesion size≥ 3cm, presence of CT bronchus sign, presence of bronchial lesion, and ≥ 6 biopsies.

Keywords: Non-guided; Flexible Bronchoscopy; Peripheral; Bronchogenic Carcinoma; Diagnostic Yield.

Please cite this article as: Elsawy SB. Diagnosis of Peripherally Located Bronchogenic Carcinoma: Utility of Non-Guided Flexible Bronchoscopy. JMA 2020; 2[3]: 631-638.

* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

The diagnosis of peripherally located lung lesions in patients thought of having lung cancer remains a challenge. The data on bronchoscopic sampling for suspected peripheral bronchogenic carcinoma is also dated with only 4 of 34 studies published after the year 2000. Fiberoptic bronchoscopy is a minimally invasive procedure with a high diagnostic yield[1].

It is probably the most important single technique in lung cancer diagnosis; therefore, a key objective should be maximizing the diagnostic yield of fiberoptic bronchoscopy [FOB][2].

Different conventional diagnostic techniques such as forceps biopsy [FB], bronchial washing [BW], bronchial brushing [BB], and transbronchial needle aspiration [TBNA] are employed during FOB. The overall diagnostic sensitivity of conventional bronchoscopic lung biopsy in peripherally located lesions is approximately 57% [3].

The diagnostic yield of bronchoscopy for peripheral lesions depends on a number of factors, including lesion size, the distance of the lesion from the hilum and on the relationship between the lesion and bronchus. The yield of bronchoscopy for lesions <3 cm varies from 14–50% compared with a diagnostic yield of 46–80% when the lesion is ≥ 3 cm. Combination of bronchial wash, brushes, transbronchial biopsy and TBNA are usually sampling methods for Peripheral lesions[4].

Visible lesions can present as an exophitic endobronchial mass, submucosal spread or a peribronchial tumor causing extrinsic compression while endobronchial involvement is frequently absent in many patients with bronchogenic carcinoma which assigned as bronchoscopically non-visible lesion[5].

When endobronchial tumor is visible the American Thoracic Society [ATS, 2013] guidelines recommended that at least 5 biopsy samples should be taken to maximize diagnostic yield and to allow for tumor phenotyping and genotyping. Additionally, in visible endobronchial tumor, BB and BW can increase the diagnostic yield of the procedure [6]. With the standard FOB [5.9 mm] the bronchoscopist can only get access to the 4-5th generation bronchi with visualization of the next 1-2 generations, covering only 1/3 of the approximately 23-generation bronchial tree. More over the majority of lesions visualized on CT-scan are therefore beyond direct bronchoscopic vision [7].

In malignant visible endobronchial tumors, the diagnostic yield of FOB is higher than peripheral non-visible tumors[8].

Despite of, many of the techniques are applied on a regular basis by bronchoscopists, a more sophisticated techniques, such as endobronchial ultrasound[9] and electromagnetic navigation bronchoscopy[10], can further increase the diagnostic yield, the identification of which technique or which combination of techniques that will offer the best and cost-effectiveness performance remains undetermined [11].

AIM OF THE WORK

Consequently, this study aimed to assess the diagnostic yield of non-guided flexible bronchoscopy biopsy techniques in diagnosis of peripherally located bronchogenic carcinoma.

PATIENTS AND METHODS

This cross-sectional study was conducted on 49 out of 85 patients with confirmed bronchogenic carcinoma, it was conducted at Chest Diseases Department, Al-Zahraa Hospital, Al-Azhar University, Cairo, Egypt, during the period from July 2016 till September 2019. All patients presented with clinical and plain chest X-ray [PCX-ray] and/or computed tomography [CT]-scan findings suspicious of bronchogenic carcinoma were evaluated for study participations [Figure 1].

Inclusion criteria

Inclusion criteria for this study were as follows: [1] all patients that had a prior CT thorax with radiological features suggestive of peripherally located bronchogenic carcinoma as reported by well experienced radiologists; [2] clinical history suspicious for malignancy such as history of smoking, presence of hemoptysis, or weight loss.

Exclusion criteria

Patients who had mediastinal adenopathy or centrally located bronchogenic carcinoma. As well as patients with severe bleeding tendencies and those in who FOB is absolutely contraindicated and/or prematurely terminated were excluded from the study.

Bronchoscopy technique

Conventional flexible bronchoscopy and all procedures were done by the author using a standard video bronchoscope and were performed via the transnasal route. Flexible FOB [FB 1T 160, Olympus; Tokyo, Japan], along with BB [BC-5C], FB [FB-15C], and TBNA [NA-411D-152] had a 6.0mm diameter and 2.8mm working channel. All cases were Premediated with 0.5 mg Atropine injected intramuscularly to decrease secretions 30 minutes before the procedure. The throat was anesthetized by spraying 5 times with 10% xylocaine [each spray contained 10mg xylocaine]. Then patients inhaled about 300mg of 2% xylocaine using nebulizer for anesthesia of the bronchial tree.

Additional small quantities of 1% xylocaine were instilled through FOB for topical bronchial anesthesia, as needed. Oxygen was administered by a nasal cannula and flows were adjusted upward from 2 L/minute to keep the oxygen saturation > 90%.

Patients were sedated with intravenous Midazolam [2.5-5mg] if not contraindicated.

According to bronchoscopic findings the lesions were categorized into either visible or non-visible. The visible lesions were categorized into two types [lobar or segmental] and the lobar bronchus locations of the lesion were also determined. Transbronchial forceps biopsy was performed for all cases in the targeted bronchopulmonary segment. Bronchial biopsy was performed by using reusable FB, whenever possible 4-6 biopsies were obtained from the centre of the most abnormal area, care was taken to avoid biopsied obvious necrotic area that could affect diagnostic yield.

The specimens were immediately fixed in 10% buffered formalin. Bronchoalveolar lavage [BAL] were obtained by aspiration of any secretion and instillation, followed by immediate aspiration of two aliquots of 20 ml of sterile isotonic saline solution [0.9%] at room temperature over the tumor or bronchial washing were also performed at the same sitting prior to the forceps biopsies.

Brushing by using a reusable sheathed brush, four-seven brushing specimens were taken from the surface of bronchoscopically-visible lesions and peripheral transbronchial needle aspiration were also done, usually, 3-5 specimens were obtained by to and from movement of the needle sheath through working channel of FOB. The TBNA and brushing specimens were immediately smeared on clean glass slides and immediately fixed with 95% ethanol for cytological examination.

In the data analysis, lesions were classified as >3cm or ≤ 3cm based on the largest dimensions of the pulmonary lesions on CT scans. CT-Bronchus sign was designated as positive if an airway was identified leading into the target lesion. An examination was considered complete if at least 3 adequate TBNA or FB specimens and 4 brushing specimens were taken.

A positive result for peripheral lung cancer was made if histology from tissue biopsy and/or BAL cytology showed the presence of malignancy. Patients with non-diagnostic results underwent further tissue sampling with alternative modalities such as CT or transthoracic ultrasound guided needle biopsy.

Ethical consideration

Ethical committee of Faculty of Medicine for Girls Al-Azhar University, Cairo, Egypt approved the study. Every participant provided his/her informed written consent before enrollment into the study. Each participant had the right to refuse participation or withdraw from the study at any point without affecting their rights in care. All the data were coded to ensure privacy.

Statistical analysis

Data were analyzed by the SPSS program version 17.0 [SPSS Inc. Chicago, USA]. The diagnostic yield of each modality was defined as the total number of patients in whom a diagnosis was obtained by this modality over the total number of patients examined.

The descriptive analysis was done for each item and the results were expressed as mean ± SD for quantitative variables, and as percentages for qualitative variables. The effect of each variable was evaluated in univariate analysis using the Chi-square [χ 2] test for categorical variables and student's t- test for continuous variables.

Multivariate logistic regression analysis was performed to identify factors predicting the diagnostic yield of each bronchoscopic sampling technique. The strength of relevance between the studied

factors and the positive yield was determined according to the value of the Beta regression coefficient [B], significance of Wald Chi-square test and the Odds ratio [Exp [B]] for each variable. Values of p< 0.05 [with a confidence limit at 95%] were considered significant.

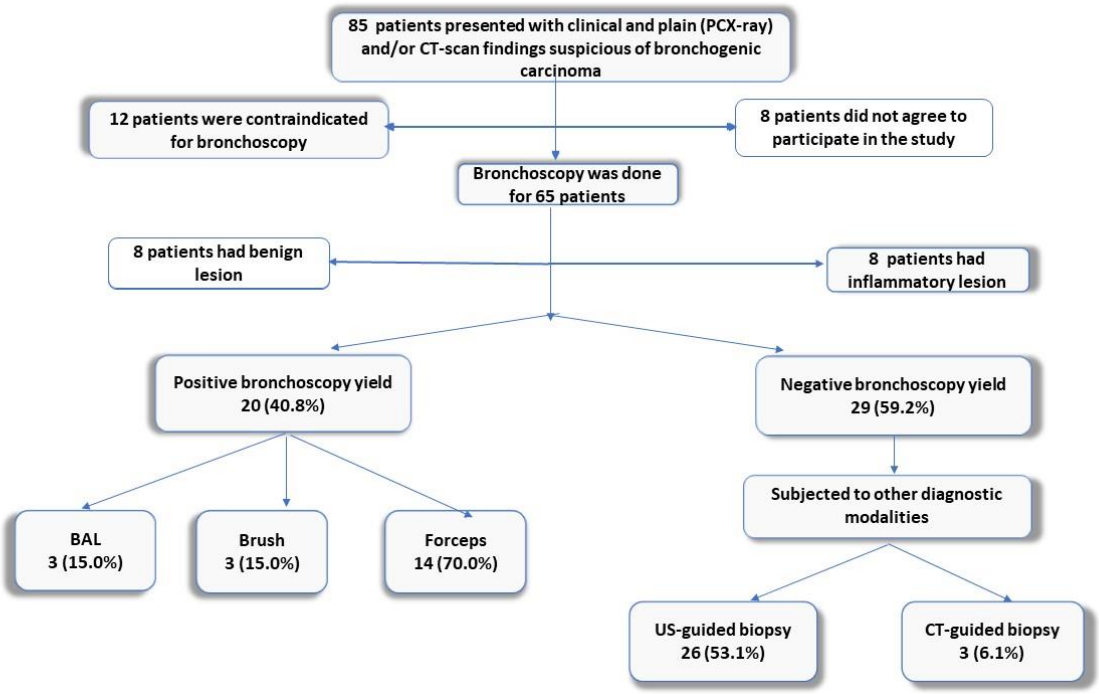

Figure [1]: Flowchart for patient's inclusion

RESULTS

A total of 49 patients met inclusion criteria and included in the study 73.5% were male and mean age was 56.96 years. Most lesions were in upper lobes 20 [40.8%]. As regard CT lesion size there was 27 55.1% lesion ≤ 3 cm and 4.9% lesion > 3 cm. Bronchus sites were segmental [44.9%], lobar [30.6%], while 24.5% had no visible lesion. The CT-Bronchus sign was identified in 55.1% patients. Diagnostic modalities other than bronchoscopy were US-guided biopsy [53.1%], CT-guided biopsy [6.1%]. Adenocarcinoma was the most common subtype of cancer [42.9%] followed by Squamous [32.7%], Large [16.3%] and SCLC [8.2%]. Repeated broncho-scopy was positive in 30.6%] patients [Table 1].

Bronchial lesions were detected in 36.7% of patients. Diagnostic yield of bronchoscopy was positive in 40.8% and negative in 59.2%. The bronchoscopic procedures done were as following; BAL in 26.5% of patients with positive yield in 15.0%, forceps in 18.4% of patients with positive yield in 70.0%, TBNA in 26.5% of patients with no positive yield [0.0%] and Bruch in 18.4% of patients with positive yield in 15.0%. Number of Biopsies ≥6 Biopsy were taken in 79.6% and < 6 biopsies were taken in 20.4% with mean ± SD [6.27 ± 1.11] [Table 2].

Lesions in the lower lobes had a high diagnostic yield [60.0%] [P0.007]. Lesions > 3cm had a diagnostic yield of 70% compared to 30 % in lesions ≤ 3 cm [P 0.001]. Cases with CT-Bronchus sign had a higher diagnostic yield [85.0%] [P 0.003]. Also, ≥ 6 Biopsy had higher diagnostic yield than those with lesions < 3cm [100.0% and 34.5% respectively] [P 0.003]. The presence of bronchial lesions and its lobar location had higher diagnostic yield [60.0%] [P0.005 and P 0.002 respectively] [Tables 3 and 4]. By logistic regression showed that CT bronchus sign, lesion size, presence of bronchial lesion, number of biopsies and lobar location were the predictor of positive bronchoscopy yield [B=2.37, 1.81, 1.73, 1.36, and 1.10 respectively] [Table 5].

Table [1]: Demographic, CT findings and types of bronchogenic carcinoma of the studied cases

Item		No. = 49
Age	Mean ± SD	56.96 ± 9.76
Sex	Male	36 [73.5%]
	Female	13 [26.5%]
Smoking Index	Median [IQR]	27 [0 - 40]
Lobar location	Upper lobes	20 [40.8%]
	Middle / lingula lobes	10 [20.4%]
	Lower lobes	19 [38.8%]
Lesion size	≤ 3 cm	27 [55.1%]
	> 3 cm	22 [44.9%]
CT bronchus Sign		27 [55.1%]
Bronchial lesions		18 [36.7%]
Type of cancer	SCLC	4 [8.2%]
	Squamous carcinoma	16 [32.7%]
	Adenocarcinoma	21 [42.9%]
	Large cell carcinoma	8 [16.3%]

CT: computed tomography, SCLC: Small cell lung cancer

Table [2]: Bronchoscopic findings and its diagnostic yield of the studied cases

Item		No. = 49
Bronchus site		
Lobar		15 [30.6%]
Segmental		22 [44.9%]
No visible lesion		12 [24.5%]
Performed bronchoscopic biopsies technique		
BAL		13 [26.5%]
Forceps		9 [18.4%]
TBNA		13 [26.5%]
Bruch		9 [18.4%]
Diagnostic bronchoscopic modalities		
BAL		3 [15.0%]
Brush		3 [15.0%]
TBNA		0 [0.0%]
Forceps		14 [70.0%]
Number of Biopsy	< 6 Biopsy	10 [20.4%]
	≥6 Biopsy	39 [79.6%]
	Mean ± SD	6.27 ± 1.11
Repeated bronchoscopy	Positive ; Negative	15 [30.6%]; 34 [69.4%]
Diagnostic yield of bronchoscopy	Positive yield; Negative yield	20 [40.8%]; 29 [59.2%]
Diagnostic Modalities	Bronchoscopy	20 [40.8%]
	US-guided biopsy	26 [53.1%]
	CT-guided biopsy	3 [6.1%]

BAL: Bronchoalveolar lavage. TBNA: Trans bronchial needle aspiration

Table [3]: Comparison of CT findings between cases with positive bronchoscopic yield and cases with negative bronchoscopic yield

Variables		Diagnostic yield of bronchoscope		Test value	P-Value
		Positive yield No. = 20	Negative yield No. = 29		
CT lobar location	Upper lobes	3 [15.0%]	17 [58.6%]	***9.79***	***0.007****
	Middle / lingula lobes	5 [25.0%]	5 [17.2%]		
	Lower lobes	12 [60.0%]	7 [24.1%]		
Lesion size	≤ 3cm	6 [30.0%]	21 [72.4%]	***8.60***	***0.003****
	> 3cm	14 [70.0%]	8 [27.6%]		
CT bronchus Sign	Positive	17[85.0%]	10 [34.5%]	***12.1***	***0.003****
	Negative	3 [15.0%]	19 [65.5%]		

Table [4]: Comparison of bronchoscopic findings, number of biopsies, and repeated bronchoscopy between cases with positive bronchoscopic yield and cases with negative bronchoscopic yield

Bronchoscopy		Diagnostic yield of bronchoscope		Test value	P-Value
		Positive yield No. [%]	Negative yield No. [%]		
Bronchial lesions	Positive	12 [60.0%]	6 [20.7%]	*7.8*	*0.005**
	Negative	8 [40.0%]	23 [79.3%]		
Bronchus site	Lobar	12 [60.0%]	3 [10.3%]	*16.2*	*0.002**
	Segmental	3 [15.0%]	19 [65.5%]		
	No visible lesion	5 [25.0%]	7 [24.1%]		
Number of Biopsy	< 6 Biopsy	0 [0.0%]	10 [34.5%]	*8.6*	*0.003**
	≥6 Biopsy	20 [100.0%]	19 [65.5%]		
	Mean ± SD	7.00 ± 0.79	5.76 ± 1.02	*4.5*	*0.005**
	Range	6.00 – 9.00	4.00 –8.00		
Repeated bronchoscopy	Positive	7 [35.0%]	8 [27.6%]	0.30	0.58
	Negative	13 [65.0%]	21 [72.4%]		

Table [5]: Logistic regression analysis for predictors of positive bronchoscopy yield

Variables	B	S.E.	Wald	P	Odds ratio [OR]	95% C.I. for OR	
						Lower	Upper
Lobar location	1.10	0.37	8.4	0.004	3.0	1.43	6.30
Lesion size	1.81	0.64	7.9	0.005	6.1	1.74	21.50
CT bronchus Sign	-2.37	0.73	10.3	0.001	0.09	0.022	0.39
Bronchial lesions	-1.74	0.64	7.3	0.007	0.17	0.049	0.61
Number of biopsy	1.36	0.40	11.3	0.001	3.8	1.76	8.60

DISUCSSION

The main finding of the current study is that the diagnostic yield of bronchoscopy in diagnosis of peripherally located bronchogenic carcinoma was 40.8%, which is lower than that reported by **De Roza et al.** [12] that is 72.0%. On the other hand, it was higher than that reported in other studies [13-15].

The bronchoscopic procedures performed in the present study were BAL [26.5%], with a diagnostic yield of 15.0%, forceps [18.4%] with 70.0% diagnostic yield, BB [18.4%] with 15.0% diagnostic yield, and TBNA [26.5%] with a no diagnostic yield at all. In the same circumstance **Govert et al.**[4] reported that cancer was diagnosed in 82.5% by TBNA, 73.7% by FB, and 63.2% by BAL. **Karahalli et al.**[16] reported that FB gave overall highest diagnostic yield [82.7%] followed by TBNA [68.6%], BB [68.4%], and BAL [31.6%].

In our study more than 6 biopsy were taken in 79.6% and < 6 biopsies were taken in 20.4%, with mean ± SD [6.27 ± 1.11]. Additionally, the higher the number of biopsies had taken the higher diagnostic yields of all bronchoscopic procedure apart from TBNA. Moreover, increasing the number of biopsies is a predictor of positive bronchoscopy yield [B=1.36]. This result is agreed with that of **Huang et al.**[14] who reported higher diagnostic accuracy with increasing number of biopsies, and as many as 10 biopsies may be needed for a maximal diagnostic yield, with no additional diagnostic yield of peripheral lesions until the fourth one**.** Other study done by **Lim et al.**[17] concluded that, performing washing after brushing during non-guided FB is a very safe, cost-effective procedure that may help improve the diagnostic yield and avoid additional invasive or expensive procedures in patients with suspected peripheral lung cancer.

The present study revealed that the presence of bronchial lesions and its lobar location had higher diagnostic yield [60.0%], and both of them were predictors of positive bronchoscopy yield. Lesions in the lower lobes had a high diagnostic yield [60.0%] when compared with other lobes. Moreover, lobar location is a predictor of positive bronchoscopy yield. Other studies reported higher diagnostic yield for lesions located in the middle lobe bronchus or lingula bronchus than other lobes bronchi[2]. Our result disagrees with **Hafez et al.**[18] as they reported significant higher yield of all used techniques for lesions located in either upper or lower lobes although lesions in the upper lobes are often technically difficult to access due to acute

angulations of the FOB needed to approach them. Also different results were reported by **Liam et al.**[13] who concluded that the diagnostic yields of all sampling techniques were not influenced by the location of the tumors; however, it is less likely in tumors located in the middle lobe or lingula. Moreover, **Das et al.**[19] reported that the diagnostic yield of the BAL was influenced by location.

Regarding CT findings, our study revealed that lesions size > 3cm had a diagnostic yield of [70%] [P 0.001], while presence of CT bronchus sign had a higher diagnostic yield [[85.0%]] Moreover, the bronchus sign and lesion size, are predictive of higher bronchoscopy yield [B=2.37, 1.81, respectively]. This higher diagnostic yield in larger lesion size and presence of bronchus sign may be easily tumor approachability offered by larger lesion and presence of bronchi leading to tumor, also it is known that 62.5% of tumors < 3cm were supplied by only one bronchus, while 60% of the tumors >3cm were supplied by ≥3 bronchi increase accessibility to tumor[14]. **De Roza et al.**[12] reported that lesions size and positive CT-Bronchus sign had a higher trend towards a better diagnostic sensitivity. This may be also explained by the fact that beyond a certain point [e.g. 3 cm], the sensitivity of bronchoscopy reaches a plateau, possibly because large lesions not visible via bronchoscope may be associated with necrotic neoplastic cells, post-obstructive pneumonia, and bronchial compression that could diminish bronchial aspiration, brushing, and BAL diagnostic yield.

These results supported by some investigators who reported that the diagnostic yield was higher if lesions are larger in size [15, 20-22]. Also, **Rivera et al.**[5] in a meta- analysis study concluded that the sensitivity for smaller lesions [<2cm] was 34% vs. 63% for larger lesions [>2cm]. Additionally, a positive CT scan Bronchus sign improves the overall yield of electromagnetic navigation bronchoscopy from 67% to 79% by multivariate analysis [23], accordingly, they recommended that, in patients with peripheral lung lesions that are difficult to reach with conventional bronchoscopy, electromagnetic navigation guidance is recommended if the equipment and the expertise are available.

In the current study bronchoscopy was repeated in 30.6 % of patients, however, it didn't increase diagnostic yield [P=0.58]. Diagnostic modalities other than bronchoscopy were US-guided biopsy 26 [53.1%], CT-guided biopsy 3 [6.1]. This was in agreement with **Hafez et al.**[24], as they showed that 60.4 % of patients were diagnosed by TUS-guided biopsy, 22.6 of patients were diagnosed via FB biopsy, and 17 % of patients were diagnosed via CT-guided biopsy. However, TUS guided biopsy was the first initial sampling procedures.

Histopathological examination revealed that adenocarcinoma was the most common subtype of cancer [42.9%] followed by Squamous [32.7%], large [16.3%] and SCLC 4[8.2%]. This is similar to the distribution of pathological classification of broncho-genic carcinoma in Egyptian patients reported by **Abu-Youssef et al.** [25]

Conclusion: The diagnostic yield of non-guided flexible bronchoscopy in the peripherally locating bronchogenic carcinoma depends on a several factors including lower lobe location, lesion size≥ 3cm, presence of CT bronchus sign, presence of bronchial lesion, and ≥ 6 biopsies. The results of this study are specific to bronchogenic carcinoma itself, and are not related to other pulmonary lesions. The main strength of this study is that it reflects the diagnostic value of bronchoscopy in a regular clinical practice in our country that has limited resources.

Financial and Non-Financial Relationships and Activities of Interest

None declared by the authors

REFERENCES

1. **Yung RC.** Tissue diagnosis of suspected lung cancer: selecting between bronchoscopy, transthoracic needle aspiration, and resectional biopsy. Respir Care Clin N Am. **2003**; 9:51-76 [DOI: 10.1016/S1078-5337 [02] 00083-7].

2. **Popovich J Jr, Kvale PA, Eichenhorn MS, Radke JR, Ohorodnik JM, Fine G.** Diagnostic accuracy of multiple biopsies from flexible fiberoptic bronchoscopy. A comparison of central versus peripheral carcinoma. Am Rev Respir Dis. **1982** May;125[5]:521-3. [DOI: 10.1164/ arrd.1982.125.5.521].

3. **Bugalho A, Ferreira D, Eberhardt R, Dias SS, Videira PA, Herth FJ, Carreiro L.** Diagnostic value of endobronchial and endoscopic ultrasound-guided fine needle aspiration for accessible lung cancer lesions after non-diagnostic conventional techniques: a prospective study. BMC Cancer. **2013**; 13:130. [DOI: 10.1186/1471-2407-13-130].

4. **Govert JA, Dodd LG, Kussin PS, Samuelson WM.** A prospective comparison of fiberoptic transbronchial needle aspiration and bronchial biopsy for broncho-

scopically visible lung carcinoma. Cancer. **1999** Jun 25; 87 [3]:129-34. [DOI: 10.1002/[sici]1097-0142 [19990 625] 87:3<129::aid-cncr5>3.0.co;2-g].

5. **Rivera MP, Detterbeck F, Mehta AC.** Diagnosis of Lung Cancer. The Guidelines. Chest **2003**; 123:129S–136S. [DOI: 10.1378/chest.123.1_suppl.129s]

6. **Rand A, Blaikley J, Booton R, Chaudhuri N, Gupta V, Khalid S, et al.** British Thoracic Society guideline for diagnostic flexible broncho-scopy in adults**.** Thorax **2013**; 68: i1–i44. [DOI: 10.1136/ thoraxjnl-2013-203618].

7. **Leong S, Shaipanich T, Stephen Lam S, Yasufuku K.** Diagnostic bronchoscopy current and future perspectives. J Thorac Dis 2013; 5[S5]: S498-S510. [DOI: 10.3978/ j.issn. 2072- 1439.2013.09.08].

8. **Shah PL, Singh S, Bower M, Livni N, Padley S, Nicholson AG.** The role of transbronchial fine needle aspiration in an integrated care pathway for the assessment of patients with suspected lung cancer. J Thorac Oncol **2006**;1: 324–327. [DOI 1556-0864/ 06/0104-0324].

9. **Herth FJ, Eberhardt R, Vilmann P, Ernst A.** Real-time endobronchial ultrasound guided trans-bronchial needle aspiration for sampling mediastinal lymph nodes. Thorax **2006**; 61: 795–798. [DOI: 10.1136/thx. 2005. 047829]

10. **Gildea TR, Mazzone PJ, Karnak D, Meziane M, Mehta AC.** Electromagnetic navigation diagnostic broncho-scopy: a prospective study. Am J Respir Crit Care Med. **2006**; 174: 982–989. [DOI: 10.1164/rccm. 200603-344OC].

11. **Hergott CA, Trembly A.** Role of bronchoscopy in the evaluation of solitary pulmonary nodules. Clin Chest Med. **2010**; 31[1]:49-63. [DOI: 10.1016/ j.ccm. 2009. 08.003].

12. **De Roza MA, Quah KH, Tay CK, Toh W, Li H, Kalyanasundaram G, Anantham D.** Diagnosis of peripheral lung lesions via conventional flexible bronchoscopy with multiplanar CT planning. Pulm Med. **2016**; 2016:5048961. [DOI: 10.1155/2016/5048961].

13. **Liam C K, Pang Y K, Poosparajah S.** Diagnostic yield of flexible bronchoscopic procedures in lung cancer patients according to tumor location. Singapore Med J. **2007;** 48 [7]: 625.

14. **Huang H, Yu-Chin L, Reury-Perng P.** The factors affecting the diagnostic yield of fiberoptic bronchoscopy in evaluating peripheral solitary pulmonary nodules or masses. Tzu Chi Med J, **2007**; 19: 21-27.

15. **Baaklini WA, Reinoso MA, Gorin AB, Sharafkanch A, Manian P.** Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. Chest **2000**; 117: 1049-1054. [DOI: 10.1378/chest.117.4.1049].

16. **Karahalli E, Yilmaz A, Türker H, Ozvaran K.** Usefulness of various diagnostic techniques during fiberoptic bronchoscopy for endoscopically visible lung cancer: should cytologic examinations be performed routinely? Respiration **2001**; 68[6]:611-4. [DOI: 10.1159/ 00005 0581].

17. **Lim JH, Kim MJ, Jeon SH, Park MH, Kim WY, Lee M, et al.** The optimal sequence of bronchial brushing and washing for diagnosing peripheral lung cancer using non-guided flexible bronchoscopy. Sci Rep. **2020** Jan 23;10[1]:1036. [DOI: 10.1038/s41598-020-58010-w].

18. **Hafez MR, Abo-Elkheir OI, Elsheikh RM.** Predictive factors for positive yield of conventional diagnostic techniques through video-assisted flexible broncho-scope in diagnosis of bronchogenic carcinoma. AAMJ **2015;** 13[2]: 151-162.

19. **Das SK, Das A, Saha SK, Biswas S.** Diagnostic yield of bronchoalveolar lavage fluid and post bronchoscopic sputum cytology in endoscopically non-visible lung cancers. J Indian Med Assoc. **2011** Oct; 109[10]:730-741. [PMID: 22482319].

20. **Labbé C, Beaudoin S, Martel S, Delage A, Joubert P, Drapeau C, Provencher S.** Diagnostic yield of non-guided flexible bronchoscopy for peripheral pulmonary neoplasia. Thoracic Cancer 6 [2015] 517–523. [DOI: 10.1111/1759-7714.12223

21. **Roth K, Hardie JA Andreassen AH Leh F, Eagan TML.** Predictors of diagnostic yield in bronchoscopy: a retrospective cohort study comparing different combinations of sampling techniques. BMC Pulm Med. **2008**, 8:2 [DOI:10.1186/1471-2466-8-2].

22. **Slade MG, Rahman NM, Stanton AE, Curry L, Slade GC, Clelland CA, Gleeson FV.** Improving standards in flexible bronchoscopy for lung cancer. Eur Respir J. **2011**; 37: 895–901. [DOI: 10.1183/09031936. 0009 7110].

23. **Seijo LM, de Torres JP, Lozano MD, Bastarrika G, Alcaide AB, Lacunza MM, Zulueta JJ.** Diagnostic yield of electromagnetic navigation bronchoscopy is highly dependent on the presence of a Bronchus sign on CT imaging: results from a prospective study. Chest. **2010**; 138 [6]:1316-21. [DOI: 10.1378/chest.09-2708].

24. **Hafez MR, Sobh ES, Elsawy SB, Abo-Elkheir OI.** The usefulness of thoracic ultrasonography in diagnosis and staging of bronchogenic carcinoma. Ultrasound. **2017** Nov; 25[4]:200-212. [DOI: 10. /1742271X 17721 264].

25. **Abu-Youssef HA, Kamel KM, Selim S, Gamal El-Deen SM.** Study of the added value of transthoracic ultrasound in staging of lung cancer. Egyptian J Chest Dis Tuberculosis **2014;** 63 [4]: 10-25 [DOI: 10. 1016/j.ejcdt.2014.04.004].