Original Article

Patterns of diagnostic procedures for lung cancer pathology in the Middle East and North Africa

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Background: Accurate pathological diagnosis is the first critical step in the management of lung cancer. This step is important to determine the histological subtype of the cancer and to identify any actionable targets. Our study aimed at evaluating the patterns of procedures used to obtain pathological diagnosis of lung cancer in the Middle East and North Africa (MENA) Region.

Methods: Data of consecutive patients with the diagnosis of non-small cell lung cancer (NSCLC) were collected from participating centers from different countries in the MENA Region. Methods of obtaining tissue diagnosis and workup were analyzed to determine the practice patterns of obtaining tissue diagnosis of lung cancer.

Results: A total of 566 patients were recruited from 10 centers in 5 countries including Saudi Arabia, United Arab Emirates (UAE), Qatar, Lebanon and Algeria. Majority of patients were males (78.1%) with a median age of 61 years (range, 22–89 years). Obtaining tissue diagnosis was successful in the first attempt in 72.3% of patients, while 16.4% and 6.3% of patients required 2nd and 3rd attempt, respectively. The success in first attempt was as follows: image guided biopsy (91%), surgical biopsy (88%), endobronchial biopsy (79%) and cytology (30%). The success in the second attempt was as follows; surgical biopsy (100%), image guided biopsy (95%), endobronchial biopsy (65%), cytology (25%).

Conclusions: More than quarter of the patients required repeated biopsy in the MENA Region. Image guided biopsy has the highest initial yield. Implementing clear process and multidisciplinary guidelines about the selection of diagnostic procedures is needed.

Keywords: Lung cancer; pathology; diagnostic procedures; work-up

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Introduction

Lung cancer is the leading cause of cancer death in the world. In the Middle East and North Africa (MENA) region, lung cancer is a major health problem and ranked in the top cancer sites in many countries in the region (1,2).

Establishing accurate pathological diagnosis is the first step of the proper management of lung cancer. This diagnosis is important for the disease management especially the selection of systemic therapy in the metastatic setting.

Knowing the histology subtype of non-small cell lung cancer is still relevant and the first step to avoid harmful treatment, such as the use of bevacizumab in squamous cell cancer, or the use of less effective treatment, such as pemetrexed in squamous histology subtype (3). This requires performing immunohistochemistry for markers to differentiate squamous form non-squamous (TTF, Napsin, P63) (4).

Furthermore, each major subtype of lung cancer harbors different actionable mutations with most of them present in non-squamous histology. This will dictate further laboratory workup based on prevailing practice (5). Staining for PDL1 has become recently a requirement to determine if the patient is candidate for first line immune therapy treatment (6). Another important utilization of the biopsy in the early phase of the patient management is staging by documenting the involvement of lymph node or an organ that may upstage the disease.

In summary, the biopsy must be adequate by having enough tissue material to discern the subtype of lung cancer and enable performing molecular studies to identify actionable targets. Therefore, selecting the type of the procedure to obtain the initial biopsy is critical to confirm diagnosis early on and avoid repeating biopsy with increasing risk of complications and delay of treatment initiation. Many procedures that are commonly used in diagnosing lung cancer includes: fiberoptic bronchoscopy with or without transbronchial needle aspiration (TBNA), endobronchial ultrasonography (EBUS), image guided transthoracic needle aspiration, mediastinoscopy, pleural fluid analysis (thoracentesis) and thoracoscopy, and surgical approaches (7).

The selection of the procedure depends on the patient condition, disease status and available expertise and equipment (8). Nevertheless, whatever is the approach used, if the biopsy is not adequate as mentioned earlier, repeating the biopsy will be indicated using similar or different approach. Therefore, the team managing lung cancer patients at the diagnosis phase should be familiar with the yield of each technique and associated risks-benefits.

In this manuscript, we are reporting the initial work-up approaches to obtain tissue diagnosis for lung cancer in the Middle East and North Africa Region.

Methods

Study design

Data of consecutive patients with non-small cell lung cancer were collected retrospectively from participating centers in different countries in the MENA Region. Methods of obtaining tissue and workup were analyzed to determine the yield of each methods and challenges encountered.

Ten centers from 5 countries participated in the study namely: Saudi Arabia (3 centers), United Arab Emirates (1 center), Qatar (1 center), Lebanon (1 center) and Algeria (4 centers).

Sample size

All consecutive NSCLC cases during the study period of January 2013 to January 2014 were included.

Ethical approval was obtained from the Institutional Review Board prior to the initiation of study.

Data acquired

A paper Clinical Research Form (CRF) was used to obtain the following data: demographic information such as age, gender, and ethnicity; information about procedures used to obtain biopsy, number of attempts, site of biopsy; information about the disease such as subtype and stage. Data were entered into excel file database then used for statistical analysis.

Statistical analysis

SAS v9.2 (SAS Institute, NC, USA) was used for statistical analysis.

Patient and disease characteristics, type of procedures were calculated as counts and proportion for categorical variables and continuous variables were reported as a mean and standard deviation. Percentage of patients who underwent one, two and three or more attempts were calculated with type of procedures. Chi-square tests used to

Table 1 Patients characteristics (N=566)

Characteristics	Value
Age (years), median [range]	61 [22–89]
Gender, n (%)	
Male	442 (78.09)
Female	114 (20.14)
Missing	10 (1.77)
Smoking	
Current	170 (30.04)
Former	113 (19.96)
Never	99 (17.49)
Missing/unknown	184 (32.51)
Nationality	
Algerian	306 (54.06)
Saudi	118 (20.85)
Lebanese	43 (7.60)
Emirati	19 (3.36)
Qataris	9 (1.59)
Others*	37 (6.54)
Missing	34 (6.01)
Number of attempts	
One attempt	409 (72.26)
Two attempts	92 (16.25)
Three attempts and more	36 (6.36)
Missing	29 (5.12)
Site of first biopsy	
Lung	468 (82.69)
Pleura	23 (4.06)
Brain	6 (1.06)
Bone	8 (1.41)
Liver	4 (0.71)
Other**	30 (5.30)
Missing	27 (4.77)

*, others include: Pakistani, Pilipino, Indian, American, and British; **, others include lymph node, supraclavicular LN, mediastinal LN, spine, skin, hepatic mass and adrenal gland.

evaluate any correlation between certain demographic and clinical features and the number of biopsy attempts.

Results

566 patients were included in the study, majority were males (78.09%) with a median age of 61 years (range, 22–89 years) (*Table 1*). Majority of the cases were diagnosed with first attempt (72.26%), however, 16.25% required two attempts and 6.36% required three or more attempts. Lung was the most common site for first biopsy (*Table 1*).

Data on methods of obtaining tissue and the yield in each attempt is depicted in *Table 2*.

The success in first attempt was attained in 72% of the patients as follows: image guided core biopsy (91%), surgical biopsy (88%), endobronchial biopsy (79%), and cytology (30%). The success in second attempt was as follows: surgical biopsy (100%), image guided core biopsy (95%), endobronchial biopsy (65%), cytology (55%) (*Table 2*).

Stage IV (27.1% *vs.* 13.0% in stage I to III, P=0.003) was the only predictor of increasing number of attempts in univariate analysis (*Table 3*).

Discussion

Our study showed that majority of lung cancer cases are diagnosed from the first attempt, but fraction of the patient requires repeated attempt of biopsy using different approaches. The best yield is with image guided biopsy and the least is in cytology which consistent with the literature (9). The yield of our initial biopsy was similar to the reports in the literature with repeat rate varies based on the procedures used (10-13).

The need to repeat the biopsy was more common in stage 4 than earlier stages which can be due to the use of better diagnostic approached such as image guided biopsy or surgery in earlier stages and the use of cytology in the advanced stages.

There are different approaches to improve the yield of the biopsy and avoid delay in diagnoses and increase risk of complications (*Table 4*). Involvement of multidisciplinary team (MDT) in the decision making to choose the best approach and site of biopsy is a must nowadays. The team should include interventional radiologist, interventional pulmonologist or gastroenterologist to be able to access hard to reach lesions or lymph nodes. The team should

Table 2 Type of procedures performed at each attempt

Procedure	1st attempt (n=566)	Required 2nd attempt	Type of specimen	Required 3rd attempt	Type of specimen
Cytology	89 (15.7%)	Yes 62 (70%); no 27 (30%)	Cytology: 19 (31%)	Yes: 7 (37%); no: 12 (63%)	Cytology 3 (42%); image 2 (29%); surgical 2 (29%)
			Endobronchial: 26 (42%)	Yes: 12 (46%); no: 14 (54%)	Cytology 6 (50%); image 5 (42%); surgical 1 (8%)
			Image: 17 (27%)	Yes: 0 (0%); no: 17 (100%)	
			Surgical: 0 (0%)		
Endobronchial biopsy	173 (30.6%)	Yes: 36 (21%); no: 137 (79%)	Cytology: 11 (28%)	Yes: 7 (64%); no: 4 (36%)	Cytology 3 (43%); image 4 (57%)
			Endobronchial: 2 (6%)	Yes: 0 (0%); no: 2 (100%)	
			Image: 14 (39%)	Yes: 2 (14%); no: 12 (86%)	Surgical 2 (100%)
			Surgical 9 (25%)	Yes: 0 (0%); no: 9 (100%)	
Image guided core biopsy	197 (34.8%)	Yes: 17 (9%); no: 180 (91%)	Cytology: 2 (12%)	Yes: 0 (0%); no: 2 (100%)	
			Endobronchial: 5 (29%)	Yes: 0 (0%); no: 5 (100%)	
			Image 4 (29%)	Yes: 2 (50%); no: 2 (50%)	Image 2 (100%)
			Surgical 5 (29%)	Yes: 0 (0%); no: 5 (100%)	
Surgical Biopsy	100 (17.7%)	Yes: 12 (12%); no: 88 (88%)	Cytology 6 (50%)	Yes: 3 (50%); no: 3 (50%)	Cytology: 3 (100%)
			Endobronchial: 4 (33%)	Yes: 1 (25%); no: 3 (75%)	Cytology: 1 (100%)
			Image: 2 (17%)	Yes: 0 (0%); no: 2 (100%)	
			Surgical: 0 (0%)	0	

select the procedure based on the highest possible yield balanced with associated risk (14). Our study did not evaluate the involvement of MDT in the decision making. It is known that multidisciplinary team approaches need to be enhanced in our region to improve patient care (15-17).

Our study did not evaluate definite reason for the inadequate biopsy and how the decision was made in the first place to select the procedure, but we recommend each center to perform root cause analysis for failures and implement intervention to reduce the rate of re-biopsy. This should be part of quality assurance plan for the whole process. *Table 4* highlights some of these approaches. Incorporating these approaches into practice may require resources and expertise to be addressed individually as one-size-fits-all recommendations will not work.

Other methods to enhance the yield of the biopsy is implementing evidence-based guidelines adapted to the local setting (18).

The use of PET scan may help identify the active disease from collapsed normal lung tissue or benign lesions, or may detect more accessible lesion that was not described with other imaging modalities (19-21).

As reported earlier on our study population, molecular studies were not performed due to inadequate specimen in 11.6% of the patients (22). Therefore, having a tissue management plan and use the more advanced techniques such as NextGen Sequencing (NGS) will help conserve tissue from small specimens (23). After confirming diagnosis of lung cancer, molecular studies can be done on liquid biopsy and avoid the need of re-biopsy in certain cases (24).

Having Rapid On-Site-Evaluation (ROSE) will determine at procedure site if adequate tissue is obtained to avoid redoing the biopsy (25,26).

Conclusions

In conclusion, selecting the initial procedure to obtain tissue diagnosis should be done carefully and proper pathological workup should minimize the need for exposing the patients for re-biopsy.

Table 3 Demographic and clinical characteristics in relation to the number of biopsy attempts

Characteristics	Overall	One attempt	Two attempts or more	P value
Gender				0.128
Male	442 (79.5)	329 (77.8)	94 (22.2)	
Female	114 (20.5)	75 (70.8)	31 (29.2)	
Overall stage				0.003*
I, II, III	113 (23.4)	94 (87.0)	14 (13.0)	
IV	370 (76.6)	256 (72.9)	95 (27.1)	
Regions				0.960
Gulf	146 (27.8)	107 (75.4)	35 (24.6)	
Non-gulf	380 (72.2)	272 (75.1)	90 (24.9)	
Smoking history				
Non-smokers	212 (55.5)	147 (72.4)	56 (27.6)	0.696
Smokers	170 (44.5)	121 (74.2)	42 (25.8)	
Site from which biopsy was taken				0.111
Lung	468 (82.7)	343 (76.9)	103 (23.1)	
Others	71 (12.5)	45 (68.2)	21 (31.8)	

*, the Chi-square statistic is significant at the 0.05 level.

Table 4 Approaches to enhance the yield of the biopsy and reduce the need for repeated biopsy

Approach	Benefits
Multidisciplinary team discussion	Determine best procedure and lesion to be taken
Adapt clinical practice guidelines	To create standard approach for common scenarios
Use of PET scan	Identify the best accessible active lesion
Tissue management plan	Proper utilization of specimen and efficient processing to minimize the use of tissue for IHC
Use of next gene sequencing	To conserve tissue especially with small specimens
Use of liquid biopsy	If histology subtype confirms but no adequate tissue for molecular studies
Rapid On-site Evaluation (ROSE)	To determine while the procedure is done if the biopsy is adequate
Quality assurance	To evaluate the reasons for inadequate biopsy and put plans to address them

PET, positron emission tomography.

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Footnote

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