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ROLE OF INVASIVE TECHNIQUES IN TISSUE DIAGNOSIS OF MEDIASTINAL MASSES

By

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ABSTRACT

Background: Mediastinal masses are an uncommon abnormalities found in clinical practice and tissue diagnosis of these masses are very important for correct therapeutic decision. **Objective:** Comparing the usefulness of invasive procedure for histological diagnosis of a mediastinal masses. **Patients and methods:** This was a prospective study of 50 patients who were admitted in Cardiothoracic Surgery Department, Al-Zahraa University Hospital, Al-Azhar University during the period between December, 2011 and April, 2014. They were diagnosed by plain X-ray and computed tomography (CT) for site detection of mediastinal masses. After taken an appropriate consent from them, they underwent fine needle aspiration (FNA) guided by CT, trans bronchial needle aspiration (TBNA), mediastinoscopy, sternotomy and thoracotomy. Cytology smears and histological sections were evaluated in all patients. **Results:** Among 50 patients, 49 were Egyptian and one patient from Ghana; 29 males and 21 females with the mean age of 43.06±3.44 years. 50% of masses were identified in patients with age more than 40 years of life. 20, 23 and 7 patients have lesion at the anterior, middle posterior parts of the mediastinum respectively. The overall sensitivity for FNA guided by CT, TBNA, mediastinoscope, sternotomy and thoracotomy were 80.0%, 66.7%, 95.0%, 100% and 100% respectively. Sarcoidosis and metastatic carcinoma were the most common entity (16%) followed by tubercular granuloma and nonHodgkin's lymphoma (NHL) (14.0%). Only one patient (2%) developed moderate pneumothorax with no mortality. **Conclusion:** FNA guided by CT and TBNA are safe, minimally invasive and cost-effective procedures, which can provide a precise diagnosis in the mediastinal masses inspite of lower sensitivity other than invasive surgical approaches like mediastinoscope, sternotomy and thoracotomy.

Key Words: Fine needle aspiration (FNA) cytology, mediastinal masses, mediastinoscopy, sternotomy, thoracotomy, trans-bronchial needle aspiration (TBNA).

INTRODUCTION

Mediastinal masses comprise a wide histopathological and radiological spectrum. The most frequent lesions encountered in the mediastinum are thymoma, neurogenic tumors and benign cysts, altogether representing 60% of patients with mediastinal masses **(Laurent, 1998).** Neurogenic tumors, germ cell neoplasms and foregut cysts represent 80% of childhood lesions, whereas primary thymic neoplasms, thyroid masses and lymphomas are the most common in adults **(Juanpere et al., 2013).**

The mediastinum is demarcated by the pleural cavities laterally, the thoracic inlet superiorly and the diaphragm inferiorly. It is further divided into anterior, middle and

posterior compartments by many anatomists **(Whiteen, 2007).** Anterior mediastinal tumors account for 50% of all mediastinal masses including thymoma, teratoma, thyroid disease and lymphoma **(Tomiyama, 2009)**. Masses of the middle mediastinum are typically congenital cysts while those arising in the posterior mediastinum are often neurogenic tumors **(Duwe, 2005).**

The first examinations required are standard radiographs, ultrasound (US) or computed tomography (CT) scan; and occasionally magnetic resonance imaging (MRI), angiography, and scintigraphy. These methods are followed by the necessary biopsy techniques (**Semin, 2008)**.

There are many methods used to perform a biopsy, depending on the individual patient, the ability of the surgeon and institution to offer these services. Procedures for the histological diagnosis of a mediastinal masses have been diverse including minimally invasive transthoracic or transbronchial fine needle aspiration (FNA) cytology, core needle biopsy (CNB), mediastino-scopey, video-assisted thoracoscopy, and more invasive open biopsy **(Nasit et al., 2013).**

None of these procedures are universally accepted either because of low diagnostic yield, or associated morbidity. So, the aim of current study was to compare the usefulness of different invasive procedures for histological diagnosis of a mediastinal masses.

PATIENTS AND METHODS

The present prospective study was carried out on 50 patients with mediastinal masses with mean age 43.06±3.44 years (29 males and 21 females) admitted in Cardiothoracic Surgery Department, Al-Zahraa University Hospital, Al-Azhar University during the period between December, 2011 and April, 2014. Our study was done with appropriate consent from the patients participated in this study after explanation for them how much this investigations are helpful in diagnosis and treatment.

Any patient with cardiac tumors, mediastinal hernia, advanced liver or renal diseases, or those had **v**ideo assisted thoracoscope as a surgical technique were excluded from this study.

Every patient was subjected to the following work- up:

1. History taking:

a. History of risk factors as regards smoking and tuberculosis.
b. History of the present complains.
c. History of fever or chest hospital admission.
d. History of living at endemic area.

2. Physical examination:

a. General examination including the following:
   - Vital signs: Blood pressure, pulse and temperature.
   - Other organs: Liver, spleen, lymph nodes.
b. Chest examination including inspection, palpation, percussion and auscultation.

3. Plain chest X- ray.

4. Computed tomography of the chest:

All cases were submitted to CT of the chest to:
- Provide information on the nature and localization of the mass.

- Exclude associated lung lesion and evaluate other parts of the chest.

5. Laboratory investigations:

a. Full blood picture and coagulation tests (prothrombin time and partial thromboplastin time).
b. Liver and kidney functions profile.
c. Tuberculin test and Ziehl Neelsen stain test.
d. Arterial blood gases.

6. Pulmonary function test.

7. Fibro optic bronchoscope.

8. Surgical biopsy was achieved by one or more of the following:

- FNA cytology.
- TBNA.
- CT guided needle biopsy.
- Mediastinoscopy.
- Mediastinotomy.
- Sternotomy.
- Thoracotomy.

The procedure of choice for diagnosis depended on:

- The location of the mass.
- The characteristics of the mass.
- The clinical manifestations**.**

Out of 50 patients, 49 patients were symptomatic with presenting clinical features of dyspnea, cough, chest pain, hoarseness of voice and weight loss. In another one patient, mediastinal masses were detected on routine physical examination. In evaluating mediastinal masses, we delivered tissues for histology. The patients were informed about the procedure. After skin cleaning, local anesthesia (10 cc of 2% xylocaine) was given, taking particular care to infiltrate the periosteum of the sternal margin. All procedures were performed under guidance of ultrasound or CT scan. Tumor size ranged from large infiltrative tumor (7 cm) to small nodules (1.5 cm).

Repeated ultrasound examination was performed to evaluate any complication such as localized hematoma or pneumothorax. In all cases, the chest radiograph was done 4 hours after biopsy, and it remained unchanged from the prebiopsy chest radiograph except in one case showing moderate pneumothorax. If the vital parameters remained normal, the patient was discharged after about 4-6 hours.

Air-dried and wet-fixed (95% alcohol) cytology smears were prepared and stained by Papanicolaou stains or hematoxylin–Eosin stain, respectively. The biopsy tissues were fixed in 10% formalin, processed, embedded in paraffin, 4 micron thin sections were cut and stained. Immunohistochemical studies were performed on biopsies by direct avidin–biotin– peroxidase method using various antibodies.

The result of histopathologic Cyto-histological correlation was done and incorrect cytological diagnosis was reviewed with special attention. The reasons for discordant cytology diagnosis and pitfalls of entities were evaluated. The patients were followed up for their definite diagnosis either by noting their response to therapy or by surgical resection of the masses.

Statistical analysis

Data were analyzed using IBM SPSS advanced statistics, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Qualitative data were expressed as frequency and percentage by Chi-square test. $\chi 2$-test (Fisher's exact test) was used to examine

the relation between qualitative variables. A probability value (P value) less than 0.05 was considered significant.

RESULTS

Preoperative data analysis: Among 50 patients participating our study, 49 Egyptian and one patient from Ghana; 29 males and 21 females with male to female ratio 1.38:1. The mean age of patients was 43.06±3.44 years (range 1-76 years), 50% of them older than 40 years. 49% of patients were presented with clinical features of dyspnea, cough, chest pain, hoarseness of voice and weight loss and one patient, mediastinal mass was detected on routine physical examination. According to the site of the mass, 23, 20 and 7 patients have lesion at the middle, anterior and posterior parts of the mediastinum respectively (Table 1).

Operative data analysis: Among 20 (40.0%) patients who have anterior mediastinal masses, FNA was done in 15 patients (11 of them were diagnosed correctly by FNA cytology guided by CT, and 4 patients were not). In four patients with negative FNA cytology guided by CT results, cytological material was inadequate for examination due to hemorrhagic smear and very scanty cellularity. Last four patients with negative FNA cytology guided by CT were undergone sternotomy.

In 23 (46.0%) patients who have middle mediastinal masses, mediastinoscope was done in 20 patients (19 of them were diagnosed correctly; whereas one patient was not). Mediastinoscope did not done to the rest of the patient, as it seems radiologically that the mass can not be reached by mediastinoscope, or it could be achieved better by another method than mediastinoscope. TBNA was done in 3 patients (two patients were diagnosed correctly and one patient was not). The remaining patients with negative mediastinoscope TBNA were undergone FNA guided by CT.

In 7 (14%) patients who have posterior mediastinal masses, FNA cytology guided by CT was done in 3 patients. All of them were diagnosed correctly, whereas other 4 patients were diagnosed definitely by thoracotomy (Ttable 2).

Sensitivity of methods: The overall sensitivity for FNA guided by CT, mediastinoscope, TBNA sternotomy and thoracotomy was 80.0%, 95.0%, 66.7%, 100% and 100% respectively (Table 3).

Histopathological outcome: Sarcoidosis and metastatic carcinoma remained the most common entity (16%), followed by TB granuloma and NHL (14.0%), then thymic hyperplasis (8.0%), teratoma (6.0%), carcinoid tumor (6.0%), thymic carcinoma (4.0%), thyroid hyperplasia (4%), bronchial cyst (2.0%), esophageal carcinoma (2.0%), thymoma (2.0%), thymic lipoma (2.0%), hemangioma (2.0%) and lastly neurogenic tumor (2%) (Table 4).

Only one of the 50 patients (2%) developed moderate pneumothorax following TBNA and managed by intercostal drainage. No mortality was recorded.

Table (1): Preoperative data of studied cases.

Data / Parameters	Frequency	%	Chi-Square	P value
Race				
• Egyptian	49	98	44.180	<0.0001
• Non Egyptian	1	2		
Sex				
• Males	29	58	2.250	0.1336
• Females	21	42		
Age				
• < 20	8	16		
• 20 - 40	17	34	8.680	0.0130
• >40	25	50		
Complain				
• Yes	49	98	44.180	<0.0001
• No	1	2		
Site of the mass				
• Anterior	20	40		
• Middle	23	46	7.412	0.0246
• Posterior	7	14		

Table (2): Invasive methods used in sampling of masses according to site of mediastinum.

Data / Parameters	Positive	Negative	Alternative method In negative cases
Anterior mediastinal mass (n =20)			
FNA guided by CT (n =15)	11	4	Sternotomy
Thoracotomy (n =5)	5	0	
Middle mediastinal mass (n =23)			
Mediastinoscope (n =20)	19	1	FNA guided by CT
TBNA (n =3)	2	1	FNA guided by CT
Posterior mediastinal mass (n =7)			
FNA guided by CT (n =3)	3	0	
Thoracotomy (n =4)	4	0	

FNA = Fine needle aspiration, TBNA = Trans bronchial needle aspiration,
CT= Computed tomography.

Table (3): Overall sensitivity of Invasive methods.

Data / Parameters	No	Results	Frequency	Sensitivity	Chi-square	P value
FNA guided by CT	20	Diagnostic	16	80.0 %	6.050	0.0139
		Non diagnostic	4			
Mediastinoscope	20	Diagnostic	19	95.0%	14.450	0.0001
		Non diagnostic	1			
TBNA	3	Positive	2	66.7 %	0.00	1.000
		Negative	1			
Sternotomy	4	Positive	4	100 %	-	-
Thoracotomy	9	Positive	9	100 %	-	-

Table (4): Histopathological diagnosis of mediasstinal masses.

Parameters / Masses	N	%	Technique	Site	Age	Sex
Sarcoidosis	8	16 %	Mediastinoscope	mid	5>40 3(20-40)	2 females 6 males
Metastatic carcinoma	8	16 %	5 Mediastinoscope 3 FNA guided by CT	2ant 6 mid	>40	8 males
Tubercloid granuloma	7	14 %	3 FNA guided by CT 3 Mediastinoscope 1 Thoracotomy	1ant 3Mid 3post	2>40 2(20-40) 3<20	3 males 4 females
Non-Hodgken lymphoma	7	14 %	4 FNA guided by CT 3 Mediastinoscope	4ant 3mid	3(20-40) 4<20	5 males 2 females
Thymic hyperplasis	4	8%	3 Sternotomy 1 Thoracotomy	ant	2>40 2(20-40)	3 males 1 female
Teratoma	3	6%	Thoracotomy	ant	3(20-40)	2 females 1 male
Carcinoid tumor	3	6%	1Thoracotomy 2 TBNP	1ant 2 mid	1>40 2(20-40)	1 male 2 females
Thymic carcinoma	2	4%	1 FNA guided by CT 1 Sternotomy	ant	1>40 1(20-40)	2 males
Thyroid hyperplasia	2	4%	2 FNA guided by CT	1ant post	>40	2 males
Bronchial cyst	1	2%	Thoracotomy	post	>40	female
Esophageal carcinoma	1	2%	FNA guided by CT	mid	>40	female
Thymoma	1	2%	FNA guided by CT	ant	>40	male
Thymic lipoma	1	2%	FNA guided by CT	ant	(20-40)	female
Hemangioma	1	2%	Thoracotomy	post	>40	male
Neurogenic tumor	1	2%	Thoracotomy	post	<20	female

DISCUSSION

Polycystic ovary syndrome is one of Mediastinum is the site of variety of lesions, ranging from inflammatory to neoplastic, benign to malignant and primary to metastatic lesions **(Karki and Chalise, 2011).** Primary mediastinal tumors are uncommon representing about 3% of tumors within the chest wall **(Vaziri et al., 2009),** as many as 25-40% of these lesions are malignant **(Nasit et al., 2013).**

Usually mediastinal masses are picked-up by clinical examination and radio-imaging appearance. Radio-imaging are widely used for detection of mediastinal masses and their extension. Tissue characterization by these techniques is not sufficient and even for distinguishing malignant from benign tumors **(Safavi et al., 2004).**

Tissue diagnosis of mediastinal masses can be performed by a variety of techniques ranging from FNA guided by CT to surgical procedures allowing biopsy as well as resection **(Desai et al., 2008).** The first priority is to provide positive histological diagnosis with the lowest possible risk **(Rendina et al., 2002).** Procedures like mediastinoscopy, thoraco-scopy, mediastinotomy, or thoracotomy are traditionally used for determining the nature of these tumors, which require intubation and general anesthesia. Open biopsy can certainly assure a definite histological diagnosis. Although the diagnostic rate might be as high as 100%, they are associated with significant morbidity, increased chance of pleural dissemination, and poor long-term results **(Nasit et al., 2013).**

We reported a prospective study comparing the usefulness of invasive procedure for histological diagnosis of a mediastinal masses. This study was done on 50 patients at Al-Zahraa University Hospital from December, 2011 and April, 2014. In this study, the mean age was 43.06±3.44 years, which was comparable to a study done at 2007 by **Bastos et al**. where the mean age was 40.3±6.32 years.

The middle mediastinum was the most commonly involved site to have a mass (46%), followed by the anterior mediastinum (40%), and lastly posterior part of the mediastinum (14%). In a study done at **2007 by Bastos et al**. on 171 patients, the antero-superior mediastinum was the most commonly involved site to have a primary cyst or tumor (58%), followed by the posterior mediastinum (24%), and the middle mediastinum (18%).

In the present study there was 29 males (58%) and 21 females (42%), which was comparable to a study done at **2007 by Bastos et al**. where there was 98 males (57%) and 73 females (43%).

The knowledge of the nature of mediastinal masses is very important for making correct diagnosis and therapeutic decisions **(Shrivastava et al., 2006).** In our study, sarcoidosis and metastatic carcinoma was reported (16%) followed by TB granuloma and NHL (14.0%). These results were lower than the studies of **Jereb and Uskrasovec (1997) and Adler et al. (1983)** who reported a higher incidence of about 72% prevalence of malignancy in their study. **Vaziri et al (2009)** showed 60% of malignancy in their study. **Herman and Colleagues (2002)** reported sensitivities of only 42% for NHL and 20% for Hodgkin's disease, as well as difficulty differentiating lymphoma from thymoma in some cases **(Ronald, 2005).**

The overall sensitivity for FNA guided by CT and TBNA was 80.0% and 66.7% respectively. These results were lower than that reported by the study of

Kulkarni (2008) that performed 83 FNA of mediastinal mass from them, adequate tissue for histological diagnosis was obtained in 80 (96%), and the biopsy was considered diagnostic. Of the 80 diagnostic biopsies, 74 biopsy samples were definitive for neoplastic pathology with a sensitivity of 92.5%.

Morrisey and Associates (1993) and Protopapas and Westcott (1996) reported the sensitivity of FNA in carcinoma of 98% and 90%, respectively. FNA is less likely to provide a specific diagnosis in cases of lymphoma, thymoma, and germ cell tumors of the mediastinum.

In a study done by **Gress (1997)**, they found that operation was avoided in 14 of 24 patients diagnosed by this method. The accuracy was 96%. They compared FNA guided by endoscopic ultrasound (EUS) and TBNA and showed that the two procedures produced similar results. EUS limited by its inability to sample anterior lymph nodes, lack of expertise in most centers, and the absence of studies based on large numbers of cases **(Ronald, 2005).**

Mediastinoscopy is an important method in the differential diagnosis of mediastinal mass since Carlens presented it in 1959. Mediastinoscopy in the skilled hands of a thoracic surgeon has proved to be a safe and cosmetically accepted procedure, with negligible complications.

In the present study, 20 patients were undergone mediastinoscopy with sensitivity of 95.0 %. All the masses were situated at the middle part of the mediastinum. The result of the pathology were 6 females and 2 males with sarcoidosis; 5 males with metastatic carcinoma; 2 males and 1 female with lymphoma, 2 males and 1 female with T.B granuloma (Table 3 and 4). **Rahman (2003)** in a study of 65 patients, recorded a positive predictive value of 100%, negative predictive value of 94.4%, with total accuracy of 98.4%. **Rodrigruez et al. (2003)** in a study of 181 patients recorded a positive predictive value of 100%, negative predictive value of 82.8%, with total sensitivity of 95.1%.

In our patients, there was no major complication in relation to the procedure, but minor complication in the form of pneumothorax that necessitate daring seen in one case with no mortality rate. Like our results**, Kulkarni (2008)** recorded no major complications, but minor complications were recorded in 5 patients. **Abdel Rahman and Abdel Rahman (2003)** recorded two minor complications in relation to the procedure in the form of mild hemorrhage, with no major complications reported, and no surgery-related mortality. **Theodosios et al. (2006)** recorded no mortality rate for cases with biopsy and 0.7% for cases with resection, and complications were noticed in 8.3% for biopsy and 15% for resection. **Bastos et al. (2007)** recorded one postoperative death (0.6%).

In spite of the numerous minimally invasive options available for histological diagnosis of mediastinal tumors and cysts, open surgical access was needed at times. Moreover, in some cases, standard sternotomy or thoracotomy may be the safest method available to obtain an adequate tissue diagnosis and to perform appropriate resection. In the present study, 13 patients have undergone open surgery in the form of sternotomy or thoracotomy (sternotomy was done to 4 patients and thoracotomy was done to 9 patients). In this study, the sensitivity and specificity of sternotomy and thoracotomy was 100%, positive predictive value was 100 % and negative predictive value was 0%, with total accuracy of 100% for both of them. In similar to our results, **Thedosios et al. (2006)** in a study of 200 patients,

recorded 100% sensitivity and specificity, with 100% total accuracy.

For sternotomy all the masses were at the anterior part of the mediastinum, 2 patients were males and 1 was female with thymic hyperplasia, and 1 male with thymic carcinoma. Thoracotomy was done to 9 patients; 5 with masses at the anterior part of the mediastinum and 4 at the posterior part.

Bastos et al. (2007), in a study of 171 patients, carried out postero-lateral thoracotomy (64 patients), sternotomy (51 patients), mediastinotomy (27 patients), antero- lateral thoracotomy (18 patients), video-assisted thoracoscopic surgery (9 patients) and mediastinoscopy (2 patients). Definitive histological diagnosis was achieved in 100 % of the cases.

CONCLUSION

The choice of the invasive diagnostic procedures depends primarily on the presence or absence of local symptoms, location, and extent of the lesion. There are many modalities to obtain a pathological diagnosis, and each modality has its advantages and limitations.

Although the diagnostic rate of sternotomy and thoracotomy was 100%, it is an invasive procedure requiring general anesthesia and a longer hospital stay. For this reason, the surgically oriented strategy is no longer considered suitable for all types of mediastinal masses. Finally, thoracic surgeons should be familiar with all surgical techniques available for the diagnosis of the mediastinal masses.

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دور الطرق التداخلية في التشخيص النسيجي لأورام الحيزوم

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خلفية البحث: تعد أورام الحيزوم من الأمراض الاقل شيوعاً في المجال الاكلينيكي و التشخيص النسيجي لهذه الأورام له دور بارز في العلاج الصحيح.

الهدف من البحث: مقارنة أهمية الطرق التداخلية في التشخيص النسيجي لأورام الحيزوم.

المرضي و طرق البحث: تمت الدراسة الحالية علي ٥٠ مريض يعانون من أورام بمنطقة الحيزوم تم حجزهم بقسم جراحة القلب و الصدر – مستشفي الزهراء الجامعي – جامعة الأزهر في الفترة بين ديسمبر ٢٠١١ و حتي أبريل ٢٠١٤. و تم تشخيصهم أولا بالأشعة العادية و المقطعية على الصدر وذلك لتحديد المنطقة المصابة بالحيزوم ، وبعد أخذ الموافقة المناسبة من المرضي ، تم اخذ عينة من النسيج المراد فحصه إما عن طريق الأشعة المقطعية أو عن طريق المنظار الشعبى أو عن طريق الجراحة سواء بالمنظار الحيزومى أو بفتح عظمة القص أو جدار الصدر، وبعد ذلك تم عمل تحليل للأنسجة وذلك للوصول الى التشخيص النهائى لكل حالة ، وقد تمت مقارنة جميع طرق التشخيص المستخدمة فى الدراسة للوصول الى أفضل طريقة فى تشخيص أمراض الحيزوم.

نتائج البحث: تمت الدراسة علي خمسين مريض (٤٩ من المصريين و مريض من دولة غانا) ٢٩ من الذكور و ٢١ من الإناث ومتوسط أعمار المرضي ٤٣,٠٦±٣,٤٤ عاما ، ونصف الحالات كانت فوق سن الأربعين. وكان عشرون من المرضي يعانون من أورام بالقسم الأمامي من الحيزوم ، و ثلاثة وعشرون من المرضي يعانون من أورام بالقسم الوسطي من الحيزوم ، بينما سبعة من المرضي كانوا يعانون من أورام بالقسم الخلفي من الحيزوم. وكانت نسبة حساسية التشخيص الكلية لطريقة أخذ عينة من النسيج المراد فحصه عن طريق الأشعة المقطعية (٨٠٪) وعن طريق المنظار الشعبى (٦٦,٧٪) وعن طريق الجراحة بالمنظار الحيزومى (٩٥٪) وعن طريق فتحة عظمة القص (١٠٠٪) وعن طريق فتح جدار الصدر (١٠٠٪).

الإستنتاج : تعتبر طريقتي أخذ عينة من النسيج المراد فحصه إما عن طريق الأشعة المقطعية أو عن طريق المنظار الشعبى من الطرق الآمنة والأقل تداخلا وإقتصادية مقارنة بطرق الجراحة سواء بالمنظار الحيزومى أو بفتح عظمة القص أو جدار الصدر علي الرغم من قلة حساسية التشخيص لهاتين الطريقتين مقارنة بالطرق الجراحية الأخرى.