ORIGINAL ARTICLE

Endoscopic ultrasonography–guided fine-needle aspiration in the management of mediastinal diseases: local experience of a novel investigation

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Objective To study the efficacy and safety of endoscopic ultrasonography–guided fine-needle aspiration in the management of mediastinal diseases in Hong Kong.

Design Retrospective review of prospectively collected data.

Setting University teaching hospital, Hong Kong.

Patients A total of 125 consecutive patients with various mediastinal and pulmonary lesions that underwent trans-oesophageal endoscopic ultrasonography–guided fine-needle aspiration from July 1998 to June 2007.

Main outcome measures The diagnostic accuracy and safety of the procedure and its influence in patient management.

Results Malignancy was confirmed in 62 (50%) of the patients and excluded in 42 (34%). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of endoscopic ultrasonography–guided fine-needle aspiration in diagnosing mediastinal malignancies were 75% (95% confidence interval, 64-83%), 100% (90-100%), 100% (93-100%), 67% (54-78%), and 83%, respectively. Eighty-six (69%) of the patients had their initial plan of invasive investigations changed. Only one (0.8%) patient developed a septic complication in a mediastinal cyst after puncturing, and was treated surgically.

Conclusions Trans-oesophageal endoscopic ultrasonography–guided fine-needle aspiration is a minimally invasive, effective, and safe method of diagnosing malignant mediastinal disease. It may reduce the need for other invasive investigations.

Introduction

Endoscopic ultrasonography (EUS) combines both endoscopy and ultrasonography (US) examination into one. By employing a high-frequency US probe, the structures around the gastro-intestinal tract can be accurately examined. The procedure has been shown to have high sensitivity and accuracy in the detection and staging of gastro-intestinal and pancreatic malignancies. In recent years, EUS and EUS-guided fine-needle aspiration (EUS-FNA) has expanded its use in aiding the diagnosis and staging of pulmonary malignancies and mediastinal diseases.[1-3] Diagnostic radial EUS and therapeutic linear-array EUS (for real-time ultrasound-guided FNA) have been introduced into Hong Kong since 1989 and 1997, respectively. However, local data on the efficacy and complication rate of this novel mode of investigation were lacking, especially in relation to pulmonary diseases. We therefore reviewed a cohort of patients who underwent EUS-FNA for mediastinal and pulmonary pathologies over a 9-year period to examine its efficacy, safety, and influence in patient management.

Key words
Biopsy, needle; Carcinoma, non–small-cell lung; Endosonography; Lung neoplasms; Mediastinum

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Methods

The records of all patients referred to a university endoscopy centre with a view to EUS-FNA for mediastinal and pulmonary pathologies between July 1998 and June 2007 were studied. Patient clinical data and procedure details were prospectively collected and relevant outcomes were reviewed retrospectively, with the approval of the hospital management. All EUS-FNA procedures were performed by an experienced endosonographer. Informed written consent was obtained from all patients, and the entire study was conducted according to the Declaration of Helsinki, 1995.

內鏡超聲引導下細針穿刺術治療縱隔病新探：本地經驗

目的 探討本地使用內鏡超聲引導下細針穿刺術治療縱隔病的效果及安全性。

設計 把前瞻性收集的數據作回顧研究。

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患者 1998年7月至2007年6月期間，所有125位患上不同縱隔病及肺病變而經食道進行內鏡超聲引導下細針穿刺術的病人。

主要結果測量 此技術的診斷準確性及安全性，以及其對治療方法的影響。

結果 62名（50%）病人確診為腫瘤，另42名（34%）證實沒有腫瘤。內鏡超聲引導下細針穿刺術用作診斷縱隔病的敏感度為75%（95%置信區間：64-83%）、特異性100%（90-100%）、陽性預測值100%（93-100%）、陰性預測值67%（54-78%）、準確性83%。其中86名（69%）病人改變其原本的侵入性檢測計劃。只有1名（0.8%）病人接受穿刺後在縱隔囊腫內有敗血症，須接受外科治療。

結論 經食道進行的內鏡超聲引導下細針穿刺術是一種微創手術，對於診斷縱隔的腫瘤病既安全又有效，還可以減少其他侵入性檢測的需要。

Patients were fasted for at least 6 hours before the EUS-FNA procedure. All procedures were performed with a curvilinear echoendoscope (GF-UC30P, Olympus Company, Japan) connected to the AI5200S ultrasound console (Acoustic Imaging Technologies Corp, Phoenix [AZ], US). Conscious sedation was achieved using intravenous diazepam and pethidine. Prophylactic antibiotics were not prescribed routinely. Thorough mediastinal examination was performed by a linear echoendoscope to define the nature of the lesion before FNA. Additional pathologies such as intra-abdominal lymphadenopathy, liver and left adrenal gland lesions were also searched for before the FNA. The locations of the mediastinal lymph nodes (MLNs) were mapped according to the American Joint Committee on Cancer classification.[4] The EUS-FNA procedure was performed with a 22-gauge FNA needle (NA-10J-1, NA-11J-KB, or NA-200H-8022, Olympus Company, Japan) under real-time EUS guidance. Negative pressure (suction) was applied via a 10-mL syringe. All aspirated material was fixed in 50% alcohol for cytological examination. No on-site cytopathologist was routinely present for immediate cytological examination. The aspirate was checked by the endosonographer for adequacy of cellularity, before ending the procedure. Day patients were observed in the recovery area after the procedure and then discharged on the same day. All patients continued to be followed up by their respective physicians or surgeons.

If the FNA cytology revealed malignant cells, it was classified as a true-positive result. Further surgical biopsy for tissue histology was usually not undertaken. If the FNA cytology was negative, but further invasive tissue biopsy or surgical specimens showed the presence of malignant cells, or tumour developed in the previous FNA site during follow-up, it was classified as a false-negative result. True-negative results were based on negative findings after surgical exploration of the mediastinum or prolonged clinical follow-up.

Results

A total of 125 patients were retrospectively studied. Their median age was 69 (range, 31-90) years, and 76% were males. Altogether 130 EUS-FNA procedures were performed. Patients were divided into different categories according to their clinical presentations: (1) lung mass with enlarged MLN (long axis of the lymph node ≥1 cm) in the computed tomography (CT) scan (CT-positive group, n=34, 27%), (2) lung mass with normal mediastinum in the CT scan (CT-negative group, n=21, 17%), (3) enlarged mediastinal mass or MLN without a peripheral lung lesion in the chest X-ray (CXR) or CT scan (central group, n=33, 26%), (4) lung shadow detected in the CXR for which EUS was used as a primary investigation before CT (EUS-first group, n=15, 12%), (5) superior vena cava obstruction (SVCO group, n=10, 8%), (6) pyrexia of unknown origin (PUO) and EUS detection of enlarged MLN (PUO group, n=4, 3%), (7) MLN incidentally detected during EUS investigation for other indications, and EUS-FNA was used to confirm the diagnosis (incidental group, n=8, 6%).

Bronchoscopy was performed prior to EUS-FNA in 58 patients, 47 of the bronchoscopies having been non-diagnostic. In all, 185 sites were sampled; with more than one site being punctured in some patients. Concerning the sites of EUS-FNA, the most commonly punctured locations were: MLN station 7 (subcarinal lymph node; n=79, 43%), followed by station 4L/5 (aortopulmonary window lymph node; n=35, 19%) and lung masses (n=34, 18%) [Table 1]. A total of 498 needle passes were undertaken, averaging 4 (range, 1-7) per procedure.

Overall FNA cytology for mediastinal lesions yielded the presence of malignant cells (true-positive) in 62 (50%) of the patients (Table 2). Forty-two (34%) of the patients were confirmed to have no mediastinal malignancy (true-negative) after surgery or prolonged clinical follow-up, but 21 (17%) were proven to have false-negative cytological results after further workup, surgery, or clinical follow-up. There was no false-positive result and the positive predictive value was

100%. Five patients had a negative EUS-FNA result initially, but malignant cells were seen after a second EUS-FNA procedure. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the cytological result in the whole group were: 75% (95% confidence interval, 64-83%), 100% (90-100%), 100% (93-100%), 67% (54-78%), and 83%, respectively. The values for different subgroups of patients are shown in Table 3. In one patient, the EUS-FNA result showed the presence of caseating granuloma, later confirmed to be tuberculosis based on the culture result. Eighty-six (69%) of the patients had their initial plan of management altered due to the EUS-FNA result. Among them, 27 had a negative EUS-FNA result and the attending physicians or surgeons decided to cease further invasive investigation after obtaining the information provided by EUS studies. In 59 patients, the EUS-FNA result showed malignant cells and no further invasive investigations such as bronchoscopy, mediastinoscopy or thoracotomy were deemed necessary. When the FNA result was negative, the need for further invasive investigation differed according to the subgroup category, due to differing pretest probabilities of malignancy (Table 3).

All the procedures were well-tolerated. Concerning the complication rate, only one (0.8%) of the patients developed an alpha-haemolytic streptococcal infection after EUS-FNA of a 7-cm, apparently solid mediastinal mass lesion (revealed by CT scan and EUS). The patient underwent surgical treatment and the final operative diagnosis was a mediastinal cyst with abscess formation.

TABLE 1. The lesion sites sampled by endoscopic ultrasonography–guided fine-needle aspiration

Site (≥1 site per patient)	No. of sites sampled (n=185)
Mediastinal lymph node stations	
2R (Upper paratracheal)	3
2L (Upper paratracheal)	4
4R (Lower paratracheal)	2
4L/5 (Aortopulmonary window)	35
7 (Subcarinal)	79
8 (Para-oesophageal)	10
9 (Pulmonary ligament)	1
10 (Hilar)	4
Lung mass	34
Pleural mass	1
Pleural effusion	1
Left adrenal gland	8
Liver	1
Celiac axis lymph node	2

TABLE 2. Cytological results of endoscopic ultrasonography–guided fine-needle aspiration (EUS-FNA)

Results	No. of patients (n=125)
Confirmed malignancy by cytology	62 (50%)
Primary lung and mediastinal tumour	
Non–small-cell lung cancer	44
Small-cell lung cancer	11
Malignant gastro-intestinal stromal tumour	1
Sarcoma	1
Diffuse large-cell lymphoma (at the same time EUS-FNA of a large intra-abdominal mass showed hepatocellular carcinoma)	1
Tumour metastasis to mediastinum	
Renal cell carcinoma	1
Metastatic small bowel adenocarcinoma	1
Prostatic cancer	1
Metastatic bone tumour	1
Granulomatous inflammation	1
Quality insufficiency	15

Discussion

Due to the close proximity of the oesophagus to the posterior mediastinum, EUS is highly sensitive for detecting lesions in the paratracheal, subcarinal, aortopulmonary and distal para-oesophageal regions of the thorax, as well as metastatic lesions in the upper abdomen. For the investigation of MLN and mediastinal tumour diseases, trans-oesophageal EUS-FNA is a minimally invasive alternative to blind transbronchial FNA, mediastinoscopy, and thoracotomy.[5] The role of this tool is growing in the management of various lung diseases and lung cancer staging.[6] The application of EUS-FNA in lung cancer staging has been studied in different patient subgroups, including those with: centrally located tumours,[7] confirmed lung cancer disease, and suspected metastatic MLNs that may or may not be evident on CT or positron emission tomography (PET) scans.[6,8-10] Since EUS-FNA helps obtain a tissue diagnosis by sampling the MLN, it is also used in patients in whom bronchoscopy or CT-guided biopsy fails to clarify the lung cancer diagnosis.[7,11,12] In a recent meta-analysis of 76 studies comparing EUS and EUS-FNA for the diagnosis of MLN disease, the pooled sensitivity and specificity for both examinations was high (EUS: 85% and 85%; EUS-FNA: 88% and 96%, respectively).[13] Due to its high diagnostic accuracy, EUS-FNA has been used as the first-line investigation for patients with suspected lung cancer before resorting to other invasive measures.[14] Another study showed it to be the most important predictor of survival in non–small-cell lung cancer (NSCLC) that could be utilised to formulate treatment plans.[15]

In the current cohort of patients with mediastinal diseases, mostly had lung cancer and attended one centre over a 9-year period. The long-term follow-

TABLE 3. Performance of endoscopic ultrasonography–guided fine-needle aspiration in the diagnosis of mediastinal malignant diseases in various patient subgroups*

Group	No.	Malignancy	Sensitivity	Specificity	PPV	NPV	Accuracy	Further test if negative
Whole group	125	62	75%	100%	100%	67%	83%	31%
CT-positive group	34	20	70%	100%	100%	36%	74%	81%
CT-negative group	21	9	64%	100%	100%	58%	76%	67%
Central group	33	15	88%	100%	100%	89%	94%	35%
EUS-first group	15	11	100%	100%	100%	100%	100%	50%
SVCO group	10	4	40%	-	100%	0%	40%	100%
PUO group	4	0	-	100%	-	100%	100%	50%
Incidental group	8	3	100%	100%	100%	100%	100%	17%

* CT denotes computed tomography, EUS endoscopic ultrasonography, SVCO superior vena cava obstruction, PUO pyrexia of unknown origin, PPV positive predictive value, and NPV negative predictive value

up data of our patients permitted assessment of the true efficacy of EUS-FNA. The cohort included different patient categories that were representative of the conditions for which EUS-FNA is used in clinical practice. The study showed that EUS-FNA enabled the diagnostic sampling of lesions in different para-oesophageal, posterior mediastinal, and intra-abdominal sites. Although there was no cytopathologist on-site to examine the FNA specimen cytology, the accuracy of the procedure was nevertheless high (83% for the whole group). A large proportion (69%) of the patients had their management plans changed to a less invasive approach, reducing the costs of management and complications. Similarly others have reported that up to 70% of scheduled surgical procedures could be avoided by the use of EUS-FNA.[16] It should be stressed that in cases in which there is a clinical suspicion, negative FNA cytology could not replace invasive or surgical biopsy, which is still the gold standard for diagnosis. However, the current study did show that the pretest probability of underlying malignant mediastinal diseases or MLN is important in formulating the clinical decision. Patients with a high probability tended to have further invasive testing if the EUS-FNA result was negative. Whereas, if the probability was low, a negative EUS-FNA result reduced resorting to further testing.

In Hong Kong, lung cancer still ranks first in terms of both cancer incidence and mortality.[17] More than 4000 cases were reported in 2006. Till now, the most promising curative treatment for NSCLC is surgery, and its operability depends heavily on accurate TNM staging, particularly of mediastinal nodes. Although CT and PET are commonly used to detect MLN metastases, their pooled sensitivity and specificity are not satisfactory, as shown in a recent study (CT: 51% and 85%; PET: 74% and 85%, respectively).[18] Even integrated PET/CT examination (sensitivity 84% and specificity 85%) cannot replace tissue diagnosis.[19] The American College of Chest Physicians suggests that in clinical practice, non-invasive investigations cannot replace invasive staging, except in patients with a peripheral, clinically stage 1 tumour and a negative PET scan.[5] Since EUS-FNA provides a tissue diagnosis in a minimally invasive way, its routine use in the lung cancer staging may reduce resorting to mediastinoscopy and avoid futile thoracotomies.[20,21] Adding EUS-FNA to mediastinoscopy is reported to reduce up to 16% of unnecessary thoracotomies.[22] The limitation of EUS-FNA is that it cannot enable complete mediastinal staging, especially for MLNs situated in the anterior mediastinum (such as in stations 2R and 4R). The latest developments in endobronchial ultrasonography (EBUS) could complement EUS and enable the whole mediastinum to be completely assessed if EUS-FNA and EBUS-FNA are used in combination.[23,24]

Previous studies indicate that the learning curve for EUS is steep. From our experience, once the basic technique of using linear EUS and FNA is acquired, it is easy to perform mediastinal FNA in comparison to other FNA procedures (such as the investigation of pancreatic lesions). We did not record the procedure duration of each case, but on average we estimated spending about 20 minutes on staging and FNA of MLNs and masses. The EUS-FNA is a very safe intervention, with a complication rate ranging from 0.003 to 2%.[25] Antibiotics are not indicated to cover the procedure, except when sampling cystic lesions.[26] In the current study, one patient developed an abscess after a large mediastinal mass was punctured in the absence of antibiotic prophylaxis. The mass lesion turned out to be a mediastinal cyst that was wrongly diagnosed as a solid mass by both CT and EUS, due to debris inside the cyst. Post EUS-FNA mediastinitis has been reported after puncturing a bronchogenic cyst and necrotic lymph nodes, or following the use of a large Trucut needle.[27-29] A prospective cohort study compared EUS-FNA against mediastinoscopy and reported complication rates of 0 and 3%, respectively.[30] Whereas, in another study transthoracic needle aspiration resulted in a pneumothorax in 20% of the patients.[31]

In Hong Kong, over the last decade, the number of endosonographers has steadily increased. However, the use of EUS in the management of lung and mediastinal diseases is still limited to a few centres. Further structured training programmes for EUS and EUS-FNA in the field of pulmonology are therefore needed, with a view to promoting awareness and utilisation of this important tool. In conclusion, EUS-FNA is an effective and safe tool for investigating various mediastinal pathologies, particularly because it can provide a cytological diagnosis to confirm underlying malignancy or metastases.

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