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Endoscopic ultrasound-guided fine needle aspiration in the evaluation of suspected lung cancer

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Summary
Background and aim: The role of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) in the diagnosis and staging of lung cancer is still not fully explored. This prospective study aimed to define the effectiveness of EUS-FNA as an adjunct to computer tomography (CT) and bronchoscopy in the evaluation of suspected lung cancer in routine clinical practice.
Methods: Over a period of 20 weeks, the data of 16 consecutive patients suspected of lung cancer on account of respiratory symptoms, and/or the findings of either a mass or mediastinal lymph nodes on helical CT, who were referred for evaluation by EUS, were prospectively collected. Fourteen of these patients underwent sequential bronchoscopy followed by EUS-FNA in the same setting.
Results: Bronchoscopy was performed in 15 patients, while EUS was performed in all 16 patients. Bronchoscopy diagnosed 9 cases of non-small-cell lung cancer (NSCLC) but was falsely negative in 3 cases of malignancies, which were all established by EUS-FNA of mediastinal lymph nodes (2 cases of NSCLC and 1 case of esophageal squamous cell cancer). EUS-FNA also diagnosed advanced NSCLC in another patient who did not undergo bronchoscopy, such that eventually 13 patients were diagnosed to have malignancies. Distant metastases were diagnosed by EUS-FNA in 4 cases of NSCLC (2 cases of left adrenal gland and 2 cases of pancreatic metastases). Two patients were diagnosed to have sarcoidosis and 1 patient was diagnosed to have pneumoconiosis eventually.
Conclusions: EUS-FNA is useful as an adjunct to CT and bronchoscopy in the evaluation of suspected lung cancer.

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Background

Lung cancer is the most common cancer in males with an age-standardized rate (ASR) of 45 per 100,000/year, and the third most common cancer in females with an ASR of 16.3 per 100,000/year, in Singapore. It is also the most frequent cause of cancer-related mortality both in the world as well as in Singapore.[1] At diagnosis, less than 30% of patients are suitable for curative surgery because of either advanced tumor stage or medical comorbidities.[2] Obtaining histological confirmation of the diagnosis of lung cancer, and accurate staging of the extent of disease, are crucial before planning either curative surgical resection or palliative radiotherapy or chemotherapy. In terms of obtaining tissue diagnosis, bronchoscopy is commonly used, but it may be falsely negative in 30%.[3] Radiologically guided percutaneous transthoracic needle biopsy is another option but it has a risk of pneumothorax of up to 30%,[4] especially for non-peripheral lung lesions. Mediastinoscopy and open surgical mediastinal staging have been the standard but are more invasive. Computer tomography (CT) though commonly used for preoperative staging, is known to miss sub-centimeter lymph nodes as well as fall to accurately detect structural invasion by tumor. Accurate staging is important both as guide to treatment as well as a guide to prognosis; the stage-dependent 5 year survival after the diagnosis of non-small-cell lung cancer (NSCLC) is follows: I: 46.9%; II: 26.1%; III: 8.4%; IV: 1.6%.[5]

Endoscopic ultrasound (EUS) is currently available to image mediastinal lesions with a high degree of accuracy, as well as to obtain tissue diagnosis with no documented complications.[6] It has been shown to detect malignant mediastinal lymphadenopathy not shown by CT[7,8] and even positron emission tomography.[8] It may also detect occult lesions in the left adrenal gland,[9] left lobe of liver[10] and pancreas.[11]

The role of EUS-guided fine needle aspiration (EUS-FNA) in obtaining tissue diagnosis of the primary tumor, as well as to assess the extent of extra-pulmonary intra-thoracic and extra-thoracic metastases, is still not fully explored. This prospective study aimed to define the effectiveness of EUS-FNA as an adjunct to CT and bronchoscopy in the evaluation of suspected lung cancer in routine clinical practice.

Methods

Patient selection

Over a 20 week period from 20 January 2006 to 9 June 2006, the data of 16 consecutive patients suspected of lung cancer on account of respiratory symptoms, and/or the findings of either a mass or mediastinal lymph nodes on helical CT who were referred for evaluation by EUS were prospectively collected. Fourteen of these patients underwent sequential bronchoscopy followed by EUS in the same setting, 1 patient underwent bronchoscopy and EUS on separate sessions and 1 patient underwent EUS without bronchoscopy.

Endoscopic procedures

Bronchoscopy: Fibreoptic bronchoscopy (BF-1T160 or BF-P160, Olympus, Tokyo, Japan) was performed by a single pulmonologist (A.T.K.H.) using a transnasal approach. A combination of intravenous midazolam and fentanyl was used for sedation. Visible endobronchial lesions were brushed and biopsied and bronchoalveolar lavage was performed for all cases undergoing bronchoscopy. Transbronchial needle aspiration (TBNA) of subcarinal lymph nodes was performed blind with a 22-gauge needle (Bard Endoscopic Technologies, Billerica, MA) if these were enlarged based on review of the thoracic CT.

EUS and FNA: Diagnostic EUS was performed with a linear-array echoendoscope (GF-UC160P, Olympus, Tokyo, Japan) using the Aloka SSD 5000 ultrasound processor (Aloka Co. Ltd., Tokyo, Japan) by 2 gastroenterologists experienced in performing EUS (A.T.L.; C.T.S.). A combination of intravenous midazolam and fentanyl was used for conscious sedation. The echoendoscope was introduced into the stomach, and screening of the left lobe and central segments of the liver, celiac axis and left adrenal gland was routinely performed. When indicated by clinical data, such as the presence of intra-abdominal lymph nodes on CT, EUS examination of the pancreas was performed. The echoendoscope was then withdrawn into the esophagus and attempts were made to identify any visible mediastinal lymph nodes, and the location was classified according to the Mountain/Dresler Regional Nodal Stations for Lung Cancer Staging.[12] For all lymph nodes, notations were made concerning the dimensions, shape, and echogenicity as well as edge characteristics. EUS-FNA was performed using a 22-gauge needle (Echo-1-22 or Echo-3-22, Cook Endoscopy, Winston-Salem, NC, USA) under Doppler guidance. When lesions were identified intra-abdominally, FNA of these lesions were performed first, followed by FNA of the mediastinal lymph nodes (contralateral nodes first, then ipsilateral nodes).

On-site cytopathologic assessment

On-site cytopathologic assessment was available to guide the FNA in 7 cases. The aspirated material was smeared onto slides, air-dried and stained with Diff-Quik (American Scientific Products, McGraw Park, Ill) and reviewed by a cytotechnologist. Additional slides were fixed in 95% ethanol for formal histopathological review by the cytopathologist. When on-site cytopathologic assessment was not available, the endoscopist assessed the cellular adequacy of the aspirate as previously reported.[13]

Statistical analysis and ethical considerations

Statistical analysis of the patients' data and clinical parameters were expressed as mean and median values and ranges and proportions. Informed written consent was obtained from all patients prior to all procedures.

Results

Demographics

Sixteen consecutive patients (13 males, 3 females) were evaluated by EUS. The median age was 68.5 years (range 46–87). Fourteen out of 15 patients who presented with

respiratory symptoms such as dyspnea or cough or hemoptysis underwent bronchoscopy and EUS-FNA at the same setting, while 1 patient had the procedures performed on separate sessions. One patient was referred for EUS evaluation of intra-abdominal lymph nodes seen on CT after presenting with abdominal pain and did not undergo bronchoscopy. In terms of CT findings, 3 patients had mediastinal lymphadenopathy only, 1 patient had a right upper lobe mass, 3 patients had right upper lobe masses and mediastinal lymphadenopathy, 3 patients had right lower lobe masses and mediastinal lymphadenopathy (of which 2 also had left adrenal masses), 2 patients had right middle lobe masses and mediastinal lymphadenopathy, 2 patients had left lower lobe masses and mediastinal lymphadenopathy (as well as intra-abdominal lymphadenopathy in 1 patient), and 2 patients had left upper lobe masses with mediastinal lymphadenopathy.

Bronchoscopy and EUS-FNA

Bronchoscopy was performed in 15 patients and it diagnosed NSCLC in 9 patients. It was falsely negative for malignancy in 3 cases. EUS was performed in 16 patients and EUS-FNA in 15 patients because 1 patient diagnosed with NSCLC by bronchoscopy did not undergo EUS-FNA due to absence of visible mediastinal lymph nodes and distant metastases (Table 1). A cellular aspirate was obtained in all the 15 cases that underwent EUS-FNA. EUS-FNA of mediastinal lymph nodes (Figs. 1 and 2) was performed in 14 cases; 1 patient with mediastinal lymphadenopathy did not undergo EUS-FNA of the mediastinal lymph nodes after the presence of left adrenal metastases was confirmed by the on-site cytotechnologist. EUS-FNA was able to diagnose the 3 cases of malignancies missed by bronchoscopy (2 cases of NSCLC and 1 case of esophageal squamous cell cancer with subcarinal lymph node metastases). In addition, EUS-FNA confirmed the presence of malignant mediastinal lymphadenopathy in 9 cases of malignancies (the results of FNA for 2 cases of NSCLC revealed reactive lymphoid hyperplasia). It also diagnosed the presence of distant metastases in 4 cases of NSCLC [2 cases of left adrenal gland metastases, one of which was not seen on CT (Fig. 3), and 2 cases of pancreatic metastases, one of which was not seen on CT]. Three patients who underwent both bronchoscopy and EUS-FNA of mediastinal lymph

Table 1 Results of bronchoscopy and EUS-FNA.

	Patient profile	Results of bronchoscopy biopsies and TBNA	Results of EUS-FNA	Diagnosis
1	72 year; male	Poorly differentiated SCC	SCC metastatic to SC and AP LN	NSCLC
2	50 year; female	Mainly bloody aspirate, with no malignant cells or granulomas	Granulomatous inflammation in mediastinal LN	Sarcoidosis
3	70 year; male	Non-small-cell carcinoma	NSCLC metastatic to pancreas	NSCLC
4	87 year; male	Non-small-cell carcinoma	NSCLC metastatic to SC and AP LN	NSCLC
5	79 year; male	Non-small-cell carcinoma	NSCLC metastatic to left adrenal gland	NSCLC
6	67 year; male	Adenocarcinoma	Adenocarcinoma metastatic to left adrenal gland	NSCLC
7	46 year; male	Non-small-cell carcinoma	Not performed	NSCLC
8	68 year; male	Inflammatory cells	FNA of SC/AP LN: reactive lymphoid hyperplasia	Pneumoconiosis
9	73 year; male	Non-small-cell carcinoma	FNA of SC/AP LN: reactive lymphoid hyperplasia	NSCLC
10	67 year; male	Inflammatory yield with no malignant cells	NSCLC metastatic to SC LN	NSCLC
11	47 year; male	Not performed	NSCLC metastatic to pancreas	NSCLC
12	59 year; male	No malignant cells seen	NSCLC metastatic to SC and AP LN	NSCLC
13	59 year; male	Moderately differentiated SCC	FNA of SC LN: reactive lymphoid hyperplasia	NSCLC
14	76 year; male	Poorly differentiated SCC	SCC metastatic to SC LN	NSCLC
15	69 year; female	Granulomatous inflammation	FNA of SC LN: granulomatous inflammation	Sarcoidosis
16	83 year; female	No malignant cells seen	Esophageal SCC metastatic to SC LN	Esophageal SCC

SCC: squamous cell carcinoma; NSCLC: non-small-cell lung cancer; SC: subcarina; AP: aortopulmonary window; LN: lymph nodes.

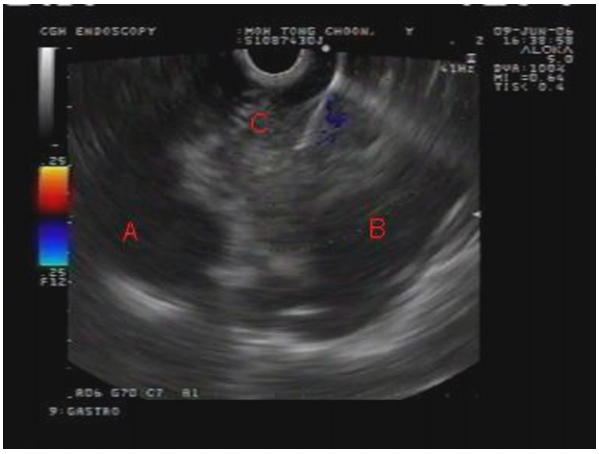

Figure 1 EUS-FNA of malignant lymph nodes in the subcarinal region: (A) left atrium; (B) right pulmonary artery; and (C) FNA of subcarinal lymph node.

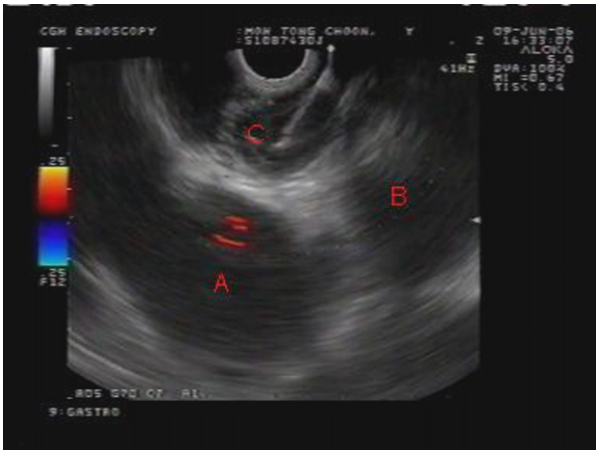

Figure 2 EUS-FNA of malignant lymph nodes in the aortopulmonary window: (A) right pulmonary artery; (B) aorta; and (C) FNA of malignant lymph node.

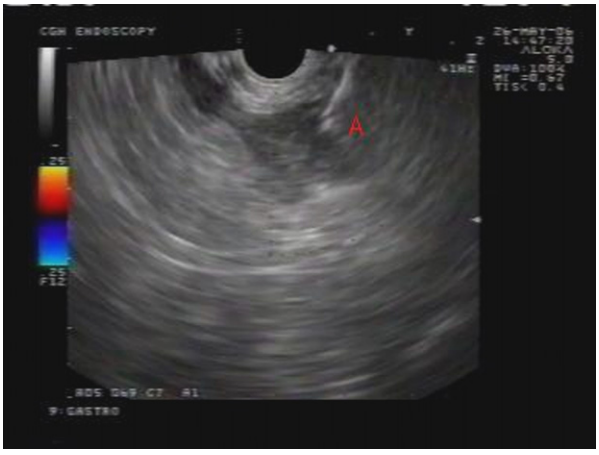

Figure 3 FNA of a left adrenal gland metastasis from lung cancer: (A) FNA of mass in body of left adrenal gland.

nodes were eventually diagnosed to have pneumoconiosis (1) and sarcoidosis (2), respectively. The former underwent a CT guided core biopsy of the lung mass after both bronchoscopy and EUS-FNA revealed only inflammatory cells. The latter two had granulomatous inflammation seen on EUS-FNA.

Clinical impact of EUS-FNA

EUS-FNA had a significant impact in terms of both tumor diagnosis and tumor staging. The diagnosis of cancer in 4 out of 13 patients was only made by EUS-FNA. EUS-FNA also confirmed the presence of distant metastases in 4 out of 13 patients, and the presence of malignant mediastinal nodal involvement in 9 out of 11 patients with malignancies who underwent mediastinal FNA (2 patients had reactive lymphoid hyperplasia). One NSCLC patient with absence of malignant mediastinal lymph nodes on EUS was found to have a malignant right apical lymph node at surgery. No procedural complications occurred.

Discussion

Accurate tumor diagnosis and staging is crucial for appropriate patient counseling and management. Among patients with lung cancer, a large proportion may present with extensive mediastinal lymph node metastases or distant metastases and are hence not suitable for surgery. Our results show that EUS-FNA is useful and effective as an adjunct to CT and bronchoscopy in the evaluation of mediastinal lymphadenoapthy, diagnosis and staging of lung cancer in routine clinical practice. The diagnosis of cancer was made only by EUS-FNA in 31% of cases, and distant metastases, i.e. stage IV disease, was confirmed in 31% of cases by EUS-FNA.

The clinical utility of EUS-FNA resides in its ability to detect and biopsy lesions that may not be visualized by CT without any complications. For instance, it has been shown that EUS can demonstrate advanced mediastinal disease in 61% of patients without CT suspicion of mediastinal lymph nodes[14]; another study showed that EUS precluded unnecessary surgery in 12% of NSCLC without CT evidence of mediastinal lymph nodes based on the presence of stage IIIA or IIIB disease detected by EUS-FNA.[15] In addition, EUS-FNA has also been shown to be very useful in terms of obtaining tissues for the purpose of achieving histological diagnoses. EUS-FNA of mediastinal masses in absence of known lung malignancy has been shown to achieve an accurate diagnosis in 94%, of which 45% were malignancies.[16] In another study, EUS-FNA was useful in confirming the diagnosis of advanced lung cancer, with a correct diagnosis made in 86%, including 24% with prior failed attempts in obtaining histological diagnoses.[17]

In terms of clinical outcome studies, preoperative EUS-FNA for patients with mediastinal lymph nodes and lung cancer being scheduled for surgical staging (i.e. mediastinoscopy or exploratory thoracotomy) has been shown to prevent 70% of scheduled surgical procedures because of the demonstration of lymph node metastases and tumor invasion (69%), or benign diagnoses (1%).[18] Preliminary

results of a study in which patients were randomized to either routine preoperative EUS-FNA for all patients vs. selective EUS-FNA showed that futile thoracotomies were reduced from 25% to 9%. These results are important because published data have shown that up to 45% of operations with curative intent for NSCLC were futile because the stage of disease was more advanced than expected preoperatively.[19]

There are limitations to the use of EUS in lung cancer. Firstly, echo features by themselves are not sufficient to differentiate benign from malignant lymph nodes. EUS features suggestive of malignant nodes are size greater than 1 cm, round or oval shape, diffusely hypoechoic and sharp edges; in the presence of 3 or 4 classic features, the sensitivity was 78% and specificity 81%. This underscores the importance of EUS-FNA, which is 100% specific, rather than EUS per se.[20] Secondly, certain parts of the mediastinum may not be that well accessed by EUS-FNA. EUS cannot access the region anterior to trachea and main bronchi, as well as the right paratracheal region, due to the intervening air. Thus mediastinoscopy, although it is more invasive, still has a role in this area.[21] In addition, real-time endobronchial ultrasound-guided transbronchial needle aspiration (real-time EBUS-TBNA), which has been recently introduced, replaces the blind nature of TBNA in obtaining tissue samples from the anterior mediastinum and may have a role as a less invasive alternative to mediastinoscopy in this respect. When EBUS-TBNA is combined with EUS-FNA, the need for more invasive tests can be potentially reduced since both the anterior (by EBUS-TBNA) and posterior (by EUS-FNA) mediastinum can be accessed. A recent preliminary study showed that using such a combined approach, the accuracy rate for the diagnosis of mediastinal cancer was 100% (95% CI: 83–100%).[22]

Although our sample size was relatively small at 16 patients, we believe that our results are sufficient to show the effectiveness of EUS-FNA in routine clinical practice. Only 1 patient in our study underwent surgery eventually so that surgical histopathological correlation could be made. In this patient, EUS did not show any mediastinal lymph nodes and hence FNA was not performed; however, the surgical specimen revealed a malignant right apical lymph node, thus reiterating the earlier point concerning the limitation of EUS in accessing lymph nodes in this region. For the patients with malignant cytology from EUS-FNA, although there was no surgical correlation, the results are unlikely to be false positives since the FNA needle did not traverse any intervening areas of malignancy when tissue specimens were obtained. However, this study is not able to state categorically whether the two EUS-FNA results, which showed reactive lymph nodes, were true results or false negatives from sampling errors. When available, on-site cytopathologic assessment could be useful in guiding the number of passes required for adequate tissue materials. Unfortunately, this was not feasible in every case due to logistical difficulties. Nonetheless, even when based simply on the assessment of the endosonographer,[13] an adequate cellular aspirate could be obtained in all cases.

We conclude that EUS-FNA is useful as an adjunct to CT and bronchoscopy in the evaluation of suspected lung cancer in routine clinical practice.

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