Clinical Impact of Endoscopic Ultrasound-Fine Needle Aspiration of Left Adrenal Masses in Established or Suspected Lung Cancer

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Introduction: Correct lung cancer staging is pivotal for optimal allocation to surgical and nonsurgical treatment. A left adrenal gland (LAG) mass is found in 5 to 16%, and malignancy preclude surgery. Endoscopic ultrasound (EUS) is superior to other imaging procedures in visualizing LAG, but the impact of EUS-fine needle aspiration (FNA) on tumor, node, metastasis (TNM)-staging, treatment, and survival is unknown.

Methods: The impact of EUS-FNA of the LAG on TNM staging, treatment, and survival was evaluated retrospectively in all patients ($n = 40$) referred to EUS during 2000–2006 for known or suspected lung cancer and where EUS disclosed an enlarged LAG. Conventional workup had preceded EUS.

Results: EUS-FNA of an enlarged LAG altered the TNM staging in 70% (downstaged: 26 of 28 patients) and treatment in 48% (gained surgery 25%, avoided surgery 5%, surgically verified benign disease 5%, no cancer and no further workup 5%, and no cancer, control computed tomography, and then no further workup 8%). A malignant LAG lesion was found in 28% and was significantly associated with shorter survival.

Conclusion: EUS-FNA of an enlarged LAG in patients with known or suspected lung cancer had a significant impact on TNM staging, treatment, and survival. The impact of routine visualization of the LAG in lung cancer workup needs to be prospectively validated.

Key Words: Diagnosis, Endoscopy, Lung cancer, Survival.

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Lung cancer is the leading cause of cancer-related mortality in the Western countries, with an estimated annual incidence of ~174,000 cases and ~162,000 deaths in the United States.[1] Most cases are non-small cell lung cancer (NSCLC), and correct staging is pivotal for optimal allocation to surgery, which is curative in case of localized disease, whereas the current recommended treatment in patients with disseminated disease involves chemo- and radiotherapy.[2] An adrenal mass is found at the initial diagnosis of NSCLC in 5 to 16% of the patients; however, the majority of these masses are benign adenomas.[3,4] Sensitivity and specificity of imaging techniques are currently insufficient to differentiate benign from malignant masses, and false-negative and false-positive rates by computed tomography (CT) scan both average 10%.[5] Adrenal masses are traditionally sampled by percutaneous biopsy, but endoscopic ultrasound (EUS) through the esophagus is superior to transabdominal ultrasound or CT scan for imaging the left adrenal gland (LAG).[6] EUS-fine needle aspiration (FNA) and endoscopic bronchial ultrasound-FNA are at present recommended as first choice procedures in invasive staging of mediastinal lymph nodes,[7] but other relevant lesions are within reach by EUS too: paraesophagal masses, liver lesions, and LAG lesions.[3,8] The feasibility, safety, yield, and clinical impact of EUS-FNA in evaluating LAG in patients with established or suspected lung cancer remains to be systematically reported.

In this study, we aimed at investigating the clinical impact of EUS-FNA in patients with an established or suspected diagnosis of lung cancer and an abnormal LAG at EUS.

PATIENTS AND METHODS

Patients and Design

A retrospective data collection was performed in patients with established or suspected lung cancer and in whom EUS disclosed an abnormal LAG ($n = 40$). Patients were referred for EUS at the Department of Surgical Gastroenterology, Gentofte Hospital, between 2000 and 2006, for either preoperative staging of established lung cancer or diagnostic evaluation of CT-verified abnormality of the LAG, paraesophagal lesions, and/or enlarged mediastinal lymph nodes. We routinely visualized the LAG in all patients undergoing EUS: if abnormal, FNA was performed for a cytologic diagnosis, and patient data were registered. Patients with right adrenal gland lesions were excluded from this study, as these lesions were examined by transabdominal ultrasound. Before EUS, all patients had undergone an initial workup at the referring department: CT, bronchoscopic biopsy sampling, and, when appropriate, transthoracic needle aspiration biopsy

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and/or pleuracentesis. Anonymized data were transferred to predefined data sheets as recoded categorical or numeral data. All but two patients were referred from the Department of Chest Medicine, Gentofte Hospital, the remaining were referred from two separate centers. All patients gave verbal, informed consent for the EUS procedure (in Denmark, written consent is not juridically required before therapy or invasive procedures). The institutional review board was not consulted because the study is a retrospective description of an established workup and thus nonexperimental. The study was conducted according to the guidelines of the Helsinki declaration and guidelines of the local Ethical Committee, Copenhagen County, Denmark.

Endpoint

Primary endpoint: clinical impact of EUS, i.e., avoidance of futile surgery or gained surgery due to downstaging as a consequence of a difference between pre- and post-EUS tumor, node, metastasis (TNM) staging. "Survival duration" was stated the June 18, 2008, by searching the regional Health Care database (Grønt System, Region Hovedstaden, Denmark) and expressed as months survived after EUS.

Secondary endpoints: complications, diagnostic yield and diagnostic values of EUS-FNA of LAG, the agreement with CT findings (dichotome variable: normal/abnormal), and identification of clinical or paraclinical variables associated with LAG malignancy.

True diagnostic values of EUS-FNA in the diagnosis of LAG metastases could not be established, because no surgical or necropsy biopsies were performed in our study. In absence of a standard procedure at present, we used "survival ≥2 years" as a proof of benignancy (i.e., true negative diagnosis), because adrenal gland metastases are associated with poor survival.

Endoscopic Ultrasound

EUS-FNA was performed on an outpatient basis with the patient in conscious sedation using midazolam and phentanyl. The EUS examination was performed with a flexible echoendoscope with a curved array transducer, an adjustable ultrasonic frequency of 5 or 10 MHz, and a penetration depth of 7 to 8 cm (an Olympus ultrasonic endoscope [GF-UC160P-OL5] connected to an Olympus processor [EU-C60] or an Olympus [GF-UC140P-AL5] ultrasonic endoscope connected to an Aloka ultrasound processor [Prosound 5000] or a Pentax [EG 3830] ultrasonic endoscope connected to an Hitachi ultrasound processor [EUB 8500]). The LAG and left liver lobe was routinely inspected first, and if a mass was identified, it was sampled by FNA first. Lymph nodes were characterized according to criteria suggestive of malignancy (round shape, hypoechoic, sharp margin, and size >1 cm). The location was classified according to the Mountain/Dressler Regional Nodal Stations for Lung Cancer Staging.[9] All lymph nodes with at least one criterion suggestive of malignancy were sampled (N3- before N2-lymph nodes). A 22-Gauge needle (MEDI-Globe, Sonotip II) was used for the biopsy. EUS-FNA of the LAG was performed through the cardia of the stomach with 1 to 3 passes of the needle. The aspirated material was smeared onto glass slides, air dried, and transported to the Department of Pathology for staining for cytologic evaluation. The patients were observed for 1 to 2 hours at the hospital after the procedure. All EUS-FNA examinations were performed by one of three experienced endosonographers. Possible complications were recorded up to 1 year after the procedure. The cytologic specimens were stained by the May-Grünwald-Giemsa method. Microscopy was performed by an experienced cytopathologist (B.G.S.). The cytologic diagnoses were categorized as follows: positive for malignancy, benign, or nondiagnostic.

Statistics

All calculations were performed using the SPSS statistical software, version 11.0 (SPSS Inc, Chicago, IL): continuous variables were presented as median and range and differences analyzed with Mann-Whitney *U* test. Discrete variables were presented as number and percentage (*n*, %) and differences analyzed with Fisher's exact test. Statistical significance was reached when $p < 0.05$.

RESULTS

Patients

Medical records and survival data were available for all patients (median age 63 [range, 38–79; women $n = 20$; staging of known NSCLC $n = 15$). Pre-EUS TNM staging suggested a surgically curable lung neoplasm in two patients (stage IB and IIB). Table 1 shows that no clinical or endosonographical parameter was significantly associated with LAG malignancy except malignancy in EUS-FNA specimens of mediastinal lesions.

Final Diagnoses

Overall, 33 patients (83%) received a final diagnosis of malignancy: NSCLC ($n = 29$, consisting of nonspecified: $n = 17$; large cell carcinoma: $n = 1$; adenocarcinoma: $n = 9$; squamous cell carcinoma: $n = 2$), small cell lung cancer (SCLC) ($n = 1$), malignant thymoma ($n = 1$), lung metastasis from femoral myosarcoma ($n = 1$), and unknown primary neoplasm with cerebral metastases ($n = 1$). In the remaining seven patients, an initial suspicion of malignancy was abolished after workup. Two patients proceeded to lobectomy, whereas workup was terminated directly or shortly after EUS in five patients who all had CT scans showing lesions in lungs, mediastinal glands, and LAG, and all had benign EUS-FNA from the two latter locations. In two patients, the pulmonary lesions were reached by EUS (showing fibrotic scarring and infection), and workup stopped hereafter. In three patients, reevaluation of the CT scan performed at a multidisciplinary meeting (chest surgeon, chest physician, radiologist, pathologist, and oncologist) with the benign EUS-FNA data available resulted in an expecting approach: control CT scan showed resolution of pulmonary tumor.

Left Adrenal Gland

EUS showed a focal lesion ($n = 36$) or an enlarged gland ($n = 4$; nonhypoechoic and preserved shape). Malignancy was found in LAG biopsies from 11 patients (27%): NSCLC ($n = 10$) and myosarcoma ($n = 1$) and was significantly associated with short survival. No between-groups differences in follow-up length were found (Table 1). Of 29 benign LAG biopsies, 27 (93%) contained representative

samples of adrenal gland tissue, resulting in a diagnostic yield of 95% (38 of 40). Benign adrenal hyperplasia was detected in two samples, and one patient (with enlarged mediastinal lymph node at CT and a reduced pulmonary mass at control CT) had a LAG neoplasm: surgical removal confirmed a benign, mature teratoma. The association and diagnostic rates of EUS-FNA outcome for 2-year survival are presented in Table 2. No complications of EUS-FNA were observed.

The majority of our patients had a CT finding of an abnormal LAG, as this was an inclusion criterion. The positive and negative predictive values of CT were 0.29 (nine malignant biopsies/31 abnormal LAG at CT) and 0.78 (seven nonmalignant [normal] biopsies/nine normal LAG at CT), respectively. The corresponding values for the ultrasonographical diagnosis of LAG by EUS were 0.31 (11 malignant biopsies/36 abnormal LAG [focal lesions] at EUS) and 1.0 (four benign biopsies/four enlarged but otherwise normal LAG at EUS).

TABLE 1. Outcome of EUS-FNA of the Left Adrenal Gland: Demographic, Radiographic, Endoscopic, and Clinical Variables

	Malignancy ($n = 11$)	No Malignancy ($n = 29$)	p^a
Women, *n* (%)	3 (27)	17 (59)	0.16
Age (yr), median (range)	62 (47–78)	63 (38–79)	0.98
Staging of NSCLC, *n* (%)	5 (46)	10 (35)	0.72
CT: normal left adrenal gland, *n* (%)	2 (18)	7 (24)	1.0
EUS: left adrenal gland			
Focal lesion, *n* (%)	11 (100)	25 (86)	0.56
Hypoechoic, *n* (%)	10 (91)	23 (92)	1.0
Normal shape, *n* (%)	0 (0)	4 (14)	0.56
Largest diameter in mm, median (range)	20 (6–60)	20 (7–50)	0.77
No. of passings, median (range)	2 (1–3)	2 (1–3)	0.90
EUS-FNA: mediastinal malignancy, *n* (%)	9/10 (90)	10/22 (45)	<0.05
Malignancy, *n* (%)	11 (100)	22 (76)	0.16
Lung cancer, *n* (%)	10 (91)	20 (69)	0.40
Surgery, *n* (%)	0 (0)	12 (41)	<0.005
Survival (mo), median (range)	6 (1–33)	26 (1–86)	<0.005
Follow-up (mo), median (range)	36 (21–86)	43 (21–86)	0.29

[a] Fisher's exact test resp. Mann-Whitney's *U* test.

CT, computed tomography; EUS-FNA, endoscopic ultrasound-fine needle aspiration; NSCLC, non-small cell lung cancer.

Mediastinum

In five patients (12%), mediastinal structures were considered normal both by EUS and CT, and no samples were obtained. Mediastinal malignancy was found in 20 patients (suspicion of lung cancer: $n = 15$): 11 of these patients (55%) had benign LAG samples (NSCLC: $n = 10$; SCLC: $n = 1$) and nine malignant LAG samples.

Clinical Impact of EUS

Figure 1 depicts the clinical course of our patients.

No Clinical Impact

Pre-EUS TNM stage was unaltered in 12 patients (stage IV: $n = 11$; stage IIIB: $n = 1$). Downstaging had no clinical impact in additionally 9 of 26 patients (31%): stage IV to IIIB (N2/N3 disease [$n = 6$], T4: mediastinal tumor invasion, $n = 1$); SCLC ($n = 1$); and stage IB but predicted postsurgical FEV_1 <0.8 L ($n = 1$).

Avoided Surgery

Two patients had LAG metastases and were thus upstaged from stage IB and IIB to stage IV. Five patients avoided further investigation or therapy because EUS (and a follow-up CT, $n = 3$) disproved intrathoracic and LAG malignancy, so totally 7 of 40 (18%) avoided futile surgery (thoracotomy + lobectomy, $n = 2$; resp. mediastinoscopy and/or video-assisted thoracoscopy FNA, $n = 5$).

Gained Surgery

The remaining 12 patients with an EUS-FNA showing the patients eligible for surgery underwent surgery, and malignancy was present in 10 patients (77%). Neither of these surgically treated patients were pre-EUS staged as eligible for surgery (downstaged from T2N3M0, $n = 1$; or stage IV, $n = 9$). Histopathological diagnoses were adenocarcinoma ($n = 5$), squamous cell carcinoma ($n = 1$), mixed subtype adenocarcinoma/squamous cell carcinoma ($n = 2$), large cell carcinoma ($n = 1$), and malignant thymoma ($n = 1$). Surgical edges were without malignancy in all but one patient (malignant infiltration of thoracic soft tissue; T3N0M0), who subsequently received neoadjuvant chemotherapy thus 9/40 (23%) gained surgical treatment. Two patients (5%) had benign lesions: infected pulmonary infarc-

TABLE 2. Outcome and Diagnostic Rates of EUS-FNA of the Left Adrenal Gland and 2-Yr Survival

	Survival ≤24 mo After EUS-FNA				
EUS-FNA of Left Adrenal Gland	**No**	**Yes**	**Total**	**Fisher's Test**	**Predictive Values**
Benign	16	13	29	$p < 0.05$	NPV: 0.55
Malignant	1	10	11		PPV: 0.91
Total	17	23	40		
	Sensitivity: 0.94	Specificity: 0.43			

EUS, endoscopic ultrasound; FNA, fine needle aspiration biopsy; PPV and NPV, positive resp. negative predictive value.

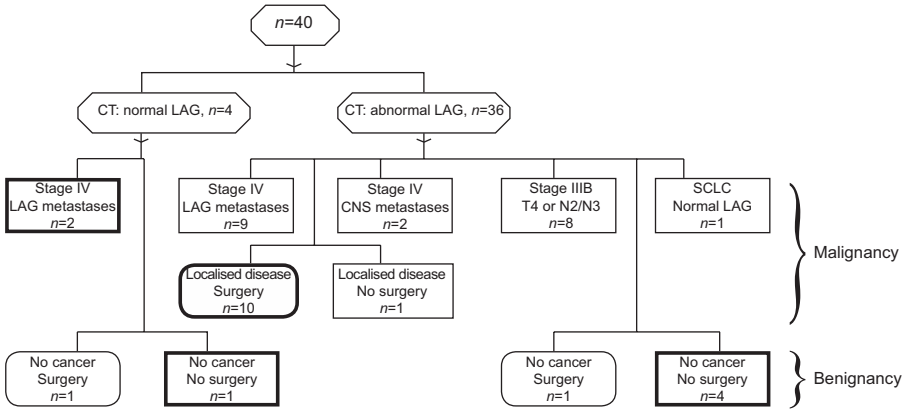

FIGURE 1. Flow-chart depicting the results of CT and EUS-FNA of the left adrenal gland (LAG), and clinical impact of adding LAG-EUS to the diagnostic work-up. Gained surgery: rounded box, fat frame. Futile surgery: rounded box, thin frame. Avoided surgery: rectangular box, fat frame. No clinical impact of EUS: rectangular box, thin frame. See text for additional information. Abbreviations: LAG, left adrenal gland; SCLC: small cell lung carcinoma; CT: computed tomography.

TABLE 3. Treatment Modality and 2-Yr Survival Rate (*n*), and Survival Duration (mo) After EUS-FNA in Patients with Malignancy ($n = 33$)

	Survival, *n*		Survival Duration (mo)		
Treatment	**2-Yr**	**Follow-Up**	**Alive**	**Dead[b]**	***p*[a]**
Surgery, $n = 10$	8 (80%)	6 (60%)	34 (22–55)	27 (15–43)	0.91
Oncology,[c] $n = 23$	3 (13%)	1 (4%)	22	8 (1–40)	0.87
Fisher's exact test, *p*	<0.0005	<0.005	0.29	0.06	

[a] Mann-Whitney *U* test.
[b] Equals follow-up duration.
[c] Chemotherapy and/or radiotherapy.
EUS-FNA, endoscopic ultrasound-fine needle aspiration.

tion (thoracotomy + lobectomy) and unspecific fibrotic tissue (video-assisted thoracoscopy + wedge resection).

Follow-Up

Table 3 shows the poor survival rates of nonsurgically treated patients: only one patient (4%) was alive at follow-up (squamous cell carcinoma, stage IIIB; follow-up duration: 22 months). Among patients with benign disease, 6 of 7 patients were alive (median follow-up duration: 46 months [range, 31–86 months]): one patient died 12 months after EUS (no surgery, aged 80 years; nonneoplastic cause of death), giving a 2-year survival of 86%.

DISCUSSION

This study is, to our best knowledge, the first to demonstrate that EUS-FNA of the LAG profoundly affected pre-EUS staging of lung cancer and survival by changing therapeutic management in patients with suspected or confirmed lung cancer and with an abnormal LAG at EUS. An adrenal gland mass is found in 5 to 16% at the time of lung cancer diagnosis,[2,3] we confirmed that EUS-FNA is a safe procedure with a high diagnostic yield in the diagnosis of left adrenal masses.[3,10–12]

The grave prognosis of metastatic lung cancer is well described,[13] and accordingly we found that malignancy of the LAG obtained by EUS-FNA was associated with short survival time and thus a high-positive predictive value for death within 2 years (Table 2). Additionally, we found that M staging by EUS-FNA of the LAG was significantly associated with both treatment modality and survival: 10 patients (25%) suspected as having LAG metastasis by CT went on to surgery after EUS-FNA was negative, and five patients (13%) found to have benign disease at EUS-FNA (assisted/confirmed by follow-up CT; $n = 3$) and thus avoided further diagnostic workup. We identified patients with N0 stage but LAG metastases, so our findings add to those recently reported by Eloubeidi et al.[14] who found that nodal staging by EUS-FNA was significantly associated with treatment modality and survival in patients with NSCLC. In our study, nodal staging by EUS-FNA was performed in the same session as the LAG evaluation, resulting in a slightly prolonged EUS procedure while avoiding further LAG workup.

The lower negative predictive value may be due to false-negative cytologic diagnoses but can also reflect the high mortality of patients with lung cancer even in absence of LAG metastases.[13,14] Except for one patient with cerebral metastases from an unknown primary carcinoma but autopsy-verified primary lung cancer, none in our population had known disseminated disease before EUS. As in similar studies, a surgical reference standard was not applicable, and postmortem LAG diagnosis does not necessarily reflect the metastatic situation at the time of EUS.[3,10–12] At present, the standard procedure is based on a fusion of data from clinical, investigative, and imaging sources.[1] A highly trained pathologist examined all specimens and experienced a satisfying yield of 95%. Stelow et al.[10] reported a 100% yield in 24 patients and Eloubeidi et al.[3] 100% in 31 patients. In the latter study, LAG tended to be larger (median 30 versus 20 mm in this study), and number of passings were higher (five versus two).[3]

Our study is a descriptive study of lung cancer workup resulting in EUS-FNA. These 40 patients constituted a minority, as more than 2000 patients received a diagnosis of lung cancer in our center during the study period. As stated in the Patients and Methods section, EUS was restricted to patients with unresolved diagnostic uncertainties or as a preoperative assessment in patients with established lung cancer,[1,2] and EUS-FNA was not performed in patients with a normal LAG when visualized by EUS. Thus, our study cannot provide reliable incidence, prevalence data on meta-

static disease to LAG, or agreement of CT findings with EUS-FNA. Ideally, EUS should have been performed in all patients with known or suspected lung cancer, but our center did not have such capacity (currently, chest physicians in our center are trained in EUS, inspired by the work of Annema et al.[15]). We hope that future, prospective studies will give us the precise frequencies of normal/abnormal findings and finding of stage IV disease by EUS-FNA. However, we have no reason to believe that our patients differ clinically from other patients with known or suspected lung cancer, which is supported by the low 2-year survival of our patients with disseminated disease (Tables 2 and 3). Our study supports that the cytologic diagnosis of an abnormal LAG identified by CT—in patients with suspected or manifest lung cancer—is efficiently achieved by EUS. The diagnostic accuracy of CT increases when combining with positron emission tomography or delayed enhanced CT,[4,5] but our data do not add to this discussion, as positron emission tomography-CT was only performed in very few patients.

We excluded patients with right adrenal gland lesions, which are most often more easily reached by FNA guided by transabdominal ultrasound than by EUS.[10] However, recent and promising case reports suggest that EUS-FNA of a right adrenal lesion should be attempted in the same session as mediastinal node staging and other sampling.[16,17]

This study is, to our knowledge, the largest report on EUS-FNA of the LAG in patients undergoing lung cancer workup. Eloubeidi et al.[3] reported in 2005 on a subgroup of patients with lung cancer: EUS-FNA confirmed LAG metastases in 60% ($n = 9$) with an abnormal LAG (pre-EUS abdominal imaging) and known ($n = 13$) or suspected ($n = 2$) lung cancer. A malignant lesion was associated with shorter survival, but data on pre- and post-EUS TNM staging, prevalence of surgery, and 2-year survival rates were unfortunately not reported.[3] In the same study, abnormal shape and larger diameter were independently associated with LAG malignancy (gastrointestinal and pulmonary cancers pooled), whereas only LAG malignancy was associated with survival in a recent study on NSCLC.[14] In our study, LAG malignancy was more prevalent when malignant mediastinal lesions were present, probably signifying progression from localized to systemic disease.[2] Neither size, shape, history of cancer, or any other included parameter was associated with LAG malignancy (Table 1).

In conclusion, our results clearly demonstrated a significant impact of EUS-FNA of the LAG on treatment modality and survival and avoided and gained surgical procedures. This is in accordance with the impact of EUS-FNA of mediastinal lesions.[12,18–22] EUS-FNA had a high diagnostic yield and accuracy for LAG lesions, it was safe, and had a high-positive predictive value of death within 2 years. As a consequence of optimized staging, allocation to correct lung cancer therapy was rationalized. Our data confirm the value of EUS in lung cancer workup as stated in recent reviews and recommendations[1,7,19,23] and suggest that the LAG should routinely be examined during EUS and punctured if a mass lesion is outlined. This suggestion needs to be prospectively evaluated.

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