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Endosonography and endosonography guided needle aspiration for left adrenal gland assessment in lung cancer patients — 10 years' experience

Abstract

Introduction: Lung cancer patients (LCP) require invasive evaluation of left adrenal glands (LAG) if distant metastases (M1b/1c) are suspected in CT or PET-CT. Only few studies showed utility of endosonography and particularly EUS-b-FNA as minimally invasive endoscopic method of LAG analysis.

Material and methods: A retrospective study of consecutive LCP was conducted in two pulmonology centers between January 2010 and December 2019.

Records of complete endosonographic staging with use of single ultrasound bronchoscope or two scopes were overviewed. The analysis included cases of enlarged LAG (body size or limbs > 10 mm) examined and sampled by EUS-b-FNA or EUS-FNA.

Results: 142 of 2596 LCP staged by complete endosonography (M: 88, F: 54 mean age 64.7) had enlarged LAG, which were biopsied by conventional EUS-FNA (52) and/or by EUS-b-FNA (90). Strong correlation with gland diameter ($P < 0.001$) was observed. The incidence of LAG metastases in analyzed group was 52.1% (74/142) and regarding histology: SCLC 76.9% (10/13), adenocarcinoma 66.7% (44/66), NSCLC 56.3% (9/16) and SCC 17.5% (7/40). A specificity and PPV for both methods were 100%. A sensitivity, accuracy and NPV for EUS-FNA were 91.7%, 96.2%, 93.3% and for EUS-b-FNA 88%, 93.3% and 87%, respectively and no significant differences for both methods were noted ($P = 0.62$, 0.44, 0.35). No severe complications after all biopsies were observed. A six months clinical follow up included all negative LCP with enlarged LAG.

Conclusions: After our study EUS-b-FNA seems to be a reasonable method of choice for LAG assesssment in LCP.

Key words: EUS, EUS-b, left adrenal, lung cancer staging

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Introduction

An exact staging of lung cancer patients has significant impact on prognosis and treatment. Adrenal glands are common sites of lung cancer metastases occurance [1, 2]. Adrenal metastases incidence ranging from 4.1% to 20% suggests that tissue verification is necessary [3, 4]. Nevertheless, little is known regarding a percentage of adrenal metastases of staged lung cancer patients (LCP) with enlarged adrenals, primarily qualified for lung resection. There is only an opinion that even a patient diagnosed with malignancy, an enlarged adrenal lesion is still more possible to be benign [5]. Various imaging techniques present adrenals as normal, consisting of a body size in width ≤ 10 mm with limbs ≤ 5 mm. A non-contrast-enhanced computed tomography (CT) describing density of adrenal glands in Haunsfield Units (HU) is useful however deficient to exclude malignancy [6]. A positron emission tomography-computed tomography (PET-CT) has a high

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diagnostic yield (sensitivity of 94% and specificity of 85%) for distant metastases in adrenal glands of LCP [7], but suspicious ones may occur false positive [8], so tissue sampling is recommended to confirm or rule out metastastic spread preventing patients to be upstaged based on radiology [9]. Conventionally, adrenal glands, especially right ones are biopsied percutaneously. The left adrenal gland (LAG) sampling is performed from a transgastric approach using ultrasound gastroscope EUS-FNA (endoscopic ultrasound guided fine needle aspiration) [10, 11]. The EUS-FNA has its advantages over percutaneous biopsy of the LAG, as no other parenchymal organs like spleen or left kidney, except the stomach wall is traversed. Sampling the LAG is a part of endosonographic mediastinal staging procedure and usually is followed by an EBUS (endobronchial ultrasound) to assess right anterior mediastinal lymph nodes. Chest physicians have valued endosonography performed by single ultrasound bronchoscope (EUS-b) as an useful tool for a few years now [12, 13]. In 2010 Herth and Hwangbo introduced EUS-b with EBUS for complete mediastinal nodal staging [14, 15]. Combination of EBUS and EUS or EBUS and EUS-b enables to reach almost the entire mediastinum to perform both a hilar and mediastinal lung cancer staging.

Material and methods

A retrospective cohort two centers study was designed to investigate the success rate of real time techniques EUS-b-FNA in comparison with conventional EUS-FNA for LAG analysis. LCP eligible for endoscopy underwent complete mediastinal lymph node staging and LAG examination using one scope (EBUS) or two scopes (EBUS and EUS). CT or PET-CT were used to assess enlarged LAGs and evaluate a suspicion of malignancy. LAG suspected in ultrasonography, which means body short axis > 15 mm and/or one or both limbs > 10 mm and/or absence of normal seagull shape, were biopsied by EUS-FNA or EUS-b-FNA with the transgastric approach. The primary study endpoint was to evaluate the ratio of LCP with a successful visibility of LAG in EUS-b and EUS and LCP with a successful EUS-b-FNA comparing to EUS-FNA procedure used to sample LAGs to obtain an adequate material for cytopathological evaluation. The secondary endpoint was both the analysis of prevalence of LAG metastases in reference to histology and location of the primary lung cancer tumor and a complication rate after LAG biopsy.

All endosonographic procedures were performed in two bronchoscopy departments according to the institutional practice by four experienced endoscopists who were well trained in EUS, EUS-b and EBUS performing over 250 procedures a year. After the informed consent was obtained, a combined procedure was performed under the mild conscious sedation based on intravenous midazolam (1–5 mg) and fentanyl (0.025–0.1 mg). A deep sedation using propofol (20–100 mg) was added if necessary. Flexible ultrasound bronchoscopes with curved linear arrays (BF-UC160F-OL8 and BF-UC180F Olympus Medical Systems Corporation, Tokyo, Japan), to visualize mediastinal and hilar structures but also left adrenals, were used for all EBUS and EUS-b examinations. Flexible ultrasound gastroscopes with integrated convex ultrasound probe (GF-UCT180F and GF-UCT160F-OL5 Olympus Medical Systems Corporation, Tokyo, Japan), which can visualize mediastinal structures and LAG were used for all EUS procedures. Dedicated ultrasound processors (CU-60, EU-ME1, EU-ME2 Olympus, Japan) were used to process imaging with power and colour doppler flow to detect blood vessels and to guide real-time sampling. Needle aspirations were performed with dedicated 22/21 gauge (G) cytological needles with suction using a 20 mL syringe during all aspirations. Every LAG was sampled 2–5 times during the EUS or EUS-b investigation. In all patients specimens were prepared both as at least 2–5 smears in alcohol solution > 90% and cell blocks fixed in Cytospin or 10% buffered formalin (pH 7.2–7.4) and then transferred to the pathology department. Rapid on-site cytology evaluation was not performed in any case. A conventional cytology was based on hematoxylin and eosin staining for all specimens but immunochemistry and molecular testing was performed additionally if necessary. Finally all cytological material was assessed by two experienced cytopathologists.

EUS-FNA procedures were performed in left sided position and then in supine position for EBUS procedure and if performed by one scope, all EBUS-TBNA and EUS-b-FNA procedures were carried out in supine position.

Statistics

The MEDCALC statistical software was used to conduct diagnostic test evaluation. A comparison of the diagnostic values of different medical tests was made with the bootstrap method (in Statistica™ Statsoft, Inc., USA environment) Asymptotic normality of maximum likelihood estimated

Table 1. A comparison of both groups EUS and EUS-b considering age and sex

Method	Patients (No)	Age (median)	Age (min–max)	Quartile 1	Quartile 3	Sex (M:F)
EUS	52	62	35–80	59.0	66.5	38:14 (73%:27%)
EUS-b	90	66.5	34–81	62.0	70.0	50:40 (56%:44%)
P-value		p = 0.001				p = 0.038

EUS — endoscopic ultrasound; EUS-b — endoscopic ultrasound by use of bronchoscope

the parameters of multinomial distribution and delta method was used to obtain the asymptotic distribution of test statistics. The bootstrap approximations of this test statistics were gathered from 2000 bootstrap replications. The significance level was set at p = 0.05.

Results

From 2010 to 2019 2596 LCP were staged by complete endosonography either by EBUS and EUS or EBUS and EUS-b. 142 (5.47%) of them (M: 88, F:54 mean age [SD] 64 [7.69]) had their LAG enlarged. The groups differed in age and sex significantly (p = 0.001, 0.038) (Table 1), but any of those features did not affect the occurrence of LAG metastases (p = 0.10, 0.14 respectively). All patients who underwent analysis were diagnosed using combination of endosonographic methods and primary lung cancer was histologically confirmed: adenocarcinoma — 66 (46.5%), squamous cell carcinoma (SCC) — 40 (28.2%), non-small cell lung carcinoma (NSCLC) — 16 (11.3%), small cell lung carcinoma (SCLC) — 13 (9.2%), carcinoid — 3 (2%), large cell carcinoma — 2 (1.4%), pleomorphic carcinoma — 1 (0.7%) and NOS — 1 (0.7%). Apart from LAG enlargement, CT or PET-CT of 26 LCP (18,3%) revealed a probability of distant metastases in brain — 13, the second lung — 5, liver — 4 and right adrenal — 4. Between years 2010 and 2019 52 LCP had their LAGs biopsied using conventional EUS-FNA. Between years 2010 and 2012 35 LCP had a complete staging procedure performed — combination of EBUS and EUS and LAG assessment. Between 2013 and 2019 EUS-FNA was performed in next 17 LCP for N staging, M1c status — LAG but mainly implemented for T4 status assessment — aorta, left atrium or esophageal infiltration. In 2012 EUS-b technique and EUS-b-FNA has been implemented into routine practice for TNM staging, including M1 and T4 status in both institutions. From 2012 to 2019 90 patients had EUS-b-FNA performed combined with EBUS. LAG was visualized by both endosonographic methods in 125/142 (88%), by EUS in 48/52 (92.3%) and by EUS-b in 77/90 (85.6%) but there were no significant differences between both methods (p = 0.68). A complete endosonography using EBUS-TBNA and EUS-FNA diagnosed N2/N3 stage in 23/52 (44.2%) LCP (sensitivity — 95.8%, accuracy — 96.1%, NPV — 96.5%) and using EBUS-TBNA and EUS-b-FNA in 55/90 (61.1%) LCP (sensitivity — 96.4%, accuracy — 97.8%, NPV — 94.6%). 66/142 (46.5%) endosonography biopsies of LAG metastases were positive, 22/142 (15.5%) of EUS-FNA, and 44/142 (31%) of EUS-b-FNA. Two false negative (FN) biopsies using EUS (2/52) (3.8%) and six FN using EUS-b technique (6/90) (6.7%) were confirmed by progression of the size of adrenals in six 6-months clinical follow up. In summary LAG metastases were diagnosed in 74/2596 (2.85%) of all LCP. The incidence of LAG metastases in analyzed group was 52.1% (74/142). The most frequent metastasizing cancer to adrenals were SCLC (10/13) (76.9%), adenocarcinoma (44/66) (66.7%) and NSCLC (9/16) (56.3%). Less frequent was SCC (7/40) (17.5%). No unexpected pheochromocytoma was found in the study group. Metastases occurred significantly more often if adrenals were enlarged (p < 0.001) (Figure 1). A primary lung cancer was located on the left in 73 (51.4%) LCP and with LAG metastases in 38 (52.1%) (upper lobe — 39/21, central — 19/11, lower lobe — 15/6) and on the right in 69 (48.6%) LCP and with LAG metastases in 35 (50.7%) (upper lobe — 37/18, lower lobe — 15/7, central — 11/7, middle lobe — 6/3). The localization of the lung tumor did not influence the occurrence of LAG metastases (p = 0.874). A benign adrenal adenoma was confirmed using endosonography in 63/142 (44.4%), by EUS-FNA in 23/142 (16.2%) and by EUS-b-FNA in 40/142 (28.2%) patients. All LCP with benign adenoma were subjected to a six months clinical follow up. Between 2010-2011 five (3.5%) EUS-FNA were non-diagnostic (adrenal tissue was absent in cytological specimen), but a six months clinical follow up did not show malignancy in them. A specificity and PPV for both

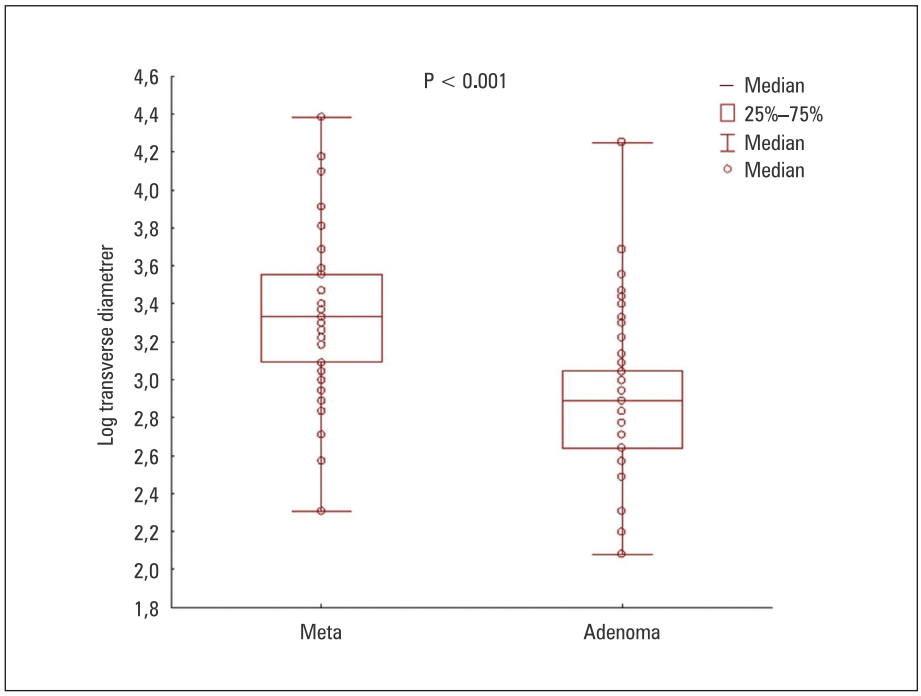

Figure 1. The incidence of malignancy and benign adenoma due to diameter of left adrenals

Table 2. Diagnostic yield of EUS-FNA and EUS-b-FNA for LAG assessment

Statistic	EUS-FNA (%/95%CI)		EUS-b-FNA (%/95%CI)		EUS-FNA and EUS-b-FNA (%/95%CI)	
Sensitivity	91.67	73–98.87	88	75.69–95.47	89.19	79.8–95.22
Specificity	100	87.66–100	100	91.19–100	100	94.72–100
NLR	0.08 (0.02–0.31)		0.12 (0.06–0.25)		0.11 (0.06–0.21)	
Disease prevalence	46.15	32.23–60.53	55.56	44.7–66.04	52.11	43.58–60.56
PPV	100		100		100	
NPV	93.33	78.79–98.14	86.96	75.89–93.39	89.47	81.54–94.24
Accuracy	96.15	86.79–99.53	93.33	86.05–97.51	94.37	89.2–97.54

EUS — endoscopic ultrasound; EUS-b — endoscopic ultrasound by use of bronchoscope; NLR — negative likelihood ratio; NPV — negative predictive value; PPV — positive predictive value

methods were 100%. A sensitivity, accuracy and NPV for EUS-FNA was 91.7%, 96.2%, 93.3% and for EUS-b-FNA 88%, 93.3% and 87%, respectively (Table 2). Neither significant differences in yield for both methods were noted (p = 0.62, 0.44, 0.35) (Table 3), nor severe complications after all biopsies performed under endosonographic guidance were observed. Due to endosonography 8 (5.6%) patients were up-staged after negative CT or PET-CT and next 32 (22.5%) were down-staged after positive CT or PET-CT findings for LAG metastases. Patients with enlarged LAG were treated as follows: chemotherapy 75 (52.8%), primary lung resection 41 (28.9%), best supportive care 12 (8.5%), chemotherapy/radiotherapy 9 (6.3%) and chemotherapy/radiotherapy/lung resection 5 (3.5%). Only 5/2596 (0.19%) LCP with confirmed metastatic LAG from the entire group underwent left adrenalectomy followed by lung resection. Ultrasonographic images of metastatic LAG obtained by EUS and EUS-b are presented in the Figure 2.

Discussion

Both accurate lung cancer mediastinal staging and finding distant metastases are prognostic factors of survival [16]. Endosonography is widely

Table 3. Differences in diagnostic yield between EUS-FNA and EUS-b-FNA

	Sensitivity	Specificity	Accuracy	PPV	NPV
EUS	91.67%	100%	96.15%	100%	93.33%
EUS-b	88.00%	100%	93.33%	100%	86.96%
Dif. EUS-EUS-b	3.67%	0.00%	2.82%	0.00%	6.38%
P-value	0.616	1	0.441	1	0.345

EUS — endoscopic ultrasound; EUS-b — endoscopic ultrasound by use of bronchoscope; NPV — negative predictive value; PPV — positive predictive value

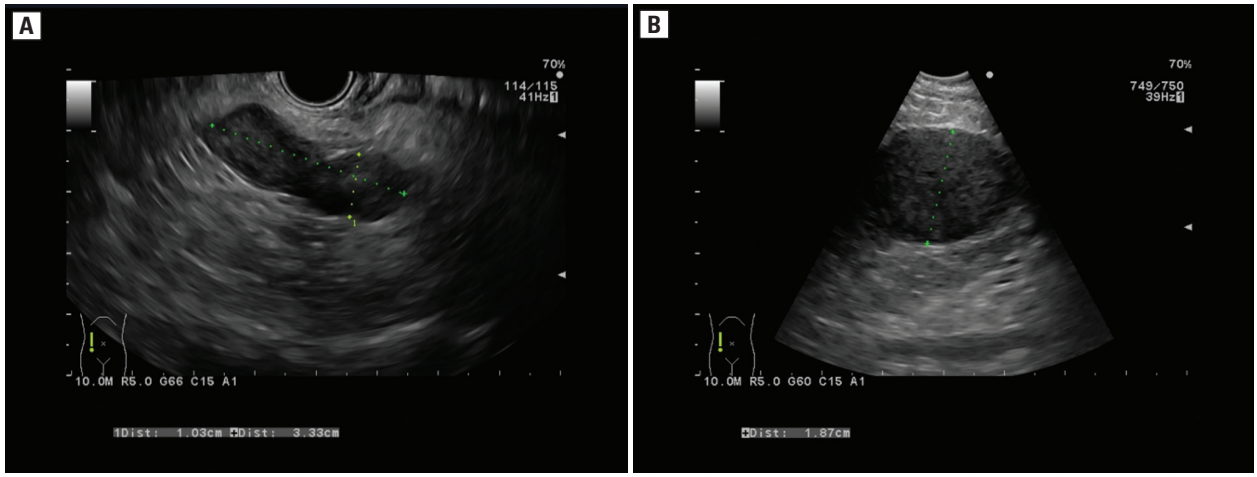

Figure 2. Metastatic, enlarged and hypoechogenic left adrenal gland in endoscopic ultrasound (EUS) (**A**) and endoscopic ultrasound by use of bronchoscope (EUS-b) (**B**) imaging

considered as the best tool both for nodal staging and adrenal assessment. The adrenals are the predilection site of lung cancer distant metastases, but data about its prevalence are limited. The largest meta-analysis, which was finally based on 6 biggest studies including 360 adrenal lesions showed that up to 50% of the LCP with adrenal lesions on imaging have metastases [19]. Nevertheless, there were only two retrospective trials including 125 patients from this meta-analysis, which showed that conventional EUS-FNA had a sensitivity to detect adrenal metastases in LCP of at least 86% [20,21].) There are also not enough data how often adrenal metastases are found during the staging of LCP, especially using EUS-b technique. In a preliminary study Crombag and Annema presented 2 NSCLC patients of 80 staged LCP with LAG metastases found using EUS-b-FNA (2.5%) [9]. Our study presenting 2596 LCP, who were staged using endoscopy during the last decade confirmed quite low (2.85%) incidence of LAG metastases. In our group of LCP with enlarged adrenals on CT scans the incidence of metastases was 52.1%, which is consistent with the data published by Crombag et al. [22] This multicenter trial enrolling 44 staged LCP showed that the incidence of LAG metastases was 54%. We presented that regarding histological type the frequency of LAG metastases was SCLC 76.9%, adenocarcinoma 66.7%, other NSCLC 56.3% and SCC 17.5%. The analysis of LCP with enlarged adrenals proved that endosonography was diagnostic in 90.9%, 46.5% revealed metastases and 44.4% — a benign adenoma. In addition, we found metastases to be more frequent in enlarged LAG ($p<0.001$) and our data are not consistent with the analysis presented by Abrams et al. based on autopsies [5]. In a prospective study Eloubeidi et al. showed on 59 patients the correlation between occurrence of malignant lesions and larger adrenals (3.1 cm), as well as benign adenomas and smaller ones (2.3 cm). Results showed that the accuracy was 68% which suggests that the size alone is not reliable enough to differentiate them and that tissue acquisition is still needed [23]. According to the guidelines of the National Institute of Health from 2002, malignancy is more likely in lesions > 4 cm in size [24]. In a review article Patil et al. made a meta-analysis of 11 studies and observed that hypoechoic adrenals,

were more suspicious of malignancy, in majority the cytological results did not confirm it [25]. To define a final modeling of malignancy, it is necessary to compare radiological and ultrasound features of adrenals in EUS or EUS-b including not only size and loss of sea-gull shape but also their echogenicity.

The primary localization of the LC was not predictor of LAG metastases (p = 0.874). One third of the cancers metastasizing to LAG were adenocarcinoma 31%. The study of Bodtger et al. specifically evaluated the impact of EUS-FNA on the clinical decision-making in patients with enlarged adrenals. Two (5%) patients were up-staged to M1c, but other 10 (28%) became the candidates for lung resection [20]. Our trial confirmed these data as we up-staged 5.6% and down-staged 22.5% LCP. We also showed that if LAG was malignant (M1c) adrenalectomy was performed only in 5/2596 (0.19%) of LCP. We confirmed that the conventional EUS gastroscope was useful to assess LAG of 92.3% patients, what was primarily reported by Chang et al. [10]. We also confirmed that LAG can be evaluated using the ultrasound bronchoscope (EUS-b) in most of cases (85.6%), which is similar to data published by Crombag et al. (85%, 89%) [9, 22]. Even though the EUS scope has its obvious advantages over ultrasound bronchoscope (EBUS): it is longer, more stable and the scanning angle is wider (120–180° compared to 60° with the EBUS), the results of our study are only slightly better for EUS and the differences between both methods are not significant (p = 0.68). And finally we presented high diagnostic yield of EUS-b-FNA for LAG assessment sensitivity — 88%, accuracy — 93.3% and NPV — 87%, similar to EUS-FNA. As no serious complications were observed in the entire group, both methods were safe and well corresponded with other studies. However, EUS--b-FNA seems to be better tolerated because it is thinner and the complete staging procedure can be performed in one supine position. Although patients from EUS group were younger and with higher percentage of men than from EUS-b group this did not influence the occurrence of adrenal metastases. It only signifies that during the last decade older and female patients are more often qualified for staging procedures and surgical or oncological treatment. The major limitations of our study are retrospective design which may cause a selection bias and no direct comparison between both endosonographic methods. Moreover, in the vast majority of cases adrenalectomy or surgical biopsy to confirm malignancy was unavailable to perform and this became the major study limitation not only of our trial [19]. This is in accordance with the most studies evaluating endosonography, where a confirmatory cytology is regarded as a reference standard to determine malignancy mostly because of advanced stage of disease. What is more understandable there was also no surgical confirmation of benign lesions although all enrolled patients were followed-up appropriately. If not assessed in histopathology all negative biopsies can be considerded as true negatives which might also introduce a bias.

Conclusions

After our study EUS-b-FNA seems to be a reasonable method of choice for enlarged LAG assessment in staged LCP.

Conflict of interest

None to declared.

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