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ULTRASOUND TIPS IN THE LUNG CANCER DIAGNOSIS: A PILOT STUDY

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Abstract – *Objective:* *The objective of this pilot study is to evaluate the ability of lung ultrasound to provide signs of suspicion of lung cancer in patients with respiratory symptoms related to a real-world setting.*

Patients and Methods: *This is a monocentric pilot study. All patients belonging to the Internal Medicine ward with respiratory symptoms including cough, chest pain or dyspnea were recruited. Patients with previous diagnoses of respiratory diseases were excluded. An ultrasound and chest radiography (CR) were performed by expert operator. Computed tomography was carried out in case of discrepant imaging or suspect of cancer. The gold standard was the discharge diagnosis.*

Results: *The final diagnosis included 51 cases of lung cancer, and 386 other diagnoses, which included pneumonia, heart failure, chronic obstructive pulmonary disease (COPD), tuberculosis, pneumothorax or fibrosis/restrictive syndrome. Consolidation areas were found in 75.4% of patients diagnosed with lung cancer, in 51% of all other diseases. Single sides pleural effusion was found in 52.9% of lung cancer (4.2% in the absence of pathology vs. 25.1% other diagnoses. A significantly higher prevalence of pleural pain and lactate were observed in cancer patients (23.5% and 34.7%, respectively). A receiver operating characteristics curve (ROC) showed a high LUS accuracy for both operators (LUS-I AUROC: 0.855 [95% CI: 0.793-0.917]; p<0.001 and LUS-II AUROC: 0.838 [95% CI: 0.774-0.902]; p<0.001), with a sensitivity and specificity of 92.2% and 87.8%, respectively.*

Conclusions: *The findings showed the lung ultrasound might be useful in the diagnosis of lung cancer in clinical practice. These data need to be supported by a large clinical trial.*

KEYWORDS: *Lung ultrasound, Lung cancer, Non-invasive diagnosis, Screening.*

INTRODUCTION

Lung cancer is the most frequent cause of cancer death in Italy[1]. The main risk factors are smoking, air pollution and particulate matter exposure[2,3]. The 5-year survival of patients with lung cancer in Italy is equal to 16%, negatively affected, above all, by advanced stages diagnoses[4]. In recent years, some specific genetic mutations have been identified which have allowed to better define some lung cancer subtypes, especially in non-smokers[5-7]. Computed tomography-associated positron emission tomography with 18-fluoro-deoxyglucose (18-FDG CT-PET) is the gold standard in solitary lung nodule diagnostic imaging, pre-operative staging and post-treatment of lung cancer[8]. In particular, it allows an accurate staging especially for the evaluation of lymphonodes and metastatic bone involvement in reference to the increase in metabolic activity of tumor cells[8,9]. Magnetic resonance imaging (MRI) may enable advantages in a view of neoplastic infiltration of the chest wall, diaphragm, vascular and nerve structures of the mediastinum and pericardium due to its mul-

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tiparametricity and multiplanarity, also in cases of inconclusive contrast enhancement computed tomography (CT)[9,10]. Lung ultrasound (LUS) played a limited role in the study of lung cancer diseases. However, improvements in technology and increasing research into non-invasive diagnostics and radiation-free have led to greater use of LUS in clinical practice[11-13]. Moreover, ultrasonography is definitely useful in the execution of endotracheal techniques, such as EndoBronchial Ultrasound-guided Transbronchial needle aspiration (EBUS-TBNA) or Transesophageal Bronchoscopic Ultrasound-Guided Fine Needle Aspiration (EUS-B-FNA). These procedures have proven suitable and effective on a high percentage of patients for histological sampling[14].

Recent studies showed the effectiveness of ultrasound in the identification of the indirect signs characterizing lung cancer at various stages. Although the localization of lung cancer at the large caliber bronchi cannot be evaluated by LUS, it is possible to promptly detect a peripheral or large volume lesions[15-17]. This could become a probably valid tool in the diagnosis phase as well as in the follow-up of the disease, in support of the validated methods.

The objective of this pilot study was to evaluate the ability of LUS to provide signs of suspicion of lung cancer in patients with respiratory signs and symptoms admitted in a general medicine practice setting.

PATIENTS AND METHODS

Patients' population

This is a single-center pilot study. All patients consecutively referred to our Department of Internal Medicine of Campania University with respiratory symptoms including cough, chest pain or dyspnea, were recruited. Previous diagnosis of respiratory diseases, pregnancy or underaged were excluded. A physical examination, routine laboratory tests, CR and LUS were performed. In case of discordant imaging or if deemed necessary for the achievement of the diagnosis, a CT has been conducted. A spirometry test was also performed to evaluate respiratory functional parameters. Upon completion of the entire clinical-instrumental diagnostic process, a final diagnosis was reached which represented the gold standard. All patients gave their consent to the scientific data treatment.

Data collection was conducted according to the Institutional policy regarding the observational pilot study and the Helsinki declaration and its amendments.

Clinical and laboratory tests

We have collected on a dedicated database all data concerning sex, age, body temperature and symptoms. We performed physical examination to detect wet or dry noises or signs of pleural effusion. We also carried out blood gas analysis to detect pH imbalance (acidosis or alkalosis), and lactates amount. Blood counts, inflammatory indices (ESV, RCP, ferritin) and the most common laboratory parameters useful for diagnosis were also evaluated.

Lung ultrasound

LUS was performed by two experienced operators blinded by the patient's clinical data. Patients were examined with the aid of two different types of ultrasound probes, respectively low frequency (3-5 MHz) and high frequency (9-15 MHz); this allowed both the superficial and deep portions of the chest to be examined. The examination was carried out with a supine and seated patient by scanning extended to the entire chest area by placing the probe in all intercostal spaces. The scans were carried out with longitudinal and transverse movements along the posterior wall, the axillary cavity and the anterior portion. The supra and subclavicular region corresponding to the pulmonary apex was also explored. All the most common ultrasound patterns were recorded: the presence of horizontal artifacts (A lines) and vertical artefacts (b lines), the pleural line for morphology and mobility, the presence of pleural effusion and areas of consolidation or clear nodular lesions. The ultrasound findings described followed the international experts consensus[18].

Radiological imaging

CR was performed in standard A-P and L-L projections and, like ultrasound, during the first 24 hours after admission. A CT was performed by experienced radiologists with cuts and dosage of millisievert appropriate to the study of the pulmonary parenchyma and mediastinum (120 Kv, 20-50 mA, 0.4-1 mSv). The evaluation of radiological images was performed blinded with respect to the clinical and ultrasound data of the patients.

Statistical analysis

Data are expressed as number and percentage for categorical variables, while continuous variables are expressed either as median and interquartile

range (IQR) or mean and standard deviation (SD), depending on their distribution. All continuous variables were previously analyzed for their distribution through the Shapiro-Wilk test and the Kolmogorov-Smirnov Goodness of Fit test. The differences between the groups were analyzed through the exact Fisher test or the chi-square test in the case of categorical variables. The continuous variables were evaluated through the non-parametric Mann–Whitney U test in the case of non-normal variables or through the Student's *t*-test, if the normal assumption was respected. The variables that emerged significant in the univariate analysis were inserted into a multivariate model of logistic regression according to the Wald Stepwise method. Finally, an analysis using ROC curves was performed to evaluate and compare the accuracy of LUS and CR in the diagnostic process. *p*-values below 0.05 were considered statistically significant. All analyses were performed with SPSS software (version 24, IBM, Armonk, NY, USA) and STATA 14 software.

RESULTS

The study population was homogeneously distributed by sex (M 51.4%), with an average age of 70 years old (IQR: 58–80). The final diagnosis included 51 cases of lung cancer, and 386 other diagnoses, which included pneumonia, heart failure, chronic obstructive pulmonary disease (COPD), tuberculosis, pneumothorax or fibrosis/restrictive syndrome). Compared to the diagnostic capacity, a high rate of diagnostic tests for lung cancer or other pathologies can be observed ($p<0.001$). The data were shown in Table 1.

The distribution of ultrasound parameters according to the presence of lung cancer or other pathologies was described in Table 2. In particular, areas of consolidation were found in 75.4% of patients diagnosed with lung cancer, significantly more prevalent especially than subjects with no diagnosis (9.3%), as well as other diagnoses made by LUS (65.3%) ($p<0.001$). The bronchogram was found in 29.4% of patients diagnosed

TABLE 1. Lung Ultrasound's diagnostic ability (n=555).

Lung Ultrasound	*Not Diagnostic (n=108)*	*Diagnostics (n=447)*	*p-value*
Diagnosis, n (%)			<0.001
Absent	47 (43.5)	71 (15.9)	
Cancer	5 (4.6)	46 (10.3)	
Other diseases*	56 (51.9)	330 (73.8)	

**Pneumonia, Heart Failure, Chronic Obstructive Pulmonary Disease (COPD), Tuberculosis, Fibrosis/Restrictive Lung Disease, Pneumothorax, Diagnostic Associations.

TABLE 2. Comparison of final diagnosis and every single parameter of lung ultrasound (n=555).

Final Diagnosis Lung ultrasound parameter	*Absent (n =118)*	*Cancer (n=51)*	*Other diseases** (n=386)*	p-*value*
Air Bronchogram, n (%)	3 (2.5)	15 (29.4)	197 (51)	<0.001
Pleural effusion, n (%)				<0.001
Absent	109 (92.4)	18 (35.3)	198 (51.3)	
Unilateral	5 (4.2)	27 (52.9)	97 (25.1)	
Bilateral	4 (3.4)	6 (11.8)	91 (23.6)	
B-profile, n (%)				<0.001
Negative	110 (93.2)	25 (49)	146 (37.8)	
Focal	7 (5.9)	23 (45.1)	171 (44.3)	
Diffuse	1 (0.8)	3 (5.9)	69 (17.9)	
Consolidations, n (%)	11 (9.3)	38 (74.5)	252 (65.3)	<0.001
Pleural Line, n (%)				<0.001
Irregular	10 (8.5)	25 (49)	182 (47.4)	

**Pneumonia, Heart Failure, Chronic Obstructive Pulmonary Disease (COPD), Tuberculosis, Fibrosis/Restrictive Lung Disease, Pneumothorax, Diagnostic Associations.

with lung cancer, significantly more prevalent especially than subjects with no diagnosis (2.5%; $p<0.001$), while it was also observed in 51% overall of all other diseases. Finally, pleural effusion was significantly prevalent in subjects with lung cancer, with a higher prevalence at the unilateral level (52.9% *vs.* 4.2% no diagnosis vs. 25.1% other diagnoses; $p<0.01$). At bilateral level, it was present in only 11.8% *vs.* 23.6% of other diagnoses, which take into account different pathologies. The B-profile, significantly negative in 93.2% of subjects with no diagnosis compared to both lung cancer and other diseases ($p<0.001$), did not show statistically significant differences between the diagnosis of lung cancer and others with regard to the focal pattern (45.1% *vs.* 44.3%). While the widespread pattern in other diagnoses is significantly higher (17.9% *vs.* 5.9% in lung cancer; $p = 0.017$). The irregularities of pleural line were significantly associated with a positive diagnosis, both for lung cancer (49%) and other pathologies (47.4%), compared to subjects with no diagnosis (8.5%; $p<0.001$). On the other hand, statistical significance was not achieved in the single comparison between lung cancer and other diseases.

A significantly higher prevalence of pleural pain is observed in cancer subjects (23.5%) compared to both the absence of diagnosis (5.1%; $p<0.001$) and other diagnoses (13.7%; $p<0.001$). Moreover, a marked leukopenia (18%) was observed both compared to subjects with absent diagnosis (10.2%; $p<0.001$) and to other diseases (5.5%; $p<0.001$). Lactates are significantly higher (≥ 2) in neoplastic subjects (34.7%). Finally, the pH balance was significantly normal in subjects with no diagnosis (72.2%, $p<0.001$), while alterations of various types (metabolic alkalosis, metabolic acidosis, alkalosis and respiratory acidosis, as well as their copresence) were observed overall in 75% of lung cancer patients. Respiratory and heart rate were significantly lower in lung cancer compared to other diseases (<16 apm in 23.5% *vs.* 14.8% in other diseases; $p<0.001$; <100 bpm in 80.4% *vs.* 69.7% in other diseases; $p<0.001$, respectively). Body temperature, on the other hand, is significantly higher in subjects with other diagnoses (39.1% *vs.* 15.7% in lung cancer; $p<0.001$). All detailed data are represented in Table 3.

We also created a receiver operating characteristics curve (ROC) to compare the accuracy, specificity, and sensitivity of LUS *vs.* lung cancer diagnosis. As shown in Figure 1 with respect to both operators, LUS was a possible accurate tool for lung cancer diagnosis (LUS-I AUROC: 0.855 [95% CI: 0.793-0.917]; $p<0.001$ and LUS-II AUROC: 0.838 [95% CI: 0.774-0.902]; $p<0.001$), with a sensitivity and specificity of 92.2% e 87.8% (LUS-I), 92.2% and 85.4% (LUS-II), respectively.

DISCUSSION

Our study aimed to evaluate the potential role of LUS in internal clinical practice in relation to lung cancer diseases. The results expressed by this pilot study demonstrated the usefulness in clinical practice of LUS in real-life setting. In particular, the method could help the clinician to identify ultrasound signs that express the presence of peripheral bronchi or pleura alteration cancer related. The ability to detect such signs has proven to be very effective with a low false negative rate. The most frequently associated signs were pleural effusion and areas of consolidation. Usually, the effusion can be the result of a pleural involvement of the tumor or less frequently of a reactive inflammation to a state of superinfection. The area of consolidation can also be a sign of the extension of the neoplasm to the peripheral bronchi or a pneumonia-like reaction that sometimes accompanies the onset of tumor symptoms. The presence of focal b lines also showed a significant association with the presence of tumor disease. Usually, the b-lines in LUS are expressions of an involvement of the interstitium by an infection or heart failure[19-21]. In the case of cancer disease, it can be a sign of a cancerous infiltration or an infection. They both can occur due to a disease related to a state of immunodepression or by the abscessualization of a small or large lesion. Thus, the clinical signs could be related to the state of the disease, complications and indirectly useful to suspect the disease. The cough, the thoracic / pleural pain and the consequent alterations of the hemogasanalytic profile, are the mirror of the involvement of the alveolar and interstitial parenchyma of the disease and can be identified by the ultrasound. Unfortunately, the most frequent localizations of lung cancer are at the central site, in the large bronchi. This makes it impossible for ultrasound to directly visualize a lesion. Only in cases of peripheral development of the primary lesions or metastases, the operators could identify the lesion. These peculiarities advise against the ultrasound use in view to the screening and early diagnosis. Furthermore, the CT-PET are the gold standard also for the detection of small lesions. In fact, these methods are not affected by the obstacle produced by the air or localization. Globally, our study showed that in the clinical practice (ward or emergency), a simple LUS could suggest a diagnostic insight of the pulmonary district. In this perspective, the LUS could be useful with sat-

TABLE 3. Comparison of final diagnosis, lung ultrasound and biochemical parameters (n=555).

Final Diagnosis Parameter	*Absent (n=118)*	*Cancer (n=51)*	*Other diseases (n=386)***	*p-value*	*Diagnostic (n=447)*	*Not diagnostic (n=108)*	*p-value*
Sex, n (%)				0.494			0.740
Male	66 (55.9)	24 (47.1)	196 (50.8)		233 (51.8)	54 (50)	
Female	52 (44.1)	27 (52.9)	190 (49.2)		217 (48.2)	54 (50)	
Cough (expectoration), n (%)	21 (17.8)	22 (43.1)	169 (43.8)	<0.001	180 (40)	32 (29.6)	0.046
Breath rate, n (%)				<0.001			0.010
<16 breaths per minute	63 (53.4)	12 (23.5)	57 (14.8)		98 (21.8)	34 (31.5)	
17-20 breaths per minute	43 (36.4)	17 (33.3)	124 (32.1)		145 (32.2)	41 (38)	
>20 breaths per minute	12 (10.2)	22 (43.1)	205 (53.1)		207 (46)	33 (30.6)	
Heart rate, n (%)				<0.001			0.079
<100 beats per minute	105 (89)	41 (80.4)	269 (69.7)		330 (73.3)	88 (81.5)	
>100 beats per minute	13 (11)	10 (19.6)	117 (30.3)		120 (26.7)	20 (18.5)	
Body temperature, n (%)				<0.001			0.162
<37°C	101(85.6)	43 (84.3)	235 (60.9)		302 (67.1)	80 (74.1)	
>37°C	17 (14.4)	8 (15.7)	151 (39.1)		148 (32.9)	28 (25.9)	
Chest physical examination, n (%)	38 (32.2)	39 (76.5)	329 (85.2)	<0.001	342 (76.2)	66 (61.1)	0.002
Pleural pain, n (%)	6 (5.1)	12 (23.5)	53 (13.7)	<0.001	59 (13.1)	12 (11.1)	0.570
White blood cells (10^3), n (%)				<0.001			<0.001
<4.2	12 (10.2)	9 (18)	21 (5.5)		26 (5.8)	17 (15.9)	
4.2-10.5	93 (78.8)	27 (54)	170 (44.2)		228 (50.9)	62 (57.9)	
>10.5	13 (11)	14 (28)	194 (50.4)		194 (43.3)	28 (26.2)	
Lactates, n (%)				<0.001			0.700
<2 mg/dL	107 (93)	32 (65.3)	258 (70.1)		318 (74.1)	79 (76)	
≥2 mg/dL	8 (7)	17 (34.7)	110 (29.9)		111 (25.9)	25 (24)	
PCR, n (%)				<0.001			0.002
<0.5 mg/dL	53 (46.1)	10 (20)	51 (13.3)		80 (18)	34 (32.3)	
0.6-1 mg/dL	18 (15.7)	13 (26)	53 (13.8)		69 (15.5)	16 (15.2)	
1.1-10 mg/dL	37 (32.2)	17 (34)	173 (45.2)		184 (41.3)	44 (41.9)	
>10 mg/dL	7 (6.1)	10 (20)	106 (27.7)		112 (25.1)	11 (10.5)	
Arterial blood gas, n (%)				<0.001			0.029
Normal	78 (72.2)	12 (25)	99(26.8)		140 (32.9)	49 (49)	
Respiratory Acidosis	3 (2.8)	3 (6.3)	38 (10.3)		37 (8.7)	7 (7)	
Metabolic acidosis	6 (5.6)	4 (8.3)	15 (4.1)		18(4.2)	7(7)	
Respiratory Alkalosis	8 (7.4)	4 (8.3)	45 (12.2)		48 (11.3)	9(9)	
Metabolic Alkalosis	4 (3.7)	5 (10.4)	21 (5.7)		27 (6.4)	3 (3)	
Mixed disorders	9 (8.3)	20 (41.7)	151 (40.9)		155 (36.5)	25 (25)	

**Pneumonia, Heart Failure, Chronic Obstructive Pulmonary Disease (COPD), Tuberculosis, Fibrosis/Restrictive Lung Disease, Pneumothorax, Diagnostic Associations.

isfactory accuracy. Ultrasound is now considered a completion of the physical examination, and this makes it even more akin to the work of the internist rather than the radiologist[22-25]. The absence of radiation, the low cost and the possibility of using portable equipment at a patient's bed allow, in expert hands, to obtain encouraging results even in a frontier field such as ultrasound of the thoracic compartment. These considerations must always be measured against the recognition of the limits of the method, which in any case cannot replace the techniques for diagnosing lung cancer suggested by the guidelines. Technological progress may eventually allow the overcoming of airborne barriers that produce artifacts that are currently exploited to indirectly identify signs of possible disease.

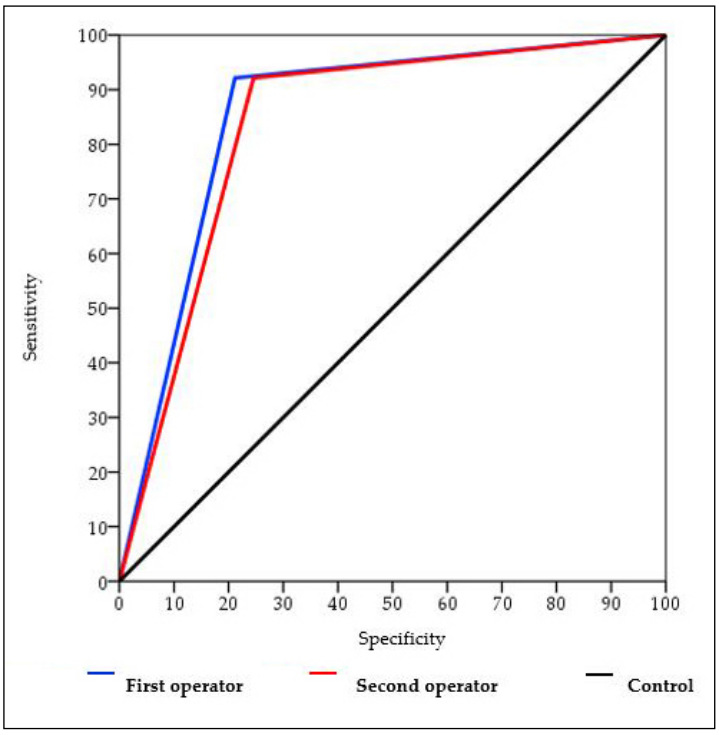

Fig. 1. ROC curve related to lung ultrasound's diagnostic ability about lung cancer comparing two different operators.

CONCLUSIONS

This pilot study may be a basis for the construction of a large multicenter trial evaluating the possibility of including LUS in the lung cancer diagnostic algorithm. Technological progress may eventually allow the overcoming of airborne barriers that produce artifacts that are currently exploited to indirectly identify signs of possible disease. In conclusion, this pilot study may be a basis for the construction of a large multicenter trial evaluating the possibility of including LUS in the lung cancer diagnostic algorithm.

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The authors declare that they have no conflict of interests.

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