Title:

The diagnostic yield using ultrasound-guided needle-aspiration for subpleural primary lung cancer is not affected by the radiological properties of the lesions resulting from computed tomography

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Naoko Iwakami, Shin-ichiro Iwakami, Takashi Dambara and Kazuhisa Takahashi planned this study. Naoko Iwakami and Shin-ichiro Iwakami reviewed the clinical data and contributed to this manuscript. Naoko Iwakami, Munechika Hara, Mitsuaki Sekiya and Shin-ichiro Iwakami performed ultrasound-guided needle-aspiration for subpleural primary lung cancers. All authors have revised this manuscript and have approved the

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Abstract

Background: It is well known that ultrasound-guided needle-aspiration (USGNA) for intrapulmonary subpleural lesion in contact with the pleura is useful and safe, and its diagnostic yield is high. However, reports concerned with the analyses of cases with intrapulmonary subpleural lesion which could not be diagnosed using USGNA are limited. The objective of this study is to clarify the radiological properties of subpleural primary lung cancer which obstruct diagnosis by USGNA.

Methods: The consecutive cases with subpleural primary lung cancer whose radiological properties could be confirmed by thoracic computed tomography (CT) without contrast enhancement (CE), and examined by USGNA at our hospital between January 1999 and December 2014 have been analyzed. All cases were given pathological diagnoses of primary lung cancer. The diagnostic yield by USGNA was calculated, and the properties of the lesions of the subjects were analyzed by means of thoracic CT without CE images and pathological findings.

Results: 87 consecutive cases (41-86 year olds, 75 males, 12 females) were analyzed. The overall diagnostic yield by USGNA was 86.2%. There was no statistically significant difference regarding the diagnostic yield concerning radiological properties such as cavities, small airspaces and low density areas in the lesions and their sizes. However, the

diagnostic yield for the cases with squamous cell carcinoma was statistically significantly low (p=0.02).

Conclusion: Although the diagnostic yield of USGNA is not distorted by the radiological properties of lesions, it is statistically significantly low in cases with squamous cell carcinoma.

Key words

Ultrasound, needle-aspiration, primary lung cancer, radiological properties, squamous cell carcinoma

Short title

Ultrasound-guided needle-aspiration

Abbreviations

USGNA: ultrasound-guided needle-aspiration

CT: computed tomography

CE: contrast enhancement

US: ultrasound

CI: confidence interval

OR: odds ratio

1. **Introduction**

Intrapulmonary subpleural lesions can be detected by ultrasound (US) when these lesions make contact with the pleura. Ultrasound-guided needle-aspiration (USGNA) for such intrapulmonary subpleural lesions can be performed by using this specific characteristic of US. USGNA for intrapulmonary subpleural lesions can be performed at the bedside or at the outpatients' clinic, and is a convenient diagnostic procedure. It is useful and safe because an operator can carry out an examination with a real-time image on a monitor [1, 2]. It is well-known that the diagnostic sensitivity of this method for cases with intrapulmonary subpleural lesions is high, even if the lesion is small or if patients have respiratory comorbidities [3-7]. On the other hand, the fact is that some cases with intrapulmonary subpleural lesions cannot be diagnosed using this procedure. It is unclear what kinds of radiological properties of the lesions using thoracic computed tomography (CT) hinder the diagnosis of intrapulmonary subpleural lesions by USGNA. In other words, it is unclear which USGNA should be chosen to make a definitive diagnosis or not in accordance with the radiological properties of the lesions by using thoracic CT.

The objective of this study is to clarify what kinds of radiological properties of subpleural primary lung cancer by using thoracic CT without contrast enhancement (CE)

hinder diagnosis of intrapulmonary subpleural lesions by using USGNA.

2. Patients and Methods

2.1. Subjects and study design

Consecutive cases with subpleural primary lung cancer examined by USGNA at Juntendo University Shizuoka Hospital (Nagaoka, Izunokuni-City, Shizuoka, Japan) between January 1999 and December 2014 have been analyzed. All cases could be confirmed the radiological properties by thoracic CT without CE and diagnosed as primary lung cancer. Subpleural primary lung cancer which was the target of USGNA in this study means that there is contact with the pleura, resulting in its being detectable by US.

USGNA was performed up to twice before diagnosing primary lung cancer. If a diagnosis could not be made using USGNA, other procedures including flexible bronchoscope, CT-guided needle biopsy and surgery were performed in order to make a diagnosis.

The diagnostic yield by USGNA was calculated, then pathological findings of the lesions and the properties of the lesions of subjects using thoracic CT without CE images were analyzed to examine features such as the size of the lesions and whether or not there

were cavities, small airspaces, and low density areas in the lesions. These radiological properties were selected because they were expected to hinder the diagnosis of subpleural primary lung cancer by USGNA. In other words, low density areas in a lesion may mean necrosis and a lesion that includes air can only be detected with difficulty by US because air such as in cavities, or in small airspaces, does not permit US penetration.

The complications caused by USGNA were also investigated using medical records.

2.2. Equipment

The equipment used in this study was a commercially available US unit (ALOKA SSD-2200) and a linear probe emitting 3.5 MHz cycles. A metallic needle (20 gauge in diameter, 150mm in length) was used for aspiration.

2.3. Procedures of USGNA

The USGNA was conducted by a respiratory physician with over ten years' experience of USGNA. A solid area in a lesion detected by ultrasound was decided as the site to obtain a specimen. An area including high echo-spots which coincided with air was avoided. The methods for the use of USGNA were as follows: after the sterilization of skin including an area for centesis by povidone-iodine, operators undertook standard precautions. Then, after the induction of subcutaneous local anesthesia using lidocaine hydrochloride, a metallic needle was introduced in the direction of the lesion, under US

guidance. After anesthesia at the parietal pleura, the injector syringe for anesthesia was removed and a 20 ml syringe fixed to a one-handed grip aspirator was fitted with a metallic needle. The patient was instructed to hold his/her breath to permit the needle to be positioned just above the lesion. Then the needle was inserted into the lesion, and moved up and down as widely as possible, visible in US images. Negative pressure during aspiration was generated by the aspirator. The correct positioning of the tip of the needle in a lesion was confirmed by the appearance of a high echo spot within the lesion in a US image. A smear was taken from the aspirated sample and fixed with 95% ethanol for cytology. Then, the residue in the needle was given a saline wash, and examined for cytology and culture. Rapid on-site evaluation was not performed.

A chest X-ray was subsequently performed to confirm the presence of complications such as pneumothorax or intrapulmonary hemorrhage.

2.4. Statistics

For the comparison of the radiological properties of lesions and positive diagnostic yields, Fisher's exact test was used. To adjust for potential confounders, binomial logistic regression analysis was performed. A p-value of <0.05 was considered statistically significant. Statistical analysis was conducted using Bell Curve Excel, Ver. 2.11 (Social Survey Research Information Co., Ltd. Japan, Tokyo).

2.5. Ethical declaration

Written informed consent regarding USGNA was obtained from all patients. This study was approved by the Ethics Committee in Juntendo University Shizuoka Hospital on 10th May 2016 (approval number: Rin-453). It conforms with the provisions of the Declaration of Helsinki.

3. Results

The characteristics of the patients, the sizes and the properties of the lesions are shown (Table 1). 87 consecutive cases (41-86 year olds, 75 males, 12 females) were analyzed in the present study. Concerning pathological diagnosis, 34 cases (39.1%) were diagnosed as adenocarcinoma, 26 cases (29.9%) were diagnosed as squamous cell carcinoma, 13 cases (14.9%) were diagnosed as small cell carcinoma and 14 cases (16.1%) were diagnosed as others. Concerning the radiological properties of lesions, 42 cases (48.3%) showed low density areas, 45 cases (51.7%) did not show low density areas; 8 cases (9.2%) showed a cavity, 79 cases (90.8%) did not show a cavity; 7 cases (8%) showed small airspaces, 80 cases (92%) did not show small airspaces; 54 cases (62.1%) displayed 5 cm and less (the minimum size of the lesion was 1cm) and 33 cases (37.9%) displayed more than 5 cm.

The diagnostic yield of USGNA for subpleural primary lung cancer is shown (Table 2) and was 86.2% (75/87) in all, 85.3% (64/75) among the males, 91.7% (11/12) among the females. Concerning the pathological diagnosis, 94.1% (32/34) of cases with adenocarcinoma, 73.1% (19/26) of cases with squamous cell carcinoma, 92.3% (12/13) of cases with small cell carcinoma, and 85.7% (12/14) of cases with others could be diagnosed by USGNA. In addition, 10 of 26 cases with squamous cell carcinoma were confirmed pathological findings of tumors which surgically resected. Necrosis in the tumors in 7 of these 10 cases was proven. Concerning the radiological properties of lesions, 86.7% (39/45) of cases did not show a low density area, 85.7% (36/42) of cases showed a low density area; 87.3% (69/79) of cases did not show a cavity, 75% (6/8) of cases showed a cavity; 87.5% (70/80) of cases did not show small airspaces, 71.4% (5/7) of cases showed small airspaces; 88.9% (48/54) of cases displayed 5 cm and less and 81.8% (27/33) of cases showed more than 5 cm which could be diagnosed by USGNA. Using Fisher's exact test, there was no statistically significant difference with regard to the diagnostic yield relating to these radiological properties of lesions. Subsequently, binomial logistic regression analysis using a forward selection method related to all the factors was performed because all factors, including the pathological findings, might be confounding factors. This analysis indicated that squamous cell carcinoma was an

independent influence on the diagnostic yield by USGNA (p=0.02).

A lung abscess as a possible complication appeared in only one case after USGNA had been performed.

4. Discussion

The usefulness and safety of USGNA has previously been reported [1-7]. It is also well known that USGNA can lead to correct diagnosis in many cases with intrapulmonary subpleural lesions, even if the lesion is small or if patients have respiratory comorbidities [3-7]. CT-guided lung biopsy which is also percutaneous lung biopsy is often used for a lesion in subpleural area. However, there are some reports concerned with systemic air embolism caused by CT-guided lung biopsy [8, 9]. On the other hand, no reports describing systemic air embolism caused by USGNA exist. Therefore, this procedure is often used to diagnose intrapulmonary subpleural lesion in our hospital even if a patient who underwent USGNA is an outpatient. In fact, 86.2% of all cases with subpleural primary lung cancer could be diagnosed by this procedure and a lung abscess as a possible complication appeared in only one case after USGNA had been performed in this study.

On the other hand, there are few reports relating to what kinds of factors of subpleural primary lung cancer are obstructions for a diagnosis using USGNA. If a special

radiological property of the lesion by using thoracic CT without CE hinders the diagnosis of subpleural primary lung cancer by USGNA, in such a case with its special radiological property of the lesion, a diagnosis employing other procedures except USGNA has to be made. Therefore, this study was planned in order to clarify these radiological properties of the lesions which hindered the diagnosis of subpleural primary lung cancer by USGNA.

Concerning the radiological properties of lesions, Montaudon *et al.* asserted that cavitation or necrosis in tumors did not influence the diagnoses of CT-guided percutaneous lung biopsy of pulmonary lesions [10]. On the other hand, there is a possibility that air in a tumor, such as cavities or small airspaces, hinder diagnosis by USGNA because air does not permit US penetration. However, there was no statistically significant difference in the diagnostic yield in these radiological properties of lesions in this study. It might be possible that a specimen could be obtained from the solid area, but not from cavities or small airspaces because cavities or small airspaces could be avoided by real-time US images. Some studies have described the relationship between the diagnostic yield and the sizes of the lesions [3-6, 11], according to which the diagnostic yield of USGNA for a malignant lesion is high even if the lesion is small, such as less than 3 cm in size [3-6]. Scisca *et al.* analyzed lesions of 1cm to 10 cm in size, and reported that the size of the lesion was not the main factor affecting the diagnostic yield of USGNA

[11]. There was also no statistically significant difference in the diagnostic yield for tumors greater than 5 cm, nor for tumors of 5 cm and less in this study. Our results suggest that USGNA should be chosen to diagnose subpleural primary lung cancer, regardless of the radiological properties of the lesions by using thoracic CT without CE if the lesion can be detected by US, because these radiological properties of the lesions do not hinder diagnosis of subpleural primary lung cancer by USGNA.

On the other hand, concerning pathological diagnosis, the diagnostic yield of cases with squamous cell carcinoma diagnosed by USGNA was statistically significantly low by binomial logistic regression analysis using a forward selection method related to all factors. Although a specimen was obtained from a solid area in a lesion detected by US, such solid area may include necrotic parts in some measure. It is supposed that the diagnostic yield for subpleural primary lung cancer by USGNA decreases if a lesion includes more necrotic parts. It is well known that squamous cell carcinoma tends to cause necrosis in a tumor [10, 12]. In fact, necrosis in the tumors in 7 of these 10 cases with squamous cell carcinoma with confirmed pathological findings of surgically resected tumors was proven. This may be related to a significant low diagnostic yield in the cases with squamous cell carcinoma. Our results suggest that other diagnostic procedures such as flexible bronchoscope or surgery should be performed in cases suspected of being cases

with squamous cell carcinoma as results of various clinical examinations, because negative results from USGNA may be falsely negative in such cases.

There are several limitations to our study. The cases showing false negatives were small in number because they were collected from a single institution. Furthermore, not all data could be evaluated by histological findings because the specimens obtained by USGNA could only be evaluated by cytological evaluation.

5. Conclusion

USGNA is a useful procedure for diagnosing subpleural primary lung cancer because the radiological properties such as the size of lesions, cavities, small airspaces and low density areas in the lesions do not affect the diagnostic yield by USGNA. In other words, USGNA should be chosen to diagnose subpleural primary lung cancer, regardless of the radiological properties of the lesions, by using thoracic CT without CE if solid parts of lesions can be detected by US and if patients are cooperative. However, the diagnostic yield of cases with squamous cell carcinoma diagnosed by USGNA is statistically significantly low. Therefore, other diagnostic procedures such as flexible bronchoscope or surgery should be performed for suspect cases, which as those with squamous cell carcinoma by results of various clinical examinations because negative results of USGNA

may be falsely negative in such cases.

Conflict of interest statement

The authors of this manuscript declare no conflicts of interest.

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Table 1: Patients' characteristics (n=87)	
Male	75 (86.2%)
Female	12 (13.8%)
	mean (range)
Age (Male)	71.1 (41-86)
Age (Female)	68.3 (55-81)
Age (Total)	70.7 (41-86)
Pathology	
Adenocarcinoma	34 (39.1%)
Squamous cell carcinoma	26 (29.9%)
Small cell carcinoma	13 (14.9%)
Others	14 (16.1%)
Properties of the lesions	
Low density areas (-)	45 (51.7%)
Low density areas (+)	42 (48.3%)
Cavity (-)	79 (90.8%)
Cavity (+)	8 (9.2%)
Small airspaces (-)	80 (92%)
Small airspaces (+)	7 (8%)
5 cm and less	54 (62.1%)
Greater than 5 cm	33 (37.9%)

Table 2: Results of ultrasound-guided needle aspiration

OR*: Odds ratio, CI: Confidence interval**

	Diagnostic yield (positive case/total)	**non-adjusted OR* (95% CI**)**	**p-Value**	**adjusted OR* (95% CI**)**	**p-Value**
Male	85.3% (64/75)	1.89 (0.22-16.15)	0.48		
Female	91.7% (11/12)				
Total	86.2% (75/87)				
Pathology					
Adenocarcinoma	94.1% (32/34)				
Squamous cell carcinoma	73.1% (19/26)			0.20 (0.05-0.77)	0.02
Small cell carcinoma	92.3% (12/13)				
Others	85.7% (12/14)				
Properties of the lesions					
Low density areas (-)	86.7% (39/45)	0.92 (0.27-3.12)	0.57		
Low density areas (+)	85.7% (36/42)				
Cavity (-)	87.3% (69/79)	0.43 (0.08-2.46)	0.30	0.27 (0.04-1.79)	0.18
Cavity (+)	75% (6/8)				
Small airspaces (-)	87.5% (70/80)	0.36 (0.06-2.09)	0.25		
Small airspaces (+)	71.4% (5/7)				
5 cm and less	88.9% (48/54)	0.56 (0.17-1.92)	0.27		
Greater than 5 cm	81.8% (27/33)				