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EBUS guided cryo biopsies in peripheral pulmonary lesions – a feasibility study

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Key words

Bronchoscopy, pulmonary lesion, cryo probe, cryo biopsy, transbronchial biopsy, lung cancer, endobronchial ultrasound

Abstract

Background: Peripheral lung lesions (PLL) are sometimes difficult to reach even with endobronchial ultrasound (EBUS) and insufficient material is often obtained by transbronchial forceps biopsy (TBB) . Cryo probes can be used for performing tissue biopsies. We evaluated safety and feasibility of the cryo probe in combination with EBUS for the diagnosis of PLL.

Methods: Patients with PLL up to 4 cm were enrolled. After identifying the lung lesion by radial EBUS, forceps and cryo biopsies were performed in a randomised order. We evaluated safety and feasibility, and compared diagnostic yield and sample size.

Results: 39 patients were randomised and the PLL was reached in 31. The overall diagnostic yield was 60.5% and in the lesions reached by EBUS it was 74.2%. In 19 cases the diagnosis was made with forceps as well as cryo biopsy and in 4 cases only with cryo biopsy. Cryo biopsies were significantly larger than forceps biopsies (11.17 mm2 vs 4.69 mm2, $p < 0.001$). We observed 1 case of moderate bleeding.

Discussion: Transbronchial cryo biopsy with EBUS-guidance is safe and useful to obtain histological samples. Larger tissue samples can be obtained by cryo probe.

Introduction

Lung cancer is one of the main causes of cancer related death worldwide (1). When detected in the early stages, curative surgical options can be considered, improving the survival significantly. Screening for lung cancer in order to detect the tumour earlier has been an often discussed topic and recently the National Lung Screening Trial was able to show an improvement in mortality data in patients screened on a yearly basis with low dose computer tomography (CT) (2). At the same time however, there was an increase of incidentally detected solitary pulmonary lesions of unknown 'histology'.

In order to obtain a definitive diagnosis of these lesions it is often mandatory to perform tissue sampling. Transthoracic CT guided needle biopsy can be performed but has a high rate of pneumothorax quoted to be between 15-43 % with 4-18 % requiring a chest drain as well as the risk of pulmonary hemorrhage with reported frequencies between 1.0 % - 27 % (3, 4). Transbronchial forceps biopsy in combination with other techniques such as brushing, needle biopsy or washings can be performed (5). The sensitivity is quite variable and depends upon the size of the lesion as well as the distance to the pleura (5, 6).

The use of guidance techniques such as endobronchial ultrasound (EBUS), virtual bronchoscopy and electromagnetic navigated bronchoscopy (ENB) improves the diagnostic yield to around 70 %, although the sensitivity depends strongly on the biopsy technique (7-12). Biopsies obtained with these conventional techniques are often small and may not be suitable for further immunohistochemical or molecular studies (13). Therefore the biopsy technique has to be improved further.

The cryo probe has been used within in the airway for tumour destruction by freezing and thawing. In the last years cryo probes have been established for airway recanalization and for sampling endobronchial lesions particularly in patients with lung cancer (14-16). Due to the simplicity of handling and the larger biopsy sizes, first reports about the use of cryo probes for transbronchial biopsies have been published (17, 18). However, in all of these trials this technique has been used in patients with diffuse or interstitial lung disease.

We assessed the safety, feasibility and efficacy of the cryo probe for transbronchial biopsies in solitary pulmonary lesions with the guidance of radial endobronchial ultrasound.

Patients and Methods

Between March and September 2010, 39 consecutive patients with a solid pulmonary lesion of less than 40 mm, who were referred to our institution for diagnostic bronchoscopy, were included in the study. All patients had a CT scan performed prior to bronchoscopy and lesion size was measured at its largest diameter. All patients were included irrespective of the position of the lesion and the relationship of the lesion to the airway. Patients with tumours suspicious of endobronchial growth, pure ground-glass lesions, mediastinal lymphadenopathy or contraindications for bronchoscopy and transbronchial biopsies were excluded. The study protocol had been approved by the ethics committee of the University of Heidelberg (S320/2009) and the study design was registered at the U.S. National Institute of Health (NCT01221493). All patients signed a study consent form.

In all 39 cases a combined rigid and flexible bronchoscopy according to our standard protocol at Thoraxklinik Heidelberg, Germany was performed by three trainees under

supervision of an experienced bronchoscopist. First, the central airways were assessed endoscopically. If endobronchial tumour growth was visible, the patient was excluded from the study. Based on the CT thorax, a radial EBUS-probe (UM-S20-20R, Olympus, Japan) with flexible guide-sheath was advanced into the suspected bronchial segments to detect the peripheral lesion. This navigation technique has been previously described in other publications (19-21). Additional fluoroscopy was used if this was considered necessary by the investigator. The duration of EBUS use for the detection of the lesion was limited to 20 min. If the lesion was not detected within the given time, the patient was considered as EBUS negative and excluded from the study.

Once the lesion was detected by EBUS, the position of the probe in relation to the lesion was noted. The miniprobe was removed whilst the guide sheath remained in position. All patients received 3 transbronchial biopsies of their lung lesion with forceps as well as 3 with the cryo probe. Patients were randomized to either receive first the forceps or the cryo biopsies according to a randomisation list with a distribution of 1:1 (**Figure 1**).

We used a commercially available reusable forceps (FB-19-C 120cm, Olympus, Japan) through the guide sheath. The correct position of the guide sheath was confirmed at the end of the 3 biopsies by EBUS to exclude dislocation.

For the cryo biopsies a flexible cryo probe of 1.2 mm (1.7 mm in addition with over sheath) in diameter and 90 cm in length (ERBE, Germany) was used. The tip of the probe was cooled with nitrous oxide to a temperature up to -89 degrees Celsius. The probe was cooled for approximately 4s and immediately thereafter retracted together with the guide sheath and bronchoscope. The frozen biopsy was then thawed in normal saline and fixed in formalin. After each cryo biopsy the lesion was located

again by radial ultrasound and fluoroscopy if required. After 6 biopsies the examination was terminated and 2 hours after the procedure a chest x-ray was performed.

All samples were separately fixed in formalin and processed in the Institute of Pathology at the University of Heidelberg. The pathologists were blinded for biopsy technique and towards the order of the biopsy. The samples were embedded in paraffin then mounted onto glass slides and HE and PAS stains were performed. A histological diagnosis was established first. If transbronchial biopsy yielded a definitive histological diagnosis it was considered TBB-success. If TBB result was non-diagnostic then additional procedures such as CT guided transthoracic needle biopsy or surgery were undertaken to confirm the diagnosis. However, if TBB yielded a plausible benign diagnosis, the patient was treated accordingly or observed for 2 years to exclude malignancy.

The length of time required for the detection of the lesion as well as for the individual biopsy techniques was recorded. Bleeding and complications such as post interventional pneumothorax as well as histological outcomes were documented.

A biopsy was assumed as overall diagnostic, if at least one of the three biopsies obtained with cryo or forceps technique was diagnostic. Diagnostic yield was calculated for each biopsy technique as the number of diagnostic procedures divided by the number of non-diagnostic procedures plus number of diagnostic procedures.

All samples underwent planimetric assessment by measuring the area of the histological specimen with a digital system (SteREO Discovery.V12 and the AxioVision 4.5 Software; Carl Zeiss Microscopy GmbH, Germany).

The artifact-free specimen area was assessed by a pathologist who was blinded to the biopsy technique applying a semi-quantitative scoring scale divided into 5 equal steps (0-20, 21-40, 41-60, 61-80 and 81-100 %) describing the relative amount of unaltered tissue.

Data were analysed by means of descriptive statistics (means and standard deviations) as well as by statistical hypothesis testing. For non-normally distributed samples, a non-parametric test (Wilcoxon matched pairs signed rank test) was used. Fisher's exact test was used to compare proportions. All p values ($p < 0.05$ was considered statistically significant) are two-sided and were not adjusted for the number of parameters evaluated. Statistical analysis was accomplished on a computer using the statistic software PRISM 6.0 (GraphPad Software, Inc., La Jolla, CA).

Results

Thirty-nine patients (28 male, 11 female) were included in this prospective study. The mean age was 68 years (range 37 to 84). One patient was excluded due to visible endobronchial tumour. The remaining 38 patients had a lung lesion of 29.7 mm ± 7.3 mm in diameter, of which 31 were malignant and 7 were benign. On average the distance to the pleura was 7 mm ± 10mm. The distribution of the lesions is described in detail in **Table 1**. The average time for EBUS examination was 7.6 min ± 6.1min. The EBUS detection rate was 81.6 %. We were not able to locate the tumour after 20 min in 7 of the 38 patients and these patients did not receive transbronchial biopsy. The detection rate was independent of the location of the lesion except for the middle lobe where all lesions could be detected by EBUS.

In the remaining 31 patients the EBUS probe was located within the lesion in 20 cases while in 11 cases the EBUS probe was located adjacent to the lesion (64.5 % and 35.5 % respectively).

All 31 EBUS positive patients received 3 transbronchial forceps biopsies and 3 transbronchial cryo biopsies according to the study protocol. The average time required for forceps biopsy was significantly shorter than the time required for the cryo biopsies (5.1 min ± 2.75 min and 11.6 min ± 4.4 min respectively, $p < 0.0001$).

The overall diagnostic yield, including lesions not biopsied as we were unable to detect them with EBUS, was 60.5 % (23 of 38 patients). The diagnostic yield of the lesions which we were able to visualize with EBUS was 74.2 % (23 of 31 patients). In 19 cases both techniques established a diagnosis. Additionally, four cases that were non-diagnostic with forceps biopsy were successfully diagnosed with cryo biopsy resulting in a diagnostic yield of 61.3 % (19/31) for forceps and 74.2 % (23/31) for cryo biopsy, respectively ($p = 0.42$). Taking only the first biopsy into account, 19 of 31 patients (61.3 %) were diagnosed by cryo biopsy and 15 by forceps biopsy (48.4 %) ($p = 0.44$). The cumulative yield after the second biopsy was 71 % (22 of 31 patients) with the cryo probe and 54.9 % (17 of 31) with forceps, however, the difference in yield between both techniques was not significant ($p = 0.29$) (**Figure 2**). It should be noted that in those four cases, where only cryo biopsy was successful in securing a diagnosis, no differences were observed in the positioning of the EBUS probe or in the size of the lesion and histological assessment. The histology of these 4 cases was 2 adenocarcinomas, 1 squamous cell carcinoma and 1 hamartoma.

The results of both biopsy techniques overall and in dependence of the final histological diagnosis are summarized in **Table 2**.

Of the 93 biopsies taken for each technique in total, 54 (58.1 %) of the cryo and 43 (46.2 %) of the forceps biopsies were diagnostic ($p = 0.14$).

Quantitative digital assessment of histological samples showed a mean sample area of 11.17 mm^2 (range 1.25 – 38.59 mm^2) for cryo biopsy and 4.69 mm^2 (range 0.53 – 22 mm^2) for forceps biopsy ($p < 0.001$). No qualitative difference was observed between cryo biopsy and forceps biopsy. Retrieval of biopsies with cryo probe did not result in more artifacts compared to forceps biopsy. Applying the semi-quantitative scoring on tissue morphology, 93 samples of the cryo biopsies and 91 samples of the forceps biopsy showed more than 80 % unaltered relative tissue area.

No severe complications were observed during this study. There was one case of moderate bleeding at the end of all 6 biopsies necessitating prolonged suction with the bronchoscope, but no other intervention. No pneumothorax was detected on chest radiograph.

Discussion

Peripheral lung lesions still pose a diagnostic dilemma. One challenge is to improve the biopsy techniques that are currently available. A recent study showed that the use of cryo probes for diagnosing endobronchial malignancy was superior over forceps biopsies (14). Cryo probes have also previously been used to perform transbronchial biopsies in interstitial lung disease (ILD) (17).

In this study we were able to show for the first time that the use of the cryo probe for transbronchial biopsies in the diagnosis of pulmonary lesions is feasible.

We combined this technique with the use of radial endobronchial ultrasound and a guide sheath in order to improve the rate of detection. In this trial our detection rate with EBUS for pulmonary lesions was 81.6%, which correlates with values described in the literature (22). In 7 of 38 patients we were not able to locate the lesion with EBUS within 20 min and these patients were therefore excluded from our study. This exclusion was necessary because the probability of a positive diagnosis in EBUS negative lesions is reported to be very low (20). In all 31 patients in whom we detected the lesion by EBUS, we were able to perform forceps biopsies and cryo biopsies and adequate specimens were obtained.

The duration of the cryo biopsies was significantly longer in comparison to forceps biopsy. The longer time was due to the need to remove the guide sheath for each biopsy, requiring repeat localization of the lesion with EBUS prior to repeat sampling. A prolonged procedure time may be acceptable in order to obtain larger samples. This might reduce the number of biopsies that need to be performed, overcoming this concern in the future.

Relevant potential complications for transbronchial forceps biopsy are iatrogenic bleeding and pneumothorax. The rates for pneumothorax after EBUS guided transbronchial forceps biopsies are reported at 0–5.1% (7). Babiak et al (17) quoted a pneumothorax incidence of nearly 5% after transbronchial biopsies with cryo probe in ILD. We did not observe any pneumothorax in our study. This may be due to the fact that we only obtained biopsies in patients in whom the lesion was reached by EBUS prior to performing the biopsy and that we additionally controlled the position of the sheath and of the biopsy instruments with fluoroscopy. Biopsy or damage of the pleura is hence minimized. Ideally 5 biopsies should be taken to optimize the diagnostic yield (11, 20), though the risk of bleeding increases with the number of biopsies taken (23). Due to the cross over design of the study we took 6 biopsies in every patient. In the study performed by Hetzel et al. an increased incidence of bleeding after endobronchial cryo biopsies was observed in comparison to forceps biopsies (14), but the number of significant haemorrhages requiring intervention did not differ to forceps biopsy. In our study we only had one moderate bleed which required no further procedures other than suction. Due to the combined use of both biopsy techniques in every patient, we could not differentiate the safety data and assign them to one of the techniques. However the number of complications in our study was very low and therefore the use of cryo biopsies for peripheral lung lesions appears to be safe. Again, this may also be due to the combined use of EBUS and guide sheath detection of the lesion prior to sampling.

Even when the lesion is detected with EBUS, a certain amount of biopsies are non-diagnostic (20, 22, 24). This is the result of a sampling error, either due to the position of the EBUS probe in relation to the lesion or due to dislocation of the biopsy tool, that can be overcome by the use of concurrent fluoroscopy. As reported in the

literature the diagnostic yield increases up to over 80% when the miniprobe can be positioned centrally within the lesion rather than adjacent to the lesion which has a yield of only 44-61 % (20, 22, 24). The diagnostic yield in all lesions in this study was 60.5 %. The diagnostic yield in the EBUS positive lesions in our study was 74.2 % (23 of 31). The distribution of diagnostic yield in relation to the position of the EBUS probe, within or adjacent to the lesion, was similar to the published literature (85% vs 54.5% respectively p=0.09). However, in the 7 EBUS negative cases we were not allowed to take any biopsies according to the study protocol.

A better diagnostic yield as well as a higher number of diagnostic biopsies was shown for the cryo probe but this was not statistically significant. The biopsy tools follow the path of the bronchus and if the bronchus is only adjacent to the tumour, forceps sampling often misses the lesion. When using a cryo probe the tissue surrounding the tip is frozen enabling biopsies also in a lateral direction. This might be one of the major advantages, especially in lesions where EBUS cannot be placed within the lesion. The position of the EBUS probe in those four cases where only cryo probe was diagnostic, were within as well as adjacent to the lesion.

Another advantage of the cryo probe may be the larger samples obtained with the procedure, supplying the pathologist with more tissue to make a correct diagnosis and to perform further molecular analyses which are crucial to personalize lung cancer treatment (13). In our study the size of the samples obtained with the cryo probe was approximately 3 times larger than those acquired with conventional forceps as has been reported in previous trials (14, 17, 18).

Cryo probe samples tend to have larger artifact free areas in comparison with forceps samples, although this trend could not be shown in our study (14, 17). The

combination of different biopsy tools usually leads to a higher diagnostic yield. In our study forceps biopsies did not add to the yield of cryo biopsies.

This study was designed to show the feasibility and safety of cryo sampling in patients with peripheral lesions. It was therefore not powered to show superiority in comparison to forceps biopsy. Safety should also be confirmed in a larger trial. Another limitation of this trial is the cross over design using both techniques in every patient. Because this was the first use of cryo probe in peripheral lung lesions excluding patients from the standard approach of forceps biopsy was not possible.

In conclusion the use of cryo probes for obtaining biopsies from peripheral lung lesions is feasible. In comparison to forceps biopsy, significantly larger samples can be obtained without affecting safety. In order to show the possible advantages of the cryo probe such as a potentially higher diagnostic yield, further larger trials in a randomized setting need to be performed.

Tables and Figures

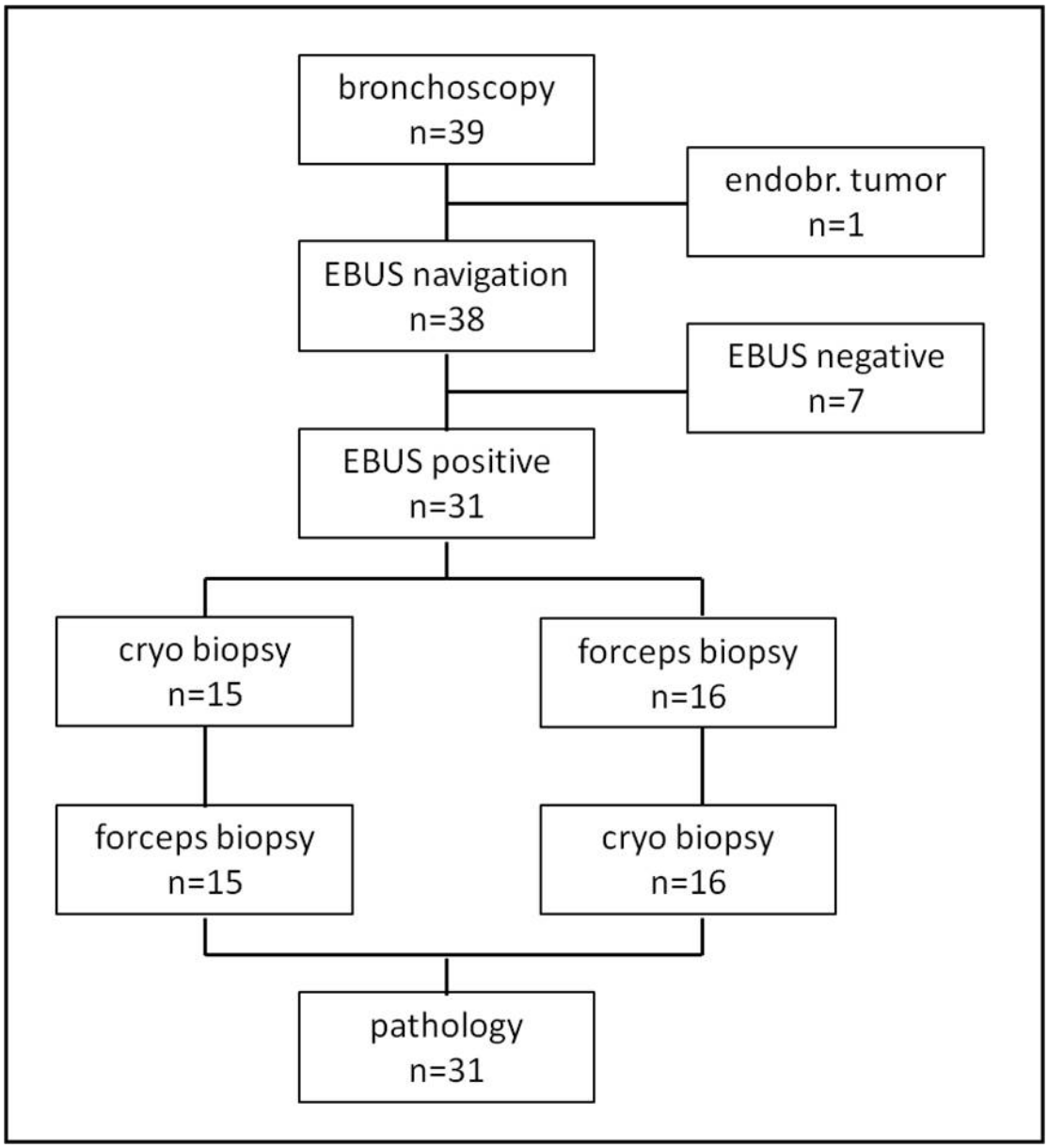
Table 1 EBUS results in relation to distribution of the lesion. Fisher's exact test

Lobes	**Position** Left/Right	**All** n	**EBUS positive** n (%)	**EBUS negative** n (%)	**P - values**
Upper	R L	13 8	11 (84.6) 6 (75.0)	2 (15.4) 2 (25.0)	1 0.64
	Total	21	17 (81.0)	4 (19.0)	1
Middle	R	5	5 (100.0)	0 (0.0)	0.57
Lower	R L	7 5	5 (71.4) 4 (80.0)	2 (19.6) 1 (20.0)	0.61 1
	Total	12	9 (75.0)	3 (25.0)	0.69
All	R L	25 13	21 (84.0) 10 (76.9)	4 (16.0) 3 (23.1)	1 0.7
	Total	38	31 (81.6)	7 (18.4)	

Table 2: Histological diagnosis of EBUS-positive lesions**.** Fisher's exact test

Diagnosis	**n**	**Cryo (%)**	**Forceps (%)**	**Total yield**	**p value**
Squamous cell	7	5 (71.4%)	4 (57.1%)	5 (71.4%)	1
Adeno	13	9 (69.2%)	7 (53.8%)	9 (69.2%)	0.69
Carcinoma	5	3 (60.0%)	3 (60.0%)	3 (60.0%)	1
Σ malignant	25	17 (68.0%)	14 (0.56%)	17 (68.0%)	0.76
COP	2	2 (100%)	2 (100%)	2 (100%)	1
Lung abscess	2	2 (100%)	2 (100%)	2 (100%)	1
Hamartoma	1	1 (100%)	0 (0%)	1 (100%)	1
Granuloma	1	1 (100%)	1 (100%)	1 (100%)	1
Σ Benign	6	6 (100%)	5 (83.3%)	6 (100%)	1
Total	31	23 (74.2 %)	19 (61.3%)	23 (74.2%)	0.42

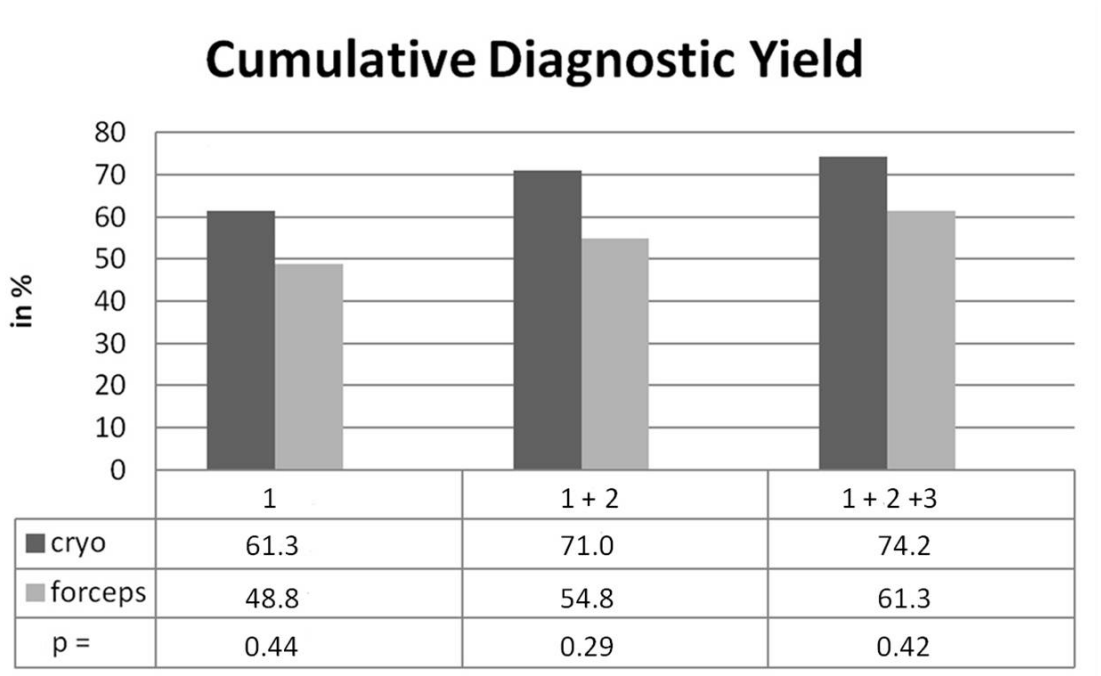
Figure 1



Legend Fig. 1

Flow diagram of EBUS and biopsy procedures performed.

Figure 2: Biopsy with cryo and forceps.



	1	1 + 2	1 + 2 +3
cryo	61.3	71.0	74.2
forceps	48.8	54.8	61.3
p =	0.44	0.29	0.42

Legend Fig. 2

Number of diagnostic specimens obtained with cryo and forceps technique after the first biopsy (1), cumulative number of diagnostic specimens after the first and second biopsy (1+2) and all three biopsies together (1+2+3).

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