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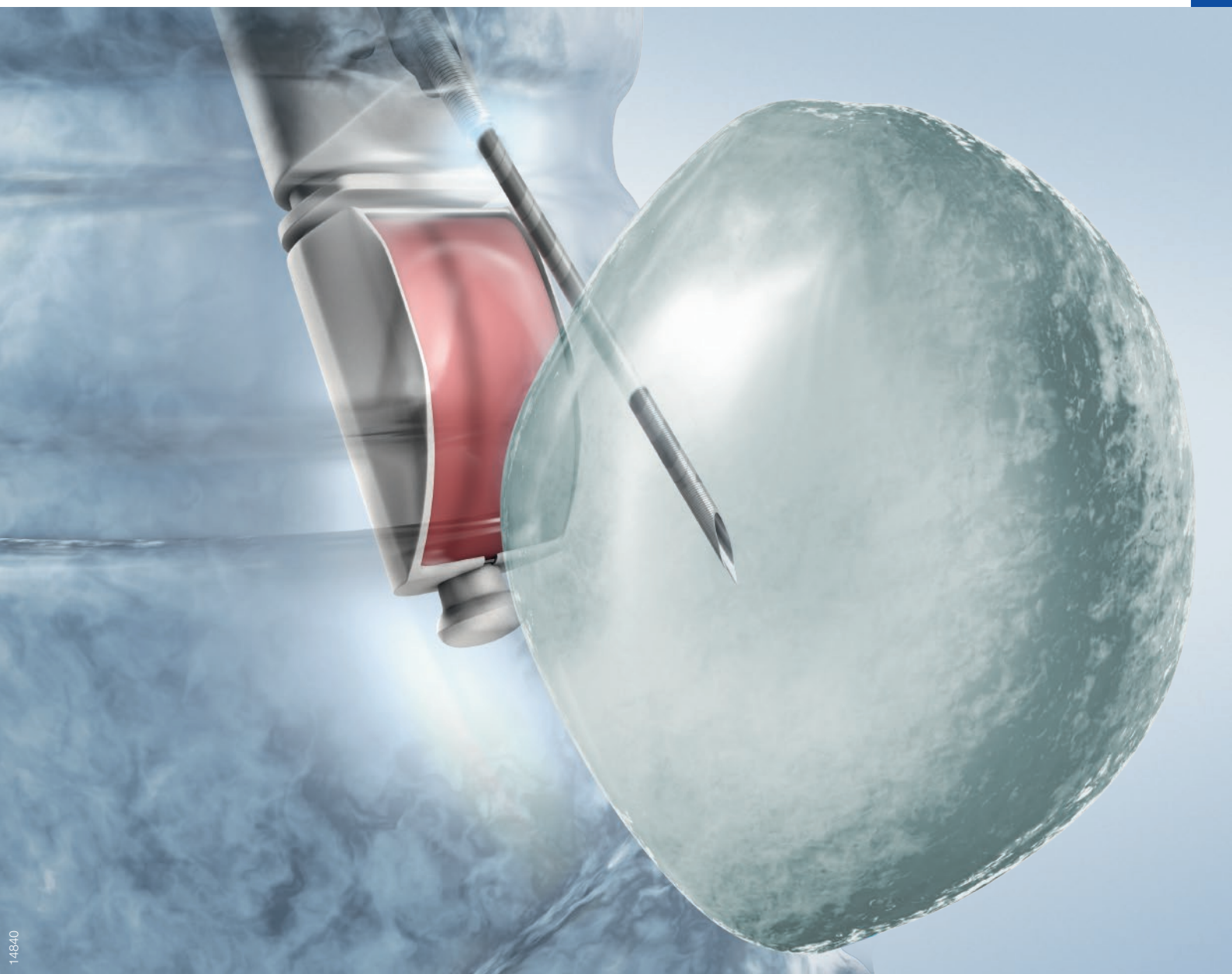
ABSTRACTS FROM OLYMPUS SYMPOSIUM

RECENT DEVELOPMENTS TO INCREASE THE YIELD OF EBUS-TBNA

World Congress for Bronchoscopy and Interventional Pulmonology

May 2016, Florence



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INTRODUCTION

EBUS-TBNA – Move Forward to the Next Level

The journey started more than ten years ago, in 2004 EBUS-TBNA was introduced into medicine. Initially ridiculed, it has now become the state-of-the-art method for the mediastinum. Over the last ten years, the evidence for EBUS-TBNA has increased rapidly. After several meta-analyses, the endoscopic technique is now quoted as the first test for the evaluation of the mediastinum, replacing mediastinoscopy. Due to the extensive work of several groups around the world, EBUS-TBNA has become the number one technique for staging and diagnosing the mediastinum in every current lung cancer guideline worldwide. Alongside the indication of lung cancer, this technique is also used for the diagnosis of non-malignant disorders like sarcoidosis with huge success.

But is it the end of the journey already? Definitely not. The technique itself, the procedure as well as the training recommendations are well established. It is especially due to the continuous work of Olympus and the experts that internationally accepted curricula have been established and implemented in several areas.

In the future we might see thinner scopes with better CCD chips, better angulation and a larger working channel. The procedure itself will remain the same.

The current focus is on the needle size. 21G and 22G are the sizes we have been using for many years already, but 19- and 25-gauge needles are also available now. What are the specific indications, what are the limitations and where are the hurdles? Sentences like “bigger is better” must be evaluated and we may have to consider choosing the needle size based on the suspected diagnosis.

Conversely, more and more ultrasound technologies are added to the processors. The most interesting technique seems to be elastography, which is included in the current EU-ME 2 model. In principle, pathophysiological processes, such as malignancy, make tissues less deformable or stiffer. Compression of surrounding structures produces a deformity or strain effect that is inversely related to the hardness of the pathologic tissue; harder tissues are less deformable than softer tissues. First applied in the field of breast ultrasound, elastography has also been used to measure tissue elasticity in thyroid and liver disease. Now we have it in our hands and it is up to us to evaluate this new option.

All topics have been discussed within the symposium in a very interactive session.

Prof. Dr. med. Felix JF Herth

This educational program, held at the World Congress for Bronchoscopy and Interventional Pulmonology (WCBIP) 2016 in Florence, Italy, brought together a group of experts in the field of EBUS-TBNA. The meeting was sponsored by Olympus, and was intended for international attendees interested in recent developments in EBUS-TBNA.

The session was chaired by:

Prof. Dr. med. Felix JF Herth
University of Heidelberg, Heidelberg, Germany

The distinguished faculty presenting at the session were:

Dr. med. Pallav L Shah
National Institute for Health Research Unit, Royal Brompton & Harefield NHS Foundation Trust, and Imperial College and Chelsea and Westminster Hospital NHS Foundation Trust, London, UK.

Dr. med. Artur Szlubowski
John Paul II Hospital, Krakow, Poland

Prof. Dr. med. Felix JF Herth
University of Heidelberg, Heidelberg, Germany

Dr. med. MSc. Aleš Rozman
University Clinic of Pulmonary and Allergic Diseases, Golnik, Slovenia

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The following abstracts provide an overview and key conclusions of the meeting.

ABSTRACT

Endobronchial Ultrasound Guided Transbronchial Needle Aspiration: Do We Need Bigger Needles?

Dr. med. Pallav L Shah [1,2]

Abstract

The development of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has transformed diagnosis and staging for lung cancer. It has also become an important diagnostic modality for benign diseases such as sarcoidosis. Over the past two years advances in the treatment of lung cancer and with the introduction of targeted therapies, there has been a need to phenotype lung cancer in more detail. Hence, there is a greater need to perform immuno-histochemistry but also to seek out potential genetic mutations for molecular targets. Hence, there is a clear need for greater tissue volume and this paper sets out the need for bigger needles.

Rationale

It is a reasonable scientific assumption that the greater the volume of tissue the more certainty that the findings observed are correct. It is an effect of sampling and multiple historical studies have shown that a fine needle aspirate may provide a diagnosis of cancer but may be insufficient to subtype the tumor. A core biopsy with greater preservation of the architecture will provide more information. Similarly, a surgical excision biopsy where the whole lesion is excised provides even more information and abundant material for additional analysis. Hence, it is only logical that the greater the volume of tissue obtained the stronger the likelihood of diagnosis and the greater the information that will be obtained. This is also akin to cryobiopsy for interstitial lung disease where larger pieces of alveolar parenchyma are obtained with better preservation of the lung architecture than with transbronchial forceps biopsy. For needle biopsy the gauge or inner diameter of the needle is a key determinant for the volume of tissue obtained.

Volume of sample = (diameter/2)^2 × length (mm) × 3.14

There are several editorials and clinical studies in the literature that claim no significant difference in diagnostic rates between different needle sizes. However, I would argue that these studies are flawed and do not have a sufficient number of patients (statistical power) to demonstrate a difference between the needle sizes. Shenk and colleagues evaluated 64 patients with mediastinal adenopathy to blind transbronchial needle aspiration (TBNA) with both a 22-gauge cytology needle and a 19-gauge Wang histology needle.[1] The sensitivity with the 22G needle was 52.7% with 26 false negative results whereas the sensitivity was 85.5% and only eight false negative results with the 19G histology needle. A small study with EBUS using the 21G and 22G needles suggested improved tissue acquisition with the 21G needle.[2] Fifty-six patients were randomized (24 to the 21G needle and 32 to the 22G needle). The samples obtained were evaluated both macroscopically and microscopically. However, with respect to histological analysis there was no statistical difference between the needles (accuracy 95.8% for 21G needle and 81.3% for 22G needle, p=0.11). This is primarily as the study is too small to show a statistical difference in sensitivity or accuracy. The more discerning finding was that only one of the 24 patients sampled with the 21G needle had inadequate material whereas six of the 32 cases sampled by the 22G needle had inadequate material for diagnosis.

The key limitations for EBUS-TBNA are in the diagnosis and classification of lymphoma. Although there are some proponents on the use of flow cytometry, some information on the histological architecture of the cells and the presence of certain features is important (particularly for Hodgkin's lymphoma). Some studies have found that flow cytometry was useful for follicular and small lymphocytic lymphoma. As with lung cancer there is increasing importance of immuno-histochemical and molecular markers and hence the amount of available tumor strengthens the accuracy of the diagnosis and furthermore improves consistency between pathologists.[3]

Herth et al has also shown the utility of a larger biopsy with a pilot trial of EBUS biopsy forceps. They evaluated 50 patients and the sensitivity was reported at 88% but inadequate material was obtained in five of the patients (10%).[4]

One of the key limitations of EBUS is in sampling small lymph nodes in Station 4L and 10L as insertion of the needle limits the angulation of the EBUS scope. The new Olympus 19G flex needle has greater flexibility with the scope angulating to 80° compared to only 40° with the conventional needle.* This in conjunction with the greater gauge promises to further improve the utility and diagnostic yield of EBUS-TBNA.

** Values obtained using an Olympus BF-UC180F scope in combination with the Olympus ViziShot 21G needle and ViziShot FLEX 19G needle. Angulation values may vary depending on the scope and needle condition*

Summary:

In summary it is apparent that larger needles will;

- Increase the volume of tissue obtained
- Reduce the number of cases where there is inadequate sampling
- Improve the proportion of samples that are suitable for molecular analysis
- Improve the diagnosis between pathologists
- `Improve the diagnostic strength where lymphoma is suspected.

The current evidence base which suggests that there is no difference in yield between needle sizes during EBUS procedures is flawed due to inadequate cases being included in the study. Future work should include adequately powered randomized controlled studies.

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ABSTRACT

19-Gauge or Nothing

Prof. Dr med. Felix JF Herth

Transbronchial needle aspiration (TBNA) of mediastinal tissue was first employed by Schieppati in patients with suspected bronchogenic or esophageal carcinoma over four decades ago, utilizing a 50 cm long, 1 mm diameter needle inserted through a rigid bronchoscope.[1,2] Subsequently, several investigators confirmed the utility and safety of TBNA. Interest in TBNA was rekindled in 1978, when Wang developed a 22-gauge needle that could be used effectively through a fiber-optic bronchoscope. Transbronchial needle aspiration offers the opportunity to pathologically stage the mediastinum in selected patients undergoing diagnostic fiber-optic bronchoscopy.[3] In the following years several groups described their results and several needles with different sizes were developed.

In 1993 Schenk reported the first trial, comparing the 19-gauge and 22-gauge needle in mediastinal staging of lung cancer. The group showed clearly that the 19-gauge needle was significantly more sensitive than the 22-gauge needle (85.5% versus 52.7% (p = 0.0001)). Several authors confirmed the results.[4]

In 2003 the success story of EBUS-TBNA started with a publication in the journal Thorax by Krasnik et al. This article gave the first description of the principle of EBUS-TBNA.[5] Yasufuku et al reported similar experience a couple of months later.[6] In 2006 Herth et al. published their experience on 502 patients that showed that EBUS-TBNA resulted in 93% diagnostic yield, a sensitivity of 94%, specificity of 100%, and accuracy of 94%, with PPV at 100% and NPV at 11%.[7]

In all the trials a 22-gauge needle was used. Over the years a 21-gauge needle was developed. Nakajima et al. performed a comparison trial using 21G and 22G needles. The quality of the histological core was evaluated by the amount of blood clots versus the actual tissue.

In 45 lesions, tumor cells were equally detected by the 21-gauge and 22-gauge needles. Two patients with adenocarcinoma were histologically diagnosed only by the 21-gauge needle. Overall the group showed no differences in diagnostic yield between the 21-gauge and 22-gauge needles during EBUS-TBNA.[8]

In 2015 the first data was presented using a 19-gauge needle through the EBUS-TBNA scope. The Toronto as well as the Heidelberg/London group showed similar results regarding the yield without any complications. The molecular analysis in particular was possible for all adenocarcinoma patients (Fig. 1).[9,10]

The next set of data will be presented during the WCBIP in Florence.

And now, which needle should be used in the daily routine? Even during the time of classical TBNA it was clearly shown that bigger is better. The amount of aspirated cells is increased by the bigger needles, and remains an important issue in patients suffering from lung cancer in order to enable molecular testing and, especially in the age of immunotherapy, the determination of checkpoint inhibitors.

For other diseases in the mediastinum, too, more tissue seems better. Even if the published data on lymphoma and sarcoidosis with 21/22 gauge needles are not as good as for lung cancer, it can be assumed, that in such indications, too, more material helps to establish the diagnosis.

And last but not least, there is another major benefit of the 19-gauge needle. The flexibility of the 19-gauge needle is dramatically improved (Fig. 2). Therefore the bending of the scope after needle insertion is improved too. This allows a better contact of the scope against the wall and this will improve the ability to puncture as well.

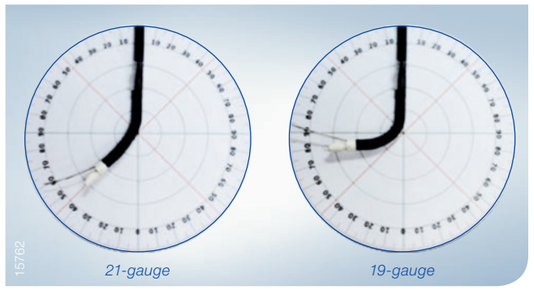
Summarizing the available data it seems to be obvious: 19-gauge or nothing for EBUS-TBNA.

Figures

Fig. 1: Results for the 19-gauge needles
(*Am J Respir Crit Care Med 191; 2015: A3726;
#Am J Respir Crit Care Med 191; 2015: A6389)

	Heidelberg/London*	Toronto#
n	20	22
Lesions sampled (n)	71	42
Yield (n)	18/20	20/22
Yield (%)	90	91
Lung cancer (n)	12	8
Sarcoidosis (n)	4	6
Lymphoma	2	
Molecular testing	kras, EGFR, ALK, BRAF, RET, ROS	
Complications (%)	0	0

Fig. 2: Improved bending of the 19-gauge needle**



** Values obtained using an Olympus BF-UC180F scope in combination with the Olympus ViziShot 21G needle and ViziShot FLEX 19G needle Angulation values may vary depending on the scope and needle condition

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ABSTRACT

EBUS Elastography

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Different tissues have different mechanical characteristics. This is the basis for physical examination by palpation. By manual application of gentle pressure on examined part of the body, tissues change their shape according to their elastic properties: Elastic ones more than stiffer tissues. The static pressure only keeps tissues deformed; for successful palpation an alternation of stress and relaxation is required in order to achieve good delineation of structures. In general, tumors are stiffer than healthy tissues and can be palpated as hard inclusions. However, only superficial structures are available for manual palpation. Ultrasound elastography extends our field of examination. Elastography is a dynamic imaging technique based on ultrasound that noninvasively assesses the stiffness of tissues by measuring tissue deformation as a response to external compression or internal pulsations and movements[1].

Elastography Images

Elastography images are calculated from normal grayscale ultrasound images by correlation-based tracking of speckles (grayscale pixels). They are usually superimposed on normal B-mode images as an additional color layer: Blue color represents the stiffest structures, green and yellow intermediate, and red the most elastic structures [Fig. 1]. The underlying B-mode image allows anatomical orientation and recognition of structures. The color map displays the distribution of relative tissue stiffness and not the absolute values within the selected area under observation. The selected area or region of interest (ROI) can be selected manually by the examiner. An additional function in the Olympus software pack enables selection of additional smaller regions within the ROI; the operator can select for example lymph nodes or other structures, obtain the average strain value from the selected area, and compare it with another selected reference area (for example normal tissue) to obtain strain ratio. Strain ratio therefore represents the relative ratio of stiffnesses between both selected areas within the ROI.

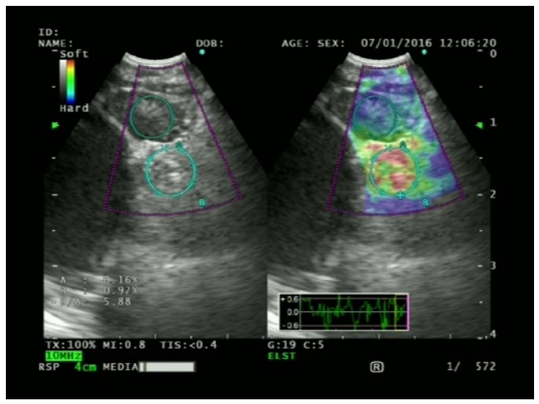

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Figure 1.
EBUS elastography image of left paratracheal 4L lymph nodes. The image on the left-hand side displays grayscale ultrasound features. The image on the right-hand side is a superimposed elastographic image with a color-coded scale (the hardest tissues are shown in blue and the softest in red). Symbol B/A represents the strain ratio, calculated between selected areas of the lymph node and the surrounding tissue.

Clinical Applications

Ultrasound elastography has previously been applied as an external procedure (for example, in the diagnosis of thyroid, breast, and prostate tumors) and as an endoscopic procedure (for example, in the diagnosis of pancreatic tumors, and nodal involvement of rectal and esophageal cancer)[2]. A meta-analysis of EUS elastography trials on the differentiation of benign and malignant lymph nodes reported a sensitivity of 88%, a specificity of 85%, and an area under the receiver operating characteristic (ROC) curve of 0.95[3]. However, only one of the included trials evaluated the strain ratio as a diagnostic standard[4]. A recent preliminary report on endobronchial ultrasound elastography suggests that this method may improve diagnostic yield[5].
Our study results described the value of the strain ratio for the mediastinal staging of patients with lung cancer[6]. The mean strain ratio for malignant lymph nodes was 18.96 ± 18.32 and 6.27 ± 7.30 for benign lymph nodes. The ROC area under the curve for the strain ratio was 0.87 (95% CI 0.78–0.96, $p < 0.0001$). A strain ratio value 8 was refined as a cut-off point with the highest ratio between sensitivity and specificity (sens. 88.24%, spec. 84.78%). However, the sensitivity and negative predictive value (NPV) of the strain ratio were still lower than for EBUS-TBNA.

The interesting feature was the high NPV (96.15%) of the strain ratio in the subgroup of normal-sized mediastinal lymph nodes in patients with lung cancer, which was comparable to the EBUS-TBNA NPV. The potential role of the elastography strain ratio may be in excluding lymph nodes with benign features from further invasive sampling. That would result in reduced invasiveness and reduced costs for mediastinal staging.

A Look into the Future

Elastography is an interesting new technology in the field of EBUS/EUS, but needs further development and refinement. In the diagnosis and staging of lung cancer we see the following fields of application:

- Better selection of sampling area within larger lesions (avoidance of necrosis),
- Selection of the most suspicious lymph node from the region for FNA,
- Less invasive mediastinal staging (reduced number of punctures),
- Quicker staging procedure.

However, the method is still not standardized and studied yet enough for routine clinical use. The biggest challenges and limitations are the following:

- Small ROI: In the case of large lesion and relative depletion of normal tissue (or presence of large vessels) there may be inaccurate assessment of relative stiffness,
- Relative, not an absolute estimation of elasticity (compression force is not known),
- Subjectivity in image (ROI, frame) selection and interpretation,
- Inter/intra-observer variability, reproducibility,
- Strong versus weak physiological movements (distance from heart, large vessels, obese patients) which generate compression on tissues in the chest,
- Vicinity or interposition of large vessels (cysts),
- Misinterpretation: Tumor necrosis in lymph nodes (soft – false negative)/calcified or fibrous lesions in benign lymph nodes (post TBC) (hard – false positive).

The technology will undoubtedly be developed and studied in the next years since several clinical trials are in progress. Their results will define the position of EBUS elastography in interventional pulmonology.

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