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Characterization of Lung Tumors that the Pulmonologist can Biopsy from the Esophagus with Endosonography (EUS-B-FNA)

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Keywords

Lung cancer · Endoscopic ultrasound · EUS-B-FNA · EUS-FNA · Endobronchial ultrasound-guided transbronchial needle aspiration

Abstract

Background: According to guidelines, it is possible to biopsy lung tumors "immediately adjacent to the esophagus" with EUS-B-FNA. However, it is unknown what "immediately adjacent" exactly means. ***Objective:*** to investigate the possibility of achieving EUS-B-FNA biopsies from a lung tumor depending on the distance from the esophagus and to establish the maximal allowable distance between the tumor and the esophagus. ***Methods:*** In a prospective observational study, we included patients with a lung tumor located maximum 6 cm from the esophagus and indication of EUS-B-FNA from the tumor. The tumors were of different sizes. In a plot presenting the tumor size-distance relationship in cases with (biopsy) versus without (non-biopsy) successful EUS-B-FNA, a separation line representing the threshold between the groups were identified and a biopsy-index equation established. The maximal tumor-size corrected distance (TSCD) was calculated using the residuals to the separation line. ***Results:*** In total, 70 patients were included. EUS-B-FNA from the lung tumor was possible in 46 patients. All tumors with a distance from the esophagus below 19 mm could be biopsied. The maximal allowable esophagus-tumor distance depended on tumor size. From the separation line, a biopsy-index equation was established with the sensitivity of 93.5%, a specificity of 100%, and total accuracy of 95.7%. The TSCD was 31 mm (sensitivity: 95.7%, specificity 75.0%, and accuracy: 88.6%). ***Conclusion:*** We established a biopsy-index equation to predict the achievability of a lung tumor using EUS-B-FNA depending on distance to esophagus and tumor size. A general maximal TSCD was 31 mm.

Introduction

In patients suspected of lung cancer, it is mandatory to obtain a tissue diagnosis to confirm or invalidate the suspicion. The biopsy, for example, can be performed by the use of endobronchial ultrasound-guided transbronchial needle aspiration via trachea (EBUS-TBNA) or esophageal ultrasound-guided fine-needle aspiration. The latter can be performed either with the use of a conventional

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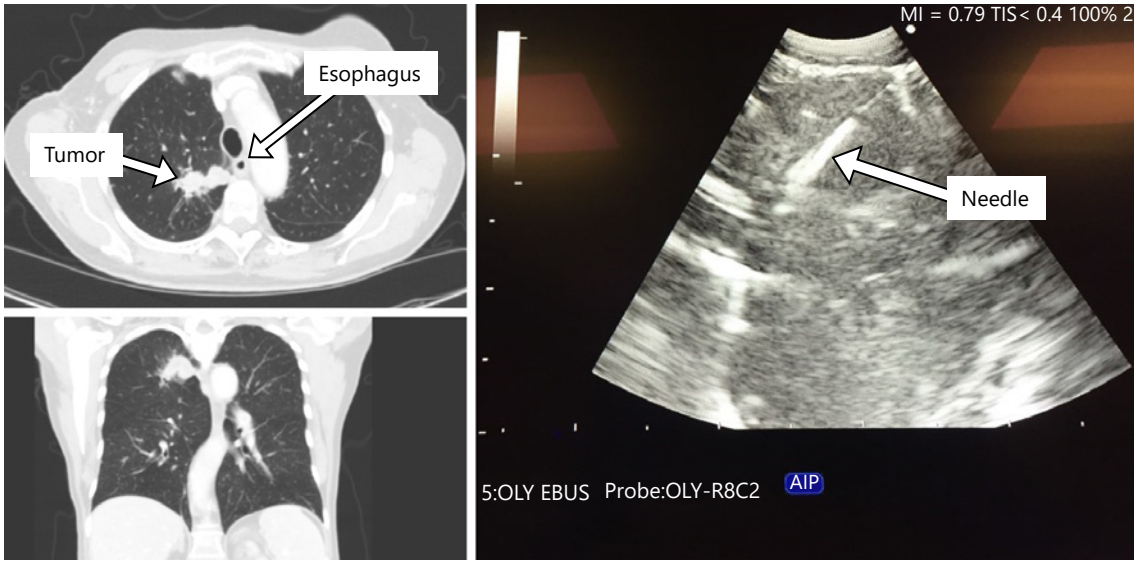

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Fig. 1. CT scan and EUS-B picture from a 77-year-old woman admitted with a 30-mm lesion in the right upper lobe. The tumor could not be visualized by bronchoscopy or EBUS. EUS-B-FNA from the lesion showed pulmonary adenocarcinoma. The distance from the esophagus to the tumor was 9 mm when measured with CT and 6 mm when measured with EUS-B. EUS-B-FNA from a slightly enlarged left adrenal gland was without metastasis. CT, computed tomography.

gastrointestinal scope (EUS-FNA) or by using the EBUS-scope in the esophagus (EUS-B-FNA) [1].

In the European guidelines for combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer [1], it is suggested that centrally located lung tumors not visible at conventional bronchoscopy should be biopsied by EUS-B-FNA "*provided that the tumor is located immediately adjacent to the esophagus*." Unfortunately, it is unknown what the term "*immediately adjacent*" covers. Studies on EUS-FNA from intrapulmonary tumors [2–11] rarely report the distance between esophagus and the lung tumor. When reported, the distances vary greatly (from below 10 up to 46 mm) [3, 4, 10, 11]. Also, there is limited evidence of the value of EUS-B-FNA for intrapulmonary tumors, and the corresponding distances to the tumor when performing EUS-B-FNA are not reported [12–16]. Consequently, it is not known which patients are suitable for EUS-B guided FNA from a centrally located lung tumor. Since ultrasound (US) has difficulties in visualizing structures in lung tissue containing air and that the length of the conventional 22 G needle is 40 mm, it is expected that only tumors with a short distance from the esophagus will be possible to biopsy with EUS-B-FNA. However, esophagus, being a muscular tube, to some extend may be moved closer to a target by bending the distal end of the endoscope, where the transducer is located. In that case, the distance between the esophagus and a lung tumor as measured by computed tomography (CT) may overestimate the actual and more relevant distance as measured by the US endoscope during the EUS-B-FNA-procedure.

Therefore, the objectives of our study were to investigate the possibility of achieving EUS-B-FNA from a lung tumor, depending on the distance from the esophagus, and to find the maximal allowable distance and describe if there is a difference between the distance measured by CT and EUS-B, reflecting a possible movement of the esophagus.

Methods

The study was a prospective, non-randomized diagnostic study with inclusion of patients with intrapulmonary lesions visualized with CT, located immediately adjacent to the esophagus and with a clinical indication for endosonography and tumor biopsy. We defined "immediately adjacent" as maximum of 6 cm in shortest distance.

Exclusion criterion: EUS-B-FNA not possible (endoscope could not enter the esophagus or big vessels between the target and the transducer). The study was performed at the Respiratory Section at the Department of Internal Medicine, Zealand University hospital, Roskilde, and Department of Respiratory Medicine, Næstved Hospital, Denmark.

During the EUS-B procedure, it was noted whether the lung lesion was visible and targetable (biopsy group) or not (non-biopsy group). If visible, the shortest distance between the transducer and the tumor was determined (esophagus-tumor distance) before insertion of the EUS-B-FNA biopsy needle. Samples were sent for cytopathological evaluation – rapid on-site evaluation was not available. Final diagnosis of the needle biopsies, and if relevant, follow-up was recorded.

Tumor size (largest diameter) and the shortest esophagus-tumor distance were measured on CT. Figure 1 shows an example of an included biopsy-group patient.

The EUS-B Procedure

Conventional bronchoscopy and EBUS-TBNA was followed by EUS-B-FNA in the same session. The patients were placed in supine position lying on the back, under conscious sedation using midazolam/fentanyl. For EUS-B, we used a flexible EBUS endoscope (Olympus BF-UC180F or UC180F; Olympus Medical Systems Europe, Ltd., Hamburg, Germany).

EUS-B was performed systematically as earlier described [13] in accordance with the structured assessment tool for EUS in examination of lung cancer patients [17]. Following identification of the intrapulmonary tumor, aspirates were performed using a 22 G needle (22-Gauge Olympus ViziShot; Olympus Medical Systems Europe, Ltd., Hamburg, Germany). The needle was inserted in the lesion under ultrasonic guidance, the stylet was removed, and suction applied. At least 2 samples were taken. The aspirates were processed for both cytological smears and cellblock analysis.

Analysis and Statistics

Primary End point

The aim of this study was to investigate the possibility of achieving a biopsy from the tumor with EUS-B-FNA, depending on distance from the esophagus, and to find the maximal allowable esophagus-to-tumor distance in order to achieve a needle biopsy with EUS-B-FNA.

The Maximal Distance and Possibility of Achieving a Needle Biopsy

The visibility of a tumor on US is a prerequisite in order to obtain a biopsy using EUS-B-FNA. The analysis presumed that the detectability of the tumor using US was dependent on both the tumor size and the tumor distance from the esophagus, that is larger objects are more likely than smaller objects to be seen at the same distance.

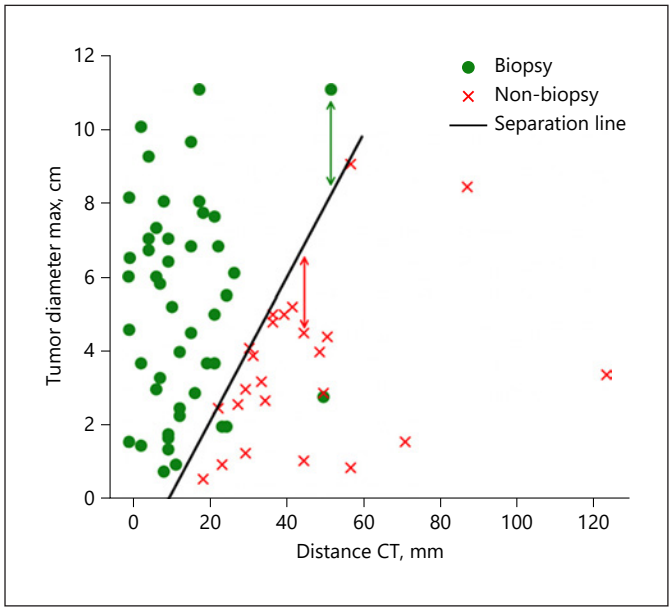

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Fig. 2. The size-distance relationship of biopsy (o) and non-biopsy (x) tumors in 2 different colors. The horizontal axis shows distance from the esophagus to the tumor in mm, and the vertical axis the tumor size expressed as diameter, in cm. The separation line is shown as the full line with the equation $y = 0.194x - 1.921$. The sensitivity concerning the separation is 93.5%, specificity 100%, and accuracy 95.7%. The red and green arrows represent examples of the residual for 2 observations, the green as a positive residual, and the red as a negative. The size of the residuals equals the biopsy index. CT, computed tomography.

As 2 variables thus logically affected the visibility of a tumor on US, accounting for tumor size was needed to assess which CT-based esophagus-tumor distance that was the maximum allowed for EUS-B-FNA. To account for the size-distance relationship of tumor achievability, tumor size and distance for the observations in the biopsy versus the non-biopsy group were plotted.

To establish a threshold of the 2 variables between the 2 groups, a separation line between the groups needed to be decided. Many different lines separating the groups can be established, but as the end point targeted the maximum allowed distance for EUS-B-FNA, a separation margin closest to the non-biopsy tumors was chosen so that none of the non-biopsy tumors were above the line. To do this, a support vector machine using an optimization algorithm was implemented in Python (3.7.7; Python Software Foundation) [18, 19] using the points along the hull of the data points belonging to the non-biopsy group. The separating vector was chosen on basis of linear error regression, maximizing total accuracy. If multiple optima

Table 1. Demographics and tumor characteristics

Tumor biopsied	Yes	No
Sex, male, *n* (%)	25 (54)	16 (67)
Age, mean (SD)	68 (9.3)	71 (8.1)
Location of tumor, lobe, *n* (%)		
RUL	17 (37)	9 (37.5)
RLL	11 (23.9)	7 (29.2)
LUL	12 (26.1)	3 (12.5)
LLL	6 (13)	5 (20.8)
Size of tumor, mean, cm (SD)	5.2 (2.8)	3.55 (2.1)

RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

were found, an average of the linear parameters would be established. Everything above this separation line is theoretically achievable using EUS-B-FNA; everything below is less likely achievable (Fig. 2 should be shown here).

The separating line and its linear function were determined, the residuals (the *y*-distances) to the line for each observation were used as an indicator of whether a tumor with a given size and distance to the esophagus would be achievable for EUS-B-FNA. From the linear function of the separation line, the residuals were calculated, expressed, and interpreted as an index equation.

If a tumor possesses characteristics (distance and size) placing it on the separation line, it should be considered as being on the limit of what can be targeted using EUS-B-FNA. That is, the residual to the separation line acts as a predictor for whether the tumor can be targeted using EUS-B-FNA (possible if index >0). The likelihood of achieving a biopsy with EUS-B-FNA from a tumor with a given size and distance was calculated as positive likelihood ratio (PLR) (sensitivity/[1 − specificity]) [20, 21] and was presented graphically as a function of the biopsy index.

In order to present a maximal possible distance for achieving a biopsy, the CT distance and the above residual index were used and a regular linear regression was performed. The tumor-size corrected maximum distance was determined using the intersect of the regression having the residual value of 0. This intersection is a theoretical distance that accounts for the variation in observed tumor size, thus named *tumor-size corrected distance* (*TSCD)*. The measure indicates a maximum distance, when correcting for the tumor size, for visualizing the tumor and obtaining a biopsy with EUS-B-FNA.

Secondary End points

Difference in the Distance Measured with CT and US

The difference between the measured distances of CT and US was calculated using paired *t* test, and a mean-difference of the distance (Bland-Altman) plot was made to assess measurement bias [22]. To affirm the observed differences, the theoretical EBUS-endoscope range of motion was determined in a technical study in which an engineer (author M.B.S.) performed measurements and calculations of theoretical movement with an EBUS endoscope and a 22 G needle (see online suppl. material 2; for all online suppl. material, see www.karger.com/doi/10.1159/000512074).

Definitions of Sample Adequacy and Diagnostic Yield

Biopsies were judged to be adequate when containing material sufficient for cytopathological evaluation. Samples in which cytopathological evaluation showed malignancy were considered to be true positive. When the cytopathological result was nonmalignant, the EUS-B biopsy result of the lung lesion was confirmed with at least a 6-month follow-up with a clinical course or CT. The diagnostic yield was defined as the number of samples in which EUS-B-FNA provided a specific diagnosis (malignant or nonmalignant) relative to the total number of samples performed with EUS-B-FNA.

Statistics

Unless otherwise specified, data were processed using SPSS (IBM, SPSS statistics, version 26). Results were reported with average ± standard deviation, and intergroup differences were analyzed using unpaired *t* test with unequal variances or paired *t* test. A p value <0.05 was considered statistically significant.

Results

In total, 70 consecutive patients were included in the study from October 1, 2017, through April 30, 2019, and EUS-B-FNA was obtained in 46 patients (65.7% = biopsy group). We observed no cases in whom the tumor was visible by EUS-B but not accessible for EUS-B-FNA biopsy. No major complications were observed. Tumor characteristics and demographics are shown in Table 1.

Eight eligible patients were excluded due to inability of introducing the EBUS endoscope in the esophagus (n = 2), and large vessels (aorta, left pulmonary artery, and the left subclavian artery) located between the tumor and the transducer (n = 6). In all of the 46 patients in the biopsy

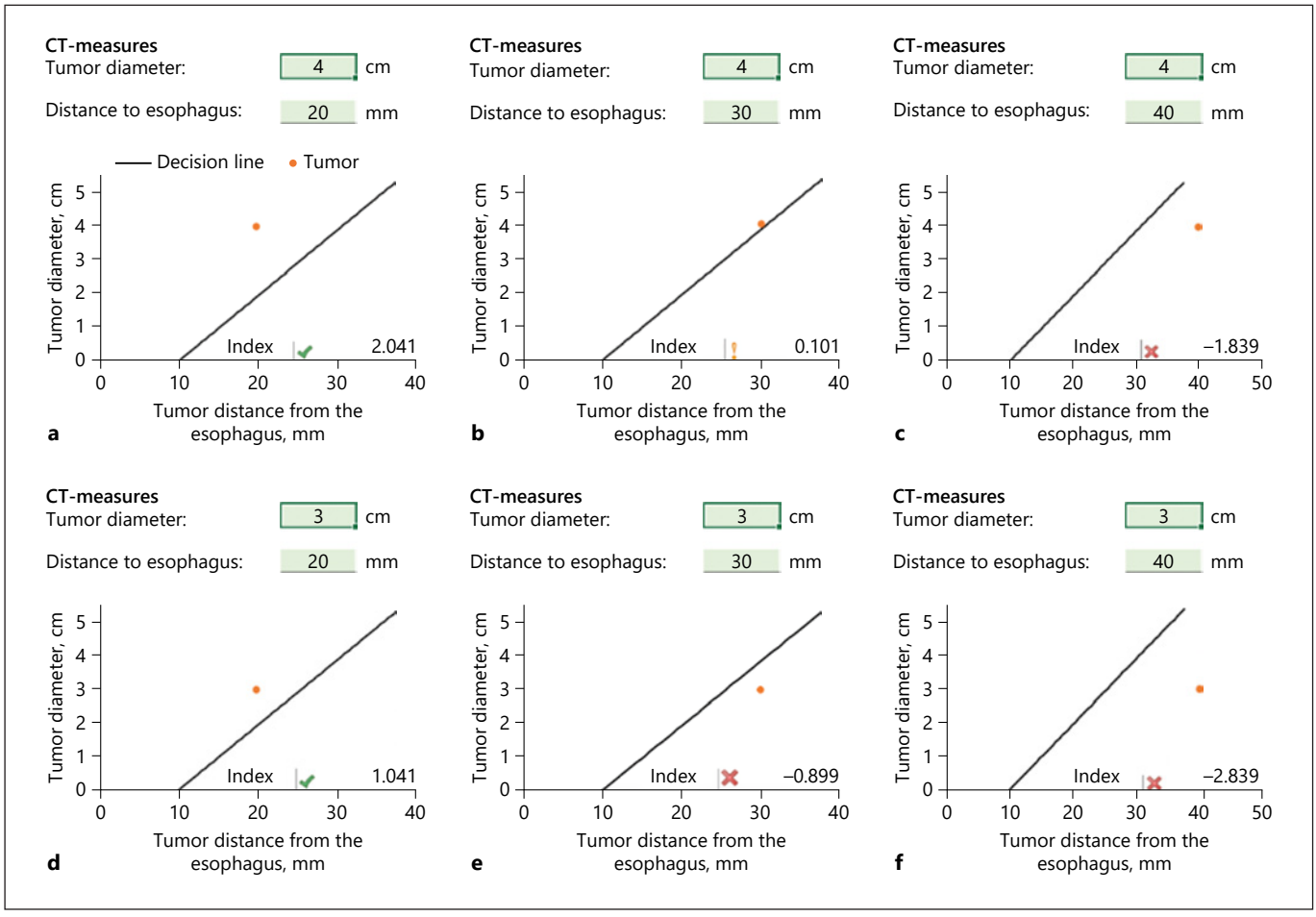

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Fig. 3. Examples of different fictive tumor sizes and distances with corresponding biopsy-index values. The interactive biopsy equation and the graphical support in the online suppl. material were used. **a–c** Tumor size 4.0 cm. **a** Distance 20 mm. Biopsy index 2.04, and thus, this tumor is likely to be achievable by EUS-B-FNA. **b** Distance 30 mm. Biopsy index 0.1, and this tumor is very close to be placed on the separation line. **c** Distance 40 mm. Biopsy index −1.84, and this tumor is unlikely to be achievable by EUS-B-FNA. **d–f** Tumor size 3.0 cm. **d** Distance 20 mm. Biopsy index 1.04, and thus this tumor is likely to be achievable by EUS-B-FNA. **e** Distance 30 mm. Biopsy index −0.89, and this tumor is unlikely to be achievable by EUS-B-FNA. **f** Distance 40 mm. Biopsy index −2.84, and this tumor is unlikely to be achievable by EUS-B-FNA.

group, cytopathological examination of the samples were adequate for evaluation. Diagnoses of the samples were NSCLC (pulmonary adenocarcinoma, $n = 16$; squamous cell carcinoma, $n = 7$; and NSCLC not otherwise specified, $n = 2$), SCLC ($n = 7$), extrapulmonary metastases ($n = 5$), carcinoma of unknown origin ($n = 1$), and nonmalignant ($n = 8$). Of these nonmalignant cases, 3 were considered false negative (malignancy was found in other lesions biopsied at the same session), whereas 5 were considered true negative (all obtained samples and 6-month follow-up were without signs of malignancy): 1 was non-TB infection, and 4 were nonspecific. Diagnostic yield was 85% (38 malignant + 1 infectious case out of 46 cases in total).

Possibility of Achieving a Biopsy and Maximal Possible Distance

The CT-measured mean distance of the biopsied tumors (biopsy group) was 14 ± 11 mm (range 0–52 mm) and was significantly lower than that in the non-biopsy group: 45 ± 22 mm (range 19–123 mm) with a mean difference of 31.3 mm ($p < 0.0001$, 95% CI: 21.2–41.4 mm). Likewise, the mean tumor size in the biopsy group of 5.2 ± 2.8 cm (range 0.8–11.0) was significantly larger than in the non-biopsy group: 3.5 ± 2.1 cm (range 0.6–9.0) with a mean difference of 1.7 cm ($p < 0.01$, 95% CI: 0.5–2.9).

Figure 2 shows the observations of size of the biopsied and non-biopsied tumors and their corresponding esopha-

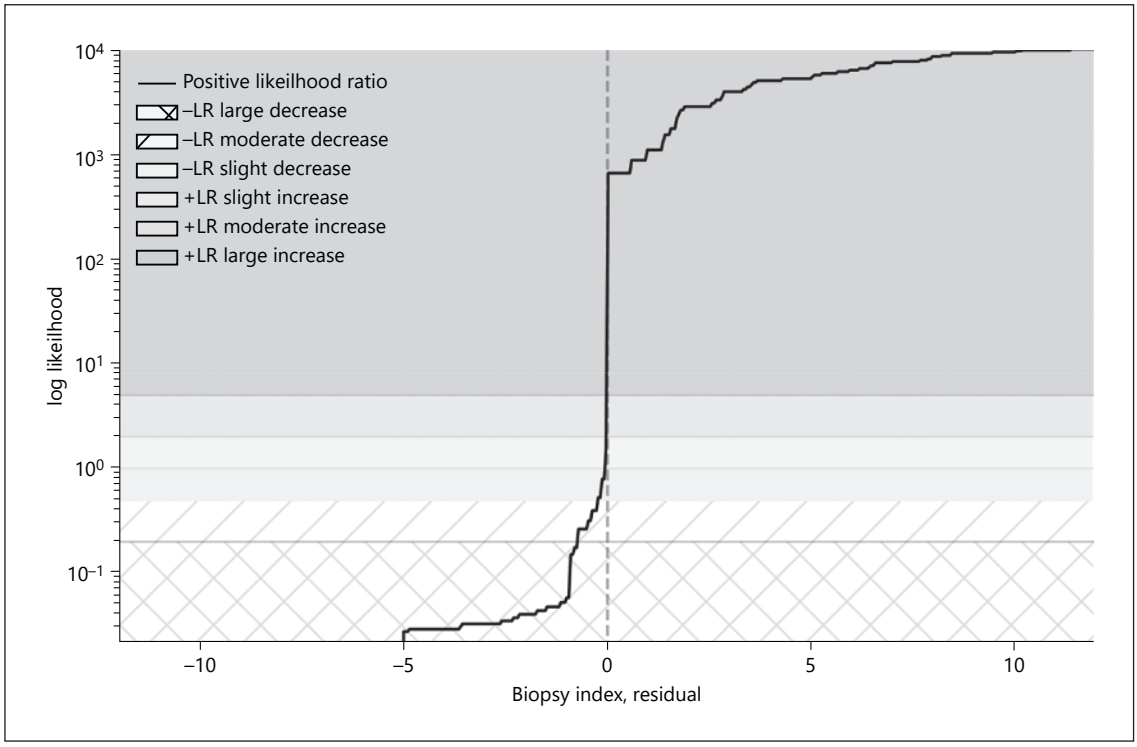

Fig. 4. The PLR as a function of the biopsy index. Interpretation of the likelihood ratios is large shift = +LR > 10 and –LR < 0.1, small shift = +LR between 5 and 10 and –LR between 0.1 and 0.2, smaller shift = +LR between 2 and 5 and –LR between 0.2 and 0.5, and rarely important shifts = +LR between 1 and 2 and –LR between 0.5 and 1. Irrelevant shifts = LR close to 1, as described by Hughes et al. [20]. The different levels for interpretation are highlighted in color. PLR, positive likelihood ratio.

gus-to-tumor distance. The 2 groups are seen to be distinct for choosing a separation line: 2 equal separating lines were found using the average of the 2, and the final separating line was determined to slope: 0.194, intercept: −1.921.

The biopsy-index equation expressed from the function of the separation line was then as follows:

$$I_{\text{biopsy}} = Ø_{tumor} - (0.194 \times d_{\text{Eso}} - 1.921)$$

where I_{biopsy} is the biopsy index, $Ø_{\text{tumor}}$ being the tumor diameter (cm), and d_{Eso} being the distance from the esophagus to the tumor (mm). With the established separation line, a threshold of 0 for separating biopsied/non-biopsied tumors regarding classifying the existing dataset for possible achievability of tumors, provided a sensitivity of 93.5% (true-positive rate, tumors assessed being biopsied, and those that were biopsied), a specificity of 100% (true-negative rate, tumors assessed not biopsied, and those that were not biopsied), and a total accuracy of 95.7%.

Figure 3 shows examples of the same curve as in Figure 2 but with fictive tumor characteristics inserted to illustrate the usability of our model. The biopsy-index equation can be used to calculate a biopsy index for a tumor with a given size and distance. An index above 0 is placed above the separation line, and an index below 0 is placed below the line. The PLR as a function of the biopsy index is illustrated graphically in Figure 4.

In order to visualize the whole range of biopsy index values, the PLR is log transformed and interpretation according to Hughes et al. [20] is marked graphically. The biopsy-index equation and interactive graphical support are accessible in the online suppl. material 1.

The determined TSCD was established at 31 mm (see Fig. 5). Using TSCD as a threshold for whether a tumor is accessible for EUS-B-FNA obtained a sensitivity of 95.7%, a specificity of 75.0%, and a total accuracy of 88.6%.

Difference in the Distance Measured with CT and US

The overall average difference between the CT and US measurements was 5.6 mm ($p < 0.0001$, CI 2.7–8.4, range = [−5, 42]). But as illustrated in Figure 6, distance presented a significant bias in the mean-difference plot, and a regression model correcting for the mean-difference had a significant regression coefficient of 1.027 (intercept: −5.49, r^2: 0.565, $p < 0.0001$).

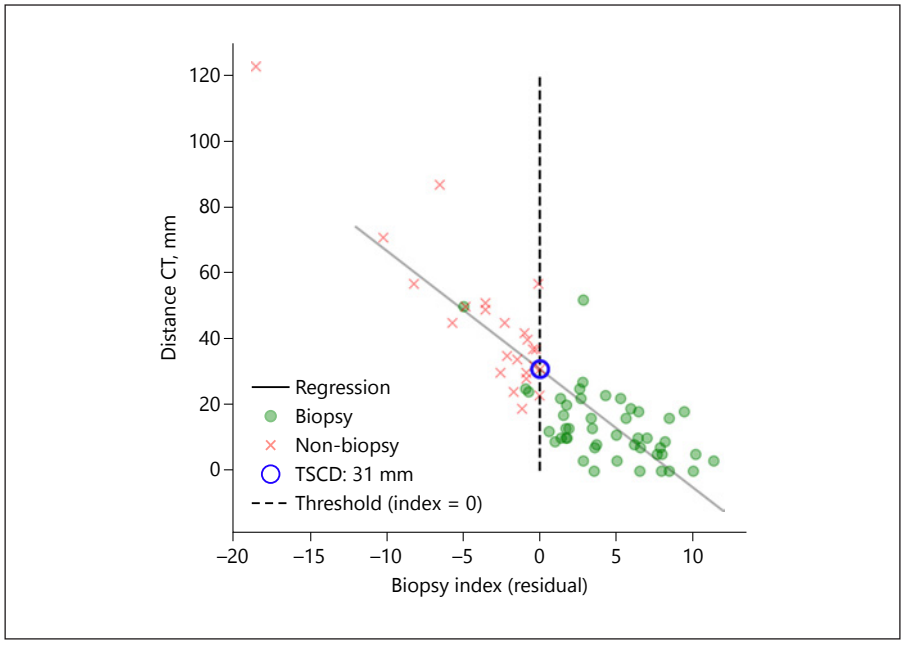

Fig. 5. The relationship of the described biopsy index (residuals to the line in Fig. 2) and CT distance with a plotted regression line of the observations (full line). The dotted vertical axis shows the threshold of 0. The TSCD, 31 mm, is highlighted in the blue circle, the exact value being the intersection between the plotted regression line and the vertical axis at 0. CT, computed tomography; TSCD, tumor-size corrected distance.

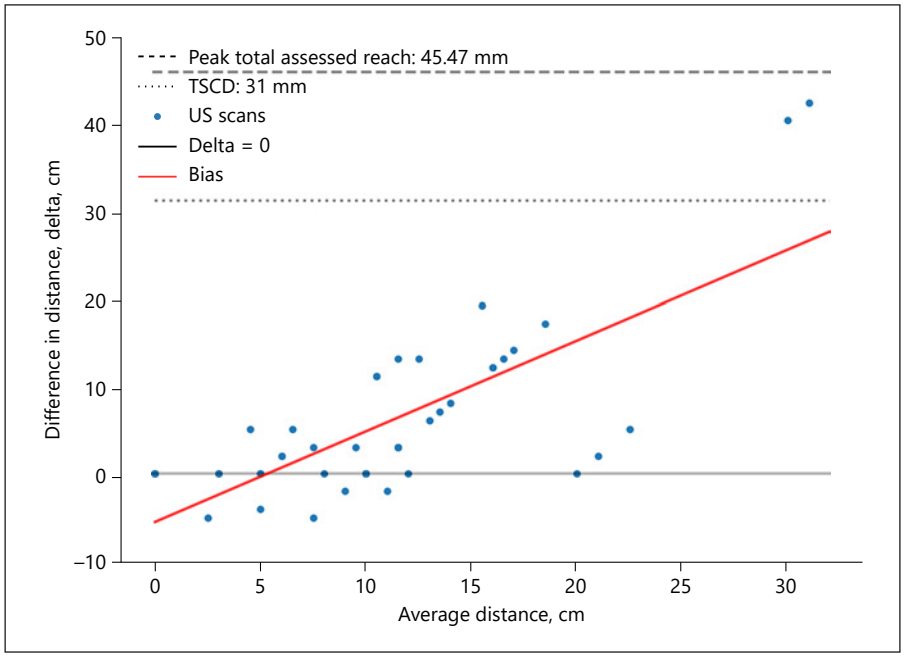

Fig. 6. A mean-difference (Bland-Altman) plot of the distances measured using EUS-B and CT scans of visible tumors. The dots (o) represent the measurements, horizontal lines: full, highlighting 0 for clarity; dashed, the theoretical full range of motion of the endoscope, based on the physical measurements; dotted, the maximum TSCD. The full red line is the linear regression of all the data, illustrating a statistically significant bias – interpreted as being caused by the esophagus being moved. CT, computed tomography; TSCD, tumor-size corrected distance; US, ultrasound.

A post hoc analysis of the differences found that at smaller distances (mean distance ≤10 mm), there was no significant difference in the measurements at CT and US (mean difference: 0.2 mm, $p = 0.8$, 95% CI: −0.9 to 1.3), and at larger distances (mean distance >10 mm), the CT measurements were significantly larger than US (mean difference 11.0 mm, $p < 0.0001$, 95% CI: 6.2–15.7). The theoretical maximal range of motion of the US probe was 45 mm (see online suppl. material 2).

Discussion

Possibility of Achieving a Biopsy and Maximal Possible Distance

Though tissue samples from centrally located lung tumors can be achieved by EUS-B-FNA [12, 13], no studies report the distance between the tumor and the esophagus, and the guidelines [1] do not mention any specific allowable maximal distance. This study is the first to report

calculations of the possibility of achieving a needle biopsy with EUS-B-FNA depending on the size of the tumor and distance from the esophagus and to report an estimation of the maximal possible distance between the lung tumor and the esophagus.

In our material, we found that accessibility of a tumor for fine-needle aspiration with EUS-B-FNA depended on both the distance from the esophagus and the tumor size. Thus, a separation line as threshold in the data obtained from the CT scan regarding distance to the esophagus and tumor size was applied (Fig. 2). From this separation line, a linear regression was applied and a biopsy-index equation was established. With this biopsy-index equation, we could establish a sensitivity of 93.5% and a specificity of 100%, with a total accuracy of 95.7%, regarding whether a tumor could be targeted for E-USB-FNA.

This equation is easily applied in a clinical practice as size and distance on CT of a given tumor can be added directly in the equation or in the online supplementary (see online suppl. material 1). The use of the equation is illustrated in Figure 3. Index results above 0 mean that the tumor is likely to be accessible by EUS-B-FNA, and results below 0 are less likely to be accessible. This knowledge can serve as a decision help for the pulmonologist when planning biopsying of a lung tumor.

However, it should be noted from the material that in the group of non-biopsied tumors, no tumors had a shorter distance from the esophagus than 19 mm, indicating that all tumors with a distance below this could be biopsied, and it is uncertain how the biopsy-index equation is applicable for distances below this level. Also, we do not know the upper limit of what distance the equation is applicable for.

In order to further simplifying the applicability of our results, we established a TSCD in an attempt to be able to disregard the size of the tumor in the assessment of whether a tumor was targetable by EUS-B-FNA (Fig. 5). This distance was, on basis of our results, established at a distance of 31 mm from the esophagus, providing a sensitivity of 95.7% and a specificity of 75.0% (88.6% total accuracy) of whether at tumor could be biopsied. Meaning that if a maximal distance of 31 mm is assumed, 95.7% of the actual accessible tumors would be biopsied but also 25% of the tumors that were not accessible would be attempted biopsied.

Using the TSCD as a general limit of distance disregarding the tumor size thus resulted in a higher sensitivity but also a lower specificity and total accuracy than a calculation with both variables. The TSCD can be used by the clinician as a pragmatic general guide of the maximal distance, and if the clinician needs a more precise prediction of a given tumor, with known size and distance, the biopsy-index equation can be used to predict achievability as a more accurate decision support.

Choosing a threshold such as the separation line depends on which conditions you want it to conform to. In this case, we chose to place the separation line in a way that would achieve a high specificity, this with a consequence of a lower sensitivity. With this approach, we chose the cautious limit as no patients in the group of non-biopsied tumors had a biopsy index above 0, and thus no patients would be exposed to the possible complications with failed biopsy attempts; on the other hand, using this threshold could have the consequence that a few tumors that turned out to be accessible by EUS-B-FNA would not have biopsies obtained using this procedure.

Difference in CT/US Distance

We found that the distance measured with CT was larger than the distance measured with US, thus it seems to be possible to move the esophagus, getting closer to the tumor. Likewise, if a tumor was located close to the esophagus based on CT, our observations indicated that there was no significant difference in CT/US distance. Whereas when the CT distance was high, there was a statistically significant bias and the difference in CT/US distance was higher (Fig. 6).

Taking the approach of considering the agreement between CT and US distances, one would expect ameasurement bias as the physical distance from the tumor to the esophagus increases. The further the distance, the more likely a difference between the modalities. The presumption is that if the tumor is far from the esophagus, the difference in measurements is larger as the physician needs to push the esophagus for visualization of the tumor.

We interpret this measurement bias as an effect of the esophagus and surrounding tissues getting pushed by the endoscope, hereby moving the esophagus with corresponding deformation and displacement of the tissues. On this background, the clinician can expect the measured CT distance to be larger than the corresponding US distance measured by the endoscope and take it into consideration when planning the biopsy of a tumor.

Additional Results

EUS-B-FNA for intrapulmonary lung tumors has been found safe and adequate in a few studies. Steinfort et al.

[12] showed that in 26 out of 27 patients, EUS-B-FNA was diagnostic predominantly with biopsies taken in the upper lobes. Skovgaard Christiansen et al. [13] showed that lung tumors located in all different lobes could be visualized and biopsied with EUS-B-FNA but with only 1 case from the right middle lobe. None of these studies reported the distance between esophagus and the lung tumor. In our material, comparable adequacy and diagnostic yield were found. Biopsies were taken from all lobes except the right middle lobe.

By biopsying centrally located lung tumors with the EUS endoscope, it could be expected that tumors at a larger distance could be expected to be achieved compared to the EBUS endoscope as the EUS endoscope is bigger, has a higher degree of motion range, and a larger ultrasound field. In the literature on EUS-FNA for intrapulmonary tumors, there exist a few cases reporting the CT-measured distances between the tumor and the EUS endoscope. The reported distance varies between below 1 cm [10], below 2 cm [3], 5–30 mm [11], and 0–46 mm [4] respectively, and the distances in our material are thus comparable with these reports. To our knowledge, there are no studies regarding the possibility of achieving a biopsy depending on neither the distance from the esophagus nor the size of the tumor.

Limitations

Our study is exploratory. We have developed a prediction model but have not tested this model in a separate population. This validation often reduces the diagnostic values [23]. Furthermore, our results are based on our material from 2 neighboring centers in the same healthcare system and should be confirmed in future studies to identify the optimal placement of the separation line and thus to develop a simple calculator of probably to succeed in sampling a central lung lesion with EUS-B-FBA. Measurement biases must be considered as the measurements of distance on CT and US respectively and are probably not at the exact same location, and the plane of the US scan is almost certainly not perpendicular to the plane of the measurements in the CT scans, that is not measuring the same physical distance.

Additionally, one could have expected the possible scenario that a tumor could be visualized without needle in the working channel of the endoscope but not with. However, in our material we did not observe any cases where insertion of the needle in the endoscope obscured visibility and biopsying of the tumor.

Conclusion

We found that the possibility of achieving a biopsy from a lung tumor with EUS-B-FNA depended on both the distance from the esophagus and the tumor size. We developed an equation to calculate a biopsy index depending on distance and size and we found a general maximal TSCD between the tumor and the esophagus of 31 mm. All tumors with a distance from the esophagus below 19 mm could be biopsied.

Also, we found that the CT-measured distance was larger than the corresponding US-measured distance to the tumor. These are all new results that directly can support the clinician planning biopsying of centrally located lung tumors.

Statement of Ethics

The study was an observational study without randomization or intervention. The study complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The regional research Ethics Committee was informed of the study and it did not need approval (J.nr. 17-000048). Patient data collection was approved by the Danish Data Protection Agency (j.nr. 2008-58-0020).

Conflict of Interest Statement

The authors have no conflicts of interest to declare concerning the content of this paper.

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Author Contributions

I.S.C., M.B.S., U.B., J.S.S., G.N.S., R.N., A.H., and P.F.C. contributed in formulation of the scientific problem, development of the methods, planning and conduction of the study. I.S.C., M.B.S., U.B., and P.F.C. contributed in conduction of the analysis of data. I.S.C., M.B.S., U.B., J.S.S., G.N.S., R.N., A.H., and P.F.C. contributed in interpretation of the results and writing of the manuscript.

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