Supplemental material:

Methods and material:

All input parameters for this decision analytical model have been collected from in-house data, literature and expert opinion. Some parameters may require more detailed elaboration to provide better reproducibility of this study.

Procedure properties:

CBCT-NB:

CBCT-NB diagnostic property parameters were gathered from Verhoeven et al. This study reports diagnostic accuracy defined as (true positive cases + true negative cases)/ total amount of procedures. The diagnostic parameters needed for the decision-analytical model are diagnostic yield (defined as amount of useful samples taken) and sensitivity, which cannot be derived from the article alone. The diagnostic accuracy post learning curve reported by Verhoeven et al can be divided in the following outcomes: 3 non diagnostic procedures; 38 true positive outcomes; 20 true negative outcomes; 0 false positive outcomes and 3 false negative outcomes. These results correspond with the 6 false negative outcomes published, but are separated as non-diagnostic and false negative, which is necessary for the model input. This provides the following input parameters: Diagnostic yield: 61/64 = 95.2%; Sensitivity: 38/41 = 92.7%; Specificity: 20/20 = 100%.

TTNB:

The collected results presented by the British thoracic society were used to gather the TTNB related procedure properties. For the decision-analytical model it was important to include papers which accurately reported the diagnostic yield (defined as number of useful samples taken). The BTS guideline was the only paper which presented this in a systematic manner. However, we excluded 5 studies in which the definition of diagnostic yield was not clearly described. These studies were not excluded in the calculation to determine sensitivity and specificity.

Delayed diagnosis:

The probability of progression to a more severe stage in case of a delayed diagnosis was based on Ten Haaf et al. This study estimated the time to progression of early stage (preclinical) lung cancer to a more advanced stage based on the NELSON trial data. The mean time to progress from one stage of lung cancer to the next (mean preclinical sojourn time) for an asymptomatic patient was presented as a Weibull distribution. We used this distribution to simulate the stage distribution over
time in patients with a false negative diagnosis. The time to delayed diagnosis in our study was assumed to be 6 months as this would be a normal period for follow-up after a biopsy with a benign diagnosis. Only stages Ia, Ib, II, IIIa, IIIb and IV were used as the article by ten Haaf et al. was based on the TNM 6th edition and no further subdivision in stages was available at that point in time.

Complications:

Complications were limited to the two most frequently and systematically reported complications, pneumothorax and bleeding. Pneumothorax rates were based on the meta-analysis studying TTNB related complications from Heerink et al. Major bleeding rates were gathered from Dibardino et al, as only this study made a clear distinction between minor and major bleedings with a clinical impact. Utility impact of TTNB and CBCT-NB were based on pneumothorax and bleeding as no specific data on the utility impact of the diagnostic procedures could be found. For pneumothorax no differentiation was made between conservative treatment or chest tube insertion, as this was already considered in the appraisal of the utility value. Utility loss due to complications of TTNB or CBCT-NB were assumed to last 2 months. This was recalculated to a yearly utility loss.

Supplemental figure 1: Markov model – part of both models, patients enter the Markov model after the decision tree in one of the possible health states (each health state has corresponding QoL values and associated costs). A yearly cycle is then run for ten years (ten cycles), in which patients can remain in the same health state or progress to death.
### Supplemental table 1: cost specification

<table>
<thead>
<tr>
<th></th>
<th>Costs (€)</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTNB personnel costs</td>
<td>254</td>
<td>Combined costs based on rate for intervention radiologist and CT technician assuming a 65 minute procedure</td>
</tr>
<tr>
<td>TTNB equipment costs</td>
<td>1,396</td>
<td>Combined costs of CT-scanner, ultrasound and x-ray equipment, disposables (lidocaine ampul, sterile cover material, core biopsy needle) and costs for pathology examination.</td>
</tr>
<tr>
<td>CBCT-NB personnel costs</td>
<td>781</td>
<td>Combined costs based on rate for intervention pulmonologist, anaesthesiologist, CT technician, endoscopy nurse assuming a 105 minute procedure</td>
</tr>
<tr>
<td>CBCT equipment costs</td>
<td>2,241</td>
<td>Combined costs of hourly rate for cone beam CT-scanner, rEBUS and ultrasound*. Cleaning costs of bronchoscope and EBUS miniprobe. disposables (lidocaine ampul, extended working catheter, TBNA needle, forceps biopsy instrument) and costs for pathology examination.</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1,422</td>
<td>Expert opinion, based on 1,5 admitted hospital days, 2 chest x-rays and 1 CT scan</td>
</tr>
<tr>
<td>Pneumothorax requiring intervention</td>
<td>3,297</td>
<td>Expert opinion, based on 3,8 admitted hospital days, chest drain insertion, 2 chest x-rays and 1 CT scan</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>1,606</td>
<td>Expert opinion, based on 1,5 admitted hospital days, and 2 CT scans</td>
</tr>
</tbody>
</table>

EBUS = endobronchial ultrasound; TBNA = transbronchial needle aspiration

Purchase costs are corrected for 10 years depreciation time, annuity factor and interest rate. All costs are corrected for hospital overhead. Costs were corrected for inflation for 2021. All cost modifications follow the dutch guidelines for cost research.
Supplemental Figure 2A and 2B: Tornado diagram evaluating costs (2A) and effects (2B) of CBCT-NB vs TTNB.

Percentage varied from base case input
Supplemental Figure 3A and 3B: Tornado diagram evaluating costs (3A) and effects (3B) of CBCT-NB vs direct treatment.
Supplemental Figure 4. Two way sensitivity analysis set at two levels of specificity: 0.94 and 1. This analysis shows which combinations of diagnostic yield and sensitivity are cost-effective compared to TTNB (figure 4A and 4B) and compared to direct treatment (figure 4C and 4D). The X- and Y- axis of figure 4A and 4B (CBCT-NB compared to TTNB) range from 80%-100%. The X- and Y-axis of figure 4C and 4D (CBCT-NB vs Direct treatment) range from 50% to 100%.

CBCT-NB: Cone beam computed tomography navigation bronchoscopy; TTNB: transthoracic needle biopsy; ICER: Incremental cost-effectiveness ratio
References


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