Cone beam CT-guided navigation bronchoscopy: a cost-effective alternative to CT-guided transthoracic biopsy for diagnosis of peripheral pulmonary nodules

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ABSTRACT

Objectives To determine if cone beam CT-guided navigation bronchoscopy (CBCT-NB) is a cost-effective diagnostic procedure in patients with a pulmonary nodule (PN) with an intermediate risk for lung cancer.

Materials and methods Two decision analytical models were developed to compare the long-term costs, survival and quality of life. In the first model, CBCT-NB was compared with CT-guided transthoracic needle biopsy (TTNB) in TTNB eligible patients. In the second model, CBCT-NB was compared with direct treatment (without pathology proven lung cancer) in patients for whom TTNB is not suitable. Input data were gathered in-house, from literature and expert opinion. Effects were expressed in quality-adjusted life years (QALYs). Sensitivity analyses were used to assess uncertainty.

Results CBCT-NB can be cost-effective in TTNB eligible patients with an incremental cost-effectiveness ratio of €18 416 in an expert setting. The probabilistic sensitivity analysis showed that in 69% and 90% of iterations CBCT-NB remained cost-effective assuming a willingness to pay (WTP) of €20 000 and €80 000 per QALY CBCT-NB dominated in the treatment strategy in which TTNB is not suitable. The probabilistic sensitivity analysis showed that in 95% of iterations CBCT-NB remained the dominant strategy, and CBCT-NB remained cost-effective in 100% of iterations assuming a WTP limit of €20 000. In the comparison between CBCT NB and TTNB, the deterministic sensitivity analysis showed that the diagnostic properties and costs of both procedures have a large impact on the outcome.

Conclusions CBCT-NB seems a cost-effective procedure when compared with TTNB and when compared with a direct treatment strategy in patients with an intermediate risk PN.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Cone beam CT-guided navigation bronchoscopy (CBCT-NB) is a navigation bronchoscopy technique used for the diagnosis of pulmonary nodules (PNs) with a high diagnostic yield and low complications, for which no cost-effectiveness research has been performed to date.

WHAT THIS STUDY ADDS
⇒ This study shows that CBCT-NB can be a cost-effective alternative to transthoracic needle biopsy (TTNB) in the diagnostic workup of PNs. Furthermore, this study shows that direct treatment is seldomly cost-effective if minimal invasive biopsy is possible.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ The diagnostic workup of PNs might be optimised by including CBCT-NB as an alternative to TTNB.

INTRODUCTION

Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related deaths worldwide,1 mainly due to the late stage (stage IV) on diagnosis in 50% of cases. The overall 5-year survival of stage IV lung cancer is less than 10%, whereas this is more than 70% for early-stage disease (stage I).2 Early diagnosis of lung cancer is therefore of vital importance in increasing survival. The potential benefit of early diagnosis by means of initiating CT screening in populations at risk has been investigated in trials such as the Dutch-Belgian lung-cancer screening trial (NELSON) and the National Lung Screening Trial (NLST).3,4 Early-stage lung cancer is generally asymptomatic and primarily detected as an incidental finding of a small peripheral nodule on CT of the chest, as long as screening programmes are not widely implemented yet. Pulmonary nodules (PNs) have been reported in 13% of all patients in which a CT of the chest was performed for a different, non-pulmonary, medical indication.5 Although a large number of PNs are detected in these
studies, there was only a 1.5% (0%–4.0%) prevalence of malignancy in the populations studied. As the majority of PN turn out to be benign, an effective work-up strategy to further these lesions is of high importance. Therefore, prediction models based on patient and nodule characteristics are used to estimate the risk of the lesion being malignant. When the calculated malignancy risk is less than 10%, CT follow-up is advised. In case the risk of malignancy is estimated to be above 10% (intermediate risk), minimal invasive biopsy is recommended, although direct treatment without invasive diagnostic procedures may be considered when the risk is estimated to be higher than 65–70% (depending on which guideline is followed).

The current, most widely available method of minimal invasive biopsy is the CT-guided transthoracic needle biopsy (TTNB), which has a diagnostic accuracy of around 90%. An important downside is a 14.6%–28.6% complication risk of a pneumothorax, requiring a chest tube insertion in 2.7%–7.3% of all patients. An additional limitation is that nodules may be inaccessible for a transthoracic approach due to anatomical constraints or because the risk of complications in combination with comorbidity of the patient prohibits its use. In current practice, these TTNB ineligible patients mostly undergo treatment without definitive pathology confirmation.

As an alternative less invasive method, several centres are exploring the possibilities of using flexible bronchoscopy with extended working catheters in combination with a cone beam CT image system in order to navigate towards lesions. The cone beam CT system can provide 3D navigation as well as confirm lesion access. Recent reports show a diagnostic accuracy in the range of TTNB with low complication rates (pneumothorax in 2%–4% of cases). Cone beam CT-guided navigation bronchoscopy (CBCT-NB) could therefore be a valuable alternative for patients who currently undergo TTNB or for those who are ineligible for TTNB due to significant comorbidity or difficult to reach lesions.

With increasing healthcare costs, it is becoming more important to assess if new techniques such as CBCT-NB are cost-effective. The potential benefits and costs of CBCT-NB have not yet been evaluated to date. In this study, we aim to determine if navigation bronchoscopy is a cost-effective procedure in the routine diagnostic workup of PNs with an intermediate risk of malignancy utilising a model-based cost-effectiveness analysis.

**METHODS AND MATERIALS**

**Decision model and comparisons**

Two decision analytical models were created in R (V.4.1.2) to compare the long-term outcomes in costs, survival and quality of life (QoL) between diagnostic and subsequent treatment strategies in the two subpopulations. A decision analytical model allows a (hypothetical) cohort of patients to walk through a diagnostic and treatment path, modelled as a flow chart, in which each decision and outcome has a probability based on the literature. A follow-up period of 10 years is then simulated using a Markov model to assess the long-term consequences in costs and QoL (online supplemental figure 1). In the first model (figure 1—model 1), a diagnostic and treatment workup including CBCT-NB as the primary diagnostic procedure was compared with a workup using TTNB as the primary diagnostic procedure.

In the second model (figure 1—model 2) patients with an intermediate risk PN who were ineligible to undergo TTNB due to anatomical constraints or comorbidity were simulated. In this model, a workup containing CBCT-NB as the primary diagnostic procedure was compared with direct treatment. Both analyses are set and modelled in the Dutch healthcare system from a healthcare perspective.

**Populations**

The modelled target population comprises patients with an average age of 65 years with an incidental PN of intermediate risk of malignancy on CT, which according to the British Thoracic Society (BTS) guidelines have an indication for a minimally invasive diagnostic procedure. Two subpopulations were defined:

1. Patients who are deemed eligible for TTNB.
2. Patients who are deemed ineligible for TTNB.

**Model structure**

**Decision tree: model 1 (CBCT-NB vs TTNB)**

The first step in the model was to divide all patients by their true pathology status, that is, having a benign or malignant lesion. The next division was based on the diagnostic properties of the two procedures under comparison. The properties used were the diagnostic yield (which was defined as the probability in which a representative sample was obtained), procedure sensitivity and specificity.

In case of an unrepresentative sample (indicating no diagnostic yield), the follow-up step was direct treatment that would result either in correct treatment in case of malignancy or incorrect treatment in case of a benign lesion. If there was a representative sample, four different outcomes would be possible. A true positive diagnosis resulted in treatment of the malignancy, while a false positive outcome resulted in overtreatment. A true negative sample was followed up with CT without subsequent treatment, while a false negative sample resulted in a delayed diagnosis and treatment with a risk of progressing to a more severe stage of disease.

**Decision tree: model 2 (CBCT-NB vs direct treatment in TTNB ineligible patients)**

The strategy containing the CBCT-NB procedure in this model followed the same steps as previously mentioned in model 1. The comparator, that is, the strategy containing direct treatment—also started by dividing patients over their true pathology. If the lesion was benign, the
outcome would result in overtreatment and in case of a malignant lesion a direct treatment would have been given correctly.

**Markov model**

A Markov model was used to simulate the consequences of the decision trees by dividing patients over different health states. The Markov model was equal in both models: patients with malignant disease were divided over health states that corresponded with six stages of lung cancer (range: Ia–IV). Patients with a malignancy who were correctly diagnosed and treated or who had direct treatment were divided over stage Ia, Ib or II, as these patients were diagnosed without a diagnostic delay (and are therefore early stage). Patients with delayed diagnoses were divided over stage Ia, Ib, II, IIIa, IIIb and IV based on the disease stage progression due to delayed diagnoses. For patients without a malignancy, two health states can be defined; (1) patients without a malignancy who received treatment (overtreatment) or (2) who correctly did not receive treatment. A yearly cycle was used for the Markov model, with a time horizon of 10 years (ten cycles). Over time, two events were possible: patients remained in the health state in which they entered the model or progressed to death. Associated QoL and healthcare costs were linked to each respective health state. Patients cannot move between health states as the associated increase in costs and loss of QoL of progressive disease is already calculated within the initial health state.

Model input

Model input was derived from the literature, expert opinion and in-house calculations. Data was selected to optimally fit the decision analytical model and Dutch data was used if possible to optimise comparability of the strategies under comparison. Details on input parameters are elaborated in supplemental text.

Probabilities

The risk of a nodule being malignant was based on the proportion of malignant diagnosis in a patient population who underwent CBCT-NB as their primary biopsy modality. The initial state of malignancy was based on the Dutch Lung Cancer Audit and distributed between stage Ia, Ib, II, IIIa, IIIb and IV based on the disease stage progression due to delayed diagnoses. For patients without a malignancy, two health states can be defined; (1) patients without a malignancy who received treatment (overtreatment) or (2) who correctly did not receive treatment. A yearly cycle was used for the Markov model, with a time horizon of 10 years (ten cycles). Over time, two events were possible: patients remained in the health state in which they entered the model or progressed to death. Associated QoL and healthcare costs were linked to each respective health state. Patients cannot move between health states as the associated increase in costs and loss of QoL of progressive disease is already calculated within the initial health state.

The risk of progression was calculated can be found in the supplemental text. Next, a treatment distribution was included for each stage of malignant disease. Probability of survival after diagnosis at a certain stage was based on 2-year and 5-year survival rates as presented in Goldstraw et al. These rates were adjusted to be used for yearly survival rates.

Risk of treatment-related mortality for video-assisted thoracoscopic surgery (VATS) and stereotactic ablative radiotherapy (SABR) was gathered from Stokes et al.
General population background mortality was based on Dutch statistics on age related death.18

A summary of the used probabilities is presented in table 1.

Procedure properties
TTNB sensitivity, specificity and diagnostic yield were derived from a systematic review as presented in the BTS guidelines, as this was the only review found that provided the amount of representative samples taken (ie, diagnostic yield) in combination with sensitivity and specificity. Complications were gathered from literature.7 8 CBCT-NB performance and complications were based on our previous publications, providing sensitivity, specificity, diagnostic yield and complication rates in an expert setting, after passing a learning curve. This setting is chosen to adequately represent the (maximum) potential of CBCT-NB.12 13 Procedure properties are presented in table 1.

Costs
Costs were calculated for diagnostic procedures and all subsequent treatments. Costs for diagnostic modalities are specified in online supplemental table 1. SABR and VATS related costs were estimated based on the literature.19 Systemic therapy prices were gathered from the Dutch healthcare institute20–22 and adjusted for longer median treatment time.23 24 An annual discount weight for costs based on Dutch guidelines was set at 4%. Costs are presented in table 2.

Utilities
Health utilities are used to reflect health-related QoL. Impact of the different diagnostic and therapeutic procedures combined with the impact of disease at a given point in time. The values range between 0 and 1, with 0 representing death and 1 resembling perfect health. Cancer stage utilities were derived from Sturza.25 In case of no malignancy at baseline, health utilities of a Dutch healthy 65 years old were used.18 Utility loss due to TTNB or CBCT-NB were based on complications and associated utility loss.26 Following VATS or SABR, an initial utility loss representing the direct impact of treatment was followed by a yearly less pronounced utility loss reflecting long-term consequences.27 28 Utilities are presented in table 2.

Outcome measures
Effects were measured as quality-adjusted life years (QALY), which consists of survival combined with QoL expressed as a health utility. A discount weight for effects was set at 1.5% corresponding to Dutch Health Authority guidelines.29

Robustness testing
The decision analytical model and decision tree were constructed according to Dutch national guidelines and international standards of treatment.5 A probabilistic sensitivity analysis was performed to assess uncertainty. A distribution was modelled around each parameter to adequately simulate the uncertainty of the model. Overall, 5000 iterations were performed with these distributions. At this number of iterations, the outcomes were stable. In each iteration, a new value from within these distributions was chosen for every individual parameter, providing 5000 possible outcomes. These combined iterations gave insight about the certainty of the model outcomes. A one-way deterministic sensitivity analysis was used to test the relative importance of individual model parameters. A two-way sensitivity analysis set at different percentages of specificity was used to assess which combinations of test properties would be cost-effective.

Data analysis
Diagnostic procedure outcomes were compared by the model based on costs in euro and effects in QALYs. Incremental cost-effectiveness ratios (ICERs) were calculated. An ICER represents the costs needed to generate an extra QALY when strategies are compared. A willingness-to-pay (WTP) threshold per QALY is dependent on disease burden and national standards. This amount was set at €20 000 and €80 000 per QALY, following the Dutch healthcare institute recommendations.30 When a strategy results in both a cost reduction and health gain, it is qualified as a dominant strategy.

RESULTS
Diagnostic pathway comparisons
Model 1 (CBCT-NB vs TTNB)
In this model, CBCT-NB appeared to be more effective with 6.853 QALY’s in comparison to TTNB with 6.829 QALYs. The total costs of the diagnostic and treatment pathway were €17561 for CBCT-NB as compared with €17103 for TTNB. The increased costs of €458 for 0.024 QALY gain per patient resulted in an ICER of €18 416 per QALY gained, which is cost-effective both using a WTP of €20 000 per QALY gained and €80 000 per QALY gained. (table 3).

Model 2 (CBCT-NB vs direct treatment in TTNB ineligible patients)
In this model, CBCT-NB as compared with direct treatment (without a definitive pathology diagnosis) appeared to be more effective (6.853 vs 6.752 QALYs) at a lower cost (€17561 vs €18 845). This resulted in a QALY gain of 0.101 and a cost reduction of €1284 per patient. CBCT-NB is therefore the dominant strategy (table 3).
| Parameter                          | Mean  | Sample size | Reference       |
|-----------------------------------|-------|-------------|-----------------|
| **Risk of malignancy**            | 73.7% | 148/202     | Verhoeven et al  |
| **Procedure characteristics**     |       |             |                 |
| CBCT-NB                           |       |             |                 |
| Diagnostic yield                  | 95.3% | 61/64       | Verhoeven et al  |
| Sensitivity                       | 92.7% | 38/41       | Verhoeven et al  |
| Specificity                       | 100%  | 20/20       | Verhoeven et al  |
| TTNB                              |       |             |                 |
| Diagnostic yield                  | 89.3% | 782/876     | Callister et al  |
| Sensitivity                       | 90.8% | 942/1038    | Callister et al  |
| Specificity                       | 94%   | 392/417     | Callister et al  |
| CBCT-NB                           |       |             |                 |
| Pneumothorax                      | 1.6%  | 4/238       | Verhoeven et al  |
| Pneumothorax requiring intervention| 1.6%  | 4/238       | Verhoeven et al  |
| Haemorrhage                       | 2.3%  | 5/238       | Verhoeven et al  |
| TTNB                              |       |             |                 |
| Pneumothorax                      | 19.7% | 1631/8275   | Heerink et al    |
| Pneumothorax requiring intervention| 5.6%  | 463/8275    | Heerink et al    |
| Haemorrhage                       | 2.8%  | 1490/8275   | Dibardino et al  |
| **Direct diagnosis, distribution**|       |             |                 |
| Stage Ia                          | 47.6% | 4569/9594   | Ismail et al     |
| Stage Ib                          | 23.8% | 2284/9594   | Ismail et al     |
| Stage II                          | 28.6% | 2744/9594   | Ismail et al     |
| **Delayed diagnosis, distribution**|      |             |                 |
| Stage Ia                          | 42.4% | –           | Ten Haaf et al/Ismail et al |
| Stage Ib                          | 18.6% | –           | Ten Haaf et al/Ismail et al |
| Stage II                          | 20.5% | –           | Ten Haaf et al/Ismail et al |
| Stage IIIa                        | 14.0% | –           | Ten Haaf et al/Ismail et al |
| Stage IIIB                        | 3.6%  | –           | Ten Haaf et al/Ismail et al |
| Stage IV                          | 0.9%  | –           | Ten Haaf et al/Ismail et al |
| **Treatment distribution**        |       |             |                 |
| Stage I–II                        |       |             |                 |
| Surgery                           | 46%   | 4554/9900   | Ismail et al     |
| Radiotherapy                      | 43.5% | 4307/9900   | Ismail et al     |
| Chemoradiotherapy                 | 2%    | 198/9900    | Ismail et al     |
| Chemotherapy                      | 7.3%  | 718/9900    | Ismail et al     |
| Chemoimmunotherapy                | 0.8%  | 74/9900     | Ismail et al     |
| Immunotherapy                     | 0.5%  | 50/9900     | Ismail et al     |
| Stage III                         |       |             |                 |
| Surgery                           | 9.3%  | 604/6524    | Ismail et al     |
| Radiotherapy                      | 12%   | 783/6524    | Ismail et al     |
| Chemoradiotherapy                 | 39.5% | 2577/6524   | Ismail et al     |
| Chemotherapy                      | 12.8% | 816/6524    | Ismail et al     |
| Chemoimmunotherapy                | 18.3% | 1191/6524   | Ismail et al     |
| Immunotherapy                     | 7.3%  | 473/6524    | Ismail et al     |
| Targeted therapy                  | 1%    | 65/6524     | Ismail et al     |
| Stage IV                          |       |             |                 |

**Continued**
Deterministic sensitivity analyses (DSA)
With the DSA, we examined the impact of single parameters on the total model outcome by adjusting them individually to –25% and +25% of the original values.

Model 1 (CBCT-NB vs TTNB)
The parameters with the highest impact on the outcome were the diagnostic characteristics (diagnostic yield, sensitivity and specificity) and the costs of both CBCT-NB and TTNB and the risk of malignancy. The alteration of other parameters resulted in minor changes in outcome. The impact of the individual parameters on the outcomes is illustrated in a tornado diagram (online supplemental figure 2). When assuming a WTP of €20,000 the minimum required diagnostic yield and sensitivity of CBCT-NB to be cost-effective are 95.1% and 92.5%. For a WTP of €80,000 per QALY, this is 92.5% and 89%. These thresholds were calculated by altering diagnostic yield and sensitivity simultaneously (ie, lowering diagnostic yield and sensitivity with the same steps until cost-effectiveness was lost). A two-way sensitivity analysis further showed which combinations of diagnostic yield and sensitivity can be cost-effective compared with TTNB at a WTP of €20,000 and €80,000 (online supplemental figure 4A,B).

Model 2 (CBCT-NB vs direct treatment)
In the DSA evaluating CBCT-NB versus direct treatment, only the risk of malignancy had a major impact on the model as can be seen in the tornado diagram (online supplemental figure 3). CBCT-NB remained dominant over direct treatment until an 80.6% risk of malignancy. CBCT-NB furthermore remained cost-effective with a WTP of €20,000 and €80,000 until an 85.2% and 89.4% risk of malignancy, respectively.

The effect of changing all other parameters were too small to affect the outcome of the model.
When looking at test properties in model 2, the minimal required diagnostic yield and sensitivity needed for CBCT-NB to remain cost-effective when compared with direct treatment were 72.2% and 69.6% when assuming a WTP of €20000 and 68.4% and 65.8% for a WTP threshold of €80000. These thresholds were also

| Table 2 Utilities and costs |
|-----------------------------|
| **Costs (€)**                | **Mean** | **Range**      |                  |
| TTNB                        | 1650     | 1237–2062      | Cost calculation|
| CBCT-NB                     | 3023     | 2267–3778      | Cost calculation|
| Pneumothorax                | 1422     | 1066–1777      | Cost calculation|
| Pneumothorax requiring intervention | 3297   | 2473–4122      | Cost calculation|
| Haemorrhage                 | 1606     | 1204–2007      | Cost calculation|
| CT follow-up                | 161      | 121–201        | Cost guideline   |
| Surgery (VATS)              | 18022    | 13517–22528    | Wolff et al 19   |
| Radiotherapy (SABR)         | 11534    | 8651–14418     | Wolff et al 19   |
| Chemotherapy                | 42951    | 32213–53689    | Dutch healthcare institute 31 |
| Targeted therapy            | 87384    | 36275–60459    | Dutch healthcare institute 32 |
| Immunotherapy               | 93279    | 69959–116599   | Dutch healthcare institute 22 23 |
| Chemo-immunotherapy         | 138627   | 103970–173283  | Dutch healthcare institute 20 21 24 |
| Chemoradiotherapy           | 20122    | 15092–25153    | Bongers et al 18  |

| Utilities (QALY) Mean SE |
|--------------------------|
| VATS 1st cycle           | 0.0346 0.026 Bendixen et al 28 |
| Other cycles             | 0.03 0.025 Bendixen et al 28 |
| SABR 1st cycle           | 0.0238 0.019 Paix et al 27 |
| Other cycles             | 0.0248 0.018 Paix et al 27 |
| Pneumothorax             | 0.023 0.017 Rickets et al 26 |
| Haemorrhage              | 0.0137 0.010 Rickets et al 26 |
| No lung cancer           | 0.852 0.014 Versteegh 39    |

**Lung cancer**
- Stage I: 0.825 0.074 Sturza 25
- Stage II: 0.825 0.074 Sturza 25
- Stage III: 0.772 0.075 Sturza 25
- Stage IV: 0.573 0.067 Sturza 25

CBCT-NB, cone beam CT-guided navigation bronchoscopy; QALY, quality-adjusted life years; SABR, stereotactic ablative radiotherapy; TTNB, transthoracic needle biopsy; VATS, video-assisted thoracoscopy.

| Table 3 Incremental analysis |
|------------------------------|
| **Test** | **Comparator** | **Incremental outcome** |
|---------|----------------|------------------------|
| Model 1: CBCT-NB versus TTNB |
| Procedure | CBCT-NB | TTNB | +458 |
| Costs (€)   | 17561    | 17103    | +0.024 |
| Effect (QALY) | 6.853 6.829 | 18.416 |
| ICER (€/QALY) | Cost-effective | 18.416 |
| Model 2: CBCT-NB versus direct treatment strategy |
| Procedure | CBCT-NB | Direct treatment | Dominant |
| Costs (€)   | 17561    | 18845 | -1284 |
| Effect (QALY) | 6.853 6.752 | +0.101 |
| ICER (€/QALY) | Dominant | x |

CBCT-NB, cone beam CT-guided navigation bronchoscopy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TTNB, transthoracic needle biopsy.
calculated by altering diagnostic yield and sensitivity simultaneously (ie, lowering diagnostic yield and sensitivity with the same steps until cost-effectiveness was lost). A two-way sensitivity analysis further showed which combinations of diagnostic yield and sensitivity can be cost-effective compared with direct treatment at a WTP of €20 000 and €80 000 (online supplemental figure 4C,D).

**Probsibilistic sensitivity analyses**

CBCT-NB resulted in health gain without increased costs in 33% of iterations when compared with TTNB and in 95% of iterations versus direct treatment. When assuming a WTP of €20 000 and €80 000 per QALY, 69% and 90% of iterations of the CBCT-NB versus TTNB model were cost-effective in favour of CBCT-NB and in 100% and 100% when compared with direct treatment (see figure 2).

**DISCUSSION**

Our decision analytical model shows that CBCT-NB can be a cost-effective diagnostic modality in the workup of intermediate risk PNs both when directly compared with CT-guided transthoracic biopsy, and when compared with direct treatment (without pathology proven malignancy) in TTNB ineligible patients. A cost-effectiveness study on electromagnetic navigation bronchoscopy (EMN) by Rickets et al. showed that EMN was expected to be cost-effective if EMN could obtain the same diagnostic accuracy as TTNB. Our study confirms these findings. CBCT-NB is an alternative navigation technique to EMN able to precisely confirm positioning of sampling tools in regard to very small peripheral PN, and has therefore the potential to obtain high diagnostic accuracy as TTNB. Our study confirms these findings. CBCT-NB is an alternative navigation technique to EMN able to precisely confirm positioning of sampling tools in regard to very small peripheral PN, and has therefore the potential to obtain high diagnostic accuracy as TTNB. Our study confirms these findings.
Study strengths and limitations

A strength of this study is that the model was constructed in a centre where there is extensive experience on both CBCT-NB and TTNB, resulting in a balanced model accurately reflecting clinical practice. Another strength is that we included a large set of parameters representing the complete disease pathway. This gave a complete view of the consequences related to the choice of diagnostic procedure. Lastly, the sensitivity analyses performed in this study highlight which of these parameters have a large impact on the outcome of the model. This is of high importance in giving a complete and nuanced perspective on how the results can be interpreted. This study also has limitations which should be discussed. First, some limitations exist regarding the comparison of diagnostic yield, sensitivity and specificity of both procedures since there are no diagnostic studies with a head-to-head analysis of CBCT-NB and TTNB. Input data for both procedures was therefore gathered from different sources. Subsequently, differences in populations might be present, which could influence the diagnostic accuracy of the procedures. Furthermore, the selected CBCT-NB data was based on published postlearning curve data, reflecting a highly experienced setting. However, this corresponds to the selected TTNB data which was obtained in referral centres by experienced physicians. Other CBCT-NB literature report a wide range of diagnostic accuracies. Reported diagnostic accuracies in the range of 70%, such as Kawakita et al (72.9%), Casal et al (70%) and our own cohort when including the learning curve (76.4%) would not be cost-effective when compared with TTNB in our model. Other centres have, however, reported higher outcomes, with Ali et al reporting a diagnostic accuracy of 90% and Pritchett et al 83.7%. These outcomes can be cost-effective in our model, depending on how these diagnostic accuracies can be divided in diagnostic yield and sensitivity (as illustrated by online supplemental figure 4). These parameters were, however, not readily available in these studies, so these statements remain estimations. When comparing CBCT-NB to direct treatment (without pathology proven disease), all the above-mentioned reported outcomes would result in cost-effectiveness in our model. Second is the absence of specific data for the patient subgroup in model 2. All applicable input parameters are therefore chosen the same as in model 1. However, in real life parameters such as background mortality, QoL and procedure related complications are most likely different for patients who are TTNB ineligible. To account for this, we varied all parameters in the DSA over a large range, which did not result in differences in outcome (see online supplemental figure 3). It is therefore likely that our conclusions will not change when specific input for this specific subpopulation would become available. Third, costs and effects in the model are based on a Dutch healthcare setting. Region or country specific costs may differ, which can make the applicability of the outcomes challenging. However, correcting for region specific differences is possible as all input data and the model structure are given, allowing interpretation in other settings.

Clinical implications

CBCT-NB is a new technique that allows both navigation support and precise confirmation of very small peripheral PN. To our knowledge, our study is the first to investigate cost-effectiveness of CBCT-NB when used as a sole tool for navigation and tissue sampling of PN. Our model indicates that CBCT-NB can be a cost-effective procedure when compared with TTNB in our experienced setting. The DSA indicates that a minimal required sensitivity and diagnostic yield to be cost-effective are ~92%, highlighting the need for further research to improve accessibility and generate a high level of competence to obtain stable high diagnostic results. Furthermore, it is important to monitor procedural outcome to analyse if CBCT-NB is used in an optimal and expedient manner. When implementing a CBCT-NB programme it is furthermore important to take the initial higher costs associated with the learning period into account.

The risk of malignancy used in the model was 73.7%, which is higher than expected but corresponds to both our current practice and to TTNB literature used in these analyses. When the models are assessed assuming a lower risk of malignancy (ie, the CT screening population), CBCT-NB becomes more cost-effective and dominates both the TTNB and direct treatment strategies, which is of interest for potential lung cancer screening programmes in the future.37

Our model shows that direct treatment without trying to obtain a definitive diagnosis is seldomly a cost-effective strategy, this holds even in patients with high risk of malignancy or in settings where there is less experience utilising CBCT-NB. When we simulated an increased risk of malignancy, the strategy containing CBCT-NB as a diagnostic modality remained cost-effective until a high risk of malignancy (85%–90%). This is opposite to the current observation in the Dutch lung cancer population where we see a high percentage of patients where curative treatments are started without obtaining a pathology proven diagnosis first.

In conclusion, our model shows that based on available evidence, CBCT-NB has the potential to be cost-effective versus TTNB and is dominant over direct treatment in patients with an intermediate risk PN.

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REFERENCES
1 Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2 Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM staging system. J Thorac Oncol 2011;6:35–43.
3 Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol 2014;15:332–41.
4 de Koning HJ, van der Aalst CM, de Jong P, et al. The Dutch lung cancer screening trial research group: the design, or conduct, or reporting, or dissemination plans of this research. J Thorac Oncol 2016;11:39–51.
5 Callister MEJ, Baldwin DR, Akram AR, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings for 36 cancers in 185 countries. The IASLC Lung Cancer Screening and Staging Project: proposals for revision of the TNM stage groupings for 36 cancers in 185 countries. J Thorac Oncol 2016;7:685–92.

Pritchett MA, Schampaert S, de Groot JAH, et al. Cone-beam CT with augmented fluoroscopy combined with electromagnetic navigation bronchoscopy for biopsy of pulmonary nodules. J Bronchology Interv Pulmonol 2018;25:274–82.
29 Verhoeven RLJ, Fütterer JJ, Hofsloot W, et al. Cone-beam CT image guidance with and without electromagnetic navigation bronchoscopy for biopsy of peripheral pulmonary lesions. J Bronchology Interv Pulmonol 2021;28:60–9.
30 Verhoeven RLJ, van der Steen W, Kong W, et al. Cone-beam CT and augmented fluoroscopy-guided navigation bronchoscopy: radiation exposure and diagnostic accuracy learning curves. J Bronchology Interv Pulmonol 2021;28:262–71.
40 A language and environment for statistical computing [program]. Vienna, Austria: R Foundation for Statistical Computing 2021.
31 Ten Haaf K, van Rosmalen J, de Koning HJ. Lung cancer detectability by test, histology, stage, and gender: estimates from the NLST and the PLCO trials. Cancer Epidemiol Biomarkers Prev 2015;24:154–61.
32 Ismail RK, Schramel FMNH, van Dartel M, et al. The Dutch lung cancer audit: nationwide quality of care evaluation of lung cancer patients. Lung Cancer 2020;149:88–77.
33 Stokes WA, Bontsrt MR, Mequid RA, et al. Post-treatment mortality after surgery and stereotactic body radiotherapy for early-stage non-small-cell lung cancer. J Clin Oncol 2018;36:642–51.
34 CBS. General background mortality. The Netherlands, 2020. Available: http://opendata.cbs.nl/statline/Table?ID=7360ned/table?tid=6183C [Accessed 15 Feb 2022].
35 Wolff HB, Alberts L, van der Linden N, et al. Cost-effectiveness of stereotactic body radiation therapy versus video assisted thoracic surgery in medically operable stage I non-small cell lung cancer: a modeling study. Lung Cancer 2020;141:89–96.
36 Zorginstituut Nederland. Pakketadvies sluisgeneesmiddel pembrolizumab (Keytruda®) bij de behandeling van niet-kleincellig longkanker, 2016.
37 Zorginstituut Nederland. Pakketadvies sluisgeneesmiddel osimertinib (Tagrisso®) bij de eerstelinjestherapie van patiënten met gevorderde of gemetastaseerde niet-kleincellig longkanker (NSCLC) met activerende EGFR-mutaties, 2019.
38 Beck M, Rodriguez-Abreu D, Robinson AG, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol 2019;37:537–46.
39 Gadgeel S, Rodriguez-Abreu D, Speranza G, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. J Clin Oncol 2020;38:1505–17.
40 Sturza J. A review and meta-analysis of utility values for lung cancer. Med Decis Making 2010;30:685–93.
41 Ricketts W, Lau KKW, Polit V, et al. Exploratory cost-effectiveness model of electromagnetic navigation bronchoscopy (ENB) compared with CT-guided biopsy (TNA) for diagnosis of malignant indeterminate peripheral pulmonary nodules. BMJ Open Respir Res 2020;7:e000595.
42 Paix A, Noel G, Falcoz P-E, et al. Cost-effectiveness analysis of stereotactic body radiotherapy and surgery for medically operable early stage non small cell lung cancer. Radiother Oncol 2018;128:534–40.
43 Bendixen M, Kronborg C, Jørgensen OD, et al. Cost-effectiveness analysis of minimally invasive surgery for lung cancer: a randomized controlled trial. Eur J Cardiothorac Surg 2019;56:754–61.
44 Zorginstituut Nederland. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg, 2016. Available: https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg
45 Versteegh MM, Ramos IC, Buyukkaramikli NC, et al. Severity-adjusted probability of being cost effective. Pharmacoeconomics 2019;37:1155–63.
46 Kawakita N, Takizawa H, Toba H, et al. Cone-beam computed tomography versus computed tomography-guided ultrathin bronchoscopic diagnosis for peripheral pulmonary lesion: a propensity score matched analysis. Respir Med 2021;26:477–84.
47 Casal RF, Sarkiss J, Jones AK, et al. Cone beam computed tomography-guided thin/ultrathin bronchoscopy for diagnosis of peripheral lung nodules: a prospective pilot study. J Thorac Oncol 2018;10:6820–9.

Kops SEP, et al. BMJ Open Respir Res 2022;9:e001280. doi:10.1136/bmjresp-2022-001280. Downloaded from http://bmjopenrespres.bmj.com/ BMJ Open Resp Res: first published as 10.1136/bmjresp-2022-001280 on 5 September 2022. Protected by copyright.
33. Ali EAA, Takizawa H, Kawakita N, et al. Transbronchial biopsy using an ultrathin bronchoscope guided by cone-beam computed tomography and virtual bronchoscopic navigation in the diagnosis of pulmonary nodules. *Respiration* 2019;98:321–8.

34. Baldwin DR, Eaton T, Kolbe J, et al. Management of solitary pulmonary nodules: how do thoracic computed tomography and guided fine needle biopsy influence clinical decisions? *Thorax* 2002;57:817–22.

35. Santambrogio L, Nosotti M, Bellaviti N, et al. CT-guided fine-needle aspiration cytology of solitary pulmonary nodules: a prospective, randomized study of immediate cytologic evaluation. *Chest* 1997;112:423–5.

36. Hayashi N, Sakai T, Kitagawa M, et al. CT-guided biopsy of pulmonary nodules less than 3 cm: usefulness of the spring-operated core biopsy needle and frozen-section pathologic diagnosis. *AJR Am J Roentgenol* 1998;170:329–31.

37. Armstrong C. Lung cancer screening recommendations from the ACCP. *Am Fam Physician* 2018;98:688–9.

38. Bongers ML, de Ruyscher D, Oberije C, et al. Model-based cost-effectiveness of conventional and innovative chemo-radiation in lung cancer. *Int J Technol Assess Health Care* 2017;33:681–90.

39. Versteegh M. Impact on the incremental cost-effectiveness ratio of using alternatives to EQ-5D in a Markov model for multiple sclerosis. *PharmacoEconomics* 2016;34:1133–44.