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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.[5]

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.[5] 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).[5 6]

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%.[5 7] 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.[8] 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.[9 10]

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).[11–13] 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)[14] 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

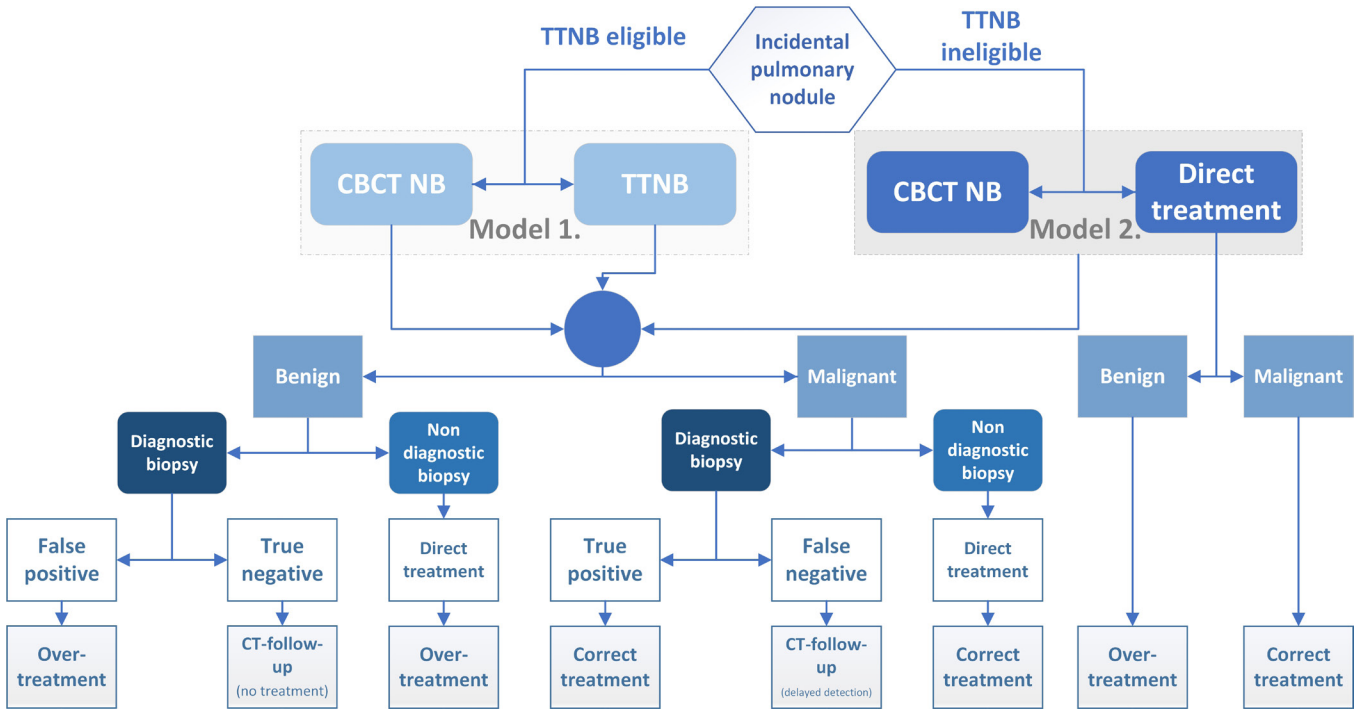

Figure 1 Decision analytical model. Model 1: CBCT-NB versus TTNB in patients with intermediate risk pulmonary nodule (PN) and eligible for TTNB. Model 2: CBCT-NB versus direct treatment in patients with intermediate risk PN and ineligible for TTNB. CBCT-NB, cone beam CT-guided navigation bronchoscopy; TTNB, transthoracic needle biopsy.

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.[15] 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.[13]

The initial state of malignancy was based on the Dutch Lung Cancer Audit and distributed between stage Ia, Ib and II lung cancer.[16] The probability of progression to a more severe stage in case of a delayed diagnosis was based on Ten Haaf *et al*.[15] This study estimated the time to progression of early-stage (preclinical) lung cancer to a more advanced stage based on the NELSON trial data.[4] Further explanation on how the 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.[16] 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*.[2] 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*.[17]

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 institute[20–22] 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.

Patient and public participation

Patients or the public were not involved in the design, conduct, reporting or dissemination of this study.

RESULTS

Diagnostic pathway comparisons

Model 1 (CBCT-NB vs TTNB)

In this model, CBCT-NB appeared to be more effective with 6.853 QALYs in comparison to TTNB with 6.829 QALYs. The total costs of the diagnostic and treatment pathway were €17 561 for CBCT-NB as compared with €17 103 for TTNB. The increased costs of €458 for an added 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 (€17 561 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).

Table 1 Input parameters: probabilities and procedure properties

Parameter	Mean	Sample size	Reference
Risk of malignancy	73.7%	148/202	Verhoeven *et al*[13]
Procedure characteristics			
CBCT-NB			
Diagnostic yield	95.3%	61/64	Verhoeven *et al*[13]
Sensitivity	92.7%	38/41	Verhoeven *et al*[13]
Specificity	100%	20/20	Verhoeven *et al*[13]
TTNB			
Diagnostic yield	89.3%	782/876	Callister *et al*[5]
Sensitivity	90.8%	942/1038	Callister *et al*[5]
Specificity	94%	392/417	Callister *et al*[5]
CBCT-NB			
Pneumothorax	1.6%	4/238	Verhoeven *et al*[12]
Pneumothorax requiring intervention	1.6%	4/238	Verhoeven *et al*[12]
Haemorrhage	2.3%	5/238	Verhoeven *et al*[12]
TTNB			
Pneumothorax	19.7%	1631/8275	Heerink *et al*[8]
Pneumothorax requiring intervention	5.6%	463/8275	Heerink *et al*[8]
Haemorrhage	2.8%	1490/8275	Dibardino *et al*[7]
Direct diagnosis, distribution			
Stage Ia	47.6%	4569/9594	Ismail *et al*[16]
Stage Ib	23.8%	2284/9594	Ismail *et al*[16]
Stage II	28.6%	2744/9594	Ismail *et al*[16]
Delayed diagnosis, distribution			
Stage Ia	42.4%	–	Ten Haaf *et al*/Ismail *et al*[15 16]
Stage Ib	18.6%	–	Ten Haaf *et al*/Ismail *et al*[15 16]
Stage II	20.5%	–	Ten Haaf *et al*/Ismail *et al*[15 16]
Stage IIIa	14.0%	–	Ten Haaf *et al*/Ismail *et al*[15 16]
Stage IIIb	3.6%	–	Ten Haaf *et al*/Ismail *et al*[15 16]
Stage IV	0.9%	–	Ten Haaf *et al*/Ismail *et al*[15 16]
Treatment distribution			
Stage I–II			
Surgery	46%	4554/9900	Ismail *et al*[16]
Radiotherapy	43.5%	4307/9900	Ismail *et al*[16]
Chemoradiotherapy	2%	198/9900	Ismail *et al*[16]
Chemotherapy	7.3%	718/9900	Ismail *et al*[16]
Chemoimmunotherapy	0.8%	74/9900	Ismail *et al*[16]
Immunotherapy	0.5%	50/9900	Ismail *et al*[16]
Stage III			
Surgery	9.3%	604/6524	Ismail *et al*[16]
Radiotherapy	12%	783/6524	Ismail *et al*[16]
Chemoradiotherapy	39.5%	2577/6524	Ismail *et al*[16]
Chemotherapy	12.8%	816/6524	Ismail *et al*[16]
Chemoimmunotherapy	18.3%	1191/6524	Ismail *et al*[16]
Immunotherapy	7.3%	473/6524	Ismail *et al*[16]
Targeted therapy	1%	65/6524	Ismail *et al*[16]
Stage IV			

Continued

Table 1 Continued

Parameter	Mean	Sample size	Reference
Surgery	0.8%	114/15 156	Ismail *et al*[16]
Radiotherapy	10.3%	1553/15 156	Ismail *et al*[16]
Chemotherapy	14.5%	2198/15 156	Ismail *et al*[16]
Chemoimmunotherapy	38%	5759/15 156	Ismail *et al*[16]
Immunotherapy	18.5%	2804/15 156	Ismail *et al*[16]
Chemoradiotherapy	4%	606/15 156	Ismail *et al*[16]
Targeted therapy	14%	2122/15 156	Ismail *et al*[16]
Treatment distribution in patients without pathology confirmation*			
VATS	51.4%	4553/8861	Ismail *et al*[16]
SABR	48.6%	4308/8861	Ismail *et al*[16]
Treatment-related mortality			
VATS	3.6%	2787/77 623	Stokes *et al*[17]
SABR	2.9%	241/8216	Stokes *et al*[17]
2-year overall survival†			
Stage Ia	93.6%	732/11 423	Goldstraw *et al*[2]
Stage Ib	89.%	666/6095	Goldstraw *et al*[2]
Stage II	77.4%	1549/6864	Goldstraw *et al*[2]
Stage IIIa	65%	2015/5756	Goldstraw *et al*[2]
Stage IIIb	46.4%	965/1798	Goldstraw *et al*[2]
Stage IV	17.1%	731/882	Goldstraw *et al*[2]
5-year overall survival†			
Stage Ia	83.7%	1837/11 423	Goldstraw *et al*[2]
Stage Ib	73%	1618/6095	Goldstraw *et al*[2]
Stage II	58.2%	2872/6864	Goldstraw *et al*[2]
Stage IIIa	41%	3219/5756	Goldstraw *et al*[2]
Stage IIIb	23.6%	1270/1798	Goldstraw *et al*[2]
Stage IV	5.5%	834/882	Goldstraw *et al*[2]

*Patients without pulmonary nodule confirmation can be in the direct treatment strategy or had a non-diagnostic biopsy.
†Survival based on TNM eighth edition.[2]
CBCT-NB, cone beam CT-guided navigation bronchoscopy; SABR, stereotactic ablative radiotherapy; TTNB, transthoracic needle biopsy; VATS, video-assisted thoracoscopy.

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 minimally 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.

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[21]
Targeted therapy	83784	36275–60459	Dutch healthcare institute[22]
Immunotherapy	93279	69959–116599	Dutch healthcare institute[20 23]
Chemo-immunotherapy	138627	103970–173283	Dutch healthcare institute[20 21 24]
Chemoradiotherapy	20122	15092–25153	Bongers *et al*[38]
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.

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 €20 000 and 68.4% and 65.8% for a WTP threshold of €80 000. These thresholds were also

Table 3 Incremental analysis

	Test	Comparator	Incremental outcome
Model 1: CBCT-NB versus TTNB			
Procedure	CBCT-NB	TTNB	
Costs (€)	17561	17103	+458
Effect (QALY)	6.853	6.829	+0.024
ICER (€/QALY)	Cost-effective		18416
Model 2: CBCT-NB versus direct treatment strategy			
Procedure	CBCT-NB	Direct treatment	
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.

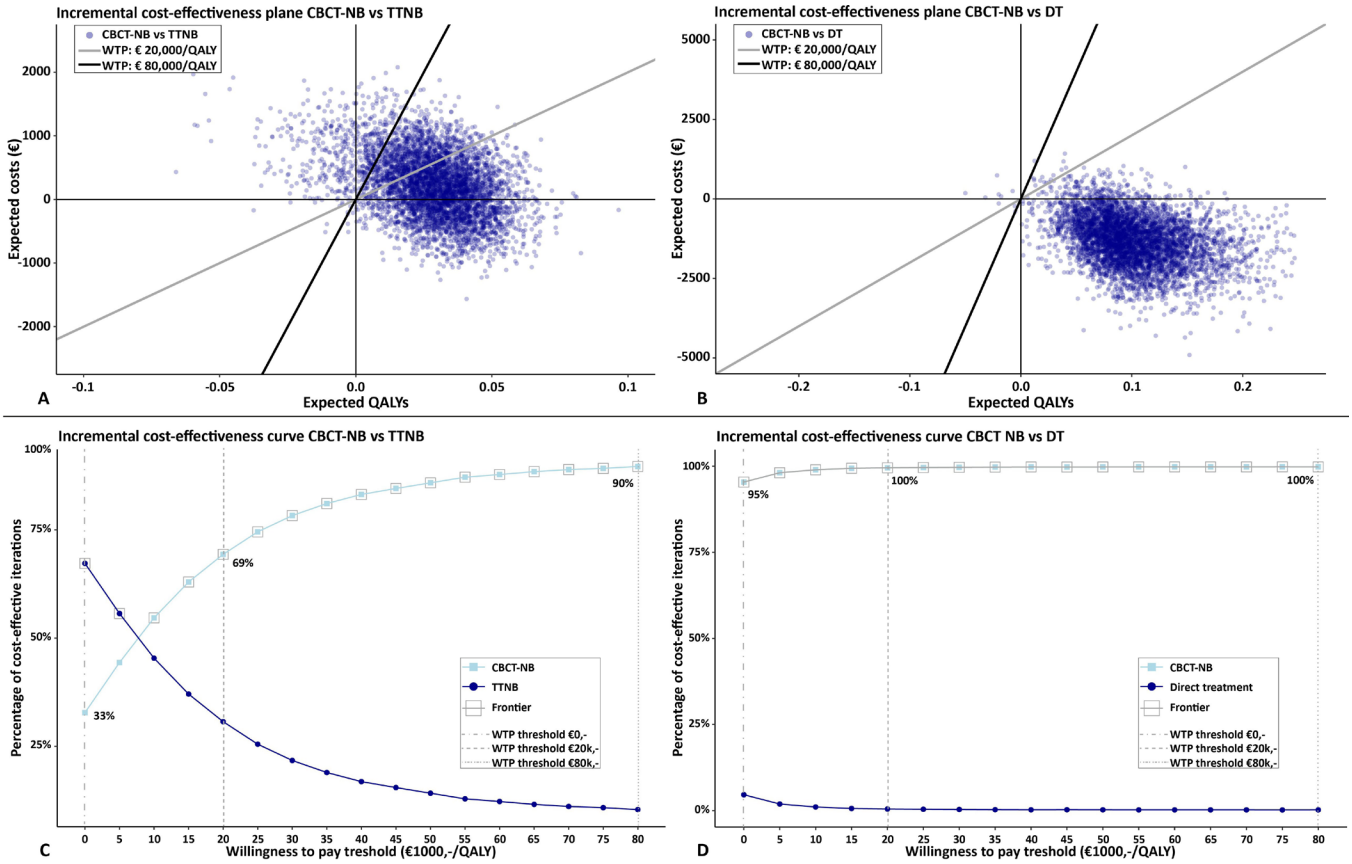

Figure 2 Cost-effectiveness planes and curves of CBCT-NB versus TTNB (A,C) and CBCT-NB versus DT (B,D). In the cost-effectiveness plane (A,B), each individual dot represents the incremental cost-effectiveness ratio of a single iteration of the probabilistic sensitivity analysis expressed in costs/QALY. Willingness-to-pay (WTP) thresholds of €20 000 and €80 000 are plotted as diagonal lines. The cost-effectiveness curves (C,D) show the probability that a strategy is cost-effective at different WTP thresholds. Different cut off points for WTP thresholds are plotted in the graph. The frontier shows the uncertainty that the optimal strategy is the most cost-effective at different thresholds. CBCT-NB, cone beam CT-guided navigation bronchoscopy; DT, direct treatment; 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).

Probabilistic 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*[26] 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 results. Partly due to these procedure characteristics, this study shows that (CBCT) navigation bronchoscopy can be cost-effective. It must be mentioned, however, that to use the CBCT-NB procedure characteristics to its full potential, an expert centre is needed and that users need to go through a learning curve.

Based on the probabilistic sensitivity analyses, there is a high likelihood that these results remain cost-effective even when taken the uncertainty of all parameters into account.

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%),[31] Casal *et al* (70%)[32] and our own cohort when including the learning curve (76.4%[13]) would not be cost-effective when compared with TTNB in our model. Other centres have, however, reported higher outcomes, with Ali *et al*[33] reporting a diagnostic accuracy of 90% and Pritchett *et al* 83.7%.[11] 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.[12 34–36] When the models are assessed assuming a lower risk of malignancy (ie, the CT screening population[3]), 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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