Cochrane Netherlands

Navigatiebronchoscopie-technieken bij verdenking op longkanker

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Pauline Heus
Johanna Damen
Kevin Jenniskens
Lotty Hooft

Samenstelling projectteam:

Onderzoekers
Cochrane Netherlands en Julius Centrum, UMC Utrecht

- Dr. P. Heus
- Dr. J.A.A. Damen
- Dr. K. Jenniskens
- Dr. M. Ghannad
- Drs. K. Luijken
- Prof. dr. L. Hooft

Zorginstituut Nederland

- Dr. I. van Beusekom
- Dr. I. de Groot

Informatiespecialist

- Drs. R. Spijker, Cochrane Netherlands en Julius Centrum, UMC Utrecht

Adviseurs

- Prof. dr. Jouke Annema, longarts, hoogleraar Pulmonale Endoscopie, Amsterdam UMC
- Dr. E.H.F.M. van der Heijden, longarts, Associate Professor Interventie Longziekten Radboudumc Nijmegen, Secretaris sectie Pulmonale Interventies NVALT, Director Thoracic Oncology Program
- Dr. D.A. Korevaar, AIOS Longziekten, epidemioloog, Amsterdam UMC

Contactgegevens
Prof. dr. Lotty Hooft
Cochrane Netherlands / Julius Centrum
Universitair Medisch Centrum Utrecht
Huispostnummer Str. 6.131
Postbus 85500
3508 GA Utrecht
T: 088 755 9301
E: cochrane@umcutrecht.nl
W: www.cochrane.nl

Lijst met gebruikte afkortingen

BI	Betrouwbaarheidsinterval
CBCT	Cone beam computer tomografie
CI	Confidence interval (betrouwbaarheidsinterval)
CT	Computer Tomografie
DTA	Diagnostische test accuratesse
EBUS	Endobronchial ultrasound (endobronchiale echografie)
EMN / ENB	Electromagnetic navigation bronchoscopy (elektromagnetische navigatiebronchoscopie)
GGO	Ground glass opacities
GS	Guide sheath
NA	Not applicable (niet van toepassing)
NPV	Negative predictive value (voorspellende waarde van een negatieve testuitslag)
PA	Pathologische anatomie
PICOT	Populatie, interventie, controle, uitkomst [*outcome*] en timing
r-EBUS	Radial endobronchial ultrasound (radiaire endobronchiale echografie)
RCT	Randomized Controlled Trial
SR	Systematische review
TTNA	Transthoracale naaldaspiratie
TTNB	Transthoracale naaldbiopsie
VB(N)	Virtual bronchoscopic navigation (virtuele navigatiebronchoscopie)

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1. Inleiding

Bij patiënten die een CT-scan ondergaan, zal bij gemiddeld 29% (range 8% tot 53%; gebaseerd op 13 Europese onderzoeken) van de patiënten bij toeval een perifere longafwijking gevonden worden, die in 1,2% (range 0,2% tot 2,4%) van het totaal maligne zal blijken.[1] Omdat het overgrote deel van de gevonden afwijkingen goedaardig zal blijken, is een goede risicostratificatie noodzakelijk. Hiervoor zijn diverse rekenmodellen ontwikkeld. Wanneer de kans op maligniteit groter dan 10% wordt ingeschat, dan is er een indicatie om met behulp van diagnostische technieken een stukje weefsel van de verdachte nodule weg te halen voor pathologisch onderzoek, waarna een gerichte behandeling kan volgen.

Vanwege een geringe grootte, perifere locatie, een locatie bij een bloedvat of omdat de procedure een te grote belasting is voor een patiënt, lukt het met de huidige technieken niet altijd om een biopt af te nemen. In dat geval worden patiënten zonder histologische uitslag behandeld. In het geval van vroege stadia longkanker bestaan curatieve behandelopties overwegend uit stereotactische radiotherapie en chirurgische resectie. In Nederland werd in 2018 64,5% van de patiënten die stereotactische radiotherapie ondergingen en 41,1% van de chirurgische patiënten behandeld zonder een sluitende pathologische diagnose voorafgaand aan de procedure (dus enkel op basis van klinische verdenking) (persoonlijke communicatie medisch inhoudelijk adviseurs met Dutch Institute for Clinical Auditing [DICA]). Er zijn aanwijzingen dat een deel van deze behandelingen mogelijk onterecht is. De meest laagdrempelig beschikbare en minimaal invasieve diagnostische procedure voor dit soort afwijkingen is op dit moment de CT-geleide punctie. Uit bovenstaande blijkt dat er, ondanks de brede beschikbaarheid van CT-geleide punctie, een aanzienlijk deel van de behandelingen wordt uitgevoerd zonder sluitende diagnose. Met behulp van nieuwe navigatiebronchoscopietechnieken is het wel mogelijk dergelijke noduli te bereiken.

De claim voor navigatiebronchoscopie is dat het toevoegen van deze techniek aan het diagnostische pad zal leiden tot minder onterechte behandelingen (operatie, stereotactische radiotherapie, chemotherapie, immuuntherapie), met minder complicaties als gevolg. Aanvullend wordt geclaimd dat navigatiebronchoscopietechnieken weliswaar een lagere diagnostische accuratesse hebben dan transthoracale naaldaspiratie (TTNA) of transthoracale naaldbiopsie (TTNB), maar minder invasief zijn en leiden tot minder ernstige complicaties.

Om te beoordelen of navigatiebronchoscopietechnieken voldoen aan de stand van de wetenschap en praktijk (ook wel duiding genoemd) heeft Zorginstituut Nederland aan Cochrane Netherlands gevraagd om een systematische review (SR) uit te voeren naar het klinisch nut van deze nieuwe technieken bij patiënten met een verdenking op longkanker.

2. Vraagstelling

De vraagstellingen bij bovengenoemde claims zijn als volgt:

1) Wat is het klinisch nut (gezondheidswinst voor de patiënt) van het inzetten van navigatiebronchoscopietechnieken voor patiënten met verdenking op longkanker?
2) Wat is de diagnostische accuratesse van navigatiebronchoscopie in vergelijking met TTNA en TTNB?

3. Methoden

Navigatiebronchoscopie is een techniek die kan worden ingezet als conventionele bronchoscopie geen optie is, bijvoorbeeld vanwege de (te perifere) ligging van longnoduli. Een volgende overweging is of een CT-geleide punctie mogelijk wordt geacht of niet. Dit is afhankelijk van de grootte van een nodule ([nog] te klein), ligging (naast een bloedvat) of aanwezigheid van comorbiditeit waardoor de techniek te belastend is voor de patiënt. Deze overweging komt ook tot uiting in de relevante onderzoekspopulaties voor de uitgangsvragen van deze systematische review. Voor de eerste uitgangsvraag betreft het onderzoekspopulaties waarvoor expliciet vermeld werd dat zowel conventionele bronchoscopie als transthoracale procedures geen opties waren, en voor de tweede uitgangsvraag populaties waarbij conventionele bronchoscopie niet mogelijk was.

3.1 Formuleren PICOT's

Na consultatie van partijen in het veld heeft het Zorginstituut de onderzoeksvraag omgezet in de volgende PICOT's (PICOT staat voor populatie, interventie, controle, uitkomst [*outcome*] en timing).

PICOT 1: Klinisch nut

Bij deze PICOT gaat het om de rol van navigatiebronchoscopie als *add-on* test, namelijk als extra mogelijkheid voor patiënten voor wie anders geen alternatief (in de vorm van conventionele bronchoscopie of CT-geleide puncties) bestaat behalve (chirurgische) behandeling.

P	Volwassen patiënten (>18 jaar), zonder klachten maar met een nodule (aangetoond middels een CT-scan) op een locatie waarbij longteam een multidisciplinair team inschat dat er geen biopt kan worden genomen middels conventionele bronchoscopie, transthoracale naaldaspiratie of transthoracale naaldbiopsie*. De noduli zijn geclassificeerd als verdacht (>10% kans op maligniteit).
I	Behandeling op basis van de pathologische (PA)-uitslag van de target nodule verkregen middels navigatiebronchoscopietechnieken.
C	Behandeling (operatie, stereotactische radiotherapie, chemotherapie, immuuntherapie) zonder biopt met PA-uitslag.
O	Cruciaal: - Percentage afname operaties/behandelingen uitgevoerd zonder pathologische uitslag - Complicaties Belangrijk: - Kwaliteit van leven
T	Minimale follow-up duur van 1 jaar
Onderzoeksopzet	De optimale onderzoeksopzet voor het bepalen van het klinisch nut van een behandeling op basis van de PA uitslag verkregen middels navigatiebronchoscopie is een RCT (*randomized controlled trial*). Voor het bepalen van het aantal complicaties kan er gebruik gemaakt worden van observationele studies of een prospectieve registratie.
Klinische relevantie-grenzen	- We hanteren voor het percentage afname operaties/behandelingen uitgevoerd een RR van 0,75. - We hanteren voor complicaties een RR van 0,75 als klinische relevantie grens. - We hanteren voor kwaliteit van leven een SMD van 0,5.
* Een multidisciplinair team kan tot deze inschatting komen bijvoorbeeld omdat dat de nodule te perifeer ligt in de longen, de nodule (nog) te klein is, de nodule naast een bloedvat ligt of omdat de huidige technieken te belastend zijn voor de patiënt vanwege comorbiditeit.	

Het Zorginstituut beschouwt, na afstemming met de veldpartijen, de volgende navigatiebronchoscopietechnieken als relevant voor duiding: elektromagnetische navigatiebronchoscopie, virtuele bronchoscopie en cone beam CT (met *augmented fluoroscopy*). Robot CT wordt in onderhavige duiding buiten beschouwing gelaten, omdat een CE-keurmerk hiervoor ontbreekt.
In aanvulling op de hierboven vermelde optimale onderzoeksopzet werd afgesproken dat, indien er geen RCTs beschikbaar blijken te zijn, er tevens gezocht zou worden naar diagnostische accuratesse onderzoeken.

PICOT 2: Diagnostische testaccuratesse

Bij deze PICOT gaat het om de rol van navigatiebronchoscopie ter vervanging van transthoracale naaldaspiratie en – biopsie (*replacement* test). De relevante onderzoekspopulatie bestaat uit patiënten bij wie conventionele bronchoscopie geen optie was, maar CT-geleide puncties wel.

P	Volwassen patiënten (>18 jaar), zonder klachten maar met een nodule (aangetoond middels een CT-scan) op een locatie waarbij een multidisciplinair team inschat dat er geen biopt kan worden genomen middels conventionele bronchoscopie*. Bij deze patiënten acht het multidisciplinaire team het wel mogelijk om een biopt te nemen middels transthoracale naaldaspiratie of transthoracale naaldbiopsie. De noduli zijn geclassificeerd als verdacht (>10% kans op maligniteit).
I	Navigatiebronchoscopietechnieken.
C	Transthoracale naaldaspiratie en transthoracale naaldbiopsie.
O	Cruciaal: • Diagnostische accuratesse • Complicaties
T	Minimale follow-up duur van 1 jaar.
Onderzoeksopzet	De optimale studieopzet voor het bepalen van diagnostische accuratesse is een vergelijkende prospectieve diagnostische accuratessestudie. Indien deze er niet zijn, dan zal ook niet rechtstreeks bewijs worden meegenomen in de beoordeling.
Klinische relevantie-grenzen	- Voor diagnostische accuratesse wordt dit in een later stadium geconsulteerd bij partijen met expertise in het veld. - We beschouwen een minimaal verschil van 10% in complicaties als klinisch relevant.
* Een multidisciplinair team kan tot deze inschatting komen bijvoorbeeld omdat de nodule te perifeer ligt in de longen.	

Ook voor deze tweede PICOT zijn elektromagnetische navigatiebronchoscopie, virtuele bronchoscopie en cone beam CT (met *augmented fluoroscopy*) de voor de duiding relevante navigatiebronchoscopietechnieken.

Omdat in onderzoeken over navigatiebronchoscopie de termen ‘diagnostische accuratesse’ en ‘diagnostische opbrengst’ door elkaar worden gebruikt, is ‘diagnostische opbrengst’ (*diagnostic yield*) ook als uitkomst meegenomen. Daarnaast werden resultaten voor de uitkomsten navigatiesucces, sensitiviteit en negatief voorspellende waarde geanalyseerd. Voor de onderhavige systematische review zijn de uitkomsten als volgt gedefinieerd (overeenkomstig de gehanteerde definities in de publicaties):

- Navigatiesucces: percentage lesies die daadwerkelijk door de navigatiebronchoscoop bereikt werden (t.o.v. het totale aantal onderzochte lesies).
- Diagnostische opbrengst: percentage lesies waarbij een diagnose (correct of incorrect) gesteld kon worden met navigatiebronchoscopie t.o.v. het totale aantal onderzochte lesies. Het totale aantal onderzochte lesies is inclusief de lesies die uiteindelijk niet met navigatiebronchoscopie bereikt konden worden.
- Percentage accurate diagnoses: percentage accuraat gestelde diagnoses met navigatiebronchoscopie (álle diagnoses, niet enkel het aantonen of uitsluiten van maligniteit) t.o.v. het totale aantal onderzochte lesies. Het totale aantal onderzochte lesies is inclusief de lesies die uiteindelijk niet met navigatiebronchoscopie bereikt konden worden.
- Sensitiviteit: percentage terecht positieve testuitslagen t.o.v. het totaal aantal lesies waarbij een diagnose maligniteit gesteld werd.
- Negatief voorspellende waarde: percentage terecht negatieve testuitslagen t.o.v. alle negatieve testuitslagen.

Specificiteit (proportie terecht negatieve testuitslagen van het totaal aantal lesies waarbij geen diagnose maligniteit gesteld werd), werd niet als uitkomst meegenomen, omdat deze in principe voor alle onderzoeken als 100% gerapporteerd zou worden. Het is immers zeer onwaarschijnlijk dat een positieve pathologische uitslag voor maligniteit o.b.v. een biopt verkregen met navigatiebronchoscopie in een later stadium een onterechte positieve testuitslag blijkt te zijn.

3.2 Identificatie en selectie van relevante onderzoeken

Aan de hand van de aldus geformuleerde onderzoeksvragen werd eerst gezocht naar SR's en meta-analyses (MA's) van relevante onderzoeken. Relevante onderzoeken waren onderzoeken waarin de drie navigatiebronchoscopietechnieken (elektromagnetische navigatie, virtuele bronchoscopie of cone beam CT) werden geëvalueerd bij asymptomatische volwassen patiënten met op basis van de CT verdachte noduli. Daarbij was de inschatting dat er bij de deelnemers geen biopt kon worden genomen via conventionele bronchoscopie (PICOT 2) en ook niet via transthoracale naaldaspiratie of –biopsie (PICOT 1). Onderzoeken met deelnemers die centrale longnoduli hadden of longnoduli met een gemiddelde of mediane diameter groter of gelijk aan drie centimeter, werden niet geselecteerd, evenals onderzoeken naar tumormarkering m.b.v. navigatiebronchoscopie en onderzoeken met minder dan 10 deelnemers.

In nauw overleg met de medisch inhoudelijk adviseurs en afgestemd met het Zorginstituut werden zoekstrategieën ontwikkeld en criteria geformuleerd voor in- en exclusie van SR's die de verschillende PICOT-vragen zouden kunnen beantwoorden. Er werd gezocht naar mogelijk geschikte SR's gepubliceerd tussen 1 januari 2015 en juni 2021. Hiertoe werden de volgende elektronische databases geraadpleegd: Epistemonikos (bevat MEDLINE en Embase) en The Cochrane Database of Systematic Reviews. Tevens werd de lijst met gepubliceerde reviews van de Cochrane Lung Cancer Group doorgenomen op de aanwezigheid van SR's die de onderzoeksvraag betreffen.

Voor de selectie van de meest geschikte review voor een bepaalde onderzoeksvraag werd de volgende procedure gehanteerd (zie ook schema van Jadad[2]).

a. De review betreft de PICOT van de onderzoeksvraag en includeerde relevante onderzoeksdesigns (afhankelijk van de PICOT zijn dat RCT's, niet-gerandomiseerde vergelijkende onderzoeken of cross-sectionele onderzoeken [diagnostische test accuratesse, DTA]).

b. Er werd gezocht in MEDLINE en tenminste één andere elektronische database.
c. De *risk of bias* bepaling is op studieniveau gerapporteerd en betrof tenminste de voor GRADE benodigde belangrijkste kwaliteitsitems (voor RCT's, niet-gerandomiseerde vergelijkende onderzoeken of cross-sectionele onderzoeken).
d. De beschrijvende gegevens en resultaten worden op studieniveau gepresenteerd (effectschattingen met 95%-BI of 2*2 tabellen).

Werd voor een bepaalde onderzoekvraag meer dan één SR geïdentificeerd, dan werd de meest complete of meest recente review geselecteerd voor verdere analyse (in overleg met het Zorginstituut). Werd alleen een SR gevonden die aan criterium a) en b) voldoet, maar niet aan c) of d), dan werd deze SR als uitgangspunt genomen en werden de daarin geïncludeerde studies verder verwerkt conform de hierna beschreven werkwijze.

Ter aanvulling op de geïdentificeerde SR's werd in MEDLINE, Embase en het Cochrane register CENTRAL gezocht naar primaire observationele onderzoeken.

De selectie van systematische reviews en primaire onderzoeken werd uitgevoerd door twee onderzoekers onafhankelijk van elkaar (één van Cochrane Netherlands, één van het Zorginstituut). Verschillen tussen twee beoordelaars werden bediscussieerd. In geval geen overeenstemming bereikt kon worden, werd een derde onderzoeker ingeschakeld, wiens/wier oordeel leidend was.

3.3 Data-extractie en analyses

Van iedere publicatie werden beschrijvende gegevens verzameld (kenmerken van de patiënten, interventie/test, controlebehandeling/diagnostische strategie), klinische uitkomsten en de resultaten (diagnostische opbrengst, percentage accurate diagnoses en effect). Tevens werd van ieder onderzoek de methodologische kwaliteit bepaald. Voor SR's werd daartoe AMSTAR-2[3] gebruikt en voor DTA onderzoeken QUADAS-2[4]. Voor RCT's zou de Cochrane Risk of Bias 2.0 tool[5] zijn gebruikt en voor niet-gerandomiseerde vergelijkende studies ROBINS-I[6]. Deze onderzoeksdesigns werden echter niet geïdentificeerd.
Aan het domein *Patient selection* van QUADAS-2 werd een extra *signalling question* toegevoegd naar het onderzoeksdesign (prospectief of niet). Het domein *Reference standard* werd enkel beoordeeld voor de uitkomsten diagnostische opbrengst en percentage accurate diagnoses. Vanwege de gehanteerde in- en exclusiecriteria werden geen applicability concerns verwacht voor dit domein en dit werd standaard als niet van toepassing gescoord. Het domein *flow and timing* werd apart beoordeeld voor de uitkomsten diagnostische opbrengst en percentage accurate diagnoses en voor de uitkomst complicaties.

Extractie van de resultaten en beoordeling van de methodologische kwaliteit werden uitgevoerd door twee onderzoekers onafhankelijk van elkaar (één van Cochrane Netherlands, één van het Zorginstituut). Verschillen tussen twee beoordelaars werden bediscussieerd. In geval geen overeenstemming bereikt kon worden, werd een derde onderzoeker ingeschakeld, wiens/wier oordeel leidend was.

Vervolgens werd gekeken of de meta-analysen van de gevonden SR's geactualiseerd konden worden of dat er nieuwe meta-analyses uitgevoerd konden worden, waarbij de methoden uit de Cochrane handboeken gevolgd werden.[5 7] Meta-analyse werd alleen uitgevoerd indien de patiënten, interventies

en uitkomsten in de verschillende studies voldoende vergelijkbaar waren (hetgeen voorgelegd werd aan de medisch inhoudelijk adviseurs). Voor DTA-onderzoeken werden resultaten voor de uitkomsten percentage accurate diagnoses en sensitiviteit gepoold aan de hand van een random effects model. Hiertoe werd eerst een logit transformatie toegepast en na pooling werden resultaten terug getransformeerd. De resultaten hiervan werden gepresenteerd in de vorm van *forest plots* inclusief 95%-betrouwbaarheidsintervallen (95%-BI) en 95%-predictieintervallen (95%-PI). Het 95%-PI geeft een schatting van het interval waarbinnen een nieuw onderzoek zal vallen. Het geeft daarmee een indicatie van de heterogeniteit tussen onderzoeken: bij grote verschillen tussen onderzoeken geïncludeerd in de meta-analyse zal het 95%-PI ook breed zijn. Het 95%-PI werd alleen berekend indien minstens vijf studies geïncludeerd waren in de meta-analyse, omdat het interval niet betrouwbaar geschat kan worden bij een lager aantal studies. Voor de berekening van het 95%-BI werd gebruik gemaakt van de Hartung-Knapp-Sidik-Jonkman correctie. Het is aangetoond dat deze correctie beter is in vergelijking met andere methoden, echter in het geval er weinig studies zijn opgenomen in de meta-analyse zal het 95-BI te conservatief (breed) zijn.[8] Om deze reden werd er niet gepoold indien het totaal aantal studies in de meta-analyse lager dan drie was. Bevindingen voor navigatiesucces, diagnostische opbrengst en negatief voorspellende waarde werden samenvattend alleen beschrijvend gepresenteerd in de vorm van een mediaan, 25^{e} en 75^{e} percentiel, minimum en maximum.
De resultaten worden gepresenteerd per PICOT-vraag en vervolgens uitgesplitst voor de drie navigatiebronchoscopietechnieken. Subgroepanalyses werden uitgevoerd met betrekking tot het al dan niet inzetten van additionele technieken tijdens de navigatie (endobronchiale echografie [*endobronchial ultrasound; EBUS*] en/of fluoroscopie). Voor PICOT 2 werd tevens nog onderscheid gemaakt in onderzoekspopulatie: onderzoeken die expliciet vermeldden dat conventionele bronchoscopie niet mogelijk was en onderzoeken waarvoor dat onduidelijk was, werden in aparte subgroepen in de analyses opgenomen. De resultaten voor de negatief voorspellende waarde werden alleen overkoepelend gerapporteerd, omdat deze uitkomst voor een relatief klein deel van de onderzoeken te berekenen was.

Aansluitend werden door twee onderzoekers onafhankelijk van elkaar aan de hand van de GRADE-methodiek *certainty of evidence* toegekend aan de uitkomsten met gepoolde resultaten.

De GRADE *levels of certainty* hebben de volgende betekenis:

High: er is veel vertrouwen dat het werkelijk effect dicht in de buurt ligt van de schatting van het effect

Moderate: er is redelijk vertrouwen in de schatting van het effect: het werkelijk effect ligt waarschijnlijk dicht bij de schatting van het effect, maar er is een mogelijkheid dat het hier substantieel van afwijkt

Low: er is beperkt vertrouwen in de schatting van het effect: het werkelijke effect kan substantieel verschillend zijn van de schatting van het effect.

Very low: er is weinig vertrouwen in de schatting van het effect: het werkelijke effect wijkt waarschijnlijk substantieel af van de schatting van het effect

Voor uitkomsten waarvoor resultaten niet gepoold werden (navigatiesucces, diagnostische opbrengst en complicaties) werd de evidence overall beoordeeld op kans op vertekening en inconsistentie, maar werd geen GRADE level of certainty toegekend. Met betrekking tot de uitkomst complicaties hebben we ons voor het waarderen van de evidence beperkt tot het optreden van bloedingen of een pneumothorax.

4. Resultaten

4.1 Selectie van onderzoeken

4.1.1 Systematische reviews

De zoekactie naar SR's werd uitgevoerd op 28 juni 2021 (Epistemonikos) en 6 juli 2021 (Cochrane Library). De zoekstrategieën zijn weergegeven in Bijlage 1A.

Er werden 151 potentieel relevante artikelen gevonden (Bijlage 2A). Daarvan vielen er op basis van de titel en/of het abstract 141 af. Van de overige 10 onderzoeken werd het volledige artikel bekeken en één ervan bleek niet relevant (Bijlage 3A). Uit de overige negen (Tabel 1) werden er op basis van de zoekdatum, de PICO-elementen en overlappende ingesloten primaire onderzoeken twee SR's geselecteerd om nader te bekijken.[9 10] De ene betrof een SR naar virtuele bronchoscopie en werd mogelijk relevant geacht voor PICOT 1,[10] de andere onderzocht de DTA van elektromagnetische navigatiebronchoscopie, passend bij PICOT 2.[9] Hoewel er meerdere SR's waren naar de DTA van virtuele bronchoscopie, was er niet één aan te wijzen die volledig was qua geïncludeerde studies en daarom werd de voorkeur gegeven aan het uitvoeren van een eigen zoekactie naar virtuele bronchoscopie. Over cone beam CT werd geen systematische review gevonden.

In evidencetabellen (Bijlage 4) wordt alle beschikbare informatie over de twee geselecteerde SR's samengevat. De AMSTAR 2-beoordelingen staan in Tabel 2 en de details van deze beoordelingen zijn terug te vinden in Bijlage 5A.
Beide SR's bleken onvoldoende bruikbaar om resultaten rechtstreeks uit over te nemen. De potentieel relevante SR voor PICOT 1 werd o.b.v. de onderzochte vergelijking alsnog terzijde gelegd.[10] Voor de review over DTA van elektromagnetische navigatiebronchoscopie was de in het artikel gepresenteerde zoekstrategie niet reproduceerbaar.[9] Er werd dan ook besloten om voor alle drie de navigatiebronchoscopietechnieken (elektromagnetische navigatiebronchoscopie, virtuele bronchoscopie en cone beam CT) voor beide PICOTs naar primaire onderzoeken te zoeken.

Tabel 1 Overzicht van systematische reviews betreffende navigatiebronchoscopie bij verdenking longkanker (n=9)

Reference	Population	Index test(s) or Intervention vs. comparison	Reference standard	Outcome(s)	Search date Number of included studies
Folch 2020[9]	Peripheral pulmonary lesions	Electromagnetic navigation bronchoscopy	Diagnosis confirmed histologically or by close clinical follow-up	Sensitivity, specificity, likelihood ratios	November 2019 N=40
Gex 2014[11]	Peripheral lung nodules or masses	Electromagnetic navigation bronchoscopy	Final diagnoses confirmed by surgery, further biopsies or extended follow-up	Navigation success, diagnostic yield and ability to identify malignancy (=accuracy)	March 2012 N=15
Giri 2021[10]	Peripheral pulmonary lesions	Virtual bronchoscopy navigation (VBN) assisted vs. non-VBN assisted	Not applicable	Diagnostic yield, total examination time, and complications	August 2020 N=6
Han 2018[12]	Peripheral pulmonary lesion defined as endobronchial lesion not detected by bronchoscopy, and the size of these lesions was limited to ≤ 3 cm in diameter	Virtual bronchoscopy	Biopsy specimen or surgical specimen; or clinical follow-up	Diagnostic yield, complications	2000-May 2016 N=24
Jiang 2020[13]	Small pulmonary lesions 3 cm in diameter for which bronchoscopic biopsy was considered unfeasible based on the imaging information.	Virtual bronchoscopy (n=9 studies); electromagnetic navigation bronchoscopy (n=1)	Not applicable	Diagnostic yield	January 1990 to October 2019 N=10
McGuire 2020[14]	Peripheral pulmonary lesions	Electromagnetic navigation bronchoscopy	As reported by included studies	Sensitivity for malignancy (true positive rate), negative predictive value for malignancy, diagnostic yield, and diagnostic accuracy for cancer	2018 N=17
Qian 2020[15]	Suspected malignant peripheral pulmonary (confirmed by CT chest)	Electromagnetic navigation bronchoscopy; virtual bronchoscopy	Pathologic diagnosis	Sensitivity, specificity, sROC curve, AUC	January 2018 N=32
Wang Memoli 2012[16]	Pulmonary nodules confirmed by radiographic evidence	Electromagnetic navigation bronchoscopy; virtual bronchoscopy	Not reported	Diagnostic yield	October 2010 N=39
Zhang 2015[17]	Radiographic evidence of pulmonary nodules	Electromagnetic navigation bronchoscopy	Biopsy or follow-up	Sensitivity, specificity, likelihood ratios, and diagnostic odds ratios (DORs); sROC curve; overall diagnostic yield	2000-2015 N=15

Tabel 2 Methodologische kwaliteit (AMSTAR-2) van de geselecteerde systematische reviews over navigatiebronchoscoopie bij verdenking longkanker (n=2)

	1. PICO comp	2. A priori study	3. Study design	4. Compr	5. Duplic	6. Duplic	7. List of	8. Details of	9. Satisfa ctory techni	10. Fundi	11. Appro priate	12. Potent ial	13. Risk of	14. Heter ogenei ty	15. Investi gation	16. Conflic t of
Folch 2020[9]	Y	PY	N	N	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	N
Giri 2021[10]	Y	N	N	PY	N	Y	N	N	Y	N	N	N	N	Y	N	Y

Y=yes, N=no, PY=partial yes, N=no

Zie Bijlage 5A voor onderbouwing van de in de tabel gepresenteerde scores.

4.1.2 Primaire onderzoeken

De zoekactie naar primaire onderzoeken werd uitgevoerd op 9 juli 2021 (MEDLINE) en 12 juli 2021 (Embase en CENTRAL). De gehanteerde zoekstrategieën staan vermeld in Bijlage 1B.
Deze zoekactie resulteerde in 2925 resultaten (Bijlage 2B). Na ontdubbelen bleven 2076 artikelen over, waarvan er 1832 op basis van titel en/of abstract niet relevant bleken. Van de overgebleven 244 werd het volledige artikel bekeken en uiteindelijk vielen er nog 164 af; de redenen hiervoor staan beschreven in Bijlage 3B. De voornaamste reden was een indextest (of interventie) of populatie die niet bij de PICOTs paste.
Tachtig publicates werden geïncludeerd. De geïncludeerde onderzoeken bestudeerden alle diagnostische testaccuratesse, diagnostische opbrengst of complicaties van navigatiebronchoscopie. Er werden geen RCT's naar klinisch nut van navigatiebronchoscopie gevonden. Vanwege overlap in onderzoekspopulaties, werden drie publicaties van Shinagawa[18-20] als één onderzoek beschouwd. Ook twee publicaties van Verhoeven[21 22] werden om dezelfde reden als één onderzoek in de analyses opgenomen, waarbij relevante informatie uit beide publicaties werd gebruikt, aangevuld met informatie verkregen na contact met de auteurs van deze drie publicaties. Uiteindelijk werden dus 77 onderzoeken geïncludeerd. Qua onderzoekspopulaties werd voor acht daarvan expliciet vermeld dat conventionele bronchoscopie én transthoracale naaldaspiratie of transthoracale naaldbiopsie niet mogelijk was en deze werden geïncludeerd voor PICOT 1 (navigatiebronchoscopie als *add-on* test). De overige 69 werden geïncludeerd voor PICOT 2 (navigatiebronchoscopie als *replacement* test).

4.2 Klinisch nut van navigatiebronchoschopie (PICOT 1)

4.2.1 Beschrijving primaire onderzoeken

Er werden geen RCT's geïdentificeerd waarin het klinisch nut van navigatiebronchoscopie bestudeerd werd. Acht onderzoeken naar de diagnostische testaccuratesse of - opbrengst van navigatiebronchoscopie als *add-on* test (bij een populatie waarvan expliciet vermeld werd dat conventionele bronchoscopie en transthoracale naaldaspiratie of transthoracale naaldbiopsie niet mogelijk waren), werden geïncludeerd.[23-30] Een overzicht van deze acht onderzoeken en hun kenmerken staat in Tabel 3. Met uitzondering van één onderzoek naar cone beam CT[25] werd in alle onderzoeken elektromagnetische navigatiebronchoscopie geëvalueerd. In drie gevallen was de studieopzet prospectief.[23 25 29] Follow-upduur was in drie onderzoeken korter dan een jaar[25 27 30] en in twee andere onderzoeken onbekend[26 29]. Het percentage maligniteiten in de onderzoeken liep uiteen van 40% tot 85% (mediaan 65%) en de gemiddelde of mediane leeftijd lag tussen 62 en 69 jaar. Drie onderzoeken maakten gebruik van EBUS en/of fluoroscopie bij de navigatiebronchoscopie.[24 26 30]

Tabel 3 Overzicht van ingesloten onderzoeken naar de diagnostische accuratesse van navigatiebronchoscopie bij verdenking op longkanker bij mensen met perifere longnoduli bij wie conventionele bronchoscopie en transthoracale naaldaspiratie of transthoracale naaldbiopsie niet mogelijk waren (n=8 onderzoeken)

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Age (yrs) & % male	Lesion size (mm), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
Electromagnetic navigation bronchoscopy (n=7)							
Andersen 2020[23]	Denmark	Prospective; Follow-up: 2 years	100 / 109; Malignancy: 51%	Age: mean (SD; range): 69 (9; 50-83); Male: 41%	Size: mean (SD): 21 (11); Type: Solid: 100%; Bronchus sign: 38%	SuperDimension; Additional: none	Histopathology; or supplementary examinations and/or control CT
Cheng 2019[24]	Hong Kong	Retrospective; Follow-up: 1 year	99 / 99; Malignancy: 63%	Age: mean (SD) 69.1 (11.4); Male: 74%	Size: median (IQR): 26 (20–37); Type: NR; Bronchus sign: 84%	NR; Additional: r-EBUS, fluoroscopy	Histopathology, cytology, or microbiology; or follow-up, additional procedures (e.g., CT-TTNA, surgical biopsy) if deemed appropriate
Mahajan 2011[26]	USA	Retrospective; Follow-up: NR	48 / 48; Malignancy: 56%	NR	Size: mean (SD): 20 (13); Type: NR; Bronchus sign: NR	SuperDimension; Additional: fluoroscopy	Histopathology, cytology, and microbiology immediately after collection; or follow-up testing (CT-guided needle biopsy, VATS, progression of lesions on follow-up chest CT)
Oh 2021[27]	South Korea	Retrospective; Follow-up: ≥3 months	90 / 100; Malignancy: 69%	Age: median (range): 66 (59–73); Male: 61%	Size: mean (SD): 27.9 (13.7); Type: 55% solid, 5% GGO, 33% partially solid, 7% consolidation; Bronchus sign: 71%	SPiN Thoracic Navigation System (SYS-4230 K; Veran Medical, St. Louis, MO); Additional: none	Histopathology (surgery) or additional CT follow-up
Pearlstein 2012[28]	USA	Retrospective; Follow-up: 2 years	104 / 104; Malignancy: 81%	Age: mean (range): 69 (44-92); Male: 62%	Size: median (range): 28 (8-100); Type: NR; Bronchus sign: NR	SuperDimension; Additional: none	Histopathology; additional diagnostic procedures or follow-up with imaging (consensus decision of a multidisciplinary thoracic oncology conference)
Seijo 2010[29]	Spain	Prospective; Follow-up: NR	51 / 51; Malignancy: 67%	Age: mean (SD): 62 (12); Male: 73%	Size: Median (IQR): 25 (15-35); Type: NR; Bronchus sign: 74%	SuperDimension; Additional: none	No details provided
Wilson 2007[30]	USA	Retrospective; Follow-up:	248 / 277; Malignancy: 40%	Age: mean (SD): 63.1 (12.9); Male: 49%	Size: mean (SD): 21 (14); Type: NR; Bronchus sign: NR	SuperDimension; Additional: fluoroscopy	Rapid on-site cytologic evaluation; nondiagnostic cases followed-up by additional diagnostic methods; follow-

		Mean (SD): 6 (5) months.					up procedures, such as surgery, mediastinoscopy, or CT-guided, fine-needle aspiration performed if clinically indicated
Cone beam CT (n=1)							
Hohenforst-Schmidt (2014)[25]	Germany	Prospective	NR / 33; Malignancy: 85%	NR	NR	DynaCT (SIEMENS AG Forchheim, Germany); Additional: none	Histology and/or follow-up

NR: not reported; SD: standard deviation; IQR: interquartile range

Tabel 4 Kans op vertekening en *applicability concerns* voor onderzoeken naar de diagnostische accuratesse van navigatiebronchoscopie bij verdenking op longkanker bij mensen met perifere longnoduli bij wie conventionele bronchoscopie en transthoracale naaldaspiratie of transthoracale naaldbiopsie niet mogelijk waren (n=8 onderzoeken)

Reference	Risk of Bias					Applicability concerns	
	Patient selection	Index test	Reference standard	Flow and timing		Patient selection	Index test
				Yield / Accurate diagnoses	Compli-cations		
Electromagnetic navigation bronchoscopy (n=7)							
Andersen 2020[23]	Low	Low	Low	Low	Low	Low	Low
Cheng 2019[24]	Low	Low	Low	Low	Unclear	Low	Low
Mahajan 2011[26]	High	Low	Low	Unclear	Unclear	Low	Low
Oh 2021[27]	High	Low	Low	High	Unclear	Low	Low
Pearlstein 2012[28]	Low	Low	Low	Low	Unclear	Low	Low
Seijo 2010[29]	Low	Low	Low	Unclear	Unclear	Low	Low
Wilson 2007[30]	Low	Low	Low	High	Unclear	Low	Low
Cone beam CT (n=1)							
Hohenforst-Schmidt (2014)[25]	Unclear	Low	Low	Unclear	Unclear	Low	Low

Tabel 4 geeft een overzicht van de kans op vertekening en *applicability concerns* in de onderzoeken (QUADAS-2; zie ook bijlage 5B voor de onderbouwing hiervan). Twee onderzoeken scoorden een hoge kans op vertekening voor het domein *patient selection*.[26 27] Voor het domein *flow and timing* werd voor twee onderzoeken voor de uitkomsten diagnostische opbrengst en percentage accurate diagnoses een hoge kans op vertekening gescoord vanwege een follow-upduur korter dan 1 jaar.[27 30] Bij een meerderheid van de onderzoeken was de kans op vertekening voor dit domein onduidelijk voor één of beide uitkomsten.

4.2.2 Resultaten

In deze paragraaf worden de resultaten gepresenteerd voor de uitkomsten diagnostische opbrengst en percentage accurate diagnoses en vervolgens voor de uitkomst complicaties. Per uitkomst rapporteren we de resultaten voor onderzoeken naar elektromagnetische navigatiebronchoscopie, virtuele bronchoscopie en cone beam CT. Voor de uitkomsten diagnostische opbrengst en percentage accurate diagnoses geven we ook het overall resultaat weer.
De resultaten uit de afzonderlijke onderzoeken op basis waarvan de uitkomsten diagnostische opbrengst en percentage accurate diagnoses werden berekend, staan in Bijlage 6A. De complicaties zoals die werden gerapporteerd door de afzonderlijke onderzoeken, zijn terug te vinden in Bijlage 6B. De samengevatte resultaten voor de uitkomsten diagnostische opbrengst en percentage accurate diagnoses, inclusief de subgroepen, worden gepresenteerd in Bijlage 7A. Bijlage 8A geeft overkoepelende evidenceprofielen voor de uitkomsten navigatiesucces, diagnostische opbrengst, percentage accurate diagnoses, sensitiviteit en de complicaties bloedingen en pneumothorax. Voor percentage accurate diagnoses en sensitiviteit wordt daarbij een GRADE level of certainty weergegeven.

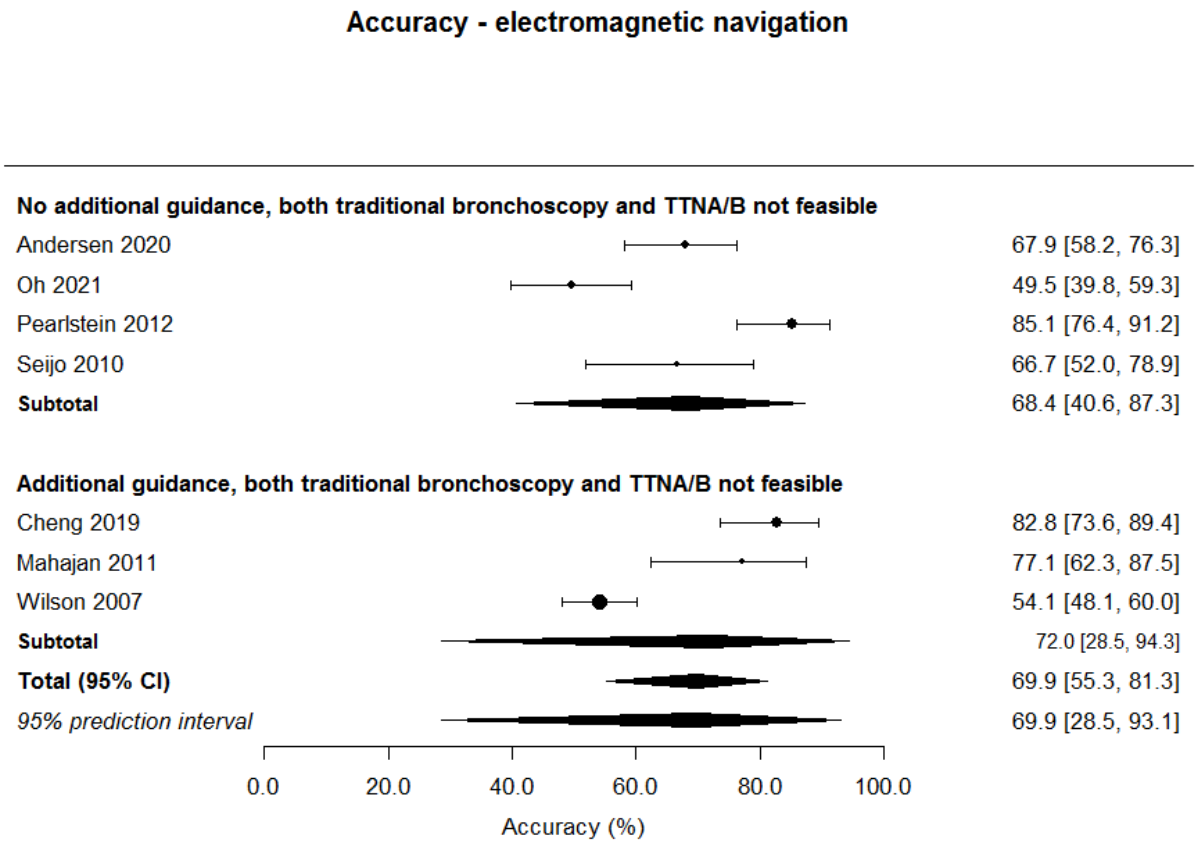
Diagnostische opbrengst en percentage accurate diagnoses

Van de acht ingesloten onderzoeken rapporteerden er vijf (568 lesies) hoe vaak een lesie werd bereikt. Dat was in 95% van de gevallen (mediaan navigatiesucces 95,3% [IQR 93,5% tot 100%]). Acht onderzoeken (827 lesies) vermeldden voor welk deel van de lesies een testuitslag werd verkregen en de mediane diagnostische opbrengst in deze onderzoeken bedroeg 70,7% (IQR 67,8% tot 91,1%). Het gepoolde percentage accurate diagnoses over zeven onderzoeken (794 lesies) bedroeg 69,9% (95%-BI 55,3% tot 81,3%; 95%-PI 28,5% tot 93,1%) en de gepoolde sensitiviteit (3 onderzoeken; 128 lesies) bedroeg 71,7% (95%-BI 33,0% tot 92,8%; 95%-PI 0,04% tot 100%). De voorspellende waarde van een negatieve testuitslag, gebaseerd op drie onderzoeken (152 lesies), was 65,3% (mediaan; IQR 60,6% tot 66,7%). Alle drie deze onderzoeken volgden patiënten tenminste één jaar om na te gaan of een negatieve testuitslag daadwerkelijk negatief was.
De *certainty of the evidence* volgens GRADE voor de gepoolde uitkomsten werd ingeschat als *low* voor de uitkomst percentage accurate diagnoses en *very low* voor de sensitiviteit, vanwege heterogeniteit en imprecisie.

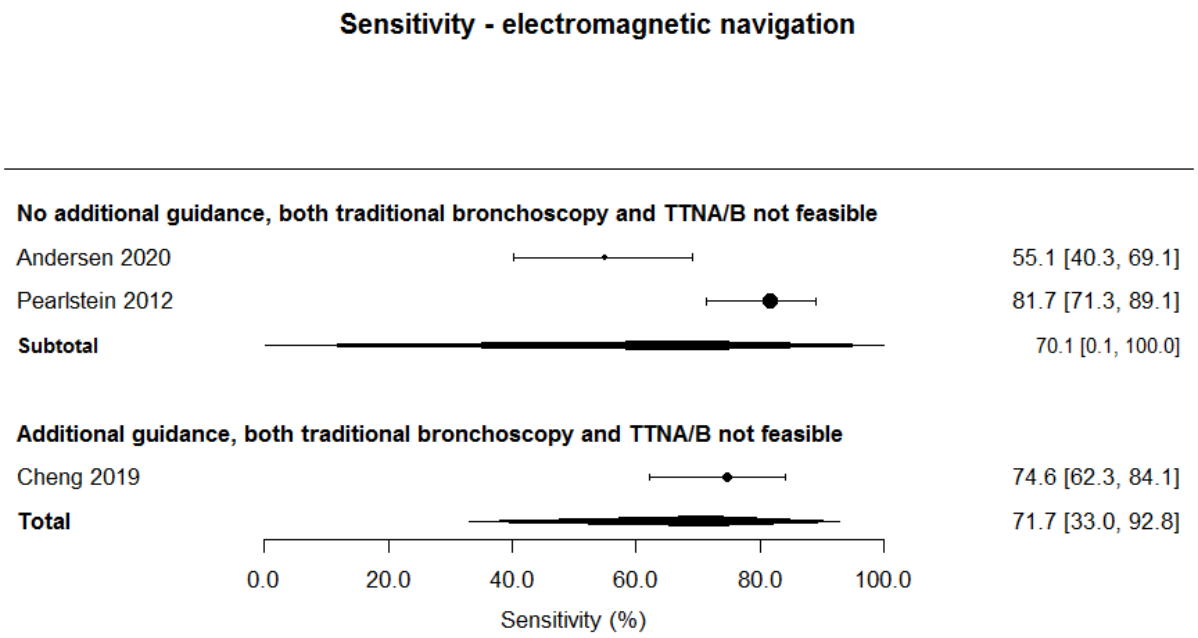
Elektromagnetische navigatiebronchoscopie

Van de zeven onderzoeken naar elektromagnetische navigatiebronchoscopie rapporteerden er vier (535 onderzochte lesies) hoe vaak een lesie werd bereikt met behulp van elektromagnetische navigatie: het mediane navigatiesucces was 97,7% (IQR: 94,9% tot 100,0%). De mediane diagnostische opbrengst,

berekend over alle zeven onderzoeken (794 lesies), was 71,7% (IQR: 67,5% tot 94,0%). Het gepoolde percentage accurate diagnoses over deze zeven onderzoeken bedroeg 69,9% (95%-BI: 55,3% tot 81,3%) (Figuur 1) en de gepoolde sensitiviteit (3 onderzoeken, 198 lesies) 71,7% (95%-BI: 33,0% to 92,8%) (Figuur 2). De bijbehorende 95%-predictieintervallen liepen respectievelijk van 28,5% tot 93,1% en van 0 tot 100%. De resultaten van de twee subgroepen verschilden niet significant van elkaar.
De *certainty of the evidence* volgens GRADE werd ingeschat als *low* voor het percentage accurate diagnoses en *very low* voor de sensitiviteit, vanwege heterogeniteit en imprecisie. Er was ook sprake van heterogeniteit voor de uitkomst diagnostische opbrengst; deze liep uiteen van 59% tot 100%.



Figuur 1 Forest plot van het percentage accurate diagnoses ("*accuracy*") van elektromagnetische navigatiebronchoscopie (met of zonder de additionele inzet van EBUS en/of fluoroscopie) bij mensen met perifere longnoduli bij wie conventionele bronchoscopie en transthoracale naaldaspiratie of transthoracale naaldbiopsie niet mogelijk waren.



Figuur 2 Forest plot van de sensitiviteit van elektromagnetische navigatiebronchoscopie (met of zonder de additionele inzet van EBUS en/of fluoroscopie) voor het aantonen van maligniteit bij mensen met perifere longnoduli bij wie conventionele bronchoscopie en transthoracale naaldaspiratie of transthoracale naaldbiopsie niet mogelijk waren.

Virtuele bronchoscopie

Er werden geen onderzoeken geïdentificeerd naar virtuele bronchoscopie bij een voor deze PICOT relevante onderzoekspopulatie.

Cone beam CT

Eén onderzoek (33 lesies) evalueerde cone beam CT (zonder inzet van additionele technieken). Dit onderzoek rapporteerde een navigatiesucces van 90,9% (95%-BI 74,5% to 97,6%) en een diagnostische opbrengst van 69,7% (95%-BI 51,1% to 83,8%). Voor beide uitkomsten verlaagt kans op vertekening de zekerheid van de resultaten. Er waren geen resultaten voor percentage accurate diagnoses of sensitiviteit.

Complicaties

Elektromagnetische navigatiebronchoscopie

In Tabel 5 staat een overzicht van de door de onderzoeken gerapporteerde complicaties die optraden tijdens of na elektromagnetische navigatiebronchoscopie. Het optreden van een bloeding en pneumothorax werden het vaakst gerapporteerd. Met uitzondering van 'geringe bloeding' (*minor bleeding*; 9%), gerapporteerd door één onderzoek,[27] lagen de mediane incidenties van deze complicaties

op 5% of lager. De manier van patiëntenselectie van de meerderheid van deze onderzoeken en onduidelijkheid rondom de vastlegging van complicaties zorgen voor kans op vertekening.

Tabel 5 Incidentie van gerapporteerde complicaties tijdens of volgend op elektromagnetische navigatiebronchoscopie bij mensen met perifere longnoduli bij wie conventionele bronchoscopie en transthoracale naaldaspiratie of transthoracale naaldbiopsie niet mogelijk waren.

Complication*	Incidence, median (range)	Number of participants	Number of studies
Bleeding			
Not specified / any	1% (0%-13%)	250	3[24 27 29]
Major bleeding	0%	100	1[27]
Moderate bleeding	3% (1%-4%)	348	2[27 30]
Minor bleeding	9%	100	1[27]
Pneumothorax			
Not defined	2% (0%-3%)	350	4[23 24 27 29]
Pneumothorax requiring chest tube insertion	4% (1%-6%)	253	3[26-28]
Pneumothorax not requiring intervention	4% (1%-6%)	297	2[26 30]
Death	0%	204	2[27 28]
Respiratory failure	1%	199	2[24 27]
Hematoma (not requiring intervention)	0.4%	248	1[30]
Hypoxemia, not requiring termination of procedure	8%	51	1[29]
Pneumonia treated with oral antibiotics	0.4%	248	1[30]

*As reported by the study. Not reported does not exclude the occurence nor the absence of complications.

Virtuele bronchoscopie

Er werden geen onderzoeken geïdentificeerd.

Cone beam CT

Levensbedreigende complicaties werden niet gerapporteerd door het enige onderzoek dat cone beam CT evalueerde in een populatie waarbij zowel conventionele bronchoscopie als transthoracale naaldaspiratie of -biopsie niet mogelijk waren.[25] Twee van de 33 deelnemers in dit onderzoek (6%) ontwikkelden een pneumothorax en één deelnemer (3%) kreeg bradycardie en hypotensie die niet levensbedreigend waren. In dit onderzoek was er onduidelijkheid over de methoden voor selectie van deelnemers en het meten van de uitkomst.

4.3 Diagnostische testacuratesse van navigatiebronchoscopie (PICOT 2)

4.3.1 Beschrijving primaire onderzoeken

Er werden 69 onderzoeken geïncludeerd naar de diagnostische testaccuratesse van navigatiebronchoscopie als *replacement* test voor transthoracale naaldaspiratie of transthoracale naaldbiopsie bij een populatie met perifere longnoduli bij wie conventionele bronchoscopie niet mogelijk was. De kenmerken van deze onderzoeken staan weergegeven in Tabel 6. Achtentwintig onderzoeken evalueerden elektromagnetische navigatiebronchoscopie,[31-58] 29 virtuele bronchoscopie[18 59-86] en drie cone beam CT[21 87 88]. In vier onderzoeken werd elektromagnetische navigatiebronchoscopie gecombineerd met cone beam CT[89-92] en in drie onderzoeken met virtuele bronchoscopie[93-95]. Twee onderzoeken combineerden virtuele bronchoscopie met cone beam CT[96 97]. Voor 24 van de onderzoeken werd expliciet vermeld dat conventionele bronchoscopie niet mogelijk was en in de overige onderzoeken ontbrak informatie over het wel of niet mogelijk zijn van conventionele bronchoscopie. Er waren in totaal 39 prospectieve onderzoeken, 29 retrospectieve en voor één onderzoek[83] was dit niet vermeld. Het percentage maligniteiten in de onderzoeken liep uiteen van 24% tot 100% (mediaan 71%) en de gemiddelde of mediane leeftijd lag tussen 51 en 75 jaar. Vijftig onderzoeken (72%) maakten gebruik van EBUS en/of fluoroscopie bij de navigatiebronchoscopie.Tabel 7 geeft een overzicht van de kans op vertekening en *applicability concerns* in de onderzoeken (QUADAS-2; zie ook bijlage 5B voor de onderbouwing hiervan). Vierentwintig onderzoeken scoorden een hoge kans op vertekening voor het domein *patient selection.*Bij twaalf onderzoeken was er een hoge kans op vertekening voor het domein *flow and timing* voor de uitkomsten diagnostische opbrengst en percentage accurate diagnoses en voor 18 was er een onduidelijke kans op vertekening. Voor de uitkomst complicaties was voor 48 van de 59 onderzoeken (81%) die naar deze uitkomst keken, de kans op vertekening onduidelijk voor dit domein door het ontbreken van informatie over de gehanteerde methode om complicaties te registreren.

Cochrane Netherlands

Tabel 6 Overzicht van ingesloten onderzoeken naar de diagnostische accuratesse van navigatiebronchoscopie bij verdenking op longkanker bij mensen met perifere longnoduli bij wie conventionele bronchoscopie niet mogelijk was (n=69 onderzoeken)

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
Electromagnetic navigation bronchoscopy (n=28)								
Al-Jaghbeer 2016[31]	USA	Retrospective; Follow-up: NR	92 / 98; Malignancies: NR	Unclear	Age: mean (range): 64 (31–90); Male: 49%	Size: 26; Type: GGO: 6%; Bronchus sign: 60%	SuperDimension, Inc., Minneapolis, MN; Additional: none	Histopathology
Bellinger 2021[32]	USA	Retrospective; Follow-up: 18 months	248 / 271; Malignancies: NR	Unclear	Age: 67.2 (10.5); Male: 50%	Size: 24.2 (12.1); Type: mass: 38%; solid nodule 56.1%; ground glass nodule: 3.7%; fiducial placement only: 1.5%; dye marking only: 0.7%; Bronchus sign: 93%	SuperDimension Navigation System® (Medtronic, Minneapolis MN).; Additional: r-EBUS at discretion of bronchoscopist, fluoroscopy	Histopathology; additional diagnostic procedures or follow-up (imaging) for benign pathology
Bertoletti 2009[33]	France	Prospective; Follow-up: 18 months	53 / NR; Malignancies: 79%	Unclear	Age: 69; Male: 89%	Size: 31.2 (14.4); Type: NR; Bronchus sign: NR	SuperDimension; Additional: none	Histopathology; follow-up for benign pathology
Bowling 2017[34]	USA	Retrospective; Follow-up: NR	14 / 14; Malignancies: 50%	Unclear	Age: 58.6; Male: 64%	Size: 23.5; Type: solid: 85.7%; semisolid: 7.1%; cavity: 7.1%; Bronchus sign: 0	CBCT Scan: Artis Zeego; Siemens Healthcare, Forchheim, Germany; ENB: superDimension navigation system 7.0 (Medtronic, Inc); Additional: none	Histopathology
Bowling 2015[35] (GA: general anesthesia; IVS: intravenous moederate sedation)	USA	Retrospective; Follow-up: NR	107 / 120; Malignancies: 60%	Unclear	Age: GA: 67 (10); IVS: 67 (14); Male: GA: 48% IV: 52%%	Size: GA group: <20: 31%, >20 ≤30: 29% >30: 40%; IVS: <20: 33%, >20 ≤30: 28%, >30: 40%; Type: NR; Bronchus sign: NR	SuperDimension Inc., Minneapolis, MN; Additional: fluoroscopy	Histopathology
Chee 2013[36]	Canada	Prospective; Follow-up: 1 year	15 / 15; Malignancies: 87%	Unclear	Age: 70 (11); Male: 40%	Size: 22 (10); Type: NR; Bronchus sign: 20%	Bronchus V4.3.4, SuperDimension; Additional: peripheral EBUS	NA (no diagnostic accuracy outcome)
Eberhardt 2007a[37]	Germany /USA	Prospective; Follow-up:	89 / 92; Malignancies: 76%	Unclear	Age: 67 (12); Male: 56%	Size: 24 (8); Type: NR; Bronchus sign: NR	SuperDimension/Bronc hus; superDimen sion	Histopathology; for benign patholoty additional procedures (CT scan guided

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
		16.1±1.8 months					Inc; Plymouth, MN; Additional: none	transthoracic needle aspiration biopsy or surgery) or clinical and radiologic follow-up
Eberhardt 2010a[39]	USA	Prospective; Follow-up: 2 years	54 / 55; Malignancies: 89%	Unclear	Age: mean (range) 65.1 (29–84) ; Male: 74%	Size: 23.3 (4.4); Type: NR; Bronchus sign: NR	Olympus ; Additional: EBUS	Histopathology; follow-up until either a definitive diagnosis obtained or diagnosis verified by other standard techniques (e.g. CT-guided fine needle aspiration or surgery)
Eberhardt 2007b[38]	Germany /USA	Prospective; Follow-up: NR	ENB: 39 ENB+EBUS: 40 / 89; Malignancies: 78%	Unclear	Age: ENB: 55 (15); ENB+EBUS: 51(12); Male: ENB: 51% ENB+EBUS: 62%	Size: ENB: 3.9 (0.9); ENB+EBUS: 4.2 (0.7); Type: NR; Bronchus sign: NR	SuperDimension, Inc., Plymouth, MN; Additional: ENB en ENB+EBUS	Histopathology; surgical biopsy in case transbronchial lung biopsy was inconclusive
Flenaugh 2016[40]	USA	Retrospective; Follow-up: 12 months	44 / 71; Malignancies: 39%	Unclear	Age: NR; Male: NR	Size: 22.1 (9.8); Type: NR; Bronchus sign: NR	Veran Medical Technologies SPiNDrive System, St Louis, MO; Additional: r-EBUS	Histopathology; additional procedures such as CT guided fine-needle aspiration, or surgery if clinically indicated; follow-up
Garwood 2016[41]	USA	Retrospective; Follow-up: 2 year	90 / 92; Malignancies: 62%	Unclear	Age: 65.6 (10.9); Male: 35%	Size: 22.7 (16.0); Type: NR; Bronchus sign: NR	SuperDimension; Additional: r-EBUS	Histopathology; follow-up
Gildea 2006[42]	Turkey	Prospective; Follow-up: mean of 10.5 months	58 / 56 lesies en 31 lymph nodes ; Malignancies: 77%	No	Age: 67.91 (9.3); Male: 60%	Size: 22.8 (12.6); Type: NR; Bronchus sign: NR	SuperDimension; Additional: none	Histopathology; for non-diagnostic ENB additional diagnostic procedures; follow-up
Gu 2017[43]	China	Retrospective; Follow-up: 12 months	78 / 84; Malignancies: 47%	Unclear	Age: mean (range): 53.52 (24–82); Male: 86%	Size: 19 (6.16); Type: NR; Bronchus sign: NR	SuperDimension; Additional: r-EBUS and X-ray	Histopathology; follow-up
Hautmann 2005[44]	Germany	Prospective; Follow-up: NR	16 / ?; Malignancies: 44%	Unclear	Age: mean (range): 63.7 (42-84); Male: 63%	Size: 22 (6); Type: NR; Bronchus sign: NR	Aurora; Northern Digital; Waterloo, ON, Canada; navigation software: Syngo;	Histopathology

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
							Siemens Medical Solutions; Erlangen, Germany); Additional: none	
Jensen 2012[45]	Spain	Retrospective; Follow-up: 6 months	92 / ?; Malignancies: NR	Unclear	Age: 67 (13); Male: 48%	Size: 26.1 (14.2); Type: NR; Bronchus sign: NR	SuperDimension; Additional: none	Histopathology; for lesions undiagnosed by bronchoscopy: surgical biopsy or stablility for 6 months on radiographic follow-up.
Lamprecht 2012[46]	Austria	Prospective; Follow-up: NR	112 / 112; Malignancies: 85%	No	Age: mean (range): 66.7 (32-87) ; Male: 67%	Size: 27.1 (1.3); Type: NR; Bronchus sign: NR	SuperDimension; Additional: none	Histopathology
Loo 2014[47]	USA	Retrospective; Follow-up: NR	40 / 50; Malignancies: NR	Unclear	Age: mean (range): 67 (53-90); Male: 30%	Size: mean (range): 26 (3-80); Type: NR; Bronchus sign: NR	SuperDimension; Additional: none	Histopathology
Ma 2020[48]	China	Retrospective; Follow-up: NA	109 / 109; Malignancies: 24%	Unclear	Age: EBUS-GS: 59.6 (12.6); ENB-EBUS: 52.8 (18.0); Male: EBUS-GS: 54% ENB-EBUS: 62%	Size: EBUS-GS: 23.2 (5.8); ENB-EBUS: 20.9 (9.6); Type: NR; Bronchus sign: EBUS-GS: 75.9% ENB-EBUS: 26.9%	Super Dimension, USA, including Super Dimension-V7 software; Additional: EBUS-GS	Final / discharge diagnosis (not further specified)
Makris 2007[49]	France	Prospective; Follow-up: 14 months	40 / 40; Malignancies: 86%	No	Age: mean (standard error) 60 (2,5); Male: 75%	Size: mean (standard error): 23.5 (1.5); Type: NR; Bronchus sign: NR	SuperDimension Bronchus, Hertzliya, Israel; Additional: none	Histopathology; additional diagnostic procedures (TTNA, surgery) or clinical and thoracic imaging follow-up, if in case EMN biopsy was inconclusive
Mukherjee 2017[50]	USA	Retrospective; Follow-up: ≥12 months	31 / 31; Malignancies: 71%	No	Age: 66 (13); Male: NR	Size: 18 (10); Type: NR; Bronchus sign: NR	Edge catheter [manufactured by Covidien (now Medtronic), Mansfield, MA] used with the superDimension navigation system version 7 (Medtronic).; Additional: C-arm fluoroscopy	Histopathology (repeat fine needle aspiration); follow-up imaging

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
Odronic 2014[51]	USA	Retrospective; Follow-up: 12 months	91 / 95; Malignancies: 38%	Unclear	Age: median (range): 66 (25-91); Male: 44%	Size: mean (range): 27 (7–71); Type: NR; Bronchus sign: NR	superDimension ; Additional: none	Histopathology; follow-up
Patrucco 2018[52]	Italy	Retrospective; Follow-up: "reasonable"	113 / 113; Malignancies: 75%	No	Age: 72.4 (10.4); Male: 69%	Size: 24.6 (10.1); Type: solid: 91%, part-solid part ground glass: 7%, GGO: 2%; Bronchus sign: 61%	SuperDimension; Additional: fluoroscopy	Histopathology; additional diagnostic procedures [i.e., fluoroscopy or CT-guided transthoracic needle aspiration (TTNA) or surgical biopsy] or a clinical-radiological follow-up
Raval 2016[53]	USA	Retrospective; Follow-up: 24 months	50 / 61; Malignancies: 40%	Unclear	Age: 67.7 (12.2); Male: 56%	Size: 19.3 (10.7); Type: NR; Bronchus sign: 52.1%	TV-EXP mapping with SPiNDrive system; Additional: none	Final diagnosis determined by repeat CT, or as recommended by the pulmonologist or tumor review board, these patients were referred to TTNA, or lung resection and biopsy.
Sato 2018[54]	Japan	Retrospective; Follow-up: 3 months	35 / 35; Malignancies: 74%	Unclear	Age: NR; Male: NR	Size: median (range): 15.28 (8-25); Type: NR; Bronchus sign: NR	superDimension; Additional: none	Surgical resection, transbronchial biopsy/cytology, or follow-up
Stenger 2020[55]	Denmark	Retrospective; Follow-up: mean of 11 months	82 / 81; Malignancies: 26%	No	Age: mean (range): 69 (38-88); Male: 52%	Size: 15.5 (4.0); Type: NR; Bronchus sign: NR	superDimension Navigation Version 7.1; Additional: none	Histopathology; additional diagnostic procedures and/or follow-up for benign or inconclusive pathology
Sun 2017[56]	China	Prospective; Follow-up: ≥12 months	40 / 40; Malignancies: 78%	No	Age: 59.0 (8.7) ; Male: 68%	Size: 21.1 (5.3); Type: NR; Bronchus sign: NR	Olympus ; Additional: r-EBUS, fluoroscopy	Histopathology; follow-up
Taton 2018[57]	Belgium	Prospective; Follow-up: 6 months	32 / NR; Malignancies: 78%	Unclear	Age: 68 (9); Male: 56%	Size: 16 (3); Type: Solid: 96.9%; non solid: 3.1%; Bronchus sign: 34.3%	olympus ; Additional: r-EBUS miniprobe, fluoroscopy	Histopathology; surgical resection, or follow-up for lesions that could not be diagnosed
Wang 2021[58]	China	Retrospective; Follow-up: ≥12 months	25 / 37; Malignancies: 35%	No	Age: 66.81 (7.57); Male: 56%	Size: 23.3 (10.08); Type: subsolid: 37.8%; solid: 62.2%; Bronchus sign: NR	SuperDimensionTM V.6 (Medtronic, Minneapolis, MN) navigation system; Additional: r-EBUS	Histopathology (video-assisted thoracoscopic surgery biopsy, percutaneous lung biopsy, bronchoscopy), or follow-up

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
Virtual bronchoscopy (n=29)								
Asahina 2005[59]	Japan	Prospective; Follow-up: NR	29 / 30; Malignancies: 77%	Unclear	Age: 62.2 (11.6); Male: 61%	Size: 18.9 (6.5); Type: NR; Bronchus sign: NR	Virtual Place; AZE; Tokyo, Japan; Additional: EBUS-GS, fluoroscopy	Histopathology; follow-up for benign pathology
Asano 2006[60]	Japan	Prospective; Follow-up: NR	37 / 38; Malignancies: 55%	Unclear	Age: median (range) 72.5 years (30-85); Male: 62%	Size: median (range) 18.5 (6-30); Type: NR; Bronchus sign: NR	Helical CT scanner (HighSpeed Nx/I; General Electric Medical Systems; Tokyo, Japan); VB performed using software (Navigator, Advantage Windows 2.0; General Electric Medical Systems); navigation system developed in cooperation with Olympos (prototype; Olympus; Tokyo, Japan); Additional: fluoroscopy	Histopathology
Asano 2008[61]	Japan	Prospective; Follow-up: NR	31 / 32; Malignancies: 53%	No	Age: median (range): 72 (42—80); Male: 71%	Size: median: 21 (10-53.5); Type: NR; Bronchus sign: NR	CT scanner: Aquilion; Toshiba, Tokyo, Japan; bronchoscopic insertion guidance system: prototype; Olympus Co., Ltd., Tokyo, Japan; Additional: EBUS-GS; fluoroscopy	Histopathology; surgery or clinical course for benign pathology
Asano 2013[62]	Japan	Prospective; Follow-up: 2 years	167 / 167; Malignancies: 86%	No	Age: median (range): 70 (43–88); Male: 62%	Size: median (range): 17.5 (7.5–29.0); Type: NR; Bronchus sign: NR	Bf-NAVI; Cybernet Systems Tokyo, Japan; Additional: X-ray fluoroscopy	Histopathology; additional diagnostic procedures or follow-up for benign pathology
Asano 2015[63]	Japan	Prospective; Follow-up: NR	59 / 59; Malignancies: NR	Unclear	Age: NR; Male: NR	Size: <20: 51%; 20-30 mm: 49%; Type: NR; Bronchus sign: 94.4%	Bf-NAVI; Additional: r-EBUS	Not specified

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
Bae 2020[64]	Republic of Korea	Prospective; Follow-up: 12 months	64 / NR; Malignancies: 64%	No	Age: 63.50 (11.30); Male: 58%	Size: 28.43 (18.20); Type: GGO: 5%; mixed opacity: 20%; solid opacity: 75%; Bronchus sign: 6%	high performance CT workstation running software program "Aquarius iNtuition Viewer"; Additional: r-EBUS with GS (K-201, Olympus)	Histopathology; follow-up for benign pathology
Bo 2019[65]	China	Prospective; Follow-up: 2 years	334 / 334; Malignancies: 49%	Unclear	Age: 58.03 (11.92); Male: 65%	Size: 21.81 (4.79); Type: NR; Bronchus sign: NR	NR; Additional: EBUS-GS	Histopathology; additional diagnostic procedures (including repeat transbronchial biopsy, transthoracic needle biopsy, positron emission computed tomography (PET/CT), surgery) or follow-up for benign pathology
Diez-Ferrer 2019[66]	Spain	Prospective; Follow-up: 2 year	55 / 55; Malignancies: 60%	Unclear	Age: 68 (10); Male: 78%	Size: 23 (13); Type: NR; Bronchus sign: 67%	Olympus; Additional: fluoroscopy	Histopathology; subsequent CT evaluation for benign pathology
Eberhardt 2010b[67]	Germany	Prospective; Follow-up: NR	25 / 25; Malignancies: 84%	Unclear	Age: 67 years (7.5); Male: 64%	Size: 28 (0.7); Type: NR; Bronchus sign: NR	LungPoint Virtual Bronchoscopic Navigation System; Additional: none	Histopathology; additional test (e.g., CT-guided fine needle aspiration or thoracoscopy) in case of inconclusive diagnosis
Fukusumi 2016[68]	Japan	Prospective; Follow-up: NR	27 / 27; Malignancies: 44%	Unclear	Age: median (range): 72 (26-87); Male: 0,56%	Size: 20.2; Type: NR; Bronchus sign: NR	UM-S20-17S; Olympus; Additional: EBUS-GS	Histopathology; for inconclusive diagnoses: open lung TT biopsy was done or stereotactic surgery or wait and see
Haidong 2017[69]	China	Retrospective; Follow-up: NR	12 / 12; Malignancies: 75%	Unclear	Age: 60 (11); Male: 68%	Size: 24 (13); Type: NR; Bronchus sign: NR	DirectPath 1.0, Cybernet systems Co. Ltd., Tokyo, Japan; Additional: EBUS-GS, fluoroscopy	Not specified
Ikezawa 2017[70]	Japan	Retrospective; Follow-up: NR	169 / 169; Malignancies: NR	Unclear	Age: median (range): Diagnosed: 71 (39–85); Non-diagnosed: 70 (39–82); Male: 36%	Size: Diagnosed: 23 (8.9); non-diagnosed: 18 (6.4); Type: pure GGO: 18.3%; mixed GGO: 81.7%; Bronchus sign: CT signs reported, compromised of both artery and	Bf-Navi; Olympus Ltd, Tokyo, Japan; or DirectPath; Cybernet System Ltd, Tokyo, Japan; Additional: EBUS-GS, X-	Histopathology; follow-up

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
						bronchus signs: type 1: 59%; type 2: 17%; type 3: 15%; type 4: 8% type 5: 2%	ray fluoroscopic guidance	
Ishida 2011[71]	Japan	Prospective; Follow-up: 2 years	102 / 102 ; Malignancies: 78%	No	Age: median (range): 69 (21-85); Male: 63%	Size: median (range): 18.0 (9.5-30.0); Type: NR; Bronchus sign: NR	UM-S20-17S; Olympus; Additional: EBUS	Histopathology; for lesions undiagnosed by bronchoscopy: other diagnostic procedures, including CT-guided fine needle aspiration or surgical intervention;, or follow-up if patients refused additional diagnostic procedures
Iwano 2011[72]	Japan	Retrospective; Follow-up: NR	122 / 122; Malignancies: 100%	Unclear	Age: median (range): 68.5 (38-84); Male: 67%	Size: median (range): 27.5 (12-58 mm) ; Type: solid: 71.3%; partly solid 22.1%; non-solid 6.6%; Bronchus sign: NR	NR; Additional: fluoroscopy	Histopathology
Kato 2018[73]	Japan	Prospective; Follow-up: NR	50 / 50; Malignancies: 82%	No	Age: 67.9 (10.2); Male: 46%	Size: 13.3 (3.9); Type: NR; Bronchus sign: bronchus sign classification 1: 62%, 2: 38%	LungPoint Satellite Planning System, Broncus Technologies Inc., Mountain View, CA, USA; Additional: multislice CT fluoroscopy	Histopathology; CT follow-up
Li 2020[74]	China	Prospective; Follow-up: 2 years	109 / 109; Malignancies: 84%	No	Age: 58.3 (10.1); Male: 55%	Size: median (range): 24.0 (7.0–68.0); Type: NR; Bronchus sign: 75.2%	DirectPath system (Cybernet System Inc., Tokyo, Japan); Additional: EBUS-GS	Histopathology; for nondiagnostic results CT-guided trans thoracic needle biopsy (TTNB) or thoracoscopic surgery, or follow-up if patients refused further examination
Maekura 2017[75]	Japan	Prospective; Follow-up: 6 months	50 / 50; Malignancies: 84%	Unclear	Age: median (range): 71 (49–85); Male: 76%	Size: 0–10: 2.2%; 11–20: 44.4%; 21–30: 53.3%; Type: NR; Bronchus sign: NR	NR; Additional: EBUS-GS, fluoroscopy	Histopathology; surgical resection, second bronchoscopy, CT-PNB, or follow-up for lesions that could not be diagnosed

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
Matsumoto 2017[76]	Japan	Retrospective; Follow-up: NA	121 / 121; Malignancies: NR	Unclear	Age: ≤70: 56.2%, >70: 43.8%; Male: 56%	Size: NR; Type: solid: 72.7%; mixed GGO: 24.8%; pure GGO: 2.5%; Bronchus sign: NR	ziostation2®, Ziosoft, Tokyo, Japan; Additional: EBUS-GS	Histopathology; for negative bronchoscopy but suspected malignancy the final diagnosis was confirmed by surgery or TTNA
Miyoshi 2018[77]	Japan	Retrospective; Follow-up: 12 months	56 / 56; Malignancies: 70%	Unclear	Age: median (range): 68 (27–84); Male: 77%	Size: NR ; Type: solid: 91.1%; mixed GGO: 7.1%; pure GGO: 1.8%; Bronchus sign: 71.4%	Olympus; Additional: fluoroscopy	Histopathology; TTNA or surgery, or follow-up for inconclusive diagnosis
Oki 2019[79]	Japan	Prospective; Follow-up: ≥12 months	310 / 310; Malignancies: 82%	Unclear	Age: median (range): UTB: 70 (35–93); TB-GS: 71 (31–88); Male: 58%	Size: median (range): UTB: 19.0 (8.8–30.0); TB-GS: 19.4 (7.0–30.0); Type: solid: 79%; others: 21%; Bronchus sign: 79%	Bf-NAVI; Cybernet Systems, Tokyo, Japan; Additional: EBUS, fluoroscopy	Histopathology; clinical and radiology follow-up
Oki 2015[78]	Japan	Prospective; Follow-up: ≥12 months	360 / 360; Malignancies: Ultrathin bronchoscopie: 80%; thin bronchoscope: 78%	Unclear	Age: median (range): UTB: 71 (34-92); thin bronchoscope : 72 (37-87); Male: UTB: 61% Thin bronchoscope : 62%%	Size: median (range): UTB: 18.9 (7.7-30.0); Thin bronchoscope: 19.1 (7.4-29.9); Type: UTB vs. thin bronchoscope: solid: 83.6% vs. 85.5%; part solid: 16.4% vs. 14.5%; Bronchus sign: UTB: 73.4%; thin bronchoscope: 74.3%	Bf-NAVI or DirectPath; Cybernet Systems; Additional: EBUS, fluoroscopy	Histopathology; follow-up
Oshige 2011[80]	Germany	Prospective; Follow-up: 6 months	57 / 57; Malignancies: 90%	No	Age: 68.9 (1.82); Male: 74%	Size: 28.4 (2.24); Type: NR; Bronchus sign: NR	Bf-NAVI, Olympus, Tokyo, Japan; Additional: EBUS-GS	Histopathology; other methods including CT-guided biopsy, surgical procedure, transbronchial needle aspiration, and a 6-month follow-up using CT image for undiagnosed cases
Shinagawa 2007[18-20]	Japan	Retrospective; Follow-up: NR	83 / 85; Malignancies: 52%	Unclear	Age: NR; Male: 49%	Size: NR; Type: NR; Bronchus sign: NR	Alato view; Toshiba, Tokyo, Japan; or Virtual Place Advance; AZE; Tokyo, Japan; Additional: real-time	Histopathology; surgery or follow-up in case of undiagnosed lesions

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
							multislice CT fluoroscopy	
Tachihara 2017[81]	Japan	Prospective; Follow-up: 2 years	31 / NR; Malignancies: group 1: 94%; group 2: 84%	Unclear	Age: median (range): X-ray group: 73 (60 to 85); non-X-ray group: 71 (60 to 82); Male: 61%	Size: median (range): X-ray group: 22 (15 to 30); non-X-ray group: 19 (12 to 30); Type: 0% GGO (exclusion criterion); Bronchus sign: 100% (inclusion criterion)	Bf-NAVI®, Olympus Medical Systems, Tokyo, Japan; Additional: EBUS (all patients); fluoroscopy (42% of patients)	Histopathology; re-bronchoscopy, CT-guided FNA, video-assisted thoracoscopy, or follow-up for bronchoscopically undiagnosed patients
Tamiya 2013[82]	Japan	Prospective; Follow-up: >6 months	68 / 68; Malignancies: 63%	Unclear	Age: median (range): 68 (31–87); Male: 65%	Size: median (range): 22 (10–30); Type: pure or mixed GGO: 47.0%; solid nodule 53.0%; Bronchus sign: NR	LungPoint (Broncus Technologies, Inc., Mountain View, CA, USA); Additional: EBUS-GS, X-ray fluoroscopy	Histopathology; additional diagnostic procedures or follow-up for benign pathology
Wong 2014[83]	Hong Kong	Unclear; Follow-up: 2 years	16 / 16; Malignancies: NR	Unclear	Age: 69.6 (6.6); Male: 56%	Size: 28.8 (9.3); Type: NR; Bronchus sign: NR	multislice CT (Lightspeed VCT, General Electric Medical Systems); set of DICOM CT data (0.625 mm, plain, soft tissue kernel) transferred to a computer equipped with advance open source processing software (OsiriX, Pixmeo, Switzerland); Additional: miniature r-EBUS	Final diagnoses were confirmed by surgery or by interval CT thorax for stability over 2 years.
Xu 2019[84]	China	Prospective; Follow-up: 6 months	55 / 55; Malignancies: 64%	Unclear	Age: 57.8 (12.3); Male: 62%	Size: 28 (1); Type: NR; Bronchus sign: NR	DirectPath V1.02, Cybernet Systems; Additional: EBUS	Histopathology; for undiagnosed lesions: additional diagnostic procedures (including CT-guided percutaneous puncture or surgical intervention) or follow-up for 6 months if patients refused further examination

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
Zhang 2020[85]	China	Retrospective; Follow-up: 12 months	20 / NR; Malignancies: 70%	No	Age: 60.7 (10.4); Male: 70%	Size: 20.3 (4.8); Type: NR; Bronchus sign: NR	virtual bronchoscopic navigation software (Direct Path, Olympus, Japan); Additional: EBUS	
Zheng 2021[86]	China	Prospective; Follow-up: ≥12 months	126 / 126, peripheral lesions 35 / 35; Malignancies: 83%	No	Age: non-fluoroscopy group 61.4 (10.8); fluoroscopy group 63.6 (9.6); Male: 65%	Size: nonfluoroscopy group 26.3 (11.4); fluoroscopy group 29.0 (11.3); Type: solid: 97%; GGO: 0% (exclusion criterion); Bronchus sign: 92%	thin-layer chest CT imaging; workstation with VBN software (DirectPath; Olympus); Additional: EBUS, fluoroscopy (50% of patients)	
Cone beam CT (n=3)								
Casal 2018[87]	USA	Prospective; Follow-up: 6 months	20 / 20; Malignancies: NR	Unclear	Age: median (range): 70 (48–86); Male: 25%	Size: median (range): 21 (11–30); Type: solid: 65%; semi-solid: 30%; ground-glass: 5%; Bronchus sign: 60%	DynaCT; Initial navigation: Olympus BF-P190 (Olympus America Inc., Cypress, USA); Additional: r-EBUS, fluoroscopy	Histopathology; benign pathology was either confirmed surgically or clinically and radiographically (6-month follow-up)
Verhoeven 2021[21 22]	Netherlands	Prospective; Follow-up: 6 months	208 / 248; Malignancies: 74	No	Age: mean (range): 65 (36 to 85); Male: 55%	Size: median (range): 13 (5-65); Type: GGO: 7.1%; part solid: 15.1%; Bronchus sign: 61%	electromagnetic navigation guidance: Medtronic SuperDimension; CBCT: Philips Allura/Azurion, Best, The Netherlands or Siemens Zeego, Forcheim, Germany); Additional: r-EBUS, augmented fluoroscopy	Histopathology; follow-up CT-guided transthoracic needle aspiration, surgical biopsy, and/or decisive clinical follow-up of at least 6 months for benign pathology
Yu 2021[88]	Taiwan	Retrospective; Follow-up: NR	53 / NR; Malignancies: 53%	No	Age: mean (range): 64.6 (31-93); Male: 57%	Size: median (range): 2.8 (1.0-6.9); Type: solid: 86.8%; semisolid/GGO: 13.2%; Bronchus sign: 75.5%	Artis Zee; Siemens Healthcare GmbH, Forchheim, Germany; Additional: EBUS (GS), C-arm fluoroscopy	Histopathology (including bronchoscopic or other diagnostic procedures), microbiological results, or clinical follow-up (≥1 year after bronchoscopy)

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
Electromagnetic navigation bronchoscopy and cone beam CT (n=4)								
Kheir 2021[89]	USA	Retrospective; Follow-up: NA	62 / 62; Malignancies: 36%	Unclear	Age: ENB: 64.5 (7.3) ENB-CBCT: 67.7 (8.2); Male: ENB: 90% ENB-CBCT: 61%	Size: median (IQR): ENB: 21.5 (16-27); ENB-CBCT: 16 (12.6 – 25.5); Type: solid: ENB: 58.1%; ENB-CBCT: 61.3%; Bronchus sign: ENB: 41.9%; ENB-CBCT: 45.2%	iLogic 7.0 ENB platform (superDimension; Medtronic); Additional: r-EBUS, fluoroscopy	Histopathology
Pritchett 2018[90]	USA	Retrospective; Follow-up: 12 months	75 / 93; Malignancies: 71%	No	Age: 70 (9); Male: 52%	Size: median (range): 16.0 (7-55); Type: NR; Bronchus sign: 39%	CBCT: Allura Xper FD20; Philips; Electromagnetic navigation system: SuperDimension; Medtronic; Additional: augmented fluoroscopy	Histopathology; more invasive diagnostic procedure or CT follow-up for undeterminate lesions
Sobieszczyk 2018[91]	USA	Retrospective; Follow-up: NR	22 / 22; Malignancies: 63%	Unclear	Age: 69 (8.8) ; Male: 36%	Size: 21 (9.8); Type: NR; Bronchus sign: NR	SuperDimension navigation system 6.0 (Medtronic; Inc.); Additional: r-EBUS, fluoroscopy	Not specified
Verhoeven 2020[92]	Netherlands	Prospective; Follow-up: ≥12 months	87 / 59 Malignancies: EMN 73%, CBCT+AF 83%	No	Age: mean/median (range): EMN: 65 (44-81), CBCT+AF: 65 (41-85); Male: EMN: 50%, CBCT+AF: 34%;	Size: mean (range?): EMN: 14.2 (7-48); CBCT and AF: 16.6 (5-43); Type: NR; Bronchus sign: EMN: 71%; CBT+AF: 63%	Primary EMN-based workflow: Medtronic's SuperDimension EMN system (version 7.0; Medtronic, Minneapolis, MN) in combination with Siemens Artis Zeego CBCT system (Siemens Healthineers, Forchheim, Germany) Primary CBCT-based workflow: Philips Allura Clarity FD20 scanner (Philips, Best, The Netherlands);; Additional: r-EBUS; augmented fluoroscopy	Histopathology; follow-up CT-guided transthoracic needle aspiration, surgical biopsy, and/or decisive clinical follow-up of at least 12 months for benign pathology

Reference	Country	Study design and duration of follow-up	Sample size (patients/ lesions) and % malignancy	Conventional bronchoscopy feasible?	Age (yrs; mean (SD) unless stated otherwise) & % male	Lesion size (mm; mean (SD) unless stated otherwise), type, and % Bronchus sign	Indextest specification & additional guidance techniques	Reference standard
Electromagnetic navigation bronchoscopy and virtual bronchoscopy CT (n=3)								
Karnak 2013[93]	Turkey	Prospective; Follow-up: ≥2 years	35 / 35; Malignancies: 56%	No	Age: 55.4 (13.60); Male: 65%	Size: 23.11 (9.42); Type: NR; Bronchus sign: NR	NR; Additional: none	Histopathology; follow-up
Ost 2016[94]	USA	Prospective; Follow-up: NR	Total 581 / 581; Malignancies: 46%	Unclear	Age: 67.1 (12.6); Male: 51%	Size: ≤20: 46.8% >20: 53,2%; Type: GGO: 4.6%; Bronchus sign: NR	NR; Additional (not in all patients): EBUS, fluoroscopy	Histopathology
Steinfort 2016[95]	Australia	Prospective; Follow-up: <12 months	236 / 245; Malignancies: 82%	Unclear	Age: 69; Male: 56%	Size: 22.8 (12.4); Type: NR; Bronchus sign: 23.2%	SuperDimension, Minneapolis, MN, USA; Additional: r-EBUS	Histopathology; subsequent invasive investigation (e.g. percutaneous or resectional biopsy) for nondiagnostic cases; and follow-up for benign etiology
Virtual bronchoscopy and cone beam CT (n=2)								
Ali 2019[96]	Japan	Prospective; Follow-up: 6 months	40 / 40; Malignancies: 63%	Unclear	Age: median (range): 75 (50–87); Male: 65%	Size: median (range): 20 (9–30); Type: solid: 70%, mixed GGO: 30%; Bronchus sign: Type A (bronchus leading to the center of the lesion): 80%, Type B (leading to the periphery of the lesion): 20%	Bf-Navi (Olympus, Tokyo, Japan) based 1-mm-thickness multidetector CT; Additional: none	Histopathology; follow-up
Kawakita 2021[97]	Japan	Retrospective; Follow-up: >6 months	CT-guided 93 / 93; CBCT 79 /79; Malignancies: CT: 70%; CBCT: 67%	Unclear	Age: median (IQR): CT-guided: 70 (62–76.5) CBCT: 73 (65–80); Male: CT-guided 55%; CBCT 60%	Size: median (IQR): CT-guided: 19 (15–23.5); CBCT: 21 (17–24); Type: CT-guided vs. CBCT groups: partially solid: 23.7% vs. 30.4%; solid 76.3% vs. 69.6%; Bronchus sign: 100% (inclusion criterion)	VBN: Bf-navi; Olympus, or SYNAPS VINCENT; Fujifilm Medical, Tokyo, Japan CBCT: Artis Zeego, Siemens; Additional: fluoroscopy	Histopathology; CT follow-up

Tabel 7 Kans op vertekening en *applicability concerns* voor onderzoeken naar de diagnostische accuratesse van navigatiebronchoscopie bij verdenking op longkanker bij mensen met perifere longnoduli bij wie conventionele bronchoscopie niet mogelijk was (n=69 onderzoeken)

Reference	Risk of Bias					Applicability concerns	
	Patient selection	Index test	Reference standard	Flow and timing		Patient selection	Index test
				Yield / Accurate diagnoses	Compli-cations		
Electromagnetic navigation bronchoscopy (n=28)							
Al-Jaghbeer 2016[31]	High	Low	Low	Low	Unclear	Low	Low
Bellinger 2021[32]	Unlcear	Unclear	Low	low	Unclear	Low	Unclear
Bertoletti 2009[33]	Low	Low	Low	Low	Unclear	Low	Low
Bowling 2017[34]	Low	Unclear	Low	Unclear	Unclear	Low	Unclear
Bowling 2015[35]	High	Low	Low	Unclear	Unclear	Low	Low
Chee 2013[36]	Unclear	Low	Low	Low	Unclear	Low	Low
Eberhardt 2007a[37]	Unclear	Low	Low	Low	Low	Low	Low
Eberhardt 2007b[38]	Low	Low	Low	Low	Low	Low	Low
Eberhardt 2010a[39]	Unclear	Low	Low	Low	Low	Low	Low
Flenaugh 2016[40]	Low	Low	Low	Low	Unclear	Low	Low
Garwood 2016[41]	Low	Low	Low	Low	Low	Low	Low
Gildea 2006[42]	Low	Low	Low	High	Unclear	Low	Low
Gu 2017[43]	Low	Low	Low	Low	Unclear	Low	Low
Hautmann 2005[44]	Unclear	Low	Low	High	Unclear	Low	Low
Jensen 2012[45]	Unclear	Low	Low	Low	Low	Low	Low
Lamprecht 2012[46]	Low	Low	Low	Low	Low	Low	Low
Loo 2014[47]	High	Low	Low	Unclear	Low	Low	Low
Ma 2020[48]	High	Low	Low	High	Unclear	Low	Low
Makris 2007[49]	Low	Low	Low	Low	Low	Low	Low
Mukherjee 2017[50]	Low	Low	Low	Low	Unclear	Low	Low
Odronic 2014[51]	High	Low	Low	Low	NA	High	Low
Patrucco 2018[52]	Low	Low	Low	Unclear	Unclear	Low	Low
Raval 2016[53]	Low	Low	Low	Low	Low	Low	Low
Sato 2018[54]	Low	Low	Unclear	High	Unclear	Low	Low
Stenger 2020[55]	Unclear	Low	Low	Low	Unclear	Low	Low
Sun 2017[56]	High	Low	Low	Low	Unclear	High	Low

Reference	Risk of Bias					Applicability concerns	
	Patient selection	Index test	Reference standard	Flow and timing		Patient selection	Index test
				Yield / Accurate diagnoses	Compli-cations		
Taton 2018[57]	Low	Low	Low	High	Unclear	Low	Low
Wang 2021[58]	Low	Low	Low	Low	Unclear	Low	Low
Virtual bronchoscopy (n=29)							
Asahina 2005[59]	Unclear	Low	Low	Low	Unclear	Low	Low
Asano 2015[63]*	High	Low	Low	Low	Unclear	High	Low
Asano 2006[60]	High	Low	Low	Low	Unclear	High	Low
Asano 2008[61]	Unclear	Low	Low	Unclear	Unclear	Unclear	Low
Asano 2013[62]	High	Low	Low	Low	Unclear	High	Low
Bae 2020[64]	High	Low	Low	Unclear	Unclear	Low	Low
Bo 2019[65]	Unclear	Low	Low	Low	Unclear	Low	Low
Diez-Ferrer 2019[66]	Low	Low	Unclear	Unclear	NA	Low	Low
Eberhardt 2010b[67]	High	Low	Low	Unclear	Unclear	High	Low
Fukusumi 2016[68]	High	Low	Low	Unclear	Unclear	High	Low
Haidong 2017[69]	High	Low	Low	Unclear	Unclear	Low	Unclear
Ikezawa 2017[70]	High	Low	Low	Unclear	Unclear	High	Low
Ishida 2011[71]	High	Low	Low	Low	Unclear	High	Low
Iwano 2011[72]	Low	Low	NA	Unclear	NA	Low	Low
Kato 2018[73]	Low	Low	Low	Unclear	Unclear	Low	Low
Li 2020[74]	High	Low	Low	Low	Unclear	High	Low
Maekura 2017[75]	High	Low	Low	High	Unclear	Low	Low
Matsumoto 2017[76]	Low	Unclear	Low	Unclear	Low	Low	Unclear
Miyoshi 2018[77]	Low	Low	Low	Low	NA	Low	Low
Oki 2019[79]	High	Low	Low	Low	Unclear	High	Unclear
Oki 2015[78]	Low	Low	Low	Low	Low	Low	Low
Oshige 2011[80]	Low	Low	Low	Low	Unclear	Low	Low
Shinagawa 2007[18-20]	High	Low	Unclear	Unclear	NA	Low	Low
Tachihara 2017[81]	Low	Low	Low	Low	Unclear	Low	Low
Tamiya 2013[82]	Low	Low	Low	Unclear	NA	Low	Low
Wong 2014[83]	Low	Low	Low	Low	Unclear	Low	Low
Xu 2019[84]	Low	Low	Low	High	Unclear	Low	Low

Reference	Risk of Bias					Applicability concerns	
	Patient selection	Index test	Reference standard	Flow and timing		Patient selection	Index test
				Yield / Accurate diagnoses	Compli-cations		
Zhang 2020[85]	High	Low	Low	Low	Unclear	Low	Low
Zheng 2021[86]	Unclear	Low	Low	Low	Unclear	Low	Low
Cone beam CT (n=2)							
Casal 2018[87]	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
Verhoeven 2021[21 22]	Low	Low	Low	High	NA	Low	Low
Yu 2021[88]	Unclear	Low	Low	Low	Unclear	Low	Low
Electromagnetic navigation bronchoscopy and cone beam CT (n=4)							
Kheir 2021[89]	High	Unclear	Low	Low	Unclear	Low	Unclear
Pritchett 2018[90]	Unclear	Low	Low	Low	Unclear	Low	Low
Sobieszczyk 2018[91]	High	Low	Unclear	High	Low	Low	Low
Verhoeven 2020[92]	Unclear	Low	Low	Low	Unclear	Low	Low
Electromagnetic navigation bronchoscopy and virtual bronchoscopy (n=3)							
Karnak 2013[93]	Low	Low	Low	Low	Unclear	Low	Low
Ost 2016[94]	Low	Low	Low	High	Unclear	Low	Low
Steinfort 2016[95]	Unclear	Low	Low	High	NA	Low	Low
Virtual bronchoscopy and cone beam CT (n=2)							
Ali 2019[96]	High	Low	Low	Low	Unclear	Low	Low
Kawakita 2021[97]	High	Low	Low	Unclear	Unclear	Low	Low

NA: not applicable

*Subpopulatie van onderzoek Ishida 2011[71], identieke QUADAS-2 beoordeling

4.3.2 Resultaten

In deze paragraaf worden de resultaten gepresenteerd voor de uitkomsten diagnostische opbrengst en percentage accurate diagnoses en vervolgens voor de uitkomst complicaties. Per uitkomst rapporteren we de resultaten voor onderzoeken naar elektromagnetische navigatiebronchoscopie, virtuele bronchoscopie, cone beam CT en onderzoeken die meer dan één navigatiebronchoscopietechniek evalueerden. Voor de uitkomsten diagnostische opbrengst en percentage accurate diagnoses geven we ook het overall resultaat weer.

De resultaten uit de afzonderlijke onderzoeken op basis waarvan de diagnostische opbrengst en het percentageaccurate diagnoses werden berekend, staan in Bijlage 6A. De complicaties zoals die werden gerapporteerd door de afzonderlijke onderzoeken, zijn terug te vinden in Bijlage 6B. De samengevatte resultaten voor de uitkomsten diagnostische opbrengst en percentage accurate diagnoses, inclusief de subgroepen, worden gepresenteerd in Bijlage 7B. Bijlage 8B geeft overkoepelende evidenceprofielen

voor de uitkomsten navigatiesucces, diagnostische opbrengst, percentage accurate diagnoses, sensitiviteit en de complicaties bloedingen en pneumothorax. Voor percentage accurate diagnoses en sensitiviteit wordt daarbij een GRADE level of certainty weergegeven.

Diagnostische opbrengst en percentage accurate diagnoses

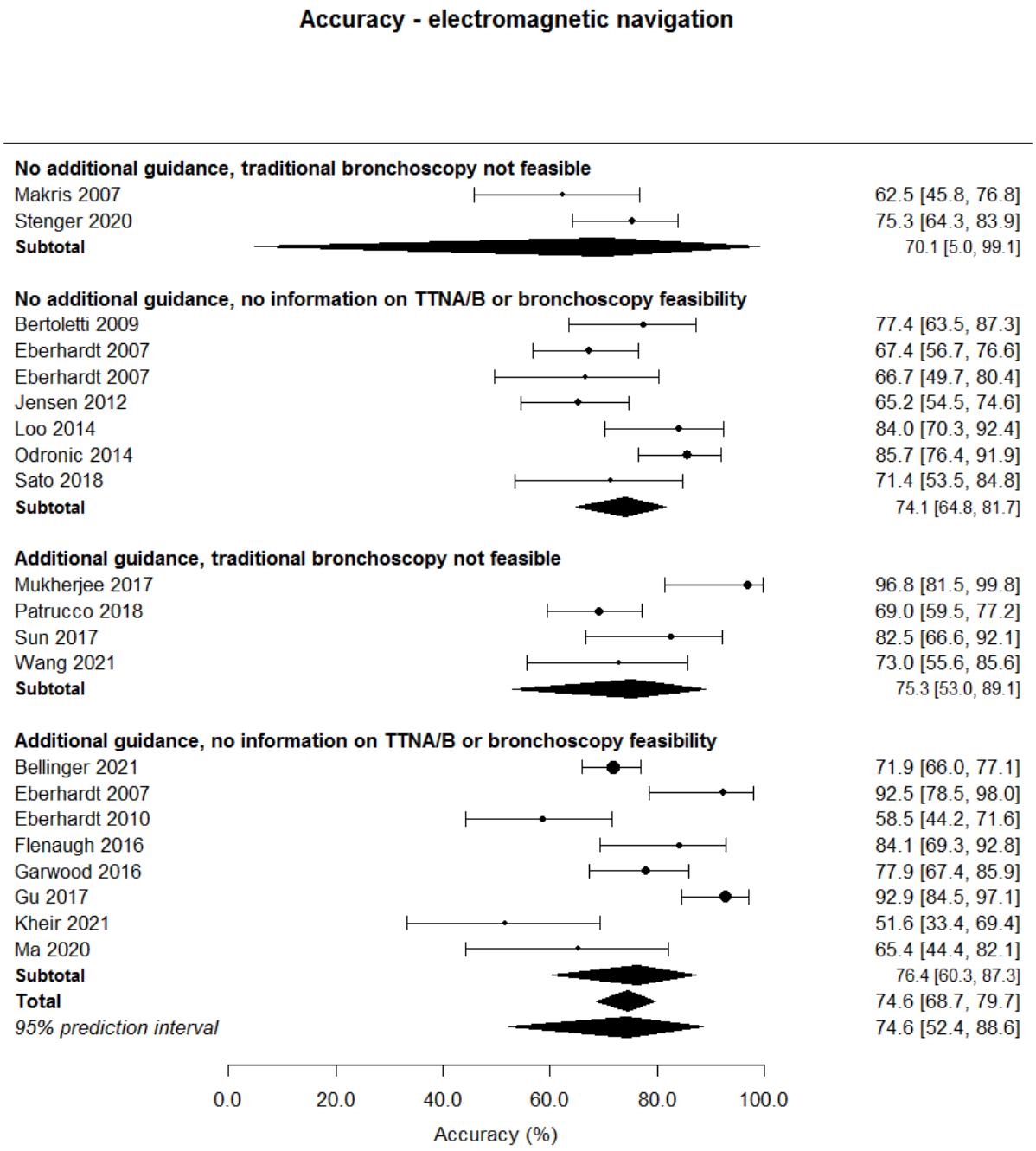
Van de 69 ingesloten onderzoeken rapporteerden er 37 (2903 lesies) hoe vaak een lesie werd bereikt. Dat was in 100% van de gevallen (mediaan; IQR 92,1% tot 100%). Tweeënzestig onderzoeken (4788 lesies) vermeldden voor welk deel van de lesies een testuitslag werd verkregen en deze diagnostische opbrengst bedroeg 78,7% (mediaan; IQR 67,7% tot 89,8%). Het gepoolde percentage accurate diagnoses over 46 onderzoeken (3519 lesies) bedroeg 73,4% (95%-BI 69,9% tot 76,6%; 95%-PI 53,3% tot 87,0%) en de gepoolde sensitiviteit (14 onderzoeken; 572 lesies) bedroeg 74,9% (95%-BI 64,6% tot 83,0%; 95%-PI 39,7% tot 93,1%). De voorspellende waarde van een negatieve testuitslag, gebaseerd op 12 onderzoeken (327 lesies), was 70,8% (mediaan; IQR 54,2% tot 83,5%). Zes hiervan volgden patiënten tenminste één jaar om na te gaan of een negatieve testuitslag daadwerkelijk negatief was en in deze zes onderzoeken (196 lesies) bedroeg de mediane voorspellende waarde van een negatieve testuitslag 70,1% (IQR 52,3% tot 83,3%).

De *certainty of the evidence* volgens GRADE voor de gepoolde uitkomsten werd ingeschat als *low* voor de uitkomst percentage accurate diagnoses en *very low* voor sensitiviteit, vanwege kans op vertekening, heterogeniteit en voor sensitiviteit ook imprecisie.

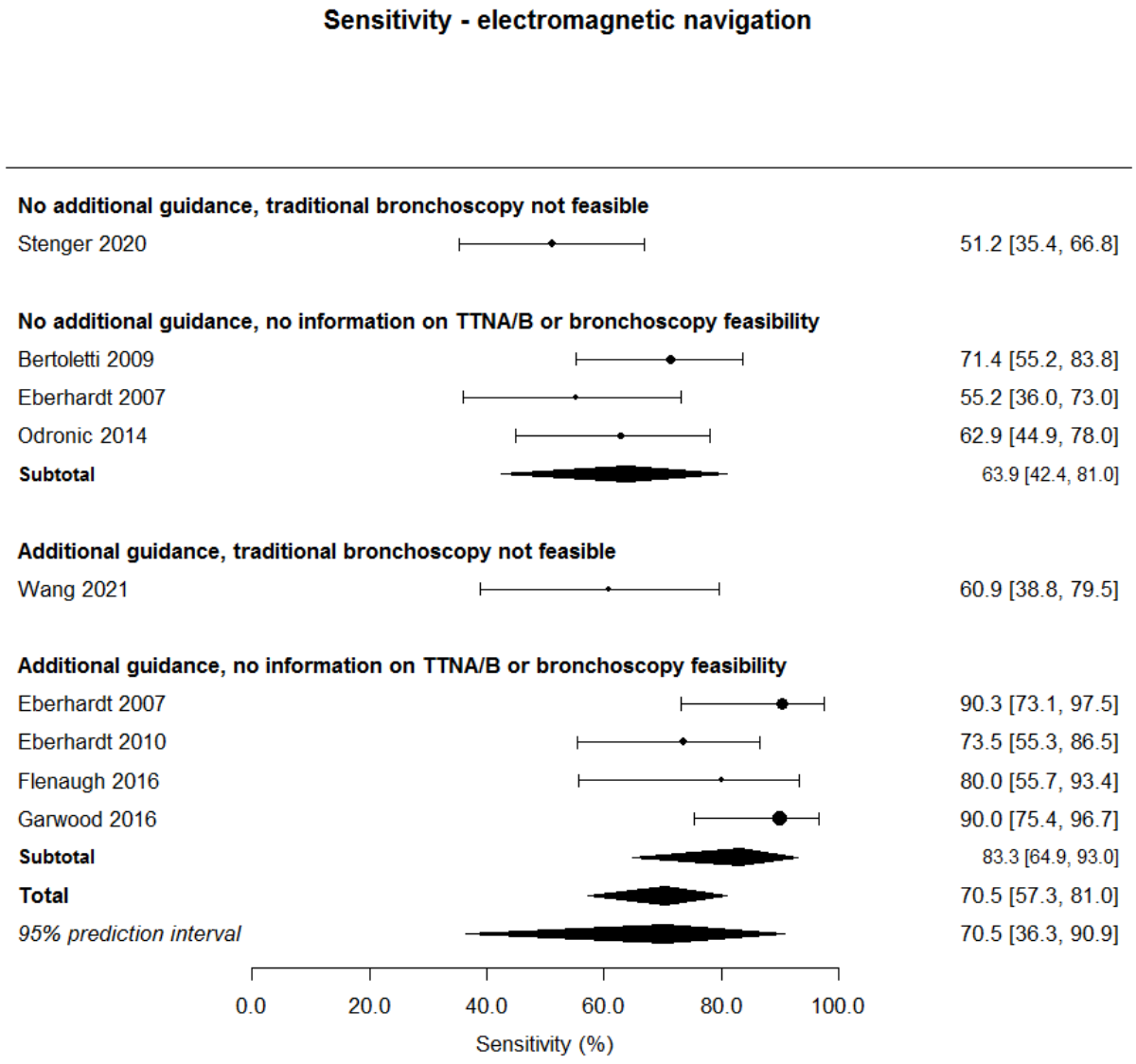
Elektromagnetische navigatiebronchoscopie

Zeventien onderzoeken (990 lesies) rapporteerden hoe vaak een lesie werd bereikt met behulp van elektromagnetische navigatie: het mediane navigatiesucces was 100% (IQR: 93,8% tot 100,0%). De mediane diagnostische opbrengst, berekend over 26 onderzoeken (1511 lesies), was 78,6% (IQR: 69,0% tot 96,7%). Het gepoolde percentage accurate diagnoses over 21 onderzoeken (1428 lesies) bedroeg 74,6% (95%-BI: 68,7% tot 79,7%) (Figuur 3) en de gepoolde sensitiviteit (9 onderzoeken; 295 lesies) 70,5% (95%-BI: 57,3% to 81,0%) (Figuur 4). De bijbehorende 95%-predictieintervallen liepen respectievelijk van 52,4% tot 88,6% en van 36,3 tot 90,9%. De resultaten van de subgroepen verschilden niet significant van elkaar.

De *certainty of the evidence* volgens GRADE werd ingeschat als *very low* voor het percentage accurate diagnoses vanwege de kans op vertekening, heterogeniteit en imprecisie, en als *low* voor de sensitiviteit, vanwege heterogeniteit en imprecisie. Kans op vertekening werd ook als beperkende factor aangemerkt voor de uitkomsten navigatiesucces en diagnostische opbrengst. Daarnaast was er sprake van heterogeniteit voor de uitkomst diagnostische opbrengst; deze liep uiteen van 34% tot 100%.



Figuur 3 Forest plot van het percentage accurate diagnoses ('*accuracy*') van elektromagnetische navigatiebronchoscopie (met of zonder de additionele inzet van EBUS en/of fluoroscopie) bij mensen met perifere longnoduli (met of zonder expliciete vermelding dat conventionele bronchoscopie niet mogelijk was).

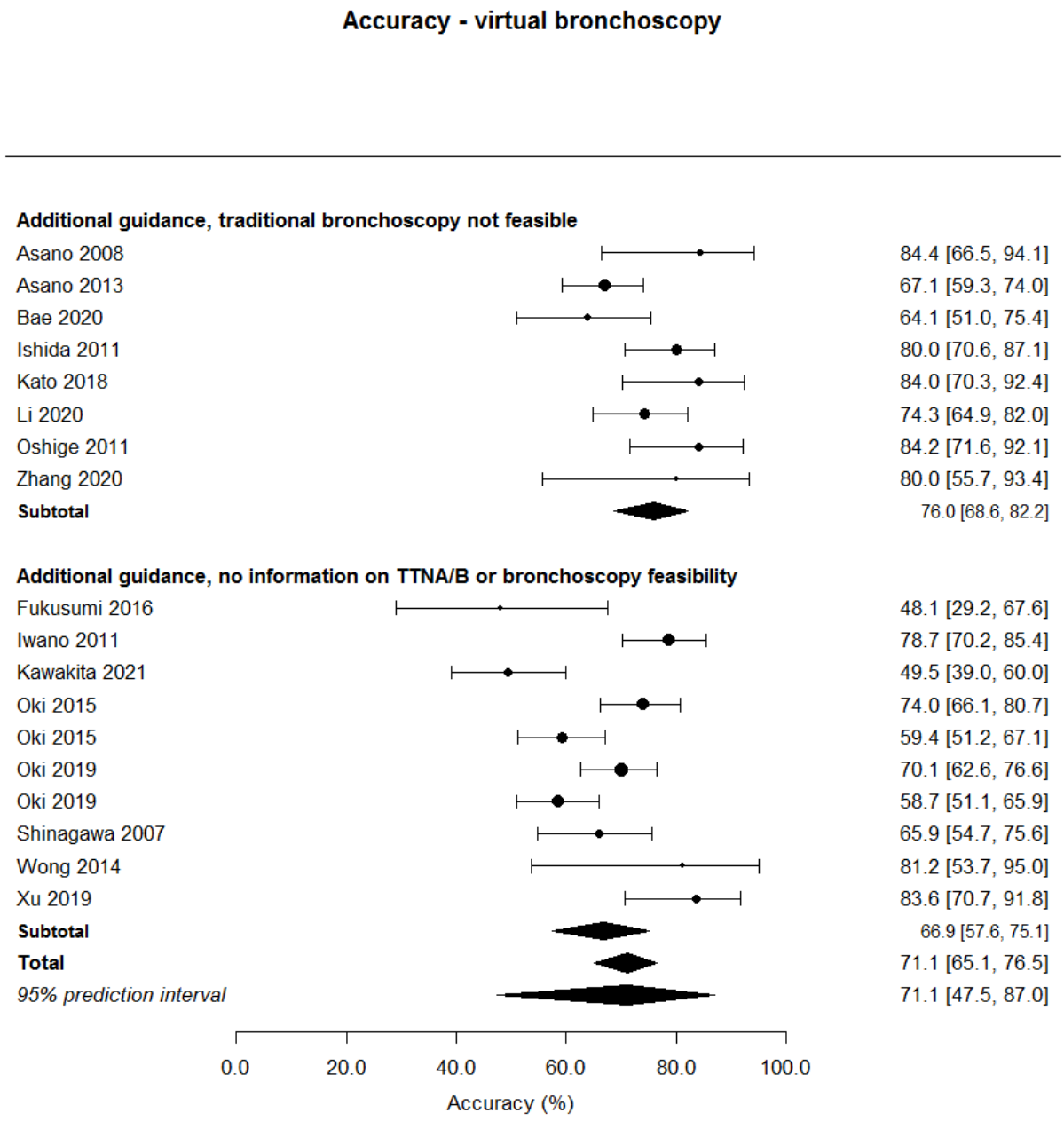


Figuur 4 Forest plot van de sensitiviteit van elektromagnetische navigatiebronchoscopie (met of zonder de additionele inzet van EBUS en/of fluoroscopie) voor het aantonen van maligniteit bij mensen met perifere longnoduli (met of zonder expliciete vermelding dat conventionele bronchoscopie niet mogelijk was).

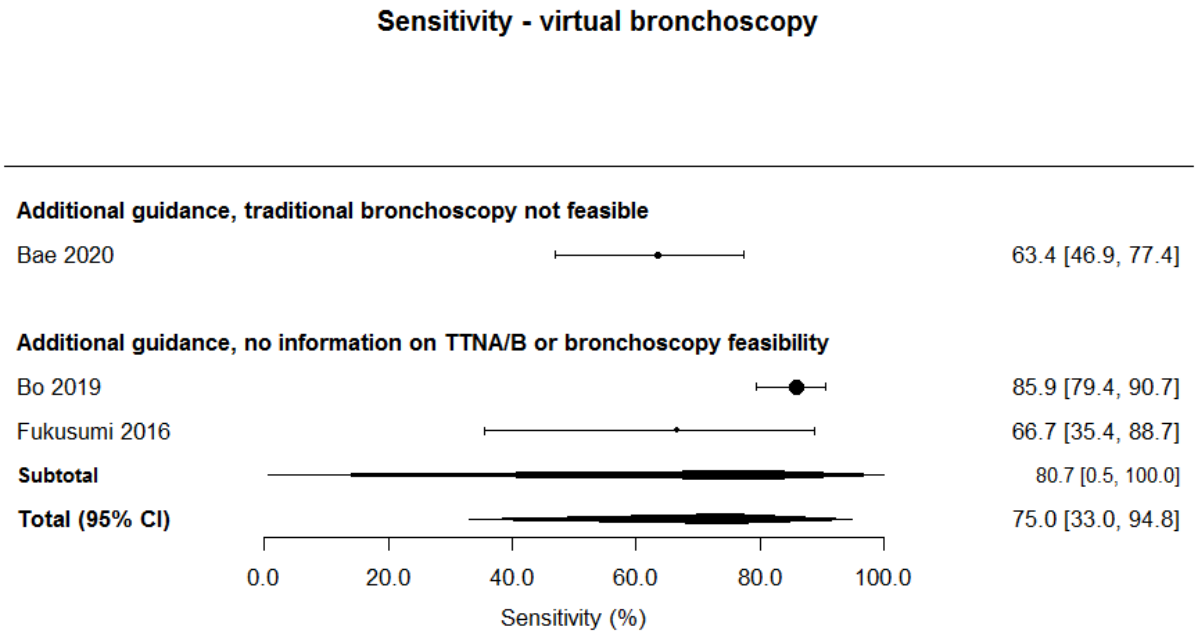
Virtuele bronchoscopie

Zeventien onderzoeken (1420 onderzochte lesies) rapporteerden hoe vaak een lesie werd bereikt met behulp van virtuele bronchoscopie: het mediane navigatiesucces was 94,7% (IQR: 92,3% tot 100,0%). De mediane diagnostische opbrengst, berekend over 27 onderzoeken (2424 lesies), was 77,8% (IQR: 67,9% tot 84,1%). Het gepoolde percentage accurate diagnoses over 18 onderzoeken (1658 lesies) bedroeg 71,1% (95%-BI: 65,1% tot 76,5%) (Figuur 5) en de gepoolde sensitiviteit (3 onderzoeken; 216 lesies) 75,0% (95%-BI: 33,0% to 94,8%) (Figuur 6). De bijbehorende 95%-predictieintervallen liepen respectievelijk van 47,5% tot 87,0% en van 0% tot 100%. De resultaten van de subgroepen verschilden niet significant van elkaar.

De *certainty of the evidence* volgens GRADE werd ingeschat als *very low* voor zowel de uitkomst percentage accurate diagnoses als voor de sensitiviteit. Voor het percentage accurate diagnoses was dit vanwege de kans op vertekening, indirectheid en heterogeniteit, en voor de sensitiviteit vanwege kans op vertekening, heterogeniteit en imprecisie. Er was ook kans op vertekening voor de uitkomsten navigatiesucces en diagnostische opbrengst.



Figuur 5 Forest plot van het percentage accurate diagnoses ('*accuracy*')van virtuele navigatiebronchoscopie (met de additionele inzet van EBUS en/of fluoroscopie) bij mensen met perifere longnoduli (met of zonder expliciete vermelding dat conventionele bronchoscopie niet mogelijk was).

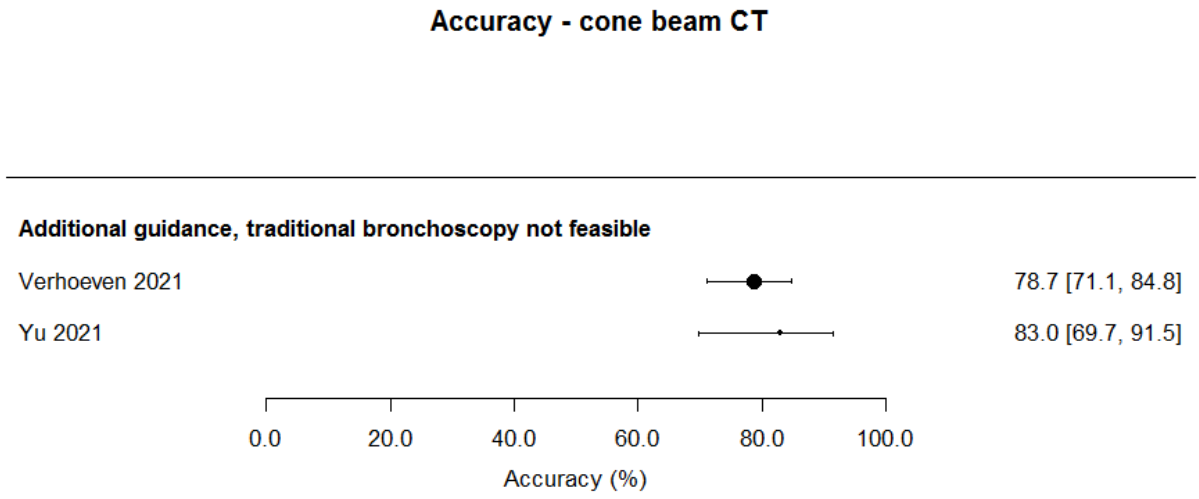


Figuur 6 Forest plot van de sensitiviteit van virtuele navigatiebronchoscopie (met de additionele inzet van EBUS en/of fluoroscopie) voor het aantonen van maligniteit bij mensen met perifere longnoduli (met of zonder expliciete vermelding dat conventionele bronchoscopie niet mogelijk was).

Cone beam CT

In één onderzoek over cone beam CT (150 onderzochte lesies) werd navigatiesucces gerapporteerd.[21] Deze bedroeg 95,3% (95%-BI 90,3% tot 97,9%). Diagnostische opbrengst werd gerapporteerd in twee onderzoeken (73 lesies) en deze was 78,4% (mediaan; IQR 74,2 tot 82,6%).[87 88] Het percentage accurate diagnoses werd beschreven in twee onderzoeken (203 lesies) en bedroeg 78,7% (95%-BI: 71,1% tot 84,8%) en 83,0% (95%-BI 69,7% tot 91,5%) (Figuur 5).[21 88] De sensitiviteit in één onderzoek (39 lesies) bedroeg 94,4% (95%-BI 80,0% to 99,0%).[88]

Certainty of the evidence volgens GRADE werd ingeschat op *low* voor zowel de uitkomst percentage accurate diagnoses als voor sensitiviteit, vanwege kans op vertekening en imprecisie. Voor de uitkomst diagnostische opbrengst was er ook kans op vertekening.



Figuur 7 Forest plot van het percentage accurate diagnoses ('*accuracy*') van cone beam CT (met de additionele inzet van EBUS en/of fluoroscopie) bij mensen met perifere longnoduli (met expliciete vermelding dat conventionele bronchoscopie niet mogelijk was).

Combinatie van navigatiebronchoscopietechnieken

Van de drie onderzoeken die elektromagnetische navigatie en virtuele bronchoscopie combineerden, presenteerde er één (57 lesies) resultaten voor navigatiesucces en dit bedroeg 76,7% (95%-BI 70,8% tot 81,8%).[95] De drie onderzoeken rapporteerden uiteenlopende resultaten voor diagnostische opbrengst: 91,4% (95%-BI 75,8% tot 97,8%),[93] 45,9% (95%-BI 39,8% tot 52,1%)[94] en 58,4% (95%-BI 51,9% tot 64,6%).[95] Sensitiviteit en percentage accurate diagnoses werden door geen van de onderzoeken beschreven.

Eén van de vier onderzoeken die elektromagnetische navigatie en cone beam CT combineerden, presenteerde een succesvolle navigaties in 84,5% (95%-BI 72,1% tot 92,2%) van de lesies.[21] Diagnostische opbrengst werd door twee onderzoeken gerapporteerd en was 82,8% (95%-BI 73,3 tot 89,6%) in het onderzoek van Pritchett[90] en 77,3% (54,2% tot 91,3%) in het onderzoek van Sobieszczyk.[91] Drie van de vier onderzoeken vonden de volgende percentages accurate diagnoses: 77,3% (95%-BI 54,2% tot 91,3%),[91] 70,7% (95%-BI 57,1% tot 81,5%)[21] en 74,2% (95%-BI 55,1% tot 87,5%)[89] (GRADE: *low certainty of evidence*). Geen van de vier onderzoeken presenteerde resultaten voor sensitiviteit.

Twee onderzoeken combineerden virtuele bronchoscopie met cone beam CT.[96 97] Eén daarvan beschreef resultaten voor navigatiesucces en dat was 100,0% (95%-BI 89,1% tot 100,0%).[96] De resultaten voor diagnostische opbrengst in beide onderzoeken liepen uiteen: 95,0% (95%-BI 81,8% tot 99,1%)[96] versus 65,8% (95%-BI 54,2% tot 75,9%).[97] Een vergelijkbaar verschil werd gezien voor het percentage accurate diagnoses: 90,0% (95%-BI 75,4% tot 96,7%)[96] versus 65,8% (95%-BI 54,2% tot 75,9%)[97] (GRADE: *very low certainty of evidence*). Sensitiviteit, gemeten in één van de onderzoeken, bedroeg 92,0% (95%-BI 72,5% to 98,6%)(GRADE: *low certainty of evidence*).

Complicaties

Elektromagnetische navigatiebronchoscopie

In Tabel 8 staat een overzicht van de door de onderzoeken gerapporteerde complicaties die optraden tijdens of na elektromagnetische navigatiebronchoscopie. Bloedingen en pneumothorax zijn de complicaties die door het grootste aantal studies werden gerapporteerd. Met uitzondering van één onderzoek dat bij 32 deelnemers incidenties van 13% en 34% rapporteerde voor 'Grade 2'- en 'Grade 1'-bloedingen,[57] lagen de mediane incidenties van bloedingen op 4% of lager. Ernstige bloedingen kwamen bij 0,4% of minder van de uitgevoerde procedures voor. Voor hemoptysis lagen de (mediane) incidenties tussen de 1% en 5%. Een pneumothorax trad op bij 3% van de procedures (mediaan; range 0%-8%; 21 onderzoeken). Eenzelfde mediane incidentie was er in zeven onderzoeken die pneumothoraxen waarvoor een interventie nodig was, rapporteerden. Vier onderzoeken keken naar pneumothoraxen waarvoor geen interventie nodig was en de mediane incidentie daarvan was 2%.

Tabel 8 Incidentie van gerapporteerde complicaties tijdens of volgend op elektromagnetische navigatiebronchoscopie bij mensen met perifere longnoduli.

Complication*	Incidence, median (range)	Number of participants	Number of studies
Bleeding			
Not specified / any	1% (0%-1%)	210	3[43 45 56]
Major bleeding	0%	31	1[50]
Moderate to severe bleeding	0,4%	270	1[32]
Grade 2 bleeding	13%	32	1[57]
Grade 1 bleeding	34%	32	1[57]
Minor bleeding	4%	90	1[41]
Hemoptysis			
Not specified / any	2% (0%-4%)	139	2[48 52]
Needing emergency department visit	1%	270	1[32]
Insignificant	5%	56	1[42]
Pneumothorax			
Not defined	3% (0%-8%)	1513	20[31 32 35-38 40 43 45-48 50-53 55 56 58 89]
Pneumothorax requiring intervention	3% (2%-6%)	342	7[33 41 42 49 54 57]
Pneumothorax not requiring intervention	2% (1%-5%)	237	4[33 39 41 49]
Death**	2% (1%-4%)	200	3[39 41 42]
Respiratory failure	0.2% (0%-1%)	745	3[37 90 94]
Fever	4% (3% to 5%)	91	2[42 54]
Chest pain	9%	56	1[42]
Emesis	7%	56	1[42]
Bradycardia, symptomatic	1%	107	1[35]
Bronchospasm or hypoxia requiring admission	2%	270	1[32]
Pneumonia or COPD exacerbation <1 week	1%	270	1[32]
Sore throat	13%	56	1[42]
Reintubation following general anesthesia	1%	107	1[35]
Perforated extended working channel	1%	89	1[37]
Repeat biopsy	2%	132	2[40 51]
Hospitalization	0%	92	1[45]

Complications			
Not specified	0%	16	1[44]
Other than pneumonia	0%	48	1[53]
Without admission	1%	270	1[32]

*As reported by the study. Not reported does not exclude the occurence nor the absence of complications.
** Of these reported deaths the majority was apparently not procedure-related. In one study 1 of 57 participants died during follow-up, no cause of death provided;[42] in another study 1 of 90 participants died before final diagnosis (cause of death not provided);[41] in the third study 2 of 53 participants died, of which one due to respiratory failure after surgery, the other as a result of B-cell lymphona of the colon.[39]

Virtuele bronchoscopie

Drie onderzoeken meldden dat er geen (ernstige) complicaties waren opgetreden tijdens of na navigatiebronchocopie.[60 61 71 83] De complicaties die door de overige onderzoeken gerapporteerd werden, staan in Tabel 9. De incidentie van bloedingen was 4% of lager, met uitzondering van één onderzoek dat een incidentie vond van 12% voor matige bloedingen gerelateerd aan virtuele navigatiebronchoscopie.[73] Een milde hemoptysis kwam in het onderzoek van Li[74] in bij 61% van de procedures voor, terwijl niet nader gespecificeerde hemoptysis over twee onderzoeken een mediane incidentie had van 1%.[69 85] De incidentie van pneumothorax was vergelijkbaar, met mediane waarden van 1% (niet nader gespecificeerde pneumothorax [9 onderzoeken] en pneumothorax waarvoor interventie nodig was [1 onderzoek]) of 2% (pneumothorax waarvoor geen interventie nodig was; 6 onderzoeken). De (mediane) incidentie van de overige gerapporteerde complicaties was maximaal 1%. De manier van patiëntenselectie van de meerderheid van de onderzoeken en onduidelijkheid rondom de vastlegging van complicaties zorgen voor kans op vertekening.

Tabel 9 Incidentie van gerapporteerde complicaties tijdens of volgend op virtuele navigatiebronchoscopie bij mensen met perifere longnoduli.

Complication*	Incidence, median (range)	Number of participants	Number of studies
Bleeding			
Not specified / any	1% (0%-4%)	1436	9[62 65 74 75 78 79 86 98]
Major bleeding	0%	86	2[59 80]
Bleeding requiring interventional therapy	0%	334	1[65]
Moderate bleeding	12%	50	1[73]
Self-limiting bleeding	4%	25	1[67]
Blood-tinged sputum	0%	64	1[64]
Hemoptysis			
Not specified / any	1% (0%-2%)	114	2[69 85]
Mild, not requiring intervention	61%	109	1[74]
Pneumothorax			
Not specified	1% (0%-3%)	1752	13[18 59 65 69 70 74 76 78-80 84 85 97]
Pneumothorax requiring intervention	1%	334	1[65]
Pneumothorax not requiring intervention	2% (1%-4%)	568	6[62 64 67 71 79 81]
Death	0%	334	1[65]
Respiratory failure	0	93	1[97]

Complication*	Incidence, median (range)	Number of participants	Number of studies
Chest pain	0.3%	305	1[78]
Emesis	1%	179	1[79]
Heart			
Arrhythmia	0%	120	1[86]
Bradycardia, symptomatic	1%	167	1[62]
Myocardial infaction	1%	179	1[79]
Hypoxemia	0%	120	1[86]
Infections	0%	109	1[74]
Nausea	1%	179	1[79]
Lidocaine intoxication	0%	120	1[86]
Pneumonia	0% (0%-1%)	810	4[59 78 79 86]

*As reported by the study. Not reported does not exclude the occurence nor the absence of complications.

Cone beam CT

Van de drie onderzoeken naar de diagnostische accuratesse van cone beam CT bij mensen met perifere longnoduli werd het ontstaan van bloedingen door één onderzoek (53 deelnemers) gerapporteerd en de incidentie was 4%.[88] Beide onderzoeken keken naar het optreden van pneumothorax. In het ene onderzoek gebeurde dit bij geen van de 53 deelnemers[88] en bij het andere onderzoek bij 1 van de 20 deelnemers (incidentie 5%).[87] Onduidelijkheid in de manier van patiëntenselectie en onduidelijkheid rondom de vastlegging van complicaties zorgden voor kans op vertekening.

Combinatie van navigatiebronchoscopietechnieken

In

Tabel 10 staan de complicaties die vermeld werden door de onderzoeken die navigatiebronchoscopietechnieken combineerden. De incidentie van bloedingen was 0,2% (1 onderzoek, 581 deelnemers) en de (mediane) incidentie van pneumothorax 3% voor de combinatie van elektromagnetische navigatiebronchoscopie met virtuele bronchoscopie. Voor elektromagnetische navigatiebronchoscopie gecombineerd met cone beam CT waren de incidenties 0% voor bloedingen (3 onderzoeken, 184 deelnemers) en 4% voor het optreden van pneumothorax (4 onderzoeken, 215 deelnemers) en voor virtuele bronchoscopie gecombineerd met cone beam CT was de incidentie van pneumothorax 2% (2 onderzoeken, 119 deelnemers). Vanwege de patiëntenselectie en flow en timing in de onderzoeken, is er kans op vertekening van de resultaten.

Tabel 10 Incidentie van gerapporteerde complicaties tijdens of volgend op combinaties van navigatiebronchoscopietechnieken bij mensen met perifere longnoduli.

Complication*	Incidence, median (range)	Number of participants	Number of studies
Electromagnetic navigation bronchoscopy and/or virtual bronchoscopy			
Bleeding	0.2%	581	1[94]
Pneumothorax	3% (2%-4%)	675	2[93 94]
Respiratory failure	0.2%	581	1[94]
Hypoxemia (refractory)	0.2%	581	1[94]
Electromagnetic navigation bronchoscopy and cone beam CT			
Bleeding	0% (0%-1%)	184	3[90-92]

Complication*	Incidence, median (range)	Number of participants	Number of studies
Pneumothorax	4% (0%-6%)	215	4[89-92]
Respiratory failure	0%	75	1[90]
Fever, minor < 4 hours	1%	87	1[92]
Infections	0%	22	1[91]
COPD exacerbation	1%	87	1[92]
Virtual bronchoscopy and cone beam CT			
Pneumothorax	2% (1%-3%)	119	2[96 97]
Respiratory failure	0%	40	1[96]

*As reported by the study. Not reported does not exclude the occurence nor the absence of complications.

5. Conclusies

PICOT 1

- Er werden geen onderzoeken geïdentificeerd betreffende het klinisch nut van het inzetten van navigatiebronchoscopie (als *add-on* test) bij patiënten met perifere longnoduli met verdenking op longkanker waarbij het multidisciplinaire team inschat dat er geen biopt kan worden genomen middels conventionele bronchoscopie, transthoracale naaldaspiratie of transthoracale naaldbiopsie. Derhalve zijn er geen resultaten voor de volgende uitkomsten: percentage afname operaties/behandelingen uitgevoerd zonder pathologische uitslag, langetermijncomplicaties en kwaliteit van leven.
- Er werden diagnostische testaccuratesse onderzoeken geïdentificeerd voor elektromagnetische navigatiebronchoscopie en cone beam CT, maar niet betreffende virtuele bronchoscopie voor het aantonen van maligniteit bij patiënten met perifere longnoduli waarbij het multidisciplinaire team inschat dat er geen biopt kan worden genomen middels conventionele bronchoscopie, transthoracale naaldaspiratie of transthoracale naaldbiopsie.
- Bij navigatiebronscopie als *add-on* test:
    - is het mediane navigatiesucces 95% (IQR 94% tot 100%; 5 onderzoeken, 568 lesies).
      Met behulp van elektromagnetische navigatie wordt een lesie in 98% (mediaan; IQR 95% tot 100%) van de gevallen bereikt (4 onderzoeken, 535 lesies). Met behulp van cone beam CT wordt een lesie in 91% (mediaan; IQR 95% tot 98%) van de gevallen bereikt (1 onderzoek, 33 lesies; kans op (selectie)bias).
    - is de mediane diagnostische opbrengst 71% (IQR 68% tot 91%; 8 onderzoeken, 827 lesies; heterogeniteit)
      Met behulp van elektromagnetische navigatiebronchoscopie kan een testuitslag worden verkregen voor 72% (mediaan; IQR 68% tot 94%) van de onderzochte lesies (7 onderzoeken, 794 lesies; heterogeniteit). Het gebruik van cone beam CT levert voor 70% (mediaan; IQR 51% tot 84%) van de onderzochte lesies een testuitslag op (1 onderzoek, 33 lesies; kans op (selectie)bias).
    - zal met behulp van elektromagnetische navigatiebronchoscopie voor 70% (95%-BI 55% tot 81%) van de onderzochte lesies een correcte testuitslag worden verkregen (7 onderzoeken, 794 lesies; GRADE: low certainty of evidence). Er werden geen onderzoeken geïdentificeerd die het percentage accurate diagnoses na cone beam CT onderzochten.
    - zal bij het gebruik van elektromagnetische navigatiebronchoscopie 28% van de maligniteiten ten onrechte niet gediagnosticeerd worden (sensitiviteit 72%, 95%-BI 33% tot 93%; 3 onderzoeken, 198 lesies; GRADE: very low certainty of evidence). Er werden geen onderzoeken geïdentificeerd die de sensitiviteit van cone beam CT onderzochten.
    - bedraagt de mediane voorspellende waarde van een negatieve testuitslag 65% (IQR 61% tot 67%; 3 onderzoeken (alle naar elektromagnetische navigatie) met tenminste 1 jaar follow-up, 152 lesies).
- De (mediane) incidentie van bloedingen gerelateerd aan de navigatiebronchoscopieprocedure is ≤3% bij elektromagnetische navigatiebronchoscopie (4 onderzoeken, 498 deelnemers; kans op bias).

Eén onderzoek (100 deelnemers) rapporteerde een hogere incidentie van 9% specifiek voor het optreden van geringe bloedingen gerelateerd aan elektromagnetische navigatiebronchoscopie. Ernst van bloedingen werd niet in alle onderzoeken nader gespecificeerd.

- De (mediane) incidentie van pneumothorax gerelateerd aan de navigatiebronchoscopieprocedure is bij elektromagnetische navigatiebronchocopie 2% en voor zowel pneumothorax complicaties waarvoor een interventie nodig is als waarvoor dat niet het geval is, is de mediane incidentie 4% (7 onderzoeken, 800 deelnemers; kans op (selectie)bias). Bij cone beam CT trad bij 6% van de procedures een pneumothorax op (1 onderzoek, 33 deelnemers; kans op bias).

PICOT 2

- Er werden geen gepaarde accuratesse onderzoeken geïdentificeerd waarin de diagnostische testaccuratesse van navigatiebronchoscopie (als *replacement* test) direct (bij dezelfde populatie) werd vergeleken met die van transthoracale naaldaspiratie of transthoracale naaldbiopsie bij patiënten met perifere longnoduli met verdenking op longkanker waarbij het multidisciplinaire team inschat dat er geen biopt kan worden genomen middels traditionele bronchoscopie.
- Bij navigatiebronchoscopie als *replacement* test voor transthoracale naaldaspiratie of - naaldbiopsie:
    - is het mediane navigatiesucces 100% (IQR 92% tot 100%; 37 onderzoeken, 2943 lesies; kans op (selectie)bias, heterogeniteit).
      Met behulp van elektromagnetische navigatie wordt een lesie in alle (mediaan 100%, IQR 94% tot 100) gevallen bereikt (17 onderzoeken, 990 lesies; kans op (selectie)bias). Met behulp van virtuele bronchoscopie wordt een lesie in 95% (mediaan; IQR 92% tot 100%) van de gevallen bereikt (17 onderzoeken, 1420 lesies; kans op (selectie)bias, indirectheid). Met behulp van cone beam CT wordt een lesie in 95% (mediaan; 95%-BI 90% tot 98%) van de gevallen bereikt (1 onderzoek, 150 lesies). Elektromagnetische navigatie leidt i.c.m. virtuele bronchoscopie tot een navigatiesucces in 77% (mediaan; IQR 71% tot 82%; 1 onderzoek, 57 lesies; kans op (selectie)bias)) en i.c.m. cone beam CT tot 85% (mediaan; IQR 95%-BI 72% tot 92%; 1 onderzoek, 31 lesies) en virtuele bronchoscopie i.c.m. cone beam CT leidt tot een navigatiesucces van 100% (mediaan; 95%-BI 89% tot 100%; 1 onderzoek, 40 lesies; kans op (selectie)bias)).
    - is de mediane diagnostische opbrengst 79% (IQR 68% tot 90%; 62 onderzoeken, 4788 lesies; kans op (selectie)bias, heterogeniteit).
      Met behulp van elektromagnetische navigatiebronchoscopie kan een testuitslag worden verkregen voor 79% (mediaan; IQR 69% tot 97%) van de onderzochte lesies (26 onderzoeken, 1511 lesies; kans op (selectie)bias, heterogeniteit). Voor virtuele bronchoscopie is de diagnostische opbrengst 78% (mediaan; IQR 68% tot 84%; 27 onderzoeken, 2424 lesies; kans op (selectie)bias, heterogeniteit). Het gebruik van cone beam CT levert voor 78% (mediaan; IQR 74% tot 83%) van de onderzochte lesies een testuitslag op (2 onderzoeken, 73 lesies; kans op (selectie)bias). Elektromagnetische navigatie gecombineerd met virtuele bronchoscopie geeft een diagnostische opbrengst van 46% tot 91% (3 onderzoeken, 358 lesies; kans op (selectie)bias), heterogeniteit) en gecombineerd met cone beam CT 77% tot 83% (2 onderzoeken, 115 lesies; kans op (selectie)bias). Virtuele bronchoscopie i.c.m. cone beam CT geeft een diagnostische

opbrengst van 66% tot 95% (2 onderzoeken, 119 lesies; kans op (selectie)bias, heterogeniteit).

- is 73% van de diagnoses accuraat gesteld (95%-BI 70% tot 77%; 45 onderzoeken, 3519 lesies; GRADE: low certainty of evidence).
  Met behulp van elektromagnetische navigatiebronchoscopie zal voor 75% (95%-BI 69% tot 80%) van de onderzochte lesies een correcte testuitslag worden verkregen (21 onderzoeken, 1428 lesies; GRADE: very low certainty of evidence). Met behulp van virtuele bronchoscopie wordt voor 71% (95%-BI 65% tot 77%) van de onderzochte lesies een correcte testuitslag verkregen (18 onderzoeken, 1658 lesies; GRADE: very low certainty of evidence) en bij gebruik van cone beam CT voor 79% tot 83% (2 onderzoeken, 203 lesies; GRADE: low certainty of evidence). Bij de combinatie van elektromagnetische navigatie en conebeam CT ligt het percentage correcte diagnoses tusssen 71% en 77% (3 onderzoeken, 182 lesies; GRADE: low certainty of evidence) en bij de combinatie van virtuele bronchoscopie met cone beam CT 66% tot 90% (2 onderzoeken, 119 lesies; GRADE: very low certainty of evidence).
- is de sensitiviteit 75% (95%-BI 65% tot 83%; 14 onderzoeken, 572 lesies; GRADE: very low certainty of evidence).
  Bij het gebruik van elektromagnetische navigatiebronchoscopie wordt 29% van de maligniteiten ten onrechte niet gediagnosticeerd (sensitiviteit 71%, 95%-BI 57% tot 81%; 9 onderzoeken, 295 lesies; GRADE: low certainty of evidence). Bij gebruik van virtuele bronchoscopie betreft het 25% van de maligniteiten (sensitiviteit 75%, 95-BI 33% tot 95%; 3 onderzoeken, 216 lesies; GRADE: very low certainty of evidence) en bij gebruik van cone beam CT 6% (sensitiviteit 94%, 95%-BI 80% tot 99%; 1 onderzoek, 39 lesies; GRADE: low certainty of evidence. Bij virtuele bronchoscopie i.c.m. cone beam CT betreft het 8% van de maligniteiten (sensitiviteit 92%, 95%-BI 73% tot 99%; GRADE: low certainty of evidence).
- bedraagt de voorspellende waarde van een negatieve testuitslag 70% (mediaan; IQR 52% tot 83%; 6 onderzoeken (5 naar elektromagnetische bronchoscopie, 1 naar virtuele bronchoscopie) met tenminste 1 jaar follow-up, 196 lesies; kans op (selectie)bias, heterogeniteit).

- De (mediane) incidentie van bloedingen gerelateerd aan de navigatiebronchoscopieprocedure is ≤4% bij elektromagnetische navigatiebronchoscopie (8 onderzoeken, 633 deelnemers; kans op (selectie)bias), ≤2% bij virtuele bronchoscopie (13 onderzoeken, 1700 deelnemers; kans op (selectie)bias), 4% bij cone beam CT (1 onderzoek, 53 deelnemers; kans op (selectie)bias), 0,2% bij elektromagnetische navigatie i.c.m. virtuele bronchoscopie (1 onderzoek, 581 deelnemers; kans op (selectie)bias) en tussen 0% en 1% bij elektromagnetische navigatie i.c.m. cone beam CT (3 onderzoeken, 184 deelnemers; kans op (selectie)bias). Enkele onderzoeken rapporteerden een hogere incidentie: 13% tot 34% (elektromagnetische navigatie; 32 deelnemers) en 12% matige bloedingen (virtuele bronchoscopie; 50 deelnemers). Ernst van bloedingen werd overigens niet in alle onderzoeken nader gespecificeerd. De incidentie van specifiek gerapporteerde ernstige bloedingen lag op 0.4% of lager voor alle navigatiebronchoscopietechnieken. Voor hemoptysis lagen de (mediane) incidenties tussen de 1% en 5% (4 onderzoeken, 465 deelnemers).

- De (mediane) incidentie van pneumothorax complicaties gerelateerd aan de navigatiebronchoscopieprocedure is bij elektromagnetische navigatiebronchocopie 3%, met mediane incidenties van 3% en 2% van pneumothorax complicaties waarvoor respectievelijk wel of geen interventie nodig is (27 onderzoeken, 1873 deelnemers; kans op bias). Bij virtuele bronchoscopie ligt de mediane incidentie op 1%, en op 1% en 2% voor pneumothorax complicaties waarvoor respectievelijk wel of geen interventie nodig is (20 onderzoeken, 2320 deelnemers; kans op bias). Bij cone beam CT is de incidentie ≤5% (twee onderzoeken, waarvan in het ene onderzoek geen pneumothorax optrad en in het andere bij één van de 20 deelnemers). Bij elektromagnetische navigatie i.c.m. virtuele bronchoscopie is de incidentie van peumothorax 2% tot 4% (2 onderzoeken, 657 deelnemers; kans op (selectie)bias), bij elektromagnetische navigatie i.c.m. cone beam CT 0 tot 6% (4 onderzoeken, 215 deelnemers; kans op (selectie)bias) en bij virtuele bronchoscopie i.c.m. cone beam CT 1 tot 3% (2 onderzoeken, 119 deelnemers; kans op (selectie)bias).

6. Discussie

Het toevoegen van navigatiebronchoscopie aan het diagnostische pad voor patiënten met longnoduli verdacht van maligniteit wordt verondersteld te leiden tot minder onterechte behandelingen (operatie, stereotactische radiotherapie, chemotherapie, immuuntherapie). Aanvullend wordt geclaimd dat navigatiebronchoscopietechnieken weliswaar een lagere diagnostische accuratesse hebben dan transthoracale naaldaspiratie of transthoracale naaldbiopsie, maar minder invasief zijn en daardoor zullen leiden tot minder ernstige complicaties als gevolg van de testprocedure (met name pneumothorax en ernstige bloedingen).

Om te kunnen aantonen of deze veronderstellingen waar zijn, is idealiter informatie nodig uit vergelijkende (bij voorkeur gerandomiseerde) onderzoeken waarin de additionele inzet van navigatiebronchoscopietechnieken vergeleken wordt met de situatie waarin deze technieken niet worden ingezet en waarbij gekeken wordt naar gezondheidswinst voor de patiënt (klinisch nut). Daarnaast dient op basis van gepaarde diagnostische testaccuratesseonderzoeken een directe vergelijking gemaakt te worden tussen navigatiebronchoscopietechnieken en transthoracale procedures voor wat betreft de vergelijkbaarheid van de diagnostische accuratesse en het optreden van (ernstige) complicaties als gevolg van de testprocedure.

In opdracht van het Zorginstituut voerden wij een SR uit naar het klinisch nut en de diagnostische testaccuratesse van navigatiebronchoscopietechnieken bij patiënten met verdenking op longkanker. Daarbij richtten we ons op de volgende navigatiebronchoscopietechnieken: elektromagnetische navigatiebronchoscopie, virtuele bronchoscopie en cone beam CT. Onderzoeken naar robot CT navigatie vielen buiten het bestek van deze opdracht. De twee uitgangsvragen (PICOT's) voor de SR belichten elk een andere rol van navigatiebronchoscopie. Bij de eerste uitgangsvraag (PICOT 1) gaat het om de rol van navigatiebronchoscopie als *add-on* test, namelijk als extra mogelijkheid voor patiënten voor wie anders geen alternatief was behalve (chirurgische) behandeling. Bij de tweede uitgangsvraag (PICOT 2) heeft navigatiebronchoscopie de rol van *replacement* test, ter vervanging van transthoracale naaldaspiratie en – biopsie. Dit onderscheid komt ook tot uiting in de geïncludeerde onderzoekspopulaties voor beide uitgangsvragen. Voor PICOT 1 waren dat onderzoeken waarvoor expliciet vermeld werd dat zowel conventionele bronchoscopie als transthoracale procedures geen opties waren, en voor PICOT 2 werden onderzoeken geïncludeerd bij een populatie bij wie conventionele bronchoscopie niet mogelijk was. Deze onderzoeken voor PICOT 2 werden in de analyses verder onderverdeeld in een groep studies waarin expliciet werd vermeld dat conventionele bronchoscopie niet mogelijk was (n=23) en een groep studies die niets vermeldden over het wel of niet mogelijk zijn van conventionele bronchoscopie in de onderzochte patiëntengroep. Voor beide PICOT's werd in subgroepanalyses de additionele inzet van (r-)EBUS en/of fluoroscopie tijdens de navigatiebronchoscopieprocedure onderzocht.
Deze SR leverde echter niet de gewenste directe evidence op. Er werden 1) geen vergelijkende onderzoeken geïdentificeerd waarin het klinisch nut van navigatiebronchoscopie als *add-on* test geëvalueerd werd, en 2) ook werden geen gepaarde diagnostische testaccuratesseonderzoeken gevonden waarin navigatiebronchoscopie (als *replacement* test) direct vergeleken werd met transthoracale naaldaspiratie of transthoracale naaldbiopsie. Wel werden 77 onderzoeken geïncludeerd naar de diagnostische testaccuratesse van navigatiebronchoscopie voor verschillende indicatiegebieden

(PICOT 1: 8 onderzoeken, 833 deelnemers, en PICOT 2: 69 onderzoeken, 6669 deelnemers) bij patiënten met kleine (gemiddeld <3cm doorsnede), perifere longnoduli verdacht van longkanker. De resultaten hiervan kunnen slechts indirect gebruikt worden om te bepalen of de *add-on* test daadwerkelijk zal leiden tot minder onterechte behandelingen en tevens kunnen de resultaten voor de *replacement* test slechts indirect vergeleken worden met resultaten uit de wetenschappelijke literatuur over complicaties bij en accuratesse van alternatieve diagnostische strategieën voor deze patiëntengroep.

De geïncludeerde onderzoeken over navigatiebronchoscopie ingezet als *add-on* test (PICOT 1) bestudeerden elektromagnetische navigatiebronchoscopie en cone-beam CT. Onderzoeken over virtuele bronchoscopie ontbraken. Beide technieken bereikten een beoogde lesie in meer dan 90% van de gevallen (mediaan navigatiesucces) en de inzet ervan leidde tot een diagnose voor 70% (cone beam CT) tot 72% (elektromagnetische navigatie) van de beoogde lesies (mediane diagnostische opbrengst). De uitkomsten percentage accurate diagnoses (elke diagnose, inclusief longkanker) en sensitiviteit (voor uitsluitend aantonen van longkanker) werden alleen in onderzoeken betreffende elektromagnetische navigatiebronchoscopie onderzocht en deze waren respectievelijk 70% en 72%. De mediane voorspellende waarde van een negatieve testuitslag (o.b.v. elektromagnetische navigatie) was 65% (IQR 61% tot 67%).
In een hypothetische populatie van 1000 patiënten bij wie een vorm van navigatiebronchoscopie als *add-on* test wordt ingezet, zal bij een prevalentie van maligniteit van 65% (mediane prevalentie in geïncludeerde onderzoeken[99]) en een sensitiviteit van 72% (met een specificiteit van 100%; zie Methoden) niemand ten onrechte de diagnose longkanker krijgen (geen fout-positieven) en bij 182 patiënten met longkanker zou de diagnose gemist zijn (fout-negatieven).

Uit onderzoeken over navigatiebronchoscopie als *replacement* test (PICOT 2) bleek dat een beoogde lesie in 100% van de gevallen bereikt werd en voor 79% van de beoogde lesies tot een testuitslag leidde. De (gepoolde) testuitslag was correct (accurate diagnose) bij 73% van de beoogde lesies die onderzocht werden (71% van de beoogde lesies onderzocht met virtuele bronchoscopie, 75% van de beoogde lesies onderzocht met elektromagnetische navigatiebronchoscopie en 83% van de beoogde lesies onderzocht met cone beam CT). De (gepoolde) sensitiviteit van navigatiebronchoscopie bedroeg 75% (71% en 75% voor respectievelijk elektromagnetische navigatie en virtuele bronchoscopie, wat inhoudt dat 25% tot 29% van de maligne lesies onterecht niet worden gediagnosticeerd; voor cone beam CT werd, gebaseerd op één onderzoek, een sensitiviteit van 94% gevonden). De mediane voorspellende waarde van een negatieve testuitslag (o.b.v. elektromagnetische of virtuele navigatiebronchocopie) was 70% (IQR 52% tot 83%).
In een hypothetische populatie van 1000 patiënten bij wie een vorm van navigatiebronchoscopie als *replacement* test wordt ingezet, zal bij een prevalentie van maligniteit van 71% (mediane prevalentie in geïncludeerde onderzoeken) en een sensitiviteit van 75% (met een specificiteit van 100%; zie Methoden) niemand ten onrechte de diagnose longkanker krijgen (geen fout-positieven) en bij 177 patiënten met longkanker zou de diagnose gemist zijn (fout-negatieven).

Het optreden van (ernstige) bloedingen of ontstaan van (ernstige) pneumothorax complicaties in relatie tot navigatiebronchoscopie lijkt beperkt, met (mediane) incidenties van 5% of minder. Voor een

aanzienlijk deel van de onderzoeken werd de ernst van de betreffende complicatie overigens niet specifiek vermeld.

Ondanks de omvang van de evidence, is er onzekerheid omtrent de resultaten, met name vanwege het ontbreken van klinisch nut studies en directe vergelijkingen van testaccuratesse. Verder treedt in de geïncludeerde studies kans op vertekening (*bias*) op en is er sprake van heterogeniteit tussen de onderzoeken.
Indien deelnemers (mogelijk) niet opeenvolgend geselecteerd werden (geen consecutieve serie patiënten), dan geeft dat kans op vertekening. Er werden veelal (retrospectief) patiënten geselecteerd die navigatiebronchoscopie (hebben) ondergaan in een bepaalde periode, maar daarvóór heeft de eigenlijke selectie al plaatsgevonden. Kenmerken van patiënt en lesie bepalen namelijk de geschiktheid voor een navigatiebronchoscopieprocedure en het hangt samen met de ervaring en voorkeur van de longarts of er wel of niet voor navigatiebronchoscopie gekozen wordt. Mogelijk is de navigatiebronchoscopie niet aangeboden aan patiënten die wel voor de procedure in aanmerking kwamen. Het excluderen van ground glass opacities (GGO's) was ook een reden om een hoge kans op vertekening te scoren voor een onderzoek, omdat deze lesies relatief moeilijker te diagnosticeren zijn. Het weglaten van dergelijke lesies uit de onderzoekspopulatie zou tot overschatting van de testaccuratesse kunnen leiden. Een andere reden voor kans op vertekening (die valt onder het QUADAS 2-domein *Reference standard*) was een onvoldoende lange follow-up duur van negatieve testuitslagen (< 1 jaar), waardoor de uitkomsten diagnostische opbrengst, percentage accurate diagnoses en sensitiviteit mogelijk niet accuraat geschat konden worden (m.n. de onterechte negatieve testuitslagen). Specifiek met betrekking tot complicaties moet opgemerkt worden dat in de grote meerderheid van de onderzoeken onduidelijk was of er systematisch gezocht werd naar complicaties (bijvoorbeeld door frequente beeldvorming) of dat enkel complicaties met een klinische manifestatie genoteerd werden. Om die reden werd voor de uitkomst complicaties voor het QUADAS 2-domein *Flow and timing* de kans op vertekening vaak als onduidelijk gescoord. Het is aannemelijk dat ernstige complicaties die klinisch van belang zijn en een interventie behoeven, over het algemeen wel gerapporteerd zullen zijn, zonder dat er systematisch naar gezocht is. Bovendien kunnen complicaties bij gebruik van bepaalde technieken (bijvoorbeeld fluoroscopie) perprocedureel direct zichtbaar worden. Daarnaast kunnen ethische overwegingen (blootstelling aan straling) een rol spelen bij het al dan niet actief zoeken naar complicaties.
De heterogeniteit die gezien werd tussen de resultaten van de verschillende onderzoeken, is waarschijnlijk gebaseerd op specifieke kenmerken van zowel de populatie (selectiebias) als de indextest. Hoewel we de onderzoeken hebben gegroepeerd aan de hand van de (on)mogelijkheid voor het uitvoeren van conventionele bronchoscopie en transthoracale naaldaspiratie en –biopsie, zijn er veel meer specifieke kenmerken waarop een populatie kan verschillen tussen de onderzoeken, bijvoorbeeld leeftijd, prevalentie maligniteit en klinische setting. Ondanks het feit dat we subgroepanalyses per navigatiebronchoscopietechniek hebben uitgevoerd, zagen we nog steeds heterogeniteit in de resultaten tussen de onderzoeken. Ervaring van degene die de navigatiebronchoscopieprocedure uitvoert, is een mogelijke factor die tot deze heterogeniteit kan leiden. Verhoeven en collega's zagen dat de leercurve in het toepassen van cone beam CT gestuurde navigatiebronchoscopie significant van invloed was op de diagnostische accuratesse.[21] De additionele inzet van (r-)EBUS en/of fluoroscopie

leidde overigens niet tot significant andere effectschattingen dan wanneer deze technieken niet naast navigatiebronchoscopie werden ingezet, zo bleek uit onze subgroepanalyses.

De resultaten uit onze systematische review kunnen indirect vergeleken worden met resultaten uit de medisch wetenschappelijke literatuur over transthoracale naaldaspiratie en –biopsie. Bij patiënten met longnoduli wordt voor deze procedures een hogere diagnostische accuratesse gerapporteerd. Zo vond een recent SR over beeldvorming gestuurde percutane transthoracale naaldbiopsie voor subsolide longnoduli op basis van 12 geïncludeerde onderzoeken een gepoolde sensitiviteit van 90% (95%-BI: 85 tot 94%).[100] Een ander SR vermeldde een percentage accurate diagnoses voor percutane naaldbiopsie van 93% (95%-BI 90% tot 96%; 15 onderzoeken).[12] De resultaten in deze reviews zijn mogelijk overschat als gevolg van een retrospectieve onderzoeksopzet bij het merendeel van de onderzoeken (92% van de onderzoeken in de ene review (Kim 2021) en 67% in de andere (Han 2018). In onze SR had 44% van de ingesloten onderzoeken een retrospectieve onderzoeksopzet.
In SR's over thransthoracale naaldaspiratie en – biopsie wordt een hogere incidentie van complicaties gerapporteerd dan wij in onze review over navigatiebronchoscopie vonden. Twee SRs beschreven een gepoolde incidentie van het totale aantal complicaties en van het aantal ernstige complicaties en deze bedroeg bij beeldvorming gestuurde percutane transthoracale naaldbiopsie voor subsolide longnoduli 43% (95%-BI: 25% tot 62%; 12 onderzoeken),[100] bij CT-geleide transthoracale longbiopsieën (32 onderzoeken) en fijne naald aspiraties (17 onderzoeken) respectievelijk 39 % (95%-BI 34% tot 44%) en 24% (95%-BI 18% to 31%)[101]. De gepoolde incidenties voor ernstige complicaties lagen aanzienlijk lager en waren respectievelijk 0,1% (95%-BI 0% tot 0,4%;), 6% (95%-BI 4% tot 7%) en 4% (95%-BI 3% tot 7%). Twee andere SR's rapporteerden specifiek over het optreden van pneumothorax en meldden beide een gepoolde incidentie van 26% op basis van 36[102] en 15 onderzoeken[12]. De incidentie van ernstige pneumothorax waarvoor een thorax drain nodig is, was 3%[12] tot 7%[102]. In één van deze SR's werd tevens een gepoolde incidentie (9 onderzoeken) van bloedingen gerapporteerd en deze bedroeg 16% (95%-BI 10% tot 25%).[12] De gepoolde incidentie (8 onderzoeken) van hemoptysis was 7% (95%-BI 6% tot 8%).

Samenvattend levert onze SR geen direct vergelijkend bewijs op m.b.t. klinisch nut of testaccuratesse om de uitgangsvragen te kunnen beantwoorden. Wel werden 77 niet-gepaarde testaccuratesse onderzoeken geïdentificeerd, waarvan de resultaten indirect vergeleken kunnen worden met kennis uit de wetenschappelijke literatuur om de potentiële rol en plaats van navigatiebronchoscopie te bepalen. Vanwege kans op vertekening en heterogeniteit in deze 77 onderzoeken, is er onzekerheid over de resultaten (*GRADE (very) low certainty of evidence*).

De populatie waarin navigatiebronchoscopie als *add-on* test zou kunnen worden ingezet, is een groep patiënten bij wie het niet mogelijk is een biopt af te nemen via de standaard diagnostische technieken, en die daardoor als enige optie een behandeling zonder PA-uitslag hebben. In deze patiëntengroep kan door navigatiebronchoscopie bij 70% wel een accurate diagnose worden gesteld, waardoor een gerichtere behandelstrategie mogelijk is.

Wat betreft de inzet van navigatiebronchoscopie als *replacement* test, is op basis van een (niet-systematische) indirecte vergelijking met bestaande literatuur de gevonden accuratesse van navigatiebronchoscopie lager dan die van transthoracale naaldaspiratie en –biopsie. Daarnaast lijkt het

totale aantal gerapporteerde complicaties aanzienlijk lager voor navigatiebronchoscopie in vergelijking met transthoracale procedures. De incidentie van ernstige complicaties (bloeding of pneumothorax waarvoor een interventie nodig is) was relatief laag voor navigatiebronchoscopie. Echter ook voor transthoracale procedures is de incidentie van ernstige complicaties laag. De afweging is of een minder invasieve test met een lagere diagnostische accuratesse opweegt tegen een vergelijkbaar aantal ernstige complicaties.

Het onderhavige rapport geeft een overzicht van de beschikbare medisch-wetenschappelijke literatuur over klinisch nut en diagnostische accuratesse van elektromagnetische navigatiebronchoscopie, virtuele bronchoscopie en cone-beam CT en biedt het Zorginstituut Nederland de gevraagde informatie voor de beoordeling of navigatiebronchoscopietechnieken voldoen aan de stand van de wetenschap en praktijk. Daarbij dienen ook de ontwikkeling van nieuwe technieken (zoals Robot CT) in overweging te worden genomen.

Referenties

1. Callister MEJ, Baldwin DR, Akram AR, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules: accredited by NICE. *Thorax* 2015;70(Suppl 2):ii1. doi: 10.1136/thoraxjnl-2015-207168
2. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. *CMAJ* 1997;156(10):1411-6. [published Online First: 1997/05/15]
3. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008. doi: 10.1136/bmj.j4008 [published Online First: 2017/09/25]
4. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. *Annals of Internal Medicine* 2011;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009
5. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). : Cochrane, 2020. Available from: www.training.cochrane.org/handbook, 2020.
6. Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919. doi: 10.1136/bmj.i4919
7. Deeks JJ, Bossuyt PMM, Gatsonis C. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.: The Cochrane Collaboration, 2010. Available from http://srdta.cochrane.org/, 2010.
8. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol* 2014;14:25. doi: 10.1186/1471-2288-14-25 [published Online First: 2014/02/20]
9. Folch EE, Labarca G, Ospina-Delgado D, et al. Sensitivity and Safety of Electromagnetic Navigation Bronchoscopy for Lung Cancer Diagnosis: Systematic Review and Meta-analysis. *Chest* 2020;158(4):1753-69. doi: 10.1016/j.chest.2020.05.534
10. Giri M, Puri A, Wang T, et al. Virtual bronchoscopic navigation versus non-virtual bronchoscopic navigation assisted bronchoscopy for the diagnosis of peripheral pulmonary lesions: a systematic review and meta-analysis. *Therapeutic advances in respiratory disease* 2021;15:17534666211017048. doi: 10.1177/17534666211017048
11. Gex G, Pralong JA, Combescure C, et al. Diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules: a systematic review and meta-analysis. *Respiration; international review of thoracic diseases* 2014;87(2):165-76. doi: 10.1159/000355710
12. Han Y, Kim HJ, Kong KA, et al. Diagnosis of small pulmonary lesions by transbronchial lung biopsy with radial endobronchial ultrasound and virtual bronchoscopic navigation versus CT-guided transthoracic needle biopsy: A systematic review and meta-analysis. *PloS one* 2018;13(1):e0191590. doi: 10.1371/journal.pone.0191590
13. Jiang S, Xie F, Mao X, et al. The value of navigation bronchoscopy in the diagnosis of peripheral pulmonary lesions: A meta-analysis. *Thoracic cancer* 2020;11(5):1191-201. doi: 10.1111/1759-7714.13373
14. McGuire AL, Myers R, Grant K, et al. The Diagnostic Accuracy and Sensitivity for Malignancy of Radial-Endobronchial Ultrasound and Electromagnetic Navigation Bronchoscopy for Sampling of Peripheral Pulmonary Lesions: Systematic Review and Meta-analysis. *Journal of Bronchology & Interventional Pulmonology* 2020;27(2):106-21. doi: https://doi.org/10.1097/lbr.0000000000000645

15. Qian K, Krimsky WS, Sarkar SA, et al. Efficiency of Electromagnetic Navigation Bronchoscopy and Virtual Bronchoscopic Navigation. *Annals of Thoracic Surgery* 2020;109(6):1731-40. doi: https://doi.org/10.1016/j.athoracsur.2020.01.019
16. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. *Chest* 2012;142(2):385-93. doi: 10.1378/chest.11-1764
17. Zhang W, Chen S, Dong X, et al. Meta-analysis of the diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules. *Journal of Thoracic Disease* 2015;7(5):799-809. doi: 10.3978/j.issn.2072-1439.2015.04.46
18. Shinagawa N, Yamazaki K, Onodera Y, et al. Factors related to diagnostic sensitivity using an ultrathin bronchoscope under CT guidance. *Chest* 2007;131(2):549-53. doi: 10.1378/chest.06-0786 [published Online First: 2007/02/14]
19. Shinagawa N, Yamazaki K, Onodera Y, et al. Virtual bronchoscopic navigation system shortens the examination time--feasibility study of virtual bronchoscopic navigation system. *Lung Cancer* 2007;56(2):201-06. doi: https://doi.org/10.1016/j.lungcan.2006.12.005
20. Shinagawa N, Yamazaki K, Onodera Y, et al. CT-guided transbronchial biopsy using an ultrathin bronchoscope with virtual bronchoscopic navigation. *Chest* 2004;125(3):1138-43. doi: 10.1378/chest.125.3.1138 [published Online First: 2004/03/10]
21. Verhoeven RLJ, van der Sterren W, Kong W, et al. Cone-beam CT and Augmented Fluoroscopy-guided Navigation Bronchoscopy: Radiation Exposure and Diagnostic Accuracy Learning Curves. *Journal of Bronchology & Interventional Pulmonology* 2021;23:23. doi: https://doi.org/10.1097/lbr.0000000000000783
22. Verhoeven RLJ, Vos S, van der Heijden E. Multi-modal tissue sampling in cone beam CT guided navigation bronchoscopy: comparative accuracy of different sampling tools and rapid on-site evaluation of cytopathology. *J Thorac Dis* 2021;13(7):4396-406. doi: 10.21037/jtd-21-518 [published Online First: 2021/08/24]
23. Andersen FD, Degn KB, Riis R. Electromagnetic navigation bronchoscopy for lung nodule evaluation. Patient selection, diagnostic variables and safety. *The clinical respiratory journal* 2020;14(6):557-63. doi: https://doi.org/10.1111/crj.13168
24. Cheng SL, Chu CM. Electromagnetic navigation bronchoscopy: the initial experience in Hong Kong. *Journal of Thoracic Disease* 2019;11(4):1697-704. doi: https://doi.org/10.21037/jtd.2018.12.17
25. Hohenforst-Schmidt W, Zarogoulidis P, Vogl T, et al. Cone Beam Computertomography (CBCT) in Interventional Chest Medicine - High Feasibility for Endobronchial Realtime Navigation. *Journal of Cancer* 2014;5(3):231-41. doi: https://doi.org/10.7150/jca.8834
26. Mahajan AK, Patel S, Hogarth DK, et al. Electromagnetic navigational bronchoscopy: an effective and safe approach to diagnose peripheral lung lesions unreachable by conventional bronchoscopy in high-risk patients. *Journal of Bronchology & Interventional Pulmonology* 2011;18(2):133-37. doi: https://doi.org/10.1097/lbr.0b013e318216cee6
27. Oh JH, Choi CM, Kim S, et al. Diagnostic yield and safety of biopsy guided by electromagnetic navigation bronchoscopy for high-risk pulmonary nodules. *Thoracic Cancer* 2021;12(10):1503-10. doi: https://doi.org/10.1111/1759-7714.13930
28. Pearlstein DP, Quinn CC, Burtis CC, et al. Electromagnetic navigation bronchoscopy performed by thoracic surgeons: one center's early success. *Annals of Thoracic Surgery* 2012;93(3):944-9; discussion 49. doi: https://doi.org/10.1016/j.athoracsur.2011.11.006
29. Seijo LM, de Torres JP, Lozano MD, et al. Diagnostic yield of electromagnetic navigation bronchoscopy is highly dependent on the presence of a Bronchus sign on CT imaging: results from a prospective study. *Chest* 2010;138(6):1316-21. doi: https://doi.org/10.1378/chest.09-2708

30. Wilson DS, Bartlett RJ. Improved diagnostic yield of bronchoscopy in a community practice: Combination of electromagnetic navigation system and rapid on-site evaluation. *Journal of Bronchology* 2007;14(4):227-32. doi: https://doi.org/10.1097/lbr.0b013e31815a7b00
31. Al-Jaghbeer M, Marcus M, Durkin M, et al. Diagnostic yield of electromagnetic navigational bronchoscopy. *Therapeutic Advances in Respiratory Disease* 2016;10(4):295-99. doi: https://doi.org/10.1177/1753465816637053
32. Bellinger C, Poon R, Dotson T, et al. Lesion characteristics affecting yield of electromagnetic navigational bronchoscopy. *Respiratory Medicine* 2021;180:106357. doi: https://doi.org/10.1016/j.rmed.2021.106357
33. Bertoletti L, Robert A, Cottier M, et al. Accuracy and feasibility of electromagnetic navigated bronchoscopy under nitrous oxide sedation for pulmonary peripheral opacities: an outpatient study. *Respiration* 2009;78(3):293-300. doi: https://doi.org/10.1159/000226128
34. Bowling MR, Brown C, Anciano CJ. Feasibility and Safety of the Transbronchial Access Tool for Peripheral Pulmonary Nodule and Mass. *Annals of Thoracic Surgery* 2017;104(2):443-49. doi: https://doi.org/10.1016/j.athoracsur.2017.02.035
35. Bowling MR, Kohan MW, Walker P, et al. The effect of general anesthesia versus intravenous sedation on diagnostic yield and success in electromagnetic navigation bronchoscopy. *Journal of Bronchology & Interventional Pulmonology* 2015;22(1):5-13. doi: https://doi.org/10.1097/lbr.0000000000000120
36. Chee A, Stather DR, Maceachern P, et al. Diagnostic utility of peripheral endobronchial ultrasound with electromagnetic navigation bronchoscopy in peripheral lung nodules. *Respirology* 2013;18(5):784-89. doi: https://doi.org/10.1111/resp.12085
37. Eberhardt R, Anantham D, Herth F, et al. Electromagnetic navigation diagnostic bronchoscopy in peripheral lung lesions. *Chest* 2007;131(6):1800-05. doi: https://doi.org/10.1378/chest.06-3016
38. Eberhardt R, Anantham D, Ernst A, et al. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. *American Journal of Respiratory & Critical Care Medicine* 2007;176(1):36-41. doi: https://doi.org/10.1164/rccm.200612-1866oc
39. Eberhardt R, Morgan RK, Ernst A, et al. Comparison of suction catheter versus forceps biopsy for sampling of solitary pulmonary nodules guided by electromagnetic navigational bronchoscopy. *Respiration* 2010;79(1):54-60. doi: https://doi.org/10.1159/000232394
40. Flenaugh E, Mohammed K. Initial experience using 4D electromagnetic navigation bronchoscopy system with tip tracked instruments for localization of peripheral lung nodules. *Int J Pulm Med* 2016;18(1):1-7.
41. Garwood SK, ClenDening P, Hevelone ND, et al. Navigational bronchoscopy at a community hospital: clinical and economic outcomes. *Lung Cancer Management* 2016;5(3):131-40. doi: https://doi.org/10.2217/lmt-2016-0015
42. Gildea TR, Mazzone PJ, Karnak D, et al. Electromagnetic navigation diagnostic bronchoscopy: a prospective study. *American Journal of Respiratory & Critical Care Medicine* 2006;174(9):982-89. doi: https://doi.org/10.1164/rccm.200603-344oc
43. Gu Y, Chen S, Shi J, et al. The introduction of electromagnetic navigation bronchoscopy for the diagnosis of small pulmonary peripheral lesions in an Asian population. *Journal of Thoracic Disease* 2017;9(9):2959-65. doi: https://doi.org/10.21037/jtd.2017.08.05
44. Hautmann H, Schneider A, Pinkau T, et al. Electromagnetic catheter navigation during bronchoscopy: validation of a novel method by conventional fluoroscopy. *Chest* 2005;128(1):382-87. doi: https://doi.org/10.1378/chest.128.1.382
45. Jensen KW, Hsia DW, Seijo LM, et al. Multicenter experience with electromagnetic navigation bronchoscopy for the diagnosis of pulmonary nodules. *Journal of Bronchology & Interventional Pulmonology* 2012;19(3):195-99. doi: https://doi.org/10.1097/lbr.0b013e3182616ece

46. Lamprecht B, Porsch P, Wegleitner B, et al. Electromagnetic navigation bronchoscopy (ENB): Increasing diagnostic yield. *Respiratory Medicine* 2012;106(5):710-15. doi: https://doi.org/10.1016/j.rmed.2012.02.002
47. Loo FL, Halligan AM, Port JL, et al. The emerging technique of electromagnetic navigation bronchoscopy-guided fine-needle aspiration of peripheral lung lesions: promising results in 50 lesions. *Cancer Cytopathology* 2014;122(3):191-99. doi: https://doi.org/10.1002/cncy.21373
48. Ma L, Fang Y, Zhang T, et al. Comparison in efficacy and safety of forceps biopsy for peripheral lung lesions guided by endobronchial ultrasound-guided sheath (EBUS-GS) and electromagnetic navigation bronchoscopy combined with EBUS (ENB-EBUS). *American Journal Of Translational Research* 2020;12(8):4604-11.
49. Makris D, Scherpereel A, Leroy S, et al. Electromagnetic navigation diagnostic bronchoscopy for small peripheral lung lesions. *European Respiratory Journal* 2007;29(6):1187-92. doi: https://doi.org/10.1183/09031936.00165306
50. Mukherjee S, Chacey M. Diagnostic Yield of Electromagnetic Navigation Bronchoscopy Using a Curved-tip Catheter to Aid in the Diagnosis of Pulmonary Lesions. *Journal of Bronchology & Interventional Pulmonology* 2017;24(1):35-39. doi: https://doi.org/10.1097/lbr.0000000000000326
51. Odronic SI, Gildea TR, Chute DJ. Electromagnetic navigation bronchoscopy-guided fine needle aspiration for the diagnosis of lung lesions. *Diagnostic Cytopathology* 2014;42(12):1045-50. doi: https://doi.org/10.1002/dc.23164
52. Patrucco F, Gavelli F, Daverio M, et al. Electromagnetic Navigation Bronchoscopy: Where Are We Now? Five Years of a Single-Center Experience. *Lung* 2018;196(6):721-27. doi: https://doi.org/10.1007/s00408-018-0161-3
53. Raval AA, Amir L. Community hospital experience using electromagnetic navigation bronchoscopy system integrating tidal volume computed tomography mapping. *Lung Cancer Management* 2016;5(1):9-19. doi: https://doi.org/10.2217/lmt-2015-0007
54. Sato T, Yutaka Y, Ueda Y, et al. Diagnostic yield of electromagnetic navigational bronchoscopy: results of initial 35 cases in a Japanese institute. *Journal of Thoracic Disease* 2018;10(Suppl 14):S1615-S19. doi: https://doi.org/10.21037/jtd.2018.04.123
55. Stenger M, Zoorob S, Hussein AA, et al. Electromagnetic navigation bronchoscopy as an adjunct diagnostic tool in the Danish lung cancer diagnostic pathway: an initial retrospective single centre series. *Journal of Thoracic Disease* 2020;12(9):4762-70. doi: https://doi.org/10.21037/jtd-20-1236
56. Sun J, Xie F, Zheng X, et al. Learning curve of electromagnetic navigation bronchoscopy for diagnosing peripheral pulmonary nodules in a single institution. *Translational Cancer Research* 2017;6(3):541-51. doi: https://doi.org/10.21037/tcr.2017.05.39
57. Taton O, Bondue B, Gevenois PA, et al. Diagnostic Yield of Combined Pulmonary Cryobiopsies and Electromagnetic Navigation in Small Pulmonary Nodules. *Pulmonary Medicine* 2018;2018:6032974. doi: https://doi.org/10.1155/2018/6032974
58. Wang N, Ma H, Huang H, et al. Electromagnetic Navigation Bronchoscopy Combined Endobronchial Ultrasound in the Diagnosis of Lung Nodules. *Medicine* 2021;100(3):e23979. doi: https://doi.org/10.1097/md.0000000000023979
59. Asahina H, Yamazaki K, Onodera Y, et al. Transbronchial biopsy using endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation. *Chest* 2005;128(3):1761-65. doi: https://doi.org/10.1378/chest.128.3.1761
60. Asano F, Matsuno Y, Shinagawa N, et al. A virtual bronchoscopic navigation system for pulmonary peripheral lesions. *Chest* 2006;130(2):559-66. doi: https://doi.org/10.1378/chest.130.2.559

61. Asano F, Matsuno Y, Tsuzuku A, et al. Diagnosis of peripheral pulmonary lesions using a bronchoscope insertion guidance system combined with endobronchial ultrasonography with a guide sheath. *Lung Cancer* 2008;60(3):366-73. doi: 10.1016/j.lungcan.2007.10.022 [published Online First: 2007/12/07]
62. Asano F, Shinagawa N, Ishida T, et al. Virtual bronchoscopic navigation combined with ultrathin bronchoscopy. A randomized clinical trial. *American Journal of Respiratory & Critical Care Medicine* 2013;188(3):327-33. doi: https://doi.org/10.1164/rccm.201211-2104ocs https://doi.org/10.1164/rccm.201211-2104oc
63. Asano F, Shinagawa N, Ishida T, et al. Virtual bronchoscopic navigation improves the diagnostic yield of radial-endobronchial ultrasound for peripheral pulmonary lesions with involved bronchi on CT. *Internal Medicine* 2015;54(9):1021-25. doi: https://doi.org/10.2169/internalmedicine.54.3497
64. Bae S, Lim S, Ahn JJ, et al. Diagnosing peripheral lung lesions using endobronchial ultrasonography with guide sheath: A prospective registry study to assess the effect of virtual bronchoscopic navigation using a computed tomography workstation. *Medicine* 2020;99(17):e19870. doi: https://doi.org/10.1097/md.0000000000019870
65. Bo L, Li C, Pan L, et al. Diagnosing a solitary pulmonary nodule using multiple bronchoscopic guided technologies: A prospective randomized study. *Lung Cancer* 2019;129:48-54. doi: https://doi.org/10.1016/j.lungcan.2019.01.006
66. Diez-Ferrer M, Morales A, Tebé C, et al. Ultrathin Bronchoscopy with and without Virtual Bronchoscopic Navigation: Influence of Segmentation on Diagnostic Yield. *Respiration* 2019;97(3):252-58. doi: https://doi.org/10.1159/000493270
67. Eberhardt R, Kahn N, Gompelmann D, et al. LungPoint--a new approach to peripheral lesions. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer* 2010;5(10):1559-63. doi: https://doi.org/10.1097/jto.0b013e3181e8b308
68. Fukusumi M, Ichinose Y, Arimoto Y, et al. Bronchoscopy for Pulmonary Peripheral Lesions With Virtual Fluoroscopic Preprocedural Planning Combined With EBUS-GS: A Pilot Study. *J Bronchology Interv Pulmonol* 2016;23(2):92-7. doi: 10.1097/lbr.0000000000000273 [published Online First: 2016/04/09]
69. Haidong H, Yunye N, Wei Z, et al. Multiple guided technologies based on radial probe endobronchial ultrasound for the diagnosis of solitary peripheral pulmonary lesions: a single-center study. *Journal of Cancer* 2017;8(17):3514-21. doi: https://doi.org/10.7150/jca.20035
70. Ikezawa Y, Shinagawa N, Sukoh N, et al. Usefulness of Endobronchial Ultrasonography With a Guide Sheath and Virtual Bronchoscopic Navigation for Ground-Glass Opacity Lesions. *Annals of Thoracic Surgery* 2017;103(2):470-75. doi: https://doi.org/10.1016/j.athoracsur.2016.09.001
71. Ishida T, Asano F, Yamazaki K, et al. Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: A randomised trial. *Thorax* 2011;66(12):1072-77. doi: https://doi.org/10.1136/thx.2010.145490
72. Iwano S, Imaizumi K, Okada T, et al. Virtual bronchoscopy-guided transbronchial biopsy for aiding the diagnosis of peripheral lung cancer. *European Journal of Radiology* 2011;79(1):155-59. doi: https://doi.org/10.1016/j.ejrad.2009.11.023
73. Kato A, Yasuo M, Tokoro Y, et al. Virtual bronchoscopic navigation as an aid to CT-guided transbronchial biopsy improves the diagnostic yield for small peripheral pulmonary lesions. *Respirology* 2018;23(11):1049-54. doi: https://doi.org/10.1111/resp.13377
74. Li S, Yan W, Chen M, et al. Virtual bronchoscopic navigation without fluoroscopy guidance for peripheral pulmonary lesions in inexperienced pulmonologist. *Chinese Journal of Cancer Research* 2020;32(4):530-39. doi: https://doi.org/10.21147/j.issn.1000-9604.2020.04.10

75. Maekura T, Sugimoto C, Tamiya A, et al. Combination of virtual bronchoscopic navigation, endobronchial ultrasound, and rapid on-site evaluation for diagnosing small peripheral pulmonary lesions: a prospective phase II study. *Journal of Thoracic Disease* 2017;9(7):1930-36. doi: https://doi.org/10.21037/jtd.2017.06.85
76. Matsumoto Y, Izumo T, Sasada S, et al. Diagnostic utility of endobronchial ultrasound with a guide sheath under the computed tomography workstation (ziostation) for small peripheral pulmonary lesions. *The clinical respiratory journal* 2017;11(2):185-92. doi: https://doi.org/10.1111/crj.12321
77. Miyoshi S, Isobe K, Shimizu H, et al. The utility of virtual bronchoscopy using a computed tomography workstation for conducting conventional bronchoscopy: A retrospective analysis of clinical practice. *Respiration* 2018;97(1):52-59. doi: https://doi.org/10.1159/000492074
78. Oki M, Saka H, Ando M, et al. Ultrathin Bronchoscopy with Multimodal Devices for Peripheral Pulmonary Lesions. A Randomized Trial. *American Journal of Respiratory & Critical Care Medicine* 2015;192(4):468-76. doi: https://doi.org/10.1164/rccm.201502-0205oc
79. Oki M, Saka H, Asano F, et al. Use of an Ultrathin vs Thin Bronchoscope for Peripheral Pulmonary Lesions: A Randomized Trial. *Chest* 2019;156(5):954-64. doi: https://doi.org/10.1016/j.chest.2019.06.038
80. Oshige M, Shirakawa T, Nakamura M, et al. Clinical application of virtual bronchoscopic navigation system for peripheral lung lesions. *Journal of Bronchology & Interventional Pulmonology* 2011;18(2):196-202. doi: https://doi.org/10.1097/lbr.0b013e3182198f24
81. Tachihara M, Tamura D, Kiriu T, et al. Sbronchoscopy using virtual navigation and endobronchial ultrasonography with a guide sheath (EBUS-GS) with or without fluoroscopy for peripheral pulmonary lesions. *Kobe Journal of Medical Sciences* 2017;63(4):E99-E104.
82. Tamiya M, Okamoto N, Sasada S, et al. Diagnostic yield of combined bronchoscopy and endobronchial ultrasonography, under LungPoint guidance for small peripheral pulmonary lesions. *Respirology* 2013;18(5):834-39. doi: https://doi.org/10.1111/resp.12095
83. Wong KY, Tse HN, Pak KK, et al. Integrated use of virtual bronchoscopy and endobronchial ultrasonography on the diagnosis of peripheral lung lesions. *Journal of Bronchology & Interventional Pulmonology* 2014;21(1):14-20. doi: https://doi.org/10.1097/lbr.0000000000000027
84. Xu C, Yuan Q, Wang Y, et al. Usefulness of virtual bronchoscopic navigation combined with endobronchial ultrasound guided transbronchial lung biopsy for solitary pulmonary nodules. *Medicine* 2019;98(7):e14248. doi: https://doi.org/10.1097/md.0000000000014248
85. Zhang H, Wang C, Zhang Y, et al. Diagnostic value of endobronchial ultrasonography with a guide sheath combined with virtual bronchoscopic biopsy for pulmonary peripheral lesions. *Iranian Journal of Radiology* 2020;17(1) doi: https://doi.org/10.5812/iranjradiol.81792
86. Zheng X, Xie F, Li Y, et al. Ultrathin bronchoscope combined with virtual bronchoscopic navigation and endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions with or without fluoroscopy: A randomized trial. *Thoracic Cancer* 2021;12(12):1864-72. doi: https://doi.org/10.1111/1759-7714.13995
87. Casal RF, Sarkiss M, Jones AK, et al. Cone beam computed tomography-guided thin/ultrathin bronchoscopy for diagnosis of peripheral lung nodules: a prospective pilot study. *Journal of Thoracic Disease* 2018;10(12):6950-59. doi: https://doi.org/10.21037/jtd.2018.11.21
88. Yu KL, Yang SM, Ko HJ, et al. Efficacy and safety of cone-beam computed tomography-derived augmented fluoroscopy combined with endobronchial ultrasound in peripheral pulmonary lesions. *Respiration* 2021;100(6):538-46. doi: https://doi.org/10.1159/000515181

89. Kheir F, Thakore SR, Uribe B, et al. Cone-Beam Computed Tomography-Guided Electromagnetic Navigation for Peripheral Lung Nodules. *Respiration* 2021;100(1):44-51. doi: https://doi.org/10.1159/000510763
90. 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. *Journal of Bronchology & Interventional Pulmonology* 2018;25(4):274-82. doi: https://doi.org/10.1097/lbr.0000000000000536
91. Sobieszczyk MJ, Yuan Z, Li W, et al. Biopsy of peripheral lung nodules utilizing cone beam computer tomography with and without trans bronchial access tool: a retrospective analysis. *J Thorac Dis* 2018;10(10):5953-59. doi: 10.21037/jtd.2018.09.16 [published Online First: 2018/12/07]
92. Verhoeven RLJ, Futterer JJ, Hoefsloot W, et al. Cone-Beam CT Image Guidance With and Without Electromagnetic Navigation Bronchoscopy for Biopsy of Peripheral Pulmonary Lesions. *Journal of bronchology & interventional pulmonology* 2020:60-69. doi: https://doi.org/10.1097/lbr.0000000000000697
93. Karnak D, Ciledag A, Ceyhan K, et al. Rapid on-site evaluation and low registration error enhance the success of electromagnetic navigation bronchoscopy. *Annals of Thoracic Medicine* 2013;8(1):28-32. doi: https://doi.org/10.4103/1817-1737.105716
94. Ost DE, Ernst A, Lei X, et al. Diagnostic Yield and Complications of Bronchoscopy for Peripheral Lung Lesions. Results of the AQuIRE Registry. *American Journal of Respiratory & Critical Care Medicine* 2016;193(1):68-77. doi: https://doi.org/10.1164/rccm.201507-1332oc
95. Steinfort DP, Bonney A, See K, et al. Sequential multimodality bronchoscopic investigation of peripheral pulmonary lesions. *Eur Respir J* 2016;47(2):607-14. doi: 10.1183/13993003.00786-2015 [published Online First: 2015/11/07]
96. 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(4):321-28. doi: https://doi.org/10.1159/000500228
97. Kawakita N, Takizawa H, Toba H, et al. Cone-beam computed tomography versus computed tomography-guided ultrathin bronchoscopic diagnosis for peripheral pulmonary lesions: A propensity score-matched analysis. *Respirology* 2021;26(5):477-84. doi: https://doi.org/10.1111/resp.14016
98. Oki M, Saka H, Asano F, et al. A randomized trial of navigational endosonographic ultrathin bronchoscopy versus thin bronchoscopy for the diagnosis of peripheral pulmonary lesions. *European Respiratory Journal* 2018;52 doi: https://doi.org/10.1183/13993003.congress-2018.pa4187
99. Oerbekke MS, Jenniskens K, Scholten R, et al. Data sources and methods used to determine pretest probabilities in a cohort of Cochrane diagnostic test accuracy reviews. *BMC Med Res Methodol* 2020;20(1):85. doi: 10.1186/s12874-020-00952-w [published Online First: 2020/04/18]
100. Kim J, Chee CG, Cho J, et al. Diagnostic accuracy and complication rate of image-guided percutaneous transthoracic needle lung biopsy for subsolid pulmonary nodules: a systematic review and meta-analysis. *Br J Radiol* 2021;94(1127):20210065. doi: 10.1259/bjr.20210065 [published Online First: 2021/10/19]
101. Heerink WJ, de Bock GH, de Jonge GJ, et al. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. *Eur Radiol* 2017;27(1):138-48. doi: 10.1007/s00330-016-4357-8 [published Online First: 2016/04/25]
102. Huo YR, Chan MV, Habib AR, et al. Pneumothorax rates in CT-Guided lung biopsies: a comprehensive systematic review and meta-analysis of risk factors. *Br J Radiol* 2020;93(1108):20190866. doi: 10.1259/bjr.20190866 [published Online First: 2019/12/21]

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Bijlage 1. Zoekstrategieën

1A: Systematic reviews

Epistemonikos (https://www.epistemonikos.org/en/)

Datum zoekactie: 28 juni 2021

(("lung cancer" OR "lung tumor" OR "lung tumour" OR "lung carcinoma" OR "lung nodules" OR "lung nodule" OR "lung malignancy" OR "lung lesion" OR "lung lesions" OR "pulmonary cancer" OR "pulmonary carcinoma" OR "pulmonary neoplasm" OR "pulmonary lesions" OR "pulmonary lesion" OR "pulmonary malignancy" OR "pulmonary tumor" OR "pulmonary tumour" OR "pulmonary nodule" OR "pulmonary nodules" OR "pulmonary neoplasm") AND (bronchoscopic OR bronchoscopy OR "cone beam" OR navigation OR fluoroscopy OR fluorescence OR "confocal" OR "optical coherence tomography"))	
Title, abstract limit systematic reviews	55

The Cochrane Library

Datum zoekactie: 6 juli 2021

#1	MeSH descriptor: [Lung Neoplasms] explode all trees	8003
#2	((lung NEAR/3 (tumor* or tumour* or carcinoma* or nodule* or malign* or lesion* or cancer or neoplasm*)) OR (pulmonary NEAR/3 (tumor* or tumour* or carcinoma* or nodule* or malign* or lesion* or cancer or neoplasm*))):ti,ab,kw	23964
#3	#1 OR #2 in Cochrane Reviews, Cochrane Protocols	96

1B: Primaire onderzoeken

MEDLINE (Ovid)

Datum zoekactie: 9 juli 2021

#	Searches	Results
1	((lung or pulmonar*) adj3 (tumor* or tumour* or carcinoma* or nodule* or malign* or lesion* or cancer or neoplasm* or opacit* or biops*)).ti,ab,kf.	260497
2	exp Lung Neoplasms/	245589
3	exp Solitary Pulmonary Nodule/	4304
4	1 or 2 or 3	348429
5	exp Cone-Beam Computed Tomography/	11478
6	exp Tomography, Optical Coherence/	37901
7	(((navigat* or virtual or fluorosc* or confocal or robot*) adj5 (bronchosc* or endomicrosc*)) or shape-sens*).ti,ab,kf.	2464
8	4 and 7	639
9	5 or 6 or 7	51769
10	4 and 9	1240

Embase (embase.com)
Datum zoekactie: 12 juli 2021

No.	Query	Results
#1	((lung OR pulmonar*) NEAR/3 (tumor* OR tumour* OR carcinoma* OR nodule* OR malign* OR lesion* OR cancer OR neoplasm* OR opacit* OR biops*)):ti,ab,kw	385798
#2	'lung cancer'/exp OR 'lung lesion'/exp OR 'lung nodule'/exp	428930
#3	#1 OR #2	535560
#4	(((navigat* OR virtual OR fluorosc* OR confocal OR robot*) NEAR/5 (bronchosc* OR endomicrosc*)):ti,ab,kw) OR 'shape sens*':ti,ab,kw	4458
#5	'optical coherence tomography'/exp OR 'cone beam computed tomography'/exp	92881
#6	#4 OR #5	97099
#7	#3 AND #6	3049
#8	#7 AND [embase]/lim	2856
#9	#7 AND [embase]/lim NOT 'conference abstract'/it	1628

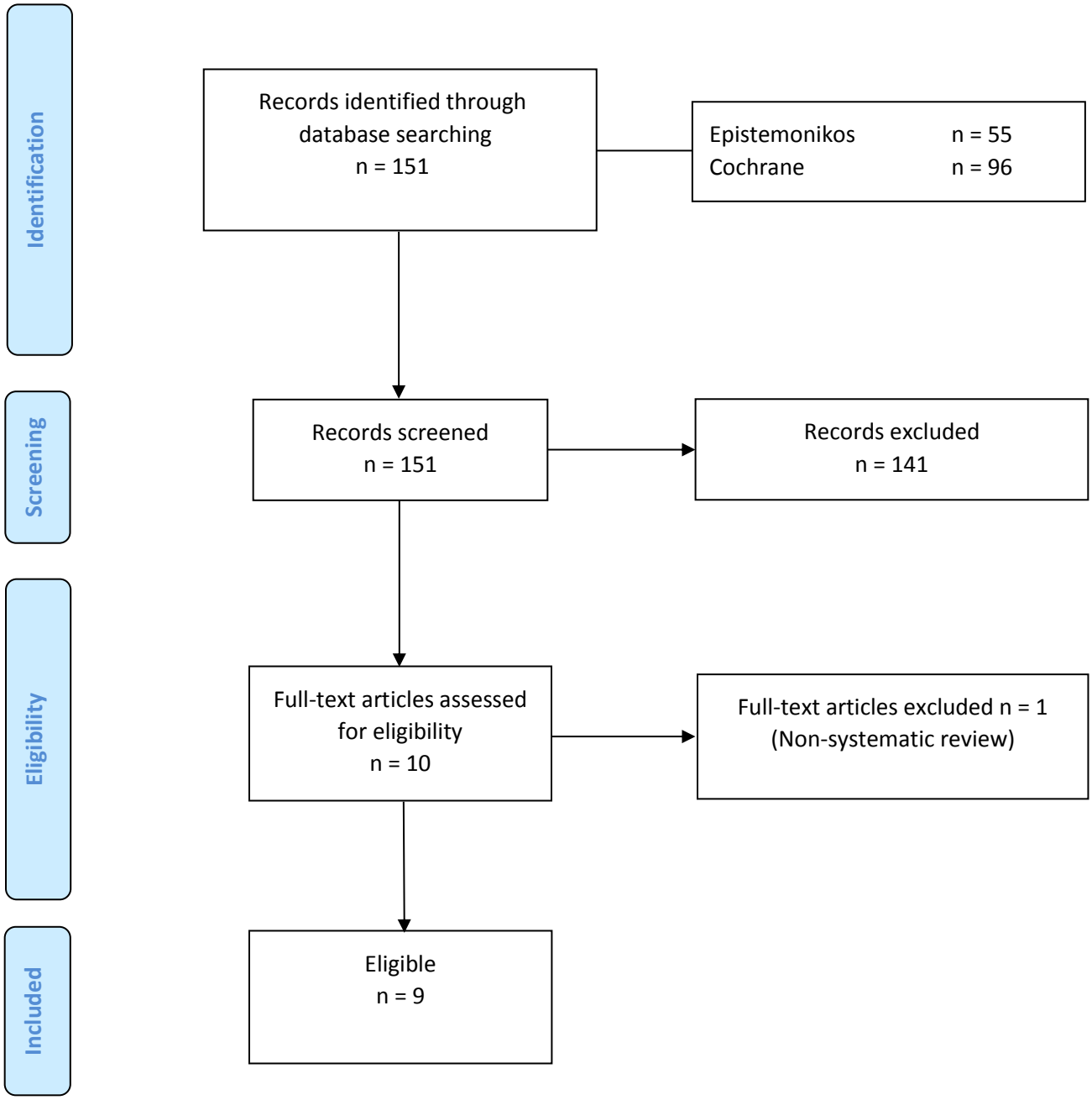
CENTRAL
Datum zoekactie: 12 juli 2021

No.	Query	Results
#1	((lung or pulmonar*) adj3 (tumor* or tumour* or carcinoma* or nodule* or malign* or lesion* or cancer or neoplasm* or opacit* or biops*)):ti,ab,kw	20414
#2	MESH DESCRIPTOR Lung Neoplasms EXPLODE ALL TREES	7957
#3	MESH DESCRIPTOR Solitary Pulmonary Nodule EXPLODE ALL TREES	82
#4	#1 OR #2 OR #3	21848
#5	MESH DESCRIPTOR Cone-Beam Computed Tomography EXPLODE ALL TREES	310
#6	MESH DESCRIPTOR Tomography, Optical Coherence EXPLODE ALL TREES	1422
#7	(((navigat* or virtual or fluorosc* or confocal or robot*) adj5 (bronchosc* or endomicrosc*)) or shape-sens*):ti,ab,kw	216
#8	#5 OR #6 OR #7	1947
#9	#4 AND #8	92
#10	(clinicaltrials OR WHO):SO	369317
#11	(conference):so	22763
#12	#10 OR #11	392079
#13	#9 NOT #12	57

Bijlage 2. Study flows

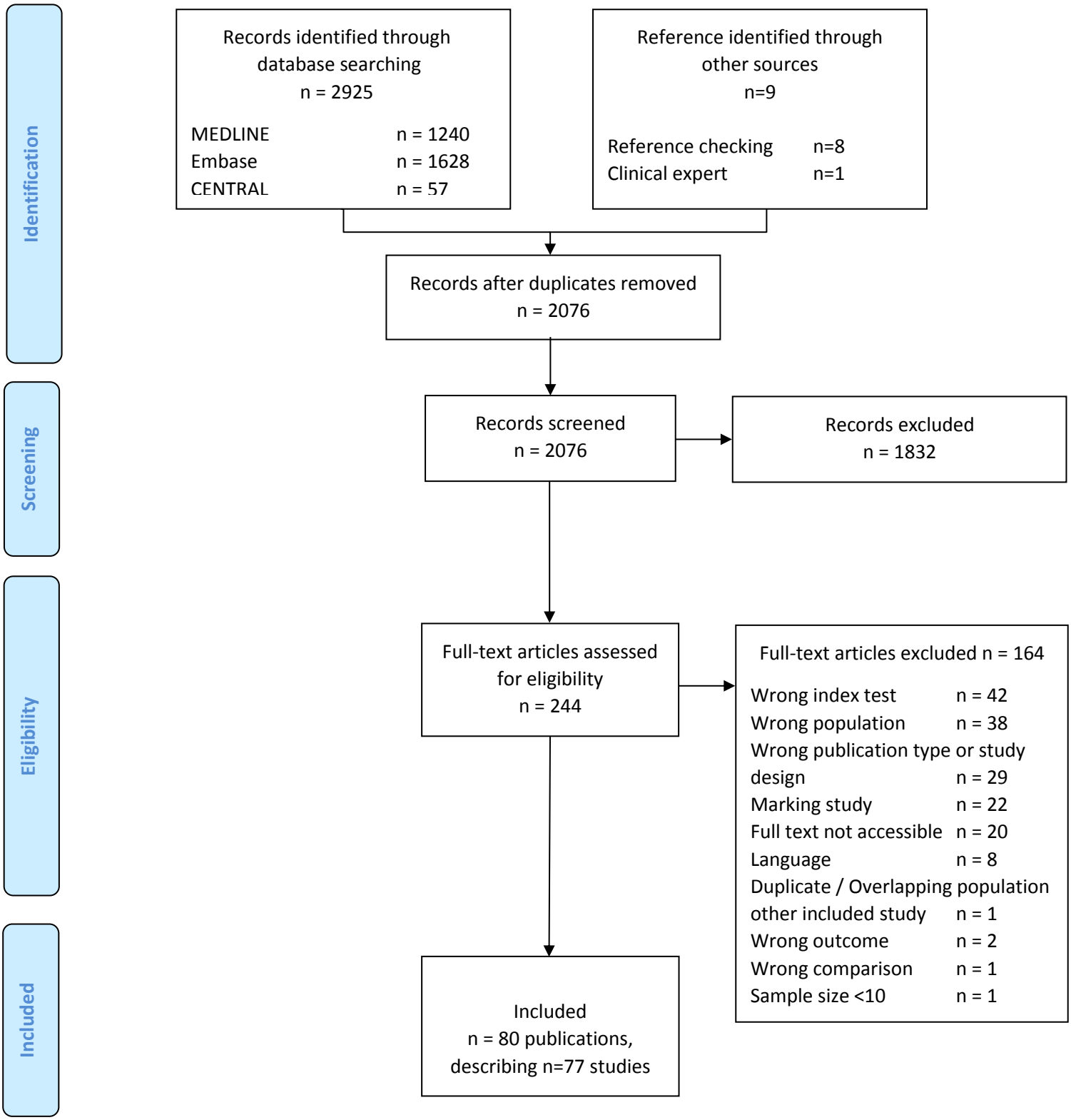
2A: Systematische reviews

Figuur. Study flow van de selectie van systematische reviews betreffende navigatiebronchscopie bij verdenking op lonkanker.



2B: Primaire onderzoeken

Figuur. Study flow van de selectie van primaire onderzoeken betreffende navigatiebronchoscopie bij verdenking op longkanker.



Bijlage 3. Uitgesloten onderzoeken

3A: Systematische reviews

Uitgesloten systematische reviews betreffende navigatiebronchoscopie bij verdenking op longkanker (n=1)

Referentie	Reden
Shaller 2020	Non-systematic review

Referentie

1. Shaller BD, Gildea TR. What is the value of electromagnetic navigation in lung cancer and to what extent does it require improvement? Expert review of respiratory medicine. 2020;14(7):1-15.

3B: Primaire onderzoeken

Uitgesloten primaire onderzoeken betreffende navigatiebronchoscopie bij verdenking op longkanker (n=164)

Referentie	Reden
[No author] 2020	Wrong publication type or study design (correction)
Abbas 2017	Wrong population
Abi-Jaoudeh 2016	Wrong intervention/index test
Aboudara 2020	Wrong comparison
Adali 2010	Wrong population
Allah 2012	Wrong population
Alvarez 2021	Wrong population
Anayama 2019	Marking study
Anayama 2021	Marking study
Andersen 2013	Full text not accessible
Andrade 2010	Wrong publication type or study design (seminar)
Asano 2004	Marking study
Asano 2015	Full text not accessible
Asano 2016	Full text not accessible
Asano 2017	Wrong population (lesion ≥3cm)
Asano 2018	Wrong publication type or study design (editorial)
Atkins 2020	Wrong population
Avasarala 2020	Wrong intervention/index test
Awais 2016	Marking study
Bakir 2008	Full text not accessible
Balbo 2013	Full text not accessible
Becker 2005	Wrong population (lesion ≥3cm)
Belanger 2019	Wrong population

Benn 2021	Wrong intervention / indextest (Robot CT)
Bessich 2020	Wrong publication type or study design (editorial)
Bhatt 2018	Wrong intervention/index test
Biswas 2017	Wrong publication type or study design (letter)
Biswas 2019	Wrong population
Bolton 2014	Wrong population
Bolton 2015	Marking study
Bolton 2015	Marking study
Bolton 2017	Wrong population
Bowling 2019	Marking study
Bowling 2019	Marking study
Brown 2016	Wrong intervention/index test
Brownback 2012	Wrong population (lesion ≥3cm)
Chaddha 2019	Wrong intervention / indextest (Robot CT)
Chan 2020	Wrong publication type or study design (surgical technique description)
Chen 2014	Full text not accessible
Chen 2016	Language
Chen 2016	Duplicate
Chen 2017	Full text not accessible
Chen 2021	Wrong intervention / indextest (Robot CT)
Cherian 2021	Wrong population (lesion ≥3cm)
Cho 2018	Marking study
Cho 2018	Marking study
Cho 2020	Sample size <10
Cicenia 2021	Wrong intervention/index test
Dale 2012	Wrong publication type or study design (cost-consequences analysis)
Deng 2018	Wrong publication type or study design (systematic review)
Duplaga 2008	Full text not accessible
Fang 2018	Full text not accessible
Fangfang 2019	Wrong publication type or study design (protocol)
Fielding 2019	Wrong intervention / indextest (Robot CT)
Fiorelli 2017	Wrong population
Folch 2016	Wrong publication type or study design (protocol)
Folch 2019	Wrong population
Furukawa 2018	Wrong outcome
Gatenby 1984	Wrong intervention/index test
Gildea 2021	Wrong population
Gulias-Soidan 2020	Wrong intervention/index test
Ha 2013	Wrong population
Hachey 2017	Marking study

Hariri 2013	Wrong publication type or study design (occasional essay)
Hassan 2015	Wrong publication type or study design (case series)
Hohenforst-Schmidt 2014	Wrong publication type or study design (phantom study)
Huang 2017	Language
Hwang 2010	Wrong intervention/index test
Hwang 2018	Wrong intervention/index test
Hwang 2018	Wrong intervention/index test
Iannelli 2018	Wrong intervention/index test
Ishige 2017	Full text not accessible
Ishiwata 2019	Wrong publication type or study design (abstract / conference contribution)
Ishiwata 2021	Wrong population
Jaconi 2015	Wrong intervention/index test
Jiao 2014	Wrong intervention/index test
Jiayuan 2015	Full text not accessible
Jin 2010	Wrong intervention/index test
Jin 2017	Full text not accessible
Karnak 2011	Language
Kato 2015	Full text not accessible
Katsis 2020	Wrong publication type or study design (abstract / conference contribution)
Katsis 2021	Wrong population
Katsis 2021	Wrong population
Kennedy 2020	Wrong publication type or study design (letter)
Khan 2013	Wrong population
Khandhar 2017	Wrong population
Kickuth 2015	Wrong intervention/index test
Kim 2015	Wrong intervention/index test
Kim 2016	Wrong intervention/index test
Kim 2017	Wrong intervention/index test
Kim 2018	Wrong intervention/index test
Kim 2018	Wrong intervention/index test
Kotlyarov 2017	Language
Krimsky 2014	Marking study
Kumar 2017	Wrong publication type or study design (letter)
Kuo 2019	Marking study
Lacasse 2004	Wrong population
Lamprecht 2009	Wrong population (lesion ≥3cm)
Lau 2019	Wrong publication type or study design (abstract / conference contribution)
Lee 2012	Wrong intervention/index test

Lee 2014	Wrong intervention/index test
Lee 2014	Wrong publication type or study design (cost effectiveness)
Lee 2018	Wrong intervention/index test
Li 2019	Language
Liewald 1998	Wrong population
Linden 2011	Wrong publication type or study design (narrative review)
Liu 2016	Full text not accessible
Liu 2019	Wrong population
Liu 2020	Wrong population
Liu 2020	Wrong population
Marino 2016	Marking study
McGuire 2020	Wrong publication type or study design (systematic review)
Mohanasundaram 2013	Wrong population (lesion ≥3cm)
Munoz-Largacha 2017	Marking study
Muñoz-Largacha 2021	Full text not accessible
Nakai 2017	Wrong intervention/index test
Okachi 2016	Wrong population
Oki 2018	Full text not accessible
Omiya 2010	Wrong population
Ost 2008	Wrong intervention/index test
Ozgul 2016	Wrong population (lesion ≥3cm)
Panchabhai 2018	Wrong population
Pertzov 2021	Wrong intervention/index test
Piao 2020	Wrong intervention/index test
Pritchett 2019	Wrong publication type or study design (letter)
Pritchett 2021	Wrong intervention/index test
Pritchett 2021	Wrong intervention/index test
Puchalski 2021	Wrong publication type or study design (narrative review)
Pupovac 2017	Marking study
Qian 2019	Marking study
Qian 2019	Language
Qian 2020	Wrong publication type or study design (systematic review)
Rickets 2020	Wrong publication type or study design (health technology assessment; hypothetical cohort)
Rojas-Solano 2018	Wrong intervention / indextest (Robot CT)
Rotolo 2016	Wrong intervention/index test
Rottgen 2005	Wrong population
Salvolini 1997	Full text not accessible
Sánchez-Font 2013	Wrong publication type or study design (abstract / conference contribution)
Sanchez-Font 2014	Wrong intervention/index test

Schwarz 2006	Wrong population (lesion ≥3cm)
Semaan 2016	Wrong outcome
Shinagawa 2013	Wrong publication type or study design (abstract / conference contribution)
Silvestri 2020	Wrong intervention/index test
Song 2021	Marking study
Stern 2019	Language
Tachihara 2007	Wrong intervention/index test
Tang 2016	Full text not accessible
Tao 2017	Full text not accessible
Tian 2020	Marking study
Towe 2017	Marking study
Towe 2019	Wrong population
Tsushima 2006	Wrong intervention/index test
Vining 2018	Marking study
Weiner 2009	Wrong intervention/index test
Xiong 2000	Wrong population
Xue 2020	Language
Yang 2020	Marking study
Yarmus 2016	Wrong intervention/index test
Yasuo 2013	Wrong publication type or study design (abstract / conference contribution)
Yasuo 2016	Wrong population
Yoon 2019	Wrong intervention/index test
Zheng 2019	Wrong publication type or study design (abstract / conference contribution)
Zuccatosta 2012	Full text not accessible

Referenties

1. [No authors listed] Correction: Exploratory cost-effectiveness model of electromagnetic navigation bronchoscopy (ENB) compared with CT-guided biopsy (TTNA) for diagnosis of malignant indeterminate peripheral pulmonary nodules. BMJ Open Respiratory Research. 2020;7(1):09.
2. Abbas A, Kadakia S, Ambur V, Muro K, Kaiser L. Intraoperative electromagnetic navigational bronchoscopic localization of small, deep, or subsolid pulmonary nodules. Journal of Thoracic & Cardiovascular Surgery. 2017;153(6):1581-1590.
3. Abi-Jaoudeh N, Fisher T, Jacobus J, Skopec M, Radaelli A, et al. Prospective Randomized Trial for Image-Guided Biopsy Using Cone-Beam CT Navigation Compared with Conventional CT. Journal of Vascular & Interventional Radiology. 2016;27(9):1342-1349.
4. Aboudara M, Roller L, Rickman O, Lentz RJ, Pannu J, et al. Improved diagnostic yield for lung nodules with digital tomosynthesis-corrected navigational bronchoscopy: Initial experience with a novel adjunct. Respirology. 2020;25(2):206-213.

5. Adali F, Uysal A, Bayramoglu S, Guner NT, Yilmaz G, Cimilli T. Virtual and fiber-optic bronchoscopy in patients with indication for tracheobronchial evaluation. Annals of Thoracic Medicine. 2010;5(2):104-109.
6. Allah MF, Hussein SR, El-Asmar AB, Zoair HM, Mohamed GA, et al. Role of virtual bronchoscopy in the evaluation of bronchial lesions. Journal of Computer Assisted Tomography. 2012;36(1):94-99.
7. Alvarez P, Rouzé S, Miga MI, Payan Y, Dillenseger JL, Chabanas M. A hybrid, image-based and biomechanics-based registration approach to markerless intraoperative nodule localization during video-assisted thoracoscopic surgery. Medical Image Analysis. 2021;69.
8. Anayama T, Hirohashi K, Okada H, Miyazaki R, Kawamoto N, et al. Simultaneous cone beam computed tomography-guided bronchoscopic marking and video-assisted thoracoscopic wedge resection in a hybrid operating room. Thoracic Cancer. 2019;10(3):579-582.
9. Anayama T, Yamamoto M, Hirohashi K, Miyazaki R, Okada H, et al. The accuracy of cone-beam computed tomography and augmented fluoroscopy-guided bronchoscopic marking of multiple small-sized pulmonary nodules in a hybrid operating room: a retrospective cohort study. Quantitative Imaging in Medicine & Surgery. 2021;11(2):725-736.
10. Andersen F, Durakovic A. [Electromagnetic navigated bronchoscopy can be applied for diagnosing peripherally located lung cancer in patients with severely reduced lung function]. Ugeskrift for Laeger. 2013;175(20):1416-1419.
11. Andrade RS. Electromagnetic navigation bronchoscopy-guided thoracoscopic wedge resection of small pulmonary nodules. Seminars in Thoracic & Cardiovascular Surgery. 2010;22(3):262-265.
12. Asano F, Ishida T, Shinagawa N, Sukoh N, Anzai M, et al. Virtual bronchoscopic navigation without X-ray fluoroscopy to diagnose peripheral pulmonary lesions: a randomized trial. BMC Pulmonary Medicine. 2017;17(1):184.
13. Asano F, Shinagawa N, Ishida T, Tsuzuku A, Tachihara M. Subgroup for which virtual bronchoscopic navigation is useful for endobronchial ultrasonography of peripheral pulmonary lesions. Respirology (Carlton, Vic). 2015;20:21.
14. Asano F, Shindoh J, Shigemitsu K, Miya K, Abe T, et al. Ultrathin bronchoscopic barium marking with virtual bronchoscopic navigation for fluoroscopy-assisted thoracoscopic surgery. Chest. 2004;126(5):1687-1693.
15. Asano F. Does virtual bronchoscopic navigation improve the diagnostic yield of transbronchial biopsy? Respirology. 2018;23(11):970-971.
16. Asano FITSNSNAMK. Virtual bronchoscopic navigation without X-ray fluoroscopy to diagnose peripheral pulmonary lesions: A randomized trial. European Respiratory Journal. 2016;48.
17. Atkins NK, Marjara J, Kaifi JT, Kunin JR, Saboo SS, et al. Role of Computed Tomography-guided Biopsies in the Era of Electromagnetic Navigational Bronchoscopy: A Retrospective Study of Factors Predicting Diagnostic Yield in Electromagnetic Navigational Bronchoscopy and Computed Tomography Biopsies. Journal of Clinical Imaging Science. 2020;10:33.
18. Avasarala SK, Machuzak MS, Gildea TR. Multidimensional Precision: Hybrid Mobile 2D/3D C-Arm Assisted Biopsy of Peripheral Lung Nodules. Journal of Bronchology & Interventional Pulmonology. 2020;27(2):153-155.
19. Awais O, Reidy MR, Mehta K, Bianco V, Gooding WE, et al. Electromagnetic Navigation Bronchoscopy-Guided Dye Marking for Thoracoscopic Resection of Pulmonary Nodules. Annals of Thoracic Surgery. 2016;102(1):223-229.

20. Bakir B, Tuzun U, Terzibasioglu E, Dursun M, Guven K, et al. [The diagnostic efficiency of multislice CT virtual bronchoscopy in detecting endobronchial tumors]. Tuberkuloz ve Toraks. 2008;56(1):43-49.
21. Balbo PE, Bodini BD, Patrucco F, Della Corte F, Zanaboni S, et al. Electromagnetic navigation bronchoscopy and rapid on site evaluation added to fluoroscopy-guided assisted bronchoscopy and rapid on site evaluation: improved yield in pulmonary nodules. Minerva Chirurgica. 2013;68(6):579-585.
22. Becker HD, Herth F, Ernst A, Schwarz Y. Bronchoscopic biopsy of peripheral lung lesions under electromagnetic guidance: a pilot study. Journal of Bronchology & Interventional Pulmonology. 2005;12(1):9-13.
23. Belanger AR, Burks AC, Chambers DM, Ghosh S, MacRosty CR, et al. Peripheral Lung Nodule Diagnosis and Fiducial Marker Placement Using a Novel Tip-Tracked Electromagnetic Navigation Bronchoscopy System. Journal of Bronchology & Interventional Pulmonology. 2019;26(1):41-48.
24. Benn BS, Romero AO, Lum M, Krishna G. Robotic-Assisted Navigation Bronchoscopy as a Paradigm Shift in Peripheral Lung Access. Lung. 2021;199(2):177-186.
25. Bessich JL, Sterman DH. Improving electromagnetic navigation: One nodule at a time. Respirology. 2020;25(2):130-131.
26. Bhatt KM, Tandon YK, Graham R, Lau CT, Lempel JK, et al. Electromagnetic Navigational Bronchoscopy versus CT-guided Percutaneous Sampling of Peripheral Indeterminate Pulmonary Nodules: A Cohort Study. Radiology. 2018;286(3):1052-1061.
27. Biswas A, Mehta HJ, Sriram PS. Diagnostic Yield of the Virtual Bronchoscopic Navigation System Guided Sampling of Peripheral Lung Lesions using Ultrathin Bronchoscope and Protected Bronchial Brush. Turkish Thoracic Journal. 2019;20(1):6-11.
28. Biswas A, Sriram PS. Localization of Peripheral Pulmonary Lesions Using Navigational Bronchoscopy and Radial Probe Endobronchial Ultrasound Confirmation. Annals of the American Thoracic Society. 2017;14(1):150-152.
29. Bolton WD, Cochran T, Ben-Or S, Stephenson JE, Ellis W, et al. Electromagnetic Navigational Bronchoscopy Reduces the Time Required for Localization and Resection of Lung Nodules. Innovations: Technology & Techniques in Cardiothoracic & Vascular Surgery. 2017;12(5):333-337.
30. Bolton WD, Howe H, rd, Stephenson JE. The utility of electromagnetic navigational bronchoscopy as a localization tool for robotic resection of small pulmonary nodules. Annals of Thoracic Surgery. 2014;98(2):471-475; discussion 475.
31. Bolton WD, Richey J, Ben-Or S, Hale AL, Ewing JA, Stephenson JE. Electromagnetic Navigational Bronchoscopy: A Safe and Effective Method for Fiducial Marker Placement in Lung Cancer Patients. American Surgeon. 2015;81(7):659-662.
32. Bolton WD, Richey J, Ben-Or S, Hale AL, Ewing JA, Stephenson JE. Electromagnetic navigational bronchoscopy: A safe and effective method for fiducial marker placement in lung cancer patients. American Surgeon. 2015;81(7):569-662.
33. Bowling MR, Folch EE, Khandhar SJ, Arenberg DA, Awais O, et al. Pleural dye marking of lung nodules by electromagnetic navigation bronchoscopy. The clinical respiratory journal. 2019;13(11):700-707.
34. Bowling MR, Folch EE, Khandhar SJ, Kazakov J, Krimsky WS, et al. Fiducial marker placement with electromagnetic navigation bronchoscopy: a subgroup analysis of the prospective, multicenter NAVIGATE study. Therapeutic Advances in Respiratory Disease. 2019;13:1753466619841234.

35. Brown J, Lee TJ, Joiner T, Wrightson W. Using Electromagnetic Navigation Bronchoscopy and Dye Injection to Aid in Video-Assisted Lung Resection. American Surgeon. 2016;82(11):1052-1054.
36. Brownback KR, Quijano F, Latham HE, Simpson SQ. Electromagnetic navigational bronchoscopy in the diagnosis of lung lesions. Journal of Bronchology & Interventional Pulmonology. 2012;19(2):91-97.
37. Chaddha U, Kovacs SP, Manley C, Hogarth DK, Cumbo-Nacheli G, et al. Robot-assisted bronchoscopy for pulmonary lesion diagnosis: results from the initial multicenter experience. BMC Pulmonary Medicine. 2019;19(1):243.
38. Chan JWY, Lau RWH, Ng CSH. Electromagnetic navigation bronchoscopy fiducial marker margin identification plus triple dye for complete lung nodule resection. JTCVS Techniques. 2020;3:329-333.
39. Chen AC, Pastis NJ, Jr, Mahajan AK, Khandhar SJ, et al. Robotic Bronchoscopy for Peripheral Pulmonary Lesions: A Multicenter Pilot and Feasibility Study (BENEFIT). Chest. 2021;159(2):845-852.
40. Chen WF, Zhong ZC, Huang P. [Application of bronchoscopy navigation in peripheral pulmonary lesions]. Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih Chinese Journal of Tuberculosis & Respiratory Diseases. 2017;40(8):622-625.
41. Chen Y, Li S, Chen H, Zhong C, Zhong N. [Electromagnetic navigation bronchoscopy real-time guidance lung biopsy for the diagnosis of small peripheral pulmonary lesions]. Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih Chinese Journal of Tuberculosis & Respiratory Diseases. 2014;37(8):579-582.
42. Chen ZB, Jin YP, Yu YM, Zhu DP, Ma HY, et al. [A study of the diagnostic value of endobronchial ultrasound guide sheath transbronchial lung biopsy combined with virtual bronchoscopic navigation in peripheral pulmonary lesions]. Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih Chinese Journal of Tuberculosis & Respiratory Diseases. 2016;39(7):509-513.
43. Chen ZB, Jin YP, Yu YM, Zhu DP, Ma HY, et al. [A study of the diagnostic value of endobronchial ultrasound guide sheath transbronchial lung biopsy combined with virtual bronchoscopic navigation in peripheral pulmonary lesions]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases. 2016;39(7):509-513.
44. Cherian S, Kaur S, Karanth S, Xian J, Estrada YMR. Diagnostic yield of electromagnetic navigational bronchoscopy: A safety net community-based hospital experience in the United States. Annals of Thoracic Medicine. 2021;16(1):102-109.
45. Cho HJ, Roknuggaman M, Han WS, Kang SK, Kang MW. Electromagnetic navigation bronchoscopy-Chungnam National University Hospital experience. Journal of Thoracic Disease. 2018;10(Suppl 6):S717-S724.
46. Cho HJ, Roknuggaman M, Han WS, Kang SK, Kang MW. Electromagnetic navigation bronchoscopy-Chungnam National University Hospital experience. Journal of Thoracic Disease. 2018;10(Suppl 6):S717-S724.
47. Cho RJ, Senitko M, Wong J, Dincer EH, Khosravi H, et al. Feasibility of Using the O-Arm Imaging System During ENB-rEBUS-guided Peripheral Lung Biopsy: A Dual-center Experience. Journal of Bronchology & Interventional Pulmonology. 2020;18:18.
48. Cicenia J, Bhadra K, Sethi S, Nader DA, Whitten P, Hogarth DK. Augmented Fluoroscopy: A New and Novel Navigation Platform for Peripheral Bronchoscopy. Journal of Bronchology & Interventional Pulmonology. 2021;28(2):116-123.

49. Dale CR, Madtes DK, Fan VS, Gorden JA, Veenstra DL. Navigational bronchoscopy with biopsy versus computed tomography-guided biopsy for the diagnosis of a solitary pulmonary nodule: a cost-consequences analysis. Journal of Bronchology & Interventional Pulmonology. 2012;19(4):294-303.
50. Deng CJ, Dai FQ, Qian K, Tan QY, Wang RW, et al. Clinical updates of approaches for biopsy of pulmonary lesions based on systematic review. BMC Pulmonary Medicine. 2018;18(1):146.
51. Duplaga M, Socha M, Wojciechowski W, Soja J, Tomaszewska R, et al. Comparison of the effectiveness of the transbronchial needle aspiration supported with the interactive virtual bronchoscopy application or with non-real time endobronchial ultrasonography in patients suspected of lung cancer [Abstract]. European Respiratory Society Annual Congress, Berlin, Germany, October 4-8. 2008:[P3396].
52. Fang F, Pan L, Bo LY, Li WP, Fu EQ, et al. [Diagnostic value of endobronchial ultrasonography with guide-sheath combined with virtual bronchoscopy navigation in peripheral lung cancer]. Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih Chinese Journal of Tuberculosis & Respiratory Diseases. 2018;41(6):472-476.
53. Fangfang X, Jian Z, Liming C, Xiaoxuan Z, Junxiang C, et al. Design of a prospective, multicenter, and cohort study of an innovative electromagnetic navigation bronchoscopy in diagnosing pulmonary nodules among Chinese population. Journal of Thoracic Disease. 2019;11(12):5592-5600.
54. Fielding DIK, Bashirzadeh F, Son JH, Todman M, Chin A, et al. First Human Use of a New Robotic-Assisted Fiber Optic Sensing Navigation System for Small Peripheral Pulmonary Nodules. Respiration. 2019;98(2):142-150.
55. Fiorelli A, Raucci A, Cascone R, Reginelli A, Di Natale D, et al. Three-dimensional virtual bronchoscopy using a tablet computer to guide real-time transbronchial needle aspiration. Interactive Cardiovascular & Thoracic Surgery. 2017;24(4):567-575.
56. Folch EE, Bowling MR, Gildea TR, Hood KL, Murgu SD, et al. Design of a prospective, multicenter, global, cohort study of electromagnetic navigation bronchoscopy. BMC Pulmonary Medicine. 2016;16(1):60.
57. Folch EE, Pritchett MA, Nead MA, Bowling MR, Murgu SD, et al. Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions: One-Year Results of the Prospective, Multicenter NAVIGATE Study. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2019;14(3):445-458.
58. Furukawa BS, Pastis NJ, Tanner NT, Chen A, Silvestri GA. Comparing Pulmonary Nodule Location During Electromagnetic Bronchoscopy With Predicted Location on the Basis of Two Virtual Airway Maps at Different Phases of Respiration. Chest. 2018;153(1):181-186.
59. Gatenby RA, Mulhern CB, Jr, Broder GJ, Moldofsky PJ. Computed-tomographic-guided biopsy of small apical and peripheral upper-lobe lung masses. Radiology. 1984;150(2):591-592.
60. Gildea TR, Folch EE, Khandhar SJ, Pritchett MA, Lemense GP, et al. The Impact of Biopsy Tool Choice and Rapid On-Site Evaluation on Diagnostic Accuracy for Malignant Lesions in the Prospective: Multicenter NAVIGATE Study. Journal of Bronchology and Interventional Pulmonology. 2021:174-183.
61. Gulias-Soidan D, Crus-Sanchez NM, Fraga-Manteiga D, Cao-González JI, Balboa-Barreiro V, González-Martín C. Cone-beam ct-guided lung biopsies: Results in 94 patients. Diagnostics. 2020;10(12).

62. Ha D, Choi H, Almeida FA, Arrossi A, Brainard J, et al. Histologic and molecular characterization of lung cancer with tissue obtained by electromagnetic navigation bronchoscopy. Journal of Bronchology & Interventional Pulmonology. 2013;20(1):10-15.
63. Hachey KJ, Digesu CS, Armstrong KW, Gilmore DM, Khullar OV, et al. A novel technique for tumor localization and targeted lymphatic mapping in early-stage lung cancer. Journal of Thoracic & Cardiovascular Surgery. 2017;154(3):1110-1118.
64. Hariri LP, Villiger M, Applegate MB, Mino-Kenudson M, Mark EJ, et al. Seeing beyond the bronchoscope to increase the diagnostic yield of bronchoscopic biopsy. American Journal of Respiratory & Critical Care Medicine. 2013;187(2):125-129.
65. Hassan T, Piton N, Lachkar S, Salaun M, Thiberville L. A Novel Method for In Vivo Imaging of Solitary Lung Nodules Using Navigational Bronchoscopy and Confocal Laser Microendoscopy. Lung. 2015;193(5):773-778.
66. Hohenforst-Schmidt W, Banckwitz R, Zarogoulidis P, Vogl T, Darwiche K, et al. Radiation exposure of patients by cone beam CT during endobronchial navigation - a phantom study. Journal of Cancer. 2014;5(3):192-202.
67. Huang H, Chen S, Pan L, Chen K, Yao F, Ma H. [Diagnostic Utility of Electromagnetic Navigation Bronchoscopy Combined with Radial Probe Endobronchial Ultrasound in Peripheral Pulmonary Lesions]. Chinese Journal of Lung Cancer. 2017;20(12):837-840.
68. Hwang EJ, Kim H, Park CM, Yoon SH, Lim HJ, Goo JM. Cone beam computed tomography virtual navigation-guided transthoracic biopsy of small (<= 1 cm) pulmonary nodules: impact of nodule visibility during real-time fluoroscopy. British Journal of Radiology. 2018;91(1087):20170805.
69. Hwang EJ, Park CM, Yoon SH, Lim HJ, Goo JM. Risk factors for haemoptysis after percutaneous transthoracic needle biopsies in 4,172 cases: Focusing on the effects of enlarged main pulmonary artery diameter. European Radiology. 2018;28(4):1410-1419.
70. Hwang HS, Chung MJ, Lee JW, Shin SW, Lee KS. C-arm cone-beam CT-guided percutaneous transthoracic lung biopsy: usefulness in evaluation of small pulmonary nodules. AJR American Journal of Roentgenology. 2010;195(6):W400-W407.
71. Iannelli G, Caivano R, Villonio A, Semeraro V, Lucarelli NM, et al. Percutaneous Computed Tomography-Guided Lung Biopsies using a Virtual Navigation Guidance: Our Experience. Cancer Investigation. 2018;36(6):349-355.
72. Ishige. [Study identified from previous review, bu no reference was provided]. 2017.
73. Ishiwata T, Ujiie H, Gregor A, Inage T, Motooka Y, et al. Pilot study using virtual 4-D tracking electromagnetic navigation bronchoscopy in the diagnosis of pulmonary nodules: a single center prospective study. Journal of Thoracic Disease. 2021;13(5):2885-2895.
74. Ishiwata T, Ujiie H, Gregor A, Motooka Y, Inage T, et al. A series of cases using combined virtual 4-D electromagnetic tip-tracked devices and endobronchial ultrasound in the diagnosis of peripheral pulmonary nodules. American Journal of Respiratory and Critical Care Medicine. 2019;199(9).
75. Jaconi M, Pagni F, Vacirca F, Leni D, Corso R, et al. C-arm cone-beam CT-guided transthoracic lung core needle biopsy as a standard diagnostic tool: an observational study. Medicine. 2015;94(12):e698.
76. Jiao DC, Li TF, Han XW, Wu G, Ma J, et al. Clinical applications of the C-arm cone-beam CT-based 3D needle guidance system in performing percutaneous transthoracic needle biopsy of pulmonary lesions. Diagnostic and Interventional Radiology. 2014;20(6):470-474.

77. Jiayuan S, Xin YXZHB. Diagnostic value of electromagnetic navigation bronchoscopy for peripheral pulmonary lesions : A randomized controlled trial. Journal of Thoracic Oncology. 2015;10(9):S396.
78. Jin KN, Park CM, Goo JM, Lee HJ, Lee Y, et al. Initial experience of percutaneous transthoracic needle biopsy of lung nodules using C-arm cone-beam CT systems. European Radiology. 2010;20(9):2108-2115.
79. Jin W, Wang L. Role of rapid on-site evaluation in electromagnetic navigation bronchoscopy-guided peripheral lung biopsy. European Respiratory Journal. 2017;50.
80. Karnak D, Çiledağ A, Ceyhan K, Atasoy Ç, Akyar S, Kayacan O. Electromagnetic navigation diagnostic bronchoscopy for peripheral lung lesions and mediastinal lymph nodes: First results. Turk Toraks Dergisi. 2011;12(2):51-56.
81. Kato A, Yasuo M, Hama M, Ichiyama T, Hanaoka M. Contribution of virtual bronchoscopic navigation to reduction of radiation exposure in computed tomography guided bronchoscopy. Respirology (Carlton, Vic). 2015;20:22.
82. Katsis J, Roller L, Aboudara M, Pannu J, Chen H, et al. Diagnostic Yield of Digital Tomosynthesis-assisted Navigational Bronchoscopy for Indeterminate Lung Nodules. Journal of Bronchology & Interventional Pulmonology. 2021;17:17.
83. Katsis J, Roller L, Aboudara M, Pannu JK, Chen H, et al. Digital tomosynthesis assisted electromagnetic navigational bronchoscopy, one year retrospective data. American Journal of Respiratory and Critical Care Medicine. 2020;201(1).
84. Katsis J, Roller L, Lester M, Johnson J, Lentz R, et al. High Accuracy of Digital Tomosynthesis-Guided Bronchoscopic Biopsy Confirmed by Intraprocedural Computed Tomography. Respiration. 2021:1-8.
85. Kennedy MP. Lung-Cancer Screening and the NELSON Trial. New England Journal of Medicine. 2020;382(22):2164-2165.
86. Khan AY, Berkowitz D, Krimsky WS, Hogarth DK, Parks C, Bechara R. Safety of pacemakers and defibrillators in electromagnetic navigation bronchoscopy. Chest. 2013;143(1):75-81.
87. Khandhar SJ, Bowling MR, Flandes J, Gildea TR, Hood KL, et al. Electromagnetic navigation bronchoscopy to access lung lesions in 1,000 subjects: First results of the prospective, multicenter NAVIGATE study. BMC Pulmonary Medicine. 2017;17(1):59.
88. Kickuth R, Reichling C, Bley T, Hahn D, Ritter C. C-Arm Cone-Beam CT Combined with a New Electromagnetic Navigation System for Guidance of Percutaneous Needle Biopsies: Initial Clinical Experience. RoFo Fortschritte auf dem Gebiet der Rontgenstrahlen und der Bildgebenden Verfahren. 2015;187(7):569-576.
89. Kim H, Kwon D, Yoon SH, Kim H, Park CM, et al. Bronchovascular injury associated with clinically significant hemoptysis after CT-guided core biopsy of the lung: Radiologic and histopathologic analysis. PLoS ONE. 2018;13(9).
90. Kim H, Park CM, Yoon SH, Hwang EJ, Lee JH, et al. Open Bronchus Sign on CT: A Risk Factor for Hemoptysis after Percutaneous Transthoracic Biopsy. Korean Journal of Radiology. 2018;19(5):880-887.
91. Kim JI, Park CM, Kim H, Lee JH, Goo JM. Non-specific benign pathological results on transthoracic core-needle biopsy: how to differentiate false-negatives? European Radiology. 2017;27(9):3888-3895.
92. Kim JI, Park CM, Lee SM, Goo JM. Rapid needle-out patient-rollover approach after cone beam CT-guided lung biopsy: effect on pneumothorax rate in 1,191 consecutive patients. European Radiology. 2015;25(7):1845-1853.

93. Kim TH, Park CM, Lee SM, McAdams HP, Kim YT, Goo JM. Percutaneous transthoracic localization of pulmonary nodules under C-arm cone-beam CT virtual navigation guidance. Diagnostic & Interventional Radiology. 2016;22(3):224-230.
94. Kotlyarov PM. Virtual bronchoscopy in differential diagnosis of neoplastic, fibrous and inflammatory abnormalities. Pulmonologiya. 2017;27(6):748-753.
95. Krimsky WS, Minnich DJ, Cattaneo SM, Sarkar SA, Harley DP, et al. Thoracoscopic detection of occult indeterminate pulmonary nodules using bronchoscopic pleural dye marking. Journal of Community Hospital Internal Medicine Perspectives. 2014;4.
96. Kumar A, Harris K. Same-Day Computed Tomographic Chest Imaging for Pulmonary Nodule Targeting with Electromagnetic Navigation Bronchoscopy: Will It Prevent Unnecessary Procedures? Annals of the American Thoracic Society. 2017;14(3):479.
97. Kuo SW, Tseng YF, Dai KY, Chang YC, Chen KC, Lee JM. Electromagnetic Navigation Bronchoscopy Localization Versus Percutaneous CT-Guided Localization for Lung Resection via Video-Assisted Thoracoscopic Surgery: A Propensity-Matched Study. Journal of Clinical Medicine. 2019;8(3):18.
98. Lacasse Y, Martel S, Hebert A, Carrier G, Raby B. Accuracy of virtual bronchoscopy to detect endobronchial lesions. Annals of Thoracic Surgery. 2004;77(5):1774-1780.
99. Lamprecht B, Porsch P, Pirich C, Studnicka M. Electromagnetic navigation bronchoscopy in combination with PET-CT and rapid on-site cytopathologic examination for diagnosis of peripheral lung lesions. Lung. 2009;187(1):55-59.
100. Lau K, Flandes J, Christensen M, Bezzi M, Lamprecht B, et al. Electromagnetic navigation bronchoscopy in the European cohort of the prospective, multicenter NAVIGATE study. Annals of Oncology. 2019;30:ii26.
101. Lee KA, Raval AA, Amir L. Cost-effectiveness of endobronchial percutaneous biopsy compared with transthoracic biopsy for diagnosis of peripheral lung lesions. Lung Cancer Management. 2014;3(2):135-148.
102. Lee SM, Park CM, Lee KH, Bahn YE, Kim JI, Goo JM. C-arm cone-beam CT-guided percutaneous transthoracic needle biopsy of lung nodules: clinical experience in 1108 patients. Radiology. 2014;271(1):291-300.
103. Lee WJ, Chong S, Seo JS, Shim HJ. Transthoracic fine-needle aspiration biopsy of the lungs using a C-arm cone-beam CT system: diagnostic accuracy and post-procedural complications. British Journal of Radiology. 2012;85(1014):e217-e222.
104. Lee Y, Park CK, Oh YH. Diagnostic performance of core needle biopsy and fine needle aspiration separately or together in the diagnosis of intrathoracic lesions under C-arm guidance. Journal of the Belgian Society of Radiology. 2018;102(1).
105. Li S, Yan W, Chen M, Sun L, Wu Q, Chen K. [Diagnostic Utility of Virtual Bronchoscopic Navigation Assisted Endobronchial Ultrasonography with Guide Sheath for Peripheral Pulmonary Lesions]. Chinese Journal of Lung Cancer. 2019;22(3):125-131.
106. Liewald F, Lang G, Fleiter T, Sokiranski R, Halter G, Orend KH. Comparison of virtual and fiberoptic bronchoscopy. Thoracic & Cardiovascular Surgeon. 1998;46(6):361-364.
107. Linden PA. Use of navigation bronchoscopy for biopsy and endobronchial fiducial placement. Innovations: Technology & Techniques in Cardiothoracic & Vascular Surgery. 2011;6(4):271-275.
108. Liu N, Kan J, Cao W, Cao J, Jiang E, et al. Metagenomic next-generation sequencing diagnosis of peripheral pulmonary infectious lesions through virtual navigation, radial EBUS, ultrathin bronchoscopy, and ROSE. Journal of International Medical Research. 2019;47(10):4878-4885.

109. Liu N, Kan J, Yu N, Cao W, Cao J, et al. Application of metagenomic next-generation sequencing technology for difficult lung lesions in patients with haematological diseases. Translational Cancer Research. 2020;9(9):5245-5254.
110. Liu W, Liu J, Liu Y, Huang H, Wei B, Sun Z. Diagnosis of peripheral pulmonary lesions using endorbronchial ultrasonography with a guide sheath combination with virtual bronchoscopic navigation. China Journal of Endoscopy. 2016;22(6):90-93.
111. Liu Y, Wang F, Zhang QC, Tong ZH. Value of virtual bronchoscopic navigation and transbronchial ultrasound-guided sheath-guided exploration in diagnosis of peripheral lung cancer. World Journal of Clinical Cases. 2020;8(16):3450-3457.
112. Marino KA, Sullivan JL, Weksler B. Electromagnetic Navigation Bronchoscopy for Identifying Lung Nodules for Thoracoscopic Resection. Annals of Thoracic Surgery. 2016;102(2):454-457.
113. McGuire AL, Myers R, Grant K, Lam S, Yee J. The Diagnostic Accuracy and Sensitivity for Malignancy of Radial-Endobronchial Ultrasound and Electromagnetic Navigation Bronchoscopy for Sampling of Peripheral Pulmonary Lesions: Systematic Review and Meta-analysis. Journal of Bronchology & Interventional Pulmonology. 2020;27(2):106-121.
114. Mohanasundaram U, Ho LA, Kuschner WG, Chitkara RK, Canfield J, et al. The diagnostic yield of navigational bronchoscopy performed with propofol deep sedation. International Scholarly Research Notices. 2013;2013.
115. Muñoz-Largacha JA, Batra H, Wei B. Navigational Bronchoscopy with Interventional Pulmonologists and Thoracic Surgeons. Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery. 2021;16(2):117-122.
116. Munoz-Largacha JA, Ebright MI, Litle VR, Fernando HC. Electromagnetic navigational bronchoscopy with dye marking for identification of small peripheral lung nodules during minimally invasive surgical resection. Journal of Thoracic Disease. 2017;9(3):802-808.
117. Nakai T, Izumo T, Matsumoto Y, Tsuchida T. Virtual fluoroscopy during transbronchial biopsy for locating ground-glass nodules not visible on X-ray fluoroscopy. Journal of Thoracic Disease. 2017;9(12):5493-5502.
118. Okachi S, Imai N, Imaizumi K, Iwano S, Ando M, et al. Factors Affecting the Diagnostic Yield of Transbronchial Biopsy Using Endobronchial Ultrasonography with a Guide Sheath in Peripheral Lung Cancer. Internal Medicine. 2016;55(13):1705-1712.
119. Oki M, Saka H, Asano F, Kitagawa C, Kogure Y, Ando M. A randomized trial of navigational endosonographic ultrathin bronchoscopy versus thin bronchoscopy for the diagnosis of peripheral pulmonary lesions. European Respiratory Journal. 2018;52.
120. Omiya H, Kikuyama A, Kubo A, Okishio K, Kawaguchi T, et al. A feasibility and efficacy study on bronchoscopy with a virtual navigation system. Journal of Bronchology & Interventional Pulmonology. 2010;17(1):11-18.
121. Ost D, Shah R, Anasco E, Lusardi L, Doyle J, et al. A randomized trial of CT fluoroscopic-guided bronchoscopy vs conventional bronchoscopy in patients with suspected lung cancer. Chest. 2008;134(3):507-513.
122. Ozgul G, Cetinkaya E, Ozgul MA, Abul Y, Gencoglu A, et al. Efficacy and safety of electromagnetic navigation bronchoscopy with or without radial endobronchial ultrasound for peripheral lung lesions. Endoscopic Ultrasound. 2016;5(3):189-195.

123. Panchabhai TS, Biswas R, Madan N, Abdelrazek H, Patel VJ, et al. Electromagnetic navigational bronchoscopy for diagnosing peripheral lung lesions in lung transplant recipients: a single-center experience. Journal of Thoracic Disease. 2018;10(8):5108-5114.
124. Pertzov B, Gershman E, Izhakian S, Heching M, Amor SM, et al. The LungVision navigational platform for peripheral lung nodule biopsy and the added value of cryobiopsy. Thoracic Cancer. 2021;12(13):2007-2012.
125. Piao Z, Han SJ, Cho HJ, Kang MW. Feasibility of electromagnetic navigation bronchoscopy-guided lung resection for pulmonary ground-glass opacity nodules. Journal of Thoracic Disease. 2020;12(5):2467-2473.
126. Pritchett MA, Bhadra K, Mattingley JS. Electromagnetic Navigation Bronchoscopy With Tomosynthesis-based Visualization and Positional Correction: Three-dimensional Accuracy as Confirmed by Cone-Beam Computed Tomography. Journal of Bronchology & Interventional Pulmonology. 2021;28(1):10-20.
127. Pritchett MA, Schampaert S. Tipping Point: Cone Beam CT With Augmented Fluoroscopy for the Biopsy and Treatment of Peripheral Nodules. Journal of Bronchology & Interventional Pulmonology. 2019;26(1):e13-e15.
128. Pritchett MA. Prospective Analysis of a Novel Endobronchial Augmented Fluoroscopic Navigation System for Diagnosis of Peripheral Pulmonary Lesions. Journal of Bronchology & Interventional Pulmonology. 2021;28(2):107-115.
129. Puchalski J. Robotic Bronchoscopy for the Diagnosis of Peripheral Lung Nodules: a Review. Current Pulmonology Reports. 2021;10(1):46-52.
130. Pupovac SS, Chaudhry A, Singh VA. Benefits of Electromagnetic Navigational Bronchoscopy for Identifying Pulmonary Nodules for Robotic Resections. Innovations: Technology & Techniques in Cardiothoracic & Vascular Surgery. 2017;12(6):418-420.
131. Qian K, Deng Y, Shen C, Feng YG, Deng B, Tan QY. Combination of electromagnetic navigation bronchoscopy-guided biopsy with a novel staining for peripheral pulmonary lesions. World Journal of Surgical Oncology. 2019;17(1):158.
132. Qian K, Feng Y, Wang R, Deng B, Tan Q. [Application of Electromagnetic Navigation Bronchoscopic Biopsy Combined with Massage Staining in Diagnosis and Treatment of Peripheral Pulmonary Lesion]. Chinese Journal of Lung Cancer. 2019;22(1):15-19.
133. Qian K, Krimsky WS, Sarkar SA, Deng Y. Efficiency of Electromagnetic Navigation Bronchoscopy and Virtual Bronchoscopic Navigation. Annals of Thoracic Surgery. 2020;109(6):1731-1740.
134. Rickets W, Lau KKW, Pollit V, Mealing S, Leonard C, et al. Exploratory cost-effectiveness model of electromagnetic navigation bronchoscopy (ENB) compared with CT-guided biopsy (TTNA) for diagnosis of malignant indeterminate peripheral pulmonary nodules. BMJ Open Respiratory Research. 2020;7(1):08.
135. Rojas-Solano JR, Ugalde-Gamboa L, Machuzak M. Robotic Bronchoscopy for Diagnosis of Suspected Lung Cancer: A Feasibility Study. Journal of Bronchology & Interventional Pulmonology. 2018;25(3):168-175.
136. Rotolo N, Floridi C, Imperatori A, Fontana F, Ierardi AM, et al. Comparison of cone-beam CT-guided and CT fluoroscopy-guided transthoracic needle biopsy of lung nodules. European Radiology. 2016;26(2):381-389.

137. Rottgen R, Schurmann D, Pinkernelle J, Herzog H, Lopez-Haninnen E, et al. [Detection of airways stenoses: comparison of virtual and flexible bronchoscopy]. Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin. 2005;177(3):338-343.
138. Salvolini L, Gasparini S, Baldelli S, Bichi S, Amici F. [Virtual bronchoscopy: the correlation between endoscopic simulation and bronchoscopic findings]. Radiologia Medica. 1997;94(5):454-462.
139. Sanchez-Font A, Giralt L, Vollmer I, Pijuan L, Gea J, Curull V. Endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions. A controlled study with fluoroscopy. Archivos de Bronconeumologia. 2014;50(5):166-171.
140. Sánchez-Font A, Vollmer I, Pijuan L, Giralt L, Curull V. Endobronchial ultrasound for the diagnosis of pheripheral pulmonary lesions. A controlled study With fluoroscopy. European Respiratory Journal. 2013;42.
141. Schwarz Y, Greif J, Becker HD, Ernst A, Mehta A. Real-time electromagnetic navigation bronchoscopy to peripheral lung lesions using overlaid CT images: the first human study. Chest. 2006;129(4):988-994.
142. Semaan RW, Lee HJ, Feller-Kopman D, Lerner AD, Mallow CM, et al. Same-Day Computed Tomographic Chest Imaging for Pulmonary Nodule Targeting with Electromagnetic Navigation Bronchoscopy May Decrease Unnecessary Procedures. Annals of the American Thoracic Society. 2016;13(12):2223-2228.
143. Shinagawa N, Asano F, Ishida T, Shindoh J, Anzai M, et al. Effect of virtual bronchoscopic navigation in combination with ultrathin bronchoscopy for diagnosing peripheral pulmonary lesions. European Respiratory Journal. 2013;42.
144. Silvestri GA, Bevill BT, Huang J, Brooks M, Choi Y, et al. An Evaluation of Diagnostic Yield From Bronchoscopy: The Impact of Clinical/Radiographic Factors, Procedure Type, and Degree of Suspicion for Cancer. Chest. 2020;157(6):1656-1664.
145. Song JW, Park IK, Bae SY, Na KJ, Park S, et al. Electromagnetic Navigation Bronchoscopy-Guided Dye Marking for Localization of Pulmonary Nodules. Annals of Thoracic Surgery. 2021;27:27.
146. Stern JB, Vieira T, Perrot L, Lefevre M, Sayah MI, et al. [The role of electromagnetic navigation bronchoscopy in the diagnosis of peripheral pulmonary lesions]. Revue des Maladies Respiratoires. 2019;36(8):946-954.
147. Tachihara M, Ishida T, Kanazawa K, Sugawara A, Watanabe K, et al. A virtual bronchoscopic navigation system under X-ray fluoroscopy for transbronchial diagnosis of small peripheral pulmonary lesions. Lung Cancer. 2007;57(3):322-327.
148. Tang C, Luo W, Zhong C, Tong D, Chen Y, et al. [The diagnostic utility of virtual bronchoscopic navigation combined with endobronchial ultrasound guided transbronchial lung biopsy for peripheral pulmonary lesions]. Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih Chinese Journal of Tuberculosis & Respiratory Diseases. 2016;39(1):38-40.
149. Tao 2017. [Study identified from previous review, bu no reference was provided]
150. Tian Y, Wang C, Yue W, Lu M, Tian H. Comparison of computed tomographic imaging-guided hook wire localization and electromagnetic navigation bronchoscope localization in the resection of pulmonary nodules: a retrospective cohort study. Scientific Reports. 2020;10(1):21459.
151. Towe CW, Ho VP, Kazakov J, Jackson T, Perry Y, et al. Severe Chronic Obstructive Pulmonary Disease Is Not Associated With Complications After Navigational Bronchoscopy Procedures. Annals of Thoracic Surgery. 2017;104(1):290-295.

152. Towe CW, Nead MA, Rickman OB, Folch EE, Khandhar SJ, et al. Safety of Electromagnetic Navigation Bronchoscopy in Patients With COPD: Results From the NAVIGATE Study. Journal of Bronchology & Interventional Pulmonology. 2019;26(1):33-40.
153. Tsushima K, Sone S, Hanaoka T, Takayama F, Honda T, Kubo K. Comparison of bronchoscopic diagnosis for peripheral pulmonary nodule under fluoroscopic guidance with CT guidance. Respiratory Medicine. 2006;100(4):737-745.
154. Vining PF, Lee TM, Bizekis CS, Zervos MD. Use of electromagnetic navigational bronchoscopy in robotic pulmonary resection. Journal of Robotic Surgery. 2018;12(4):613-616.
155. Weiner GM, Schulze K, Geiger B, Ebhardt H, Wolf KJ, Albrecht T. CT bronchoscopic simulation for guiding transbronchial needle aspiration of extramural mediastinal and hilar lesions: initial clinical results. Radiology. 2009;250(3):923-931.
156. Xiong M, Zhang W, Wang D, Xu J. CT virtual bronchoscopy: imaging method and clinical application. Chinese Medical Journal. 2000;113(11):1022-1025.
157. Xue M, Wang J, Han Y, Zhu Y, Zhang N, et al. [Clinical Application of Electromagnetic Navigation Bronchoscopy on the Diagnosis of Peripheral Lung Lesions]. Chinese Journal of Lung Cancer. 2020;23(6):446-450.
158. Yang SM, Yu KL, Lin KH, Liu YL, Sun SE, et al. Localization of Small Pulmonary Nodules Using Augmented Fluoroscopic Bronchoscopy: Experience from 100 Consecutive Cases. World Journal of Surgery. 2020;44(7):2418-2425.
159. Yarmus LB, Arias S, Feller-Kopman D, Semaan R, Wang KP, et al. Electromagnetic navigation transthoracic needle aspiration for the diagnosis of pulmonary nodules: A safety and feasibility pilot study. Journal of Thoracic Disease. 2016;8(1):186-194.
160. Yasuo M, Kobayashi T, Hama M, Ichiyama T, Horiuchi T, et al. Combination of virtual bronchoscopic navigation with conventional transbronchial needle aspiration in the diagnosis of peribronchial pulmonary lesions located in the middle third of the lungs. Respiratory Investigation. 2016;54(5):355-363.
161. Yasuo M, Kobayashi T, Tokoro Y, Horiuchi T, Ichiyama T, et al. Prospective comparative study of chest computed tomography guided bronchoscopy with or without virtual bronchoscopic navigation. American Journal of Respiratory and Critical Care Medicine. 2013;187.
162. Yoon SH, Park CM, Lee KH, Lim KY, Suh YJ, et al. Analysis of Complications of Percutaneous Transthoracic Needle Biopsy Using CT-Guidance Modalities In a Multicenter Cohort of 10568 Biopsies. Korean Journal of Radiology. 2019;20(2):323-331.
163. Zheng X, Xie F, Sun J. OA01.07 Ultrathin Bronchoscopy Combined with VBN and EBUS for the Diagnosis of PPLs With or Without Fluoroscopy: A Randomized Trial. Journal of Thoracic Oncology. 2019;14(10):S207.
164. Zuccatosta L, Bonifazi M, Sediari M, Mei F, Gasparini S. Successful diagnosis of bilateral peripheral pulmonary nodules using Electromagnetic Navigation Bronchoscopy. Rassegna di Patologia dell'Apparato Respiratorio. 2012;27(1):52-54.

Bijlage 4. Evidencetabellen Systematische reviews

Folch, 2020	
• **Methods**	
• **Design**	Systematic review and meta-analysis
• **Source of funding and competing interest**	”The authors have reported to CHEST that no funding was received for this study.” “The authors have reported to CHEST the following: E. E. F. is a scientific consultant for Boston Scientific and Medtronic, is an educational consultant for Cook Medical and Pinnacle Biologics, and his institution has received a research grant from Intuitive Surgical. S J. K. is a consultant, advisor, and speaker for Medtronic, Boston Scientific, and Auris Robotics. A. M. is scientific consultant for Boston Scientific and an educational consultant for Olympus America, Cook Medical, and Pnnacle Biologics; and has received a research grant from Olympus and Intuitive Surgical.”
• **Search date**	November 2019
• **Searched databases and other sources**	“A highly sensitive database search was conducted without language restriction, using the following databases: PubMed (MEDLINE), Embase, LILACS (www.scielo.org), Clinical Trials (ClinicalTrials.gov), Cochrane Central Register of Controlled Trials, ScienceDirect (www.sciencedirect.com), Scirus (www.scirus. com/srsapp), ISI Web of Knowledge (www.isiwebofknowledge.com), and Google Scholar (http://scholar.google.com). References from the included studies were also manually searched along with the abstracts of potential studies presented in conferences from 2014 through 2019 by the American Thoracic Society, American College of Chest Physicians, European Respiratory Society, and American Association for Bronchology & Interventional Pulmonology.”
• **Included study designs**	In the protocol it was stated that observational studies will be included and case series excluded, however, also RCTs were included.
• **Number of included studies and participants**	A total of 40 studies were included in the qualitative and quantitative analyses. A total of 3,342 participants were extracted from the selected articles.
• **Study characteristics**	
• **Inclusion criteria**	(1) ENB used for diagnosis of PPLs, (2) diagnosis confirmed histologically or by close clinical follow-up, and (3) studies that stated a clear reference standard for establishing diagnostic sensitivity.
• **Exclusion criteria**	Review papers, letters, or studies in which data to calculate sensitivity for malignancy was insufficient.
• **Index test(s)**	Electromagnetic navigation bronchoscopy

• **Reference standard**	Combinations of: Surgery, follow-up, thoracotomy, CT fine needle aspiration, mediastinoscopy, PET scan, open lung biopsy, TTNA Target condition(s): Lung cancer
• **Results**	
• **Diagnostic accuracy (sensitivity, specificity, and/or other relevant measures like predictive values, AUC, LR, DOR)**	Sensitivity: 0.77 (95% CI 0.72 to 0.82) (random), 0.76 (95% CI 0.74 to 0.78) (fixed) Specificity: 1.00 (95% CI 0.99 to 1.00) Negative likelihood ratio: 0.2 (95% CI 0.1 to 0.3) Positive likelihood ratio: 15.8 (95% CI 10.3 to 24.2) AUC: 0.95 (SE 0.01)
• **Subgroups**	Subgroup: high risk of bias (9 studies) Sensitivity: 0.67 (95% CI 0.59 to 0.74) Subgroup: Low risk of bias (31 studies) Sensitivity: 0.77 (95% CI 0.71 to 0.82) Subgroup: Super Dimension navigation system (38 studies) Sensitivity: 0.78 (95% CI 0.73 to 0.83) Subgroup: Other navigation system (2 studies) Sensitivity: 0.70 (95% CI 0.54 to 0.84) Subgroup: General anesthesia (16 studies) Sensitivity: 0.74 (95% CI 0.66 to 0.81) Subgroup: Conscious sedation (15 studies) Sensitivity: 0.75 (95% CI 0.65 to 0.84) Subgroup: Mixed group of general anesthesia and conscious sedation (4 studies) Sensitivity: 0.74 (95% CI 0.65 to 0.81) Subgroup: EBN with rapid on-site examination (20 studies) Sensitivity: 0.72 (95% CI 0.66 to 0.76) reported in table. 0.76 (95% CI 0.69 to 0.83) reported in text. Subgroup: EBN without rapid on-site examination (14 studies) Sensitivity: 0.74 (95% CI 0.65 to 0.80) reported in table. 0.81 (95% CI 0.74 to 0.88) reported in text.

	Subgroup: EBN with fluoroscopy (19 studies) Sensitivity: 0.71 (95% CI 0.60 to 0.79) reported in table. 0.74 (95% CI 0.65 to 0.81) reported in text. Subgroup: EBN without fluoroscopy (15 studies) Sensitivity: 0.74 (95% CI 0.69 to 0.77) reported in table. 0.83 (95% CI 0.72 to 0.89) reported in text. Subgroup: EBN with r-EBUS (unclear number of studies) Sensitivity: 0.80 (95% CI 0.74 to 0.83) Subgroup: EBN without r-EBUS (unclear number of studies) Sensitivity: 0.72 (95% CI 0.66 to 0.76) Subgroup: EBN with one sampling technique (7 studies) Sensitivity: 0.67 (95% CI 0.53 to 0.79) Subgroup: EBN with two sampling techniques (11 studies) Sensitivity: 0.72 (95% CI 0.60 to 0.83) Subgroup: EBN with three sampling technique (19 studies) Sensitivity: 0.83 (95% CI 0.76 to 0.89) Subgroup: EBN with four sampling technique (1 study) Sensitivity: 0.91 (95% CI 0.82 to 0.96) Subgroup: EBN with five sampling technique (2 studies) Sensitivity: 0.72 (95% CI 0.69 to 0.76) "A subgroup analysis of studies over time showed no differences in sensitivity when studies were grouped in 2-year intervals" Results for other accuracy measures such as specificity were not reported.
• **Adverse events**	2.0% (95% CI 1.0% to 3.0%) pneumothorax 1.0% (95% CI 0.6% to 1.3%) minor bronchopulmonary bleeding 0.8% (95% CI 0.5% to 1.1%) major bronchopulmonary bleeding 0.6% (95% CI 0.4% to 0.9%) acute respiratory failure
• **Limitations**	

• **Limitations**	AMSTAR 2: The PICO components are clearly described and there is a review protocol that includes all essential information, except for the search strategy. No rationale for included study designs is provided and the search strategy is not reproducible. Study selection and data-extraction were performed in duplicate, however a list of excluded studies is lacking. Also, included studies are not described in sufficient detail. Risk of bias assessment and meta-analyses were done appropriately, however funding sources of included studies were not reported. The authors reported their funding sources but did not explain how they managed their potential conflicts of interest. Finally, there is selective reporting of outcomes in the review. In the protocol, diagnostic yield and diagnostic accuracy were reported as outcomes, but in the review, only sensitivity was reported, and complications were added as outcome. QUADAS 2: For patient selection, 18 studies scored a low risk of bias, 22 studies scored a high risk of bias and no studies scored unclear risk of bias. All studies scored a low risk of bias for index test. For reference standard, 38 studies scored a low risk of bias, no studies scored a high risk of bias, and 2 studies scored an unclear risk of bias. Finally, for flow and timing, 1 study scored a low risk of bias, 37 studies a high risk of bias, and 2 studies unclear risk of bias.
• **Other comments**	

Giri 2021. Virtual bronchoscopic navigation versus non-virtual bronchoscopic navigation assisted bronchoscopy for the diagnosis of peripheral pulmonary lesions: a systematic review and meta-analysis	
• **Methods**	
• **Design**	Systematic review and meta-analysis
• **Source of funding and competing interest**	Supported by grants from Chongqing Science and Technology Commission project cstc2017shmsA130044
• **Search date**	26 August 2020
• **Searched databases and other sources**	PubMed, Embase, Cochrane library, and Web of Sciences databases. Reference list of retrieved studies.
• **Included study designs**	Randomized controlled trials
• **Number of included studies and participants**	Six RCTs with 1626 patients (813 patients in virtual bronchoscopy navigation group and 813 patients in non-virtual bronchoscopy navigation group respectively)
• **Study characteristics**	
• **Inclusion criteria**	All studies that met the following criteria:

	(a) RCTs; (b) Patients were randomized to either virtual bronchoscopy navigation or non-virtual bronchoscopy navigation for peripheral pulmonary lesions; and (c) reporting any of the following outcomes: total diagnostic yield, total examination time, diagnostic yield according to the lesion size, nature of lesion, lesion location in the lung lobe, distance from the hilum, bronchus sign, and complications
• **Exclusion criteria**	Non-comparatives studies, case reports, conference papers, and review papers
• **Intervention(s)**	Virtual bronchoscopic navigation assisted (VBNA)
• **Comparator(s)**	Non- virtual bronchoscopic navigation assisted (NVBNA)
• **Results**	
Treatment initiation not informed by histopathology results	Not assessed
• **Complications**	Any complication VBN-assisted vs. non-VBN-assisted: 2.1% (15/723) vs. 2.5% (18/724); RR 0.84 (95% CI 0.42 to 1.67); 5 studies Also reported per study:

Study	VBNA	NVBNA
Asano et al. 2013	Pneumothorax not requiring drainage (n = 1) Hemorrhage (n = 2) Transient bradycardia (n = 1) No severe adverse events	Pneumothorax not requiring drainage (n = 1) Xylocaine intoxication (n = 1) Pneumonia (n = 1) No severe adverse events
Asano et al. 2017	Hyperventilation (n = 1) No severe adverse effect	Hemorrhage (n = 2) Pneumonia (n = 1) No severe adverse effect
Bo et al. 2019	Pneumothorax (n = 5) Hemorrhage (n = 3)	Pneumothorax (n = 7) Hemorrhage (n = 4)

	No severe adverse events	No severe adverse events
Chen et al. 2016	No severe adverse events	No severe adverse events
Ishida et al. 2011	No severe or moderate adverse events	Mild pneumothorax that did not require chest drainage (n = 1)
Xu et al. 2019	Pneumothorax requiring intervention (n = 2)	Hemorrhage (n = 1)

• **Quality of life**	Not assessed
• **Diagnostic yield**	VBN-assisted vs. non-VBN-assisted: 74.2% (603/813) vs. 69.5% (565/813); RR 1.07 (95% CI 0.98 to 1.17); 6 studies <u>Subgroup: lesion size ≤20 mm</u> VBN-assisted vs. non-VBN-assisted: 64.0% (240/375) vs. 54.6% (212/388); RR 1.18 (95% CI 1.05 to 1.32); 5 studies <u>Subgroup: lesion size > 20 mm</u> VBN-assisted vs. non-VBN-assisted: 86.7% (313/361) vs. 84.4% (298/353); RR 1.01 (95% CI 0.96 to 1.06); 5 studies Also subgroup analyses conducted for nature of lesion (benign, malignant), location of lesion (bilateral lower lobe, right middle lobe), distance from hilum (peripheral third, central or intermediate third), bronchus sign (absent, present).
• **Diagnostic test accuracy measures**	Not assessed
• **Limitations**	
• **Limitations**	AMSTAR 2: No systematic review protocol was available, and there was no rationale for including only RCTs. The quality of the search was moderate: trial registries and grey literature were not searched, and no experts in the field were contacted. It is unclear whether study selection was performed in duplicate, but data-extraction was performed in duplicate. No list of excluded studies was provided, and description of included studies was limited. Methods for meta-analyses were appropriate but the impact of bias on the results was not explored. It was not possible to study the presence of publication bias due to the low number of included studies. Cochrane Risk of bias tool: • randomisation: all studies low risk • allocation concealment: 6 studies unclear risk • performance bias: 3 studies high risk, 3 studies unclear risk • detection bias: 3 studies unclear risk • attrition bias: 1 study unclear risk

- reporting bias: 1 study unclear risk
- other bias; 1 study unclear risk
- no study at low risk of bias for all items

- **Other comments**

Bijlage 5. Overzicht van de kans op vertekening (risk of bias) in de geïncludeerde onderzoeken

5A: Systematische reviews (AMSTAR-2)

Folch 2020

Domain	Instructions (Check all that apply)	Judgement	Comments (optional)
PICO components	1. Did the research questions and inclusion criteria for the review include the components of PICO? For Yes: ☒ Population ☒ Index test(s) ☒ Reference standard ☒ Target condition	☒Yes ☐No	"In patients with peripheral pulmonary lesion suspected of lung cancer, what is the sensitivity and safety of electromagnetic navigation bronchoscopy compared to surgery or longitudinal follow up?"
Protocol	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☒ review question(s) ☐ a search strategy ☒ inclusion/exclusion criteria ☒ a risk of bias assessment For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☒ a meta-analysis/synthesis plan, if appropriate, *and* ☒ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐Yes ☒Partial Yes ☐No	Search strategy not provided in protocol, but databases are specified.
Study design explanation	3. Did the review authors explain their selection of the study designs for inclusion in the review? For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only cross sectional studies ☐ OR *Explanation for* including both cross sectional studies and case control studies	☐Yes ☒No	Observational studies were included, case series were excluded. No rationale provided.
Comprehensive search strategy	4. Did the review authors use a comprehensive literature search strategy? For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question) ☒ provided key words and/or search strategy ☒ justified publication restrictions (e.g. language) For Yes, should also have (all the following): ☒ searched the reference lists / bibliographies of included studies	☐Yes ☐Partial Yes ☒No	Search strategy is provided, but only studies with MeSH terms were identified so more recent studies are missed. No publication restrictions applied.

	☐ included/consulted content experts in the field ☒ where relevant, searched for grey literature ☒ conducted search within 24 months of completion of the review		
Duplicate study selection	5. Did the review authors perform study selection in duplicate? For Yes, either ONE of the following: ☒ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☒Yes ☐No	
Duplicate data extraction	6. Did the review authors perform data extraction in duplicate? For Yes, either ONE of the following: ☒at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☒Yes ☐No	"Two independent reviewers extracted data from each study"
Details of excluded studies	7. Did the review authors provide a list of excluded studies and justify the exclusions? For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐Yes ☐Partial Yes ☒No	
Description of included studies	8. Did the review authors describe the included studies in adequate detail? For Partial Yes (ALL the following): ☒ described populations ☐ described index test(s) ☐ described reference standard ☐ described target condition ☒ described research designs For Yes, should also have ALL the following: ☐ described population in detail (including setting and prevalence) ☐ described index test(s) in detail (including thresholds) ☐ described reference standard in detail (including thresholds) ☐ described the target condition in detail (including definitions for classification)	☐Yes ☐Partial Yes ☒No	Limited description of included studies provided in Table 1.
Risk of bias assessment	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB from ☒ patient selection, *and* ☒ lack of blinding of index test and reference standard For Yes, must have assessed RoB using QUADAS 2 tool	☒Yes ☐Partial Yes ☐No	
Funding sources	10. Did the review authors report on the sources of funding for the studies included in the review? For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐Yes ☒No	

Meta-analyses	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☒ The authors justified combining the data in a meta-analysis ☒ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present (i.e. bivariate model [Reitsma] or hierarchical summary ROC model [Rutter and Gatsonis]). ☒ AND investigated the causes of any heterogeneity	☒Yes ☐No ☐No meta-analysis conducted	
Impact of bias on meta-analysis	12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? For Yes: ☐ included only low risk of bias studies ☒ OR, if the pooled estimate was based on studies at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☒Yes ☐No ☐No meta-analysis conducted	
Risk of bias and interpretation results	13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? For Yes: ☐ included only low risk of bias studies ☒ OR, if studies with moderate or high RoB were included the review provided a discussion of the likely impact of RoB on the results	☒Yes ☐No	
Heterogeneity	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? For Yes: ☐ There was no significant heterogeneity in the results ☒ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☒Yes ☐No	
Publication bias	15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? For Yes: ☒ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☒Yes ☐No ☐No meta-analysis conducted	
Conflicts of interest	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☐Yes ☒No	"The authors have reported to CHEST that no funding was received for this study." "The authors have reported to CHEST the following: E. E. F. is a scientific consultant for Boston Scientific and Medtronic, is an educational consultant for Cook Medical and Pinnacle Biologics, and his institution has received a research grant from Intuitive Surgical. S J. K. is a consultant,

			advisor, and speaker for Medtronic, Boston Scientific, and Auris Robotics. A. M. is scientific consultant for Boston Scientific and an educational consultant for Olympus America, Cook Medical, and Pnnacle Biologics; and has received a research grant from Olympus and Intuitive Surgical."

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Domain	Instructions (Check all that apply)	Judgement	Comments (optional)
PICO components	1. Did the research questions and inclusion criteria for the review include the components of PICO? For Yes: ☒ Population ☒ Intervention ☒ Comparator group ☒ Outcome Optional (recommended) ☐ Timeframe for follow up	☒Yes ☐No	
Protocol	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐Yes ☐Partial Yes ☒No	
Study design explanation	3. Did the review authors explain their selection of the study designs for inclusion in the review? For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI	☐Yes ☒No	
Comprehensive search strategy	4. Did the review authors use a comprehensive literature search strategy? For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question)	☐Yes ☒Partial Yes ☐No	No restrictions were applied for study language

	☒ provided key words and/or search strategy ☐ justified publication restrictions (e.g. language) For Yes, should also have (all the following): ☒ searched the reference lists / bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☒ conducted search within 24 months of completion of the review		
Duplicate study selection	5. Did the review authors perform study selection in duplicate? For Yes, either ONE of the following: ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☐Yes ☒No	No info is given regarding screening in duplicate.
Duplicate data extraction	6. Did the review authors perform data extraction in duplicate? For Yes, either ONE of the following: ☒at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☒Yes ☐No	
Details of excluded studies	7. Did the review authors provide a list of excluded studies and justify the exclusions? For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐Yes ☐Partial Yes ☒No	Other than mentioning it in the PRISMA diagram, the list of excluded studies is not provided.
Description of included studies	8. Did the review authors describe the included studies in adequate detail? For Partial Yes (ALL the following): ☐ described populations ☐ described interventions ☐ described comparators ☒ described outcomes ☒ described research designs For Yes, should also have ALL the following: ☐ described population in detail ☐ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☐ described study's setting ☐ timeframe for follow-up	☐Yes ☐Partial Yes ☒No	
Risk of bias assessment (RCTs)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB from ☒ unconcealed allocation, *and* ☒ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality) For Yes, must also have assessed RoB from:	☒Yes ☐Partial Yes ☐No ☐Includes only NRSI	

	☒ allocation sequence that was not truly random, *and* ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome		
Risk of bias assessment (NRSI)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB: ☐ from confounding, *and* ☐ from selection bias For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐Yes ☐Partial Yes ☐No ☒Includes only RCTs	
Funding sources	10. Did the review authors report on the sources of funding for the studies included in the review? For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐Yes ☒No	
Meta-analyses (RCTs)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☐ The authors justified combining the data in a meta-analysis ☒ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☒ AND investigated the causes of any heterogeneity	☐Yes ☒No ☐No meta-analysis conducted ☐Includes only NRSI	
Meta-analyses (NRSI)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐Yes ☐No ☐No meta-analysis conducted ☒Includes only RCTs	
Impact of bias on meta-analysis	12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐Yes ☒No ☐No meta-analysis conducted	
Risk of bias and interpretation results	13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐Yes ☒No	
Heterogeneity	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	☒Yes ☐No	Subgroup analyses were performed to

	For Yes: ☐ There was no significant heterogeneity in the results ☒ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review		explore heterogeneity.
Publication bias	15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐Yes ☒No ☐No meta-analysis conducted	"We did not assess the publication bias owing to the limited number of studies (<10 studies) included in each analysis. Tests for funnel plot asymmetry were evaluated visually, but not used to assess for publication bias, as the number of studies identified was <10"
Conflicts of interest	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? For Yes: ☒ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☒Yes ☐No	

5B: Primaire onderzoeken (QUADAS-2)

Ali 2019

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	No	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	Exclusion criteria not stated
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		

A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	Yes	
• Were all patients included in the analysis?	Yes	No exclusions reported
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
Were all patients included in the analysis?	Yes	**See comment above**
Could the patient flow have introduced bias?	**Unclear risk**	

Al-Jaghbeer 2016

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	No	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	Exclusion criteria not stated
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	

B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	Yes	
• Were all patients included in the analysis?	Yes	No exclusions reported
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	.
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	**See comment above**
Could the patient flow have introduced bias?	**Unclear risk**	

Andersen 2020

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	

• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	Exclusion criteria not stated
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	All patients had an X-ray examination performed 2 hours after the procedure

		to check for pneumothorax.
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	

Asahina 2005

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low Risk**	

B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**Unclear risk**	

Asano 2006

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	Consecutive mentioned
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	No	GGO excluded
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**High concern**	

DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**Unclear concern**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	

Could the patient flow have introduced bias?	**Unclear**	

NA: not applicable

Asano 2008

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Unclear concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	

DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	"No complications were observed"
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Asano 2013

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	No	GGO excluded
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**High concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		

• Were the index test results interpreted without knowledge of the results of the reference standard?	No	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear**	

NA: not applicable

Bae 2020

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	No	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	No	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	Low risk	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	NA	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		

• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Unclear	Not described
• Did all patients receive the same reference standard?	Yes	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Unclear risk	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	.
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

Bellinger 2021

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	No	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	Exclusion not reported
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	Rapid on-site pathology is available on cases.
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Unclear risk**	

B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	**Yes**	
• Were the reference standard results interpreted without knowledge of the results of the index test?	**Yes**	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	Yes	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Low risk	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	.
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

Bertoletti 2009

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		

• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	No	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	Follow-up duration was 18 months
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	

Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear**	

Bo 2019

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	Consecutive not mentioned
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		

• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**Low concern**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Bowling 2017

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	

Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	Rapid on site
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	

• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Bowling 2015

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		

Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	
• Did all patients receive a reference standard?	No	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Casal 2018

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		

• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Unclear	
• Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	
• Did all patients receive a reference standard?	Unclear	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Cochrane Netherlands

Chee 2013

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	No	clinical decision to surgically resect the lesion with a high suspicion for lung cancer excluded
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	

• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Cheng 2019

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	NA	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**	

B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear**	

NA: not applicable

Diez-Ferrer 2019

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	Consecutive
• Was there a prospective study design?	Yes	Prospective
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		

• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Unclear	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**Low concern**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	Duration of follow-up is unclear
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	NA	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	NA	
• Were all patients included in the analysis?	NA	
Could the patient flow have introduced bias?	**NA**	

NA: not applicable

Eberhardt 2010b Lungpoint

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	Consecutive mentioned
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	No	GGO excluded
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**High concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		

• Was there an appropriate interval between index test(s) and reference standard?	Unclear	Follow up duration is notreported.
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Eberhardt 2007a

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	

Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**Low concern**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	

Eberhardt 2007b Multimodality Bronchoscopic Diagnosis of Peripheral Lung Lesions

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	
• Did all patients receive a reference standard?	Yes	

• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	

NA: not applicable

Ebeherhardt 2010a Comparison of Suction Catheter versus Forceps Biopsy for Sampling of Solitary Pulmonary Nodules Guided by Electromagnetic Navigational Bronchoscopy

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	Consecutive not mentioned
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low**	
B. Concerns regarding applicability		

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	2 years of follow-up
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Low risk	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	In all patients, a chest X-ray was performed after the procedure to evaluate iatrogenic pneumothorax after transbronchial lung biopsy
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	

NA: not applicable

Flenaugh 2016

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	consecutive mentioned
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	12 months
• Did all patients receive a reference standard?	Yes	

• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	No	3 cases were excluded from follow-up
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	Radiological surveillance was completed a
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Fukusumi 2016

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	Consecutive mentioned
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	No	GGO excluded
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**High concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low**	
B. Concerns regarding applicability		

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**Low**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	Follow-up duration not described
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Garwood 2016

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		

• Was a consecutive or random sample of patients enrolled?	Yes	Consecutive mentioned
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	Low concern	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	2 years
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	

• Were all patients included in the analysis?	No	Follow up was available in 84/86 patients
Could the patient flow have introduced bias?	Low risk	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	Unclear risk	

NA: not applicable

Gildea 2006

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	'All subjects..."
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	

DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low Risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	10,5 months
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	No	2 patients did not complete follow-up
Could the patient flow have introduced bias?	**High risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Gu 2017

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	

• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	12 months of FU
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	

A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	**Yes**	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	**Yes**	
Could the patient flow have introduced bias?	**Unlear risk**	

NA: not applicable

Haidong 2017

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		

• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Hautman 2005

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	

• Did the study avoid inappropriate exclusions?	Unclear	Exclusion criteria are not reported
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	Nothing reported on FU duration
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	Yes	
• Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	**High risk**	

A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	**No complications occurred during bronchoscopy**
• Were all patients included in the analysis?	**Yes**	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Hohenforst-Schmidt 2014

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	No	
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		

• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

Ikezawa 2017

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		

Are there concerns that the included patients do not match the review question?	**High concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Yes risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	Number of non malignant individuals not specified
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Ishida 2011

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	No	GGO excluded
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**High concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low** risk	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low** concern	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**Unclear**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		

• Was there an appropriate interval between index test(s) and reference standard?	Yes	2 jaar
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	No	1 lost to follow-up
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Iwano 2010

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	Low concern	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	Low risk	

B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	NA	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias? omu	**NA**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	NA	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	NA	
• Were all patients included in the analysis?	NA	
Could the patient flow have introduced bias?	**NA**	

NA: not applicable

Jensen 2012

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		

• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	Nothing on exclusion criteria reported, but probably not an issue
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	

• Did all patients receive the same reference standard?	No	KJ: changed from yes to no, as some patients received (radiological) FU
• Were all patients included in the analysis?	No	8 patients were excluded
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	**Yes**	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Yes	
• Were all patients included in the analysis?	**Yes**	
Could the patient flow have introduced bias?	**Low risk**	

NA: not applicable

Karnak 2013

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	No worrisome exclusions in my opinion
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	

B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	At least two years of FU (mean 2,1 years)
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	**Yes**	Confirmed by radiological follow-up and Positron Emission Tomography
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	**Yes**	Probably all patients included based on the context in which pneumothorax is described
Could the patient flow have introduced bias?	**Unlear risk**	

NA: not applicable

Kato 2018

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		

• Was there an appropriate interval between index test(s) and reference standard?	Unclear	Follow-up period notmentioned
• Did all patients receive a reference standard?	No	
• Did all patients receive the same reference standard?	Yes	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unlcear concern**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear concern**	

NA: not applicable

Kawakita 2021

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	.
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low risk**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	More than 6 months, but not further specified how long
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Kheir 2021

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	

Could the selection of patients have introduced bias?	**High risk**	Authors report a retrospective design, yet talk about assigning ENB or ENB-CBCT. Also the distribution on diagnostic interventions is equal, which would be peculiar for a consecutive retrospective series
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Unlcear	Rapid on site
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low Risk**	

A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Lamprecht 2012

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	NA	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	

• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	No	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	

NA: not applicable

Li 2020

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	Consecutive mentioned
• Was there a prospective study design?	No	
• Was a case-control design avoided?	NA	
• Did the study avoid inappropriate exclusions?	No	GGO excluded
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**High concern**	

DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Loo 2014

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		

• Was there an appropriate interval between index test(s) and reference standard?	Unclear	Nothing reported on FU duration
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	Probably not
• Were all patients included in the analysis?	No	Because they report that in 3 patients no follow-up information was available. Though this is unlikely to have impacted the results
Could the patient flow have introduced bias?	**Unclear risk**	**Mostly due to unknown FU duration**
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Yes	
• Were all patients included in the analysis?	**Yes**	
Could the patient flow have introduced bias?	**Low risk**	

NA: not applicable

Ma 2020

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	Exclusion: difficulty in complying with clinical instructions and procedures.
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	

DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**High risk**	Unclear how sample size in EBUS-GS group switches from 93 to 83
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Maekura 2017

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	Six months follow-up
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	

• Were all patients included in the analysis?	No	5 were excluded, though the impact of this may be limited
Could the patient flow have introduced bias?	**High risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Mahajan 2011

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	Consecutive not mentioned
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		

A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	Follow-up duration not reported
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Makris 2007

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	

• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	No	1 patient lost-to-follow-up
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		

• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	

NA: not applicable

Matsumoto 2017

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	Consecutive mentioned
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low risk**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	Rapid on site
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	

Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	1 year
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**Unclear risk**	

Miyoshi 2018

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	Consecutive mentioned
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	

DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	12 months
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low concern**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	NA	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	NA	
• Were all patients included in the analysis?	NA	

Could the patient flow have introduced bias?	**NA**	

NA: not applicable

Mukherjee 2017

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	Nothing on exclusion criteria reported, but probably not an issue
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	

DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	At least 1 year
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	**Unclear**	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	**Yes**	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Odronic 2014

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	"all cases indentified..."
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	

• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	12 months
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	NA	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	NA	
• Were all patients included in the analysis?	NA	
Could the patient flow have introduced bias?	**NA**	

NA: not applicable

Oh 2021

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	No	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	Exclusion criteria not stated
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	Follow-up duration could be short (at least 3 months)
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	Yes	
• Were all patients included in the analysis?	Yes	No exclusions reported
Could the patient flow have introduced bias?	**High risk**	

A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Oki 2019

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	No	GGO excluded
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**High concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**	Some proportion get different types of navigation guidance (virtual, fluorescence) but no further specification on how many patients received this
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		

• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Oki 2015

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		

Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	No	A chest radiograph was obtained

		routinely to identify pneumothorax 2 hours after the procedures
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	

NA: not applicable

Oshige 2011

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	Cases deemed benign on CT image and clinical inference were excluded from bronchoscopic procedures
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	

• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Ost 2016

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	For selection, yes, but for flow patients are not all included in the analysis

Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	In a secondary analysis follow-up data was used to determine diagnosis
• Did all patients receive the same reference standard?	Yes	For the primary analysis, all was based on histopathology
• Were all patients included in the analysis?	No	Indeterminate cases (for which bronchoscopy did not arrive at a diagnosis, n=44) were excluded for calculation of max sensitivity and included as FN for min sensitivity
Could the patient flow have introduced bias?	**High risk**	

A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Patrucco 2018

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	

B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	Follow-up duration not described
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	No	5 patients /113 lost to follow-up
Could the patient flow have introduced bias?	Unclear	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Pearlstein 2012

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	Consecutive mentioned
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	

DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	Follow-up duration 2 year
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	No	3 patients insuffient follow-up
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	

• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Pritchett 2018

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	

DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear**	

NA: not applicable

Raval 2016

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low Risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	

• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	Two years follow-up to see whether benign diagnoses were indeed benign
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	**Low risk**	Two patients were excluded because EMN was not possible.
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	

Sato 2018

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Unclear	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	NA	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	3 months?
• Did all patients receive a reference standard?	Yes	

• Did all patients receive the same reference standard?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**High risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unlcear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Seijo 2010

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	

DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	Follow-up duration not mentioned
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	No	1 pt lost to follow up
Could the patient flow have introduced bias?	Unclear risk	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Shinagawa 2007

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	No	

• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low risk**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Unclear	Not described
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Unclear	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	NA	**Geen complicaties beschreven**
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	NA	
• Were all patients included in the analysis?	NA	
Could the patient flow have introduced bias?	**NA**	

NA: not applicable

Sobieszczyk 2018

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Unclear	

• Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	Follow-up duration was 6 months
• Did all patients receive a reference standard?	yes	
• Did all patients receive the same reference standard?	Yes	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**High risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Yes	**Chest X-ray examination was performed 2 hours after the procedure**
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low**	

NA: not applicable

Steinfort 2016

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**Unclear risk**	

B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**High risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	NA	**Geen complicaties beschreven**

• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	NA	
• Were all patients included in the analysis?	NA	
Could the patient flow have introduced bias?	**NA**	

NA: not applicable

Stenger 2020

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	

• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	No	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Sun 2017

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	No	GGO excluded
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**High concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		

A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	Follow-up duration at least 12 months
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Low risk	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Tachihara 2007

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	

• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low risk**	

A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**Unclear**	

NA: not applicable

Tamiya 2013

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	

• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	NA	**No complications described**
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	NA	
• Were all patients included in the analysis?	NA	
Could the patient flow have introduced bias?	**NA**	

NA: not applicable

Taton 2018

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	

B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	6 months
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	High risk	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	

• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Verhoeven 2020

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Unclear**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	

B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	No	8/87 excluded from analysis
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	No mention (in methods), so no or unclear
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	No mention (in methods), so no or unclear
• Were all patients included in the analysis?	No	8/87 were excluded from analysis)
Could the patient flow have introduced bias?	**Unclear risk**	**Unclear risk**

NA: not applicable

Verhoeven 2021 (Cone-beam CT and Augmented Fluoroscopy-guided Navigation Bronchoscopy: Radiation Exposure and Diagnostic Accuracy Learning Curves)

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		

Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	Follow-up of benign lesions <1 yr
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	**High risk**	Follow-up of benign lesions <1 yr
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	NA	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	NA	

• Were all patients included in the analysis?	NA	
Could the patient flow have introduced bias?	**NA**	

NA: not applicable

Verhoeven 2021 - Multi-modal tissue sampling in cone beam CT guided navigation bronchoscopy: comparative accurate diagnoses of different sampling tools and rapid on-site evaluation of cytopathology

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	Rapid on site
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		

Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	Follow-up < 1yr
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	Having a reference standard was inclusion criterion (patients without follow-up were excluded).
Could the patient flow have introduced bias?	**High risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	NA	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	NA	
• Were all patients included in the analysis?	NA	
Could the patient flow have introduced bias?	**NA**	

NA: not applicable

Wang 2021

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	Randomized
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	

DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	Yes	
• Were all patients included in the analysis?	No	1 patient was excluded due to being lost to follow-up
Could the patient flow have introduced bias?	**Low risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	**Not mentioned**
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	

• Were all patients included in the analysis?	No	One patient was excluded due to being lost to follow-up after at least 12 months.
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Wilson 2007

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	Consecutive mentioned
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		

Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	Mean follow-up period 6 maanden
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**High risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Wong 2014

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Unclear	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		

• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Low**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear**	

NA: not applicable

Xu 2019

DOMAIN 1: PATIENT SELECTION	Judgement	Comments (optional)
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	No	

• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**High risk**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Yu 2021

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Yes	
• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	Exclusion criteria not stated
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	Yes	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Low risk	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

Zhang 2020

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	No	

• Was there a prospective study design?	No	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Unclear	Exclusion criteria not stated
Could the selection of patients have introduced bias?	**High risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	
• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	Yes	
• Were all patients included in the analysis?	Yes	No exclusions reported
Could the patient flow have introduced bias?	Low risk	

A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	
• Were all patients included in the analysis?		**See comment above**
Could the patient flow have introduced bias?	**Unclear risk**	

Zheng 2021

DOMAIN 1: PATIENT SELECTION	**Judgement**	**Comments (optional)**
A. Risk of Bias		
• Was a consecutive or random sample of patients enrolled?	Unclear	
• Was there a prospective study design?	Yes	
• Was a case-control design avoided?	Yes	
• Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	**Unclear risk**	
B. Concerns regarding applicability		
Are there concerns that the included patients do not match the review question?	**Low concern**	
DOMAIN 2: INDEX TEST – Navigation bronchoscopy		
A. Risk of Bias		
• Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
• If a threshold was used, was it pre-specified?	NA	
Could the conduct or interpretation of the index test have introduced bias?	**Low**	
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**	
DOMAIN 3: REFERENCE STANDARD		
A. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Is the reference standard likely to correctly classify the target condition?	Yes	

• Were the reference standard results interpreted without knowledge of the results of the index test?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**	
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the review question?	**NA**	
DOMAIN 4: FLOW AND TIMING		
A1. Risk of Bias – Diagnostic yield / accurate diagnoses		
• Was there an appropriate interval between index test(s) and reference standard?	Yes	
• Did all patients receive a reference standard?	Yes	
• Did all patients receive the same reference standard?	No	
• Were all patients included in the analysis?	No	However, excluded patients (low number) were for reason of bronchoscopically visible lesion (n=4), cough (n=1) or technical problem (n=1)
Could the patient flow have introduced bias?	**Low**	
A2. Risk of Bias – Complications		
• After navigation bronchoscopy, was imaging being done to detect complications (i.e pneumothorax and bleeding)	Unclear	
• After navigation bronchoscopy, was imaging being done on indication (rather than standard imaging for all participants)?	Unclear	Probably yes
• Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	**Unclear risk**	

NA: not applicable

Bijlage 6. Resultaten individuele onderzoeken

6A: Navigatiesucces, diagnostische opbrengst, percentage accurate diagnoses, sensitiviteit en negatief voorspellende waarde

PICOT 1

Reference	Population	Index test add on	Navigation success (95% CI)	Yield (95% CI)	Accurate diagnoses (95% CI)	Sensitivity (95% CI)	Negative predictive value (95% CI)
Electromagnetic navigation							
Andersen 2020	Both traditional bronchoscopy and TTNA/B not feasible	No		88.1% (80.1% to 93.2%)	67.9% (58.2% to 76.3%)	55.1% (40.3% to 69.1%)	68.1% (55.7% to 78.5%)
Cheng 2019	Both traditional bronchoscopy and TTNA/B not feasible	Yes		71.7% (61.6% to 80.1%)	82.8% (73.6% to 89.4%)	74.6% (62.3% to 84.1%)	65.3% (50.3% to 77.9%)
Mahajan 2011	Both traditional bronchoscopy and TTNA/B not feasible	Yes	100.0% (90.8% to 100.0%)	100.0% (90.8% to 100.0%)	77.1% (62.3% to 87.5%)		
Oh 2021	Both traditional bronchoscopy and TTNA/B not feasible	No	93.5% (86.5% to 97.1%)	68.2% (58.4% to 76.7%)	49.5% (39.8% to 59.3%)		
Pearlstein 2012	Both traditional bronchoscopy and TTNA/B not feasible	No	100.0% (95.4% to 100.0%)	100.0% (95.4% to 100.0%)	85.1% (76.4% to 91.2%)	81.7% (71.3% to 89.1%)	55.9% (38.1% to 72.4%)
Seijo 2010	Both traditional bronchoscopy and TTNA/B not feasible	No		66.7% (52.0% to 78.9%)	66.7% (52.0% to 78.9%)		
Wilson 2007	Both traditional bronchoscopy and TTNA/B not feasible	Yes	95.3% (92.0% to 97.4%)	59.1% (53.1% to 64.9%)	54.1% (48.1% to 60.0%)		
Cone-Beam CT							
Hohenforst-Schmidt 2014	Both traditional bronchoscopy and TTNA/B not feasible	No	90.9% (74.5% to 97.6%)	69.7% (51.1% to 83.8%)			

PICOT 2

Reference	Population	Index test add on	Navigation success (95% CI)	Yield (95% CI)	Accurate diagnoses (95% CI)	Sensitivity (95% CI)	Negative predictive value (95% CI)
Electromagnetic navigation							
Al-Jaghbeer 2016	No information on TTNA/B or bronchoscopy feasibility	No		60.2% (49.8% to 69.8%)			
Bellinger 2021	No information on TTNA/B or bronchoscopy feasibility	Yes			71.9% (66.0% to 77.1%)		
Bertoletti 2009	No information on TTNA/B or bronchoscopy feasibility	No			77.4% (63.5% to 87.3%)	71.4% (55.2% to 83.8%)	
Bowling 2015	No information on TTNA/B or bronchoscopy feasibility	Yes	93.8% (86.5% to 97.5%)	69.1% (58.8% to 77.9%)			
Bowling 2017	No information on TTNA/B or bronchoscopy feasibility	No		78.6% (48.8% to 94.3%)			
Chee 2013	No information on TTNA/B or bronchoscopy feasibility	Yes		73.3% (44.8% to 91.1%)			
Eberhardt 2007a	No information on TTNA/B or bronchoscopy feasibility	No		67.4% (56.7% to 76.6%)	67.4% (56.7% to 76.6%)		
Eberhardt 2007b	No information on TTNA/B or bronchoscopy feasibility	No	100.0% (88.8% to 100.0%)	100.0% (88.8% to 100.0%)	66.7% (49.7% to 80.4%)	55.2% (36.0% to 73.0%)	43.5% (23.9% to 65.1%)
Eberhardt 2007b	No information on TTNA/B or bronchoscopy feasibility	Yes	100.0% (89.1% to 100.0%)	100.0% (89.1% to 100.0%)	92.5% (78.5% to 98.0%)	90.3% (73.1% to 97.5%)	75.0% (42.8% to 93.3%)
Eberhardt 2010a	No information on TTNA/B or bronchoscopy feasibility	Yes	100.0% (91.6% to 100.0%)	75.5% (61.4% to 85.8%)	58.5% (44.2% to 71.6%)	73.5% (55.3% to 86.5%)	40.0% (17.5% to 67.1%)
Flenaugh 2016	No information on TTNA/B or bronchoscopy feasibility	Yes		93.2% (80.3% to 98.2%)	84.1% (69.3% to 92.8%)	80.0% (55.7% to 93.4%)	84.0% (63.1% to 94.7%)
Garwood 2016	No information on TTNA/B or bronchoscopy feasibility	Yes	89.5% (80.6% to 94.8%)	82.6% (72.5% to 89.6%)	77.9% (67.4% to 85.9%)	90.0% (75.4% to 96.7%)	88.6% (72.3% to 96.3%)
Gildea 2006	Traditional bronchoscopy not feasible	No		71.4% (57.6% to 82.3%)			
Gu 2017	No information on TTNA/B or bronchoscopy feasibility	Yes		96.4% (89.2% to 99.1%)	92.9% (84.5% to 97.1%)		
Hautmann 2005	No information on TTNA/B or bronchoscopy feasibility	No	100.0% (75.9% to 100.0%)				
Jensen 2012	No information on TTNA/B or bronchoscopy feasibility	No			65.2% (54.5% to 74.6%)		
Kheir 2021	No information on TTNA/B or bronchoscopy feasibility	Yes			51.6% (33.4% to 69.4%)		

Reference	Population	Index test add on	Navigation success (95% CI)	Yield (95% CI)	Accurate diagnoses (95% CI)	Sensitivity (95% CI)	Negative predictive value (95% CI)
Lamprecht 2012	Traditional bronchoscopy not feasible	No	90.2% (82.7% to 94.8%)	83.9% (75.5% to 89.9%)			
Loo 2014	No information on TTNA/B or bronchoscopy feasibility	No		98.0% (88.0% to 99.9%)	84.0% (70.3% to 92.4%)		
Ma 2020	No information on TTNA/B or bronchoscopy feasibility	Yes	100.0% (84.0% to 100.0%)	65.4% (44.4% to 82.1%)	65.4% (44.4% to 82.1%)		
Makris 2007	Traditional bronchoscopy not feasible	No		62.5% (45.8% to 76.8%)	62.5% (45.8% to 76.8%)		
Mukherjee 2017	Traditional bronchoscopy not feasible	Yes	100.0% (86.3% to 100.0%)	96.8% (81.5% to 99.8%)	96.8% (81.5% to 99.8%)		
Odronic 2014	No information on TTNA/B or bronchoscopy feasibility	No	100.0% (95.0% to 100.0%)	100.0% (95.0% to 100.0%)	85.7% (76.4% to 91.9%)	62.9% (44.9% to 78.0%)	81.2% (69.6% to 89.2%)
Ost 2016	No information on TTNA/B or bronchoscopy feasibility	Mixture		59.1% (43.3% to 73.3%)			
Patrucco 2018	Traditional bronchoscopy not feasible	Yes	100.0% (95.9% to 100.0%)	69.0% (59.5% to 77.2%)	69.0% (59.5% to 77.2%)		
Raval 2016	No information on TTNA/B or bronchoscopy feasibility	No	100.0% (92.6% to 100.0%)	78.7% (66.0% to 87.7%)			
Sato 2018	No information on TTNA/B or bronchoscopy feasibility	No	71.4% (53.5% to 84.8%)	71.4% (53.5% to 84.8%)	71.4% (53.5% to 84.8%)		
Stenger 2020	Traditional bronchoscopy not feasible	No	100.0% (94.4% to 100.0%)	100.0% (94.4% to 100.0%)	75.3% (64.3% to 83.9%)	51.2% (35.4% to 66.8%)	66.7% (53.2% to 78.0%)
Sun 2017	Traditional bronchoscopy not feasible	Yes	100.0% (89.1% to 100.0%)	82.5% (66.6% to 92.1%)	82.5% (66.6% to 92.1%)		
Taton 2018	No information on TTNA/B or bronchoscopy feasibility	Yes	90.6% (73.8% to 97.5%)	34.4% (19.2% to 53.2%)			
Wang 2021	Traditional bronchoscopy not feasible	Yes	100.0% (88.3% to 100.0%)	100.0% (88.3% to 100.0%)	73.0% (55.6% to 85.6%)	60.9% (38.8% to 79.5%)	59.1% (36.7% to 78.5%)
Virtual bronchoscopy							
Asahina 2005	No information on TTNA/B or bronchoscopy feasibility	Yes	80.0% (60.9% to 91.6%)	63.3% (43.9% to 79.5%)			
Asano 2006	No information on TTNA/B or bronchoscopy feasibility	Yes	94.7% (80.9% to 99.1%)	81.6% (65.1% to 91.7%)			
Asano 2008	Traditional bronchoscopy not feasible	Yes	93.8% (77.8% to 98.9%)	84.4% (66.5% to 94.1%)	84.4% (66.5% to 94.1%)		
Asano 2013	Traditional bronchoscopy not feasible	Yes		67.1% (59.3% to 74.0%)	67.1% (59.3% to 74.0%)		

Reference	Population	Index test add on	Navigation success (95% CI)	Yield (95% CI)	Accurate diagnoses (95% CI)	Sensitivity (95% CI)	Negative predictive value (95% CI)
Asano 2015	No information on TTNA/B or bronchoscopy feasibility	Yes		76.3% (63.1% to 86.0%)			
Bae 2020	Traditional bronchoscopy not feasible	Yes		96.9% (88.2% to 99.5%)	64.1% (51.0% to 75.4%)	63.4% (46.9% to 77.4%)	50.0% (33.2% to 66.8%)
Bo 2019	No information on TTNA/B or bronchoscopy feasibility	Yes		74.3% (69.1% to 78.8%)		85.9% (79.4% to 90.7%)	
Diez-Ferrer 2019	No information on TTNA/B or bronchoscopy feasibility	Yes		81.8% (68.6% to 90.5%)			
Eberhardt 2010b	No information on TTNA/B or bronchoscopy feasibility	No	100.0% (83.4% to 100.0%)	80.0% (58.7% to 92.4%)			
Fukusumi 2016	No information on TTNA/B or bronchoscopy feasibility	Yes	100.0% (84.5% to 100.0%)	63.0% (42.5% to 79.9%)	48.1% (29.2% to 67.6%)	66.7% (35.4% to 88.7%)	55.6% (22.7% to 84.7%)
Haidong 2017	No information on TTNA/B or bronchoscopy feasibility	Yes		91.7% (59.8% to 99.6%)			
Ikezawa 2017	No information on TTNA/B or bronchoscopy feasibility	Yes	92.3% (86.9% to 95.7%)	68.6% (61.0% to 75.4%)			
Ishida 2011	Traditional bronchoscopy not feasible	Yes	92.0% (84.4% to 96.2%)		80.0% (70.6% to 87.1%)		
Iwano 2011	No information on TTNA/B or bronchoscopy feasibility	Yes			78.7% (70.2% to 85.4%)		
Kato 2018	Traditional bronchoscopy not feasible	Yes		84.0% (70.3% to 92.4%)	84.0% (70.3% to 92.4%)		
Kawakita 2021	No information on TTNA/B or bronchoscopy feasibility	Yes		49.5% (39.0% to 60.0%)	49.5% (39.0% to 60.0%)		
Li 2020	Traditional bronchoscopy not feasible	Yes	90.8% (83.4% to 95.3%)	90.8% (83.4% to 95.3%)	74.3% (64.9% to 82.0%)		
Maekura 2017	No information on TTNA/B or bronchoscopy feasibility	Yes		77.8% (62.5% to 88.3%)			
Matsumoto 2017	No information on TTNA/B or bronchoscopy feasibility	Yes	100.0% (96.2% to 100.0%)	77.7% (69.0% to 84.5%)			
Miyoshi 2018	No information on TTNA/B or bronchoscopy feasibility	Yes					
Oki 2015	No information on TTNA/B or bronchoscopy feasibility	Yes	100.0% (96.9% to 100.0%)	74.0% (66.1% to 80.7%)	74.0% (66.1% to 80.7%)		
Oki 2015	No information on TTNA/B or bronchoscopy feasibility	Yes	100.0% (97.0% to 100.0%)	59.4% (51.2% to 67.1%)	59.4% (51.2% to 67.1%)		

Reference	Population	Index test add on	Navigation success (95% CI)	Yield (95% CI)	Accurate diagnoses (95% CI)	Sensitivity (95% CI)	Negative predictive value (95% CI)
Oki 2019	No information on TTNA/B or bronchoscopy feasibility	Yes	100.0% (97.4% to 100.0%)	70.1% (62.6% to 76.6%)	70.1% (62.6% to 76.6%)		
Oki 2019	No information on TTNA/B or bronchoscopy feasibility	Yes	100.0% (97.4% to 100.0%)	58.7% (51.1% to 65.9%)	58.7% (51.1% to 65.9%)		
Oshige 2011	Traditional bronchoscopy not feasible	Yes	93.0% (82.2% to 97.7%)	84.2% (71.6% to 92.1%)	84.2% (71.6% to 92.1%)		
Shinagawa 2007	No information on TTNA/B or bronchoscopy feasibility	Yes		65.9% (54.7% to 75.6%)	65.9% (54.7% to 75.6%)		
Tachihara 2017	No information on TTNA/B or bronchoscopy feasibility	Yes	84.6% (53.7% to 97.3%)				
Tachihara 2017	No information on TTNA/B or bronchoscopy feasibility	Yes	94.4% (70.6% to 99.7%)				
Tamiya 2013	No information on TTNA/B or bronchoscopy feasibility	Yes					
Wong 2014	No information on TTNA/B or bronchoscopy feasibility	Yes		81.2% (53.7% to 95.0%)	81.2% (53.7% to 95.0%)		
Xu 2019	No information on TTNA/B or bronchoscopy feasibility	Yes		83.6% (70.7% to 91.8%)	83.6% (70.7% to 91.8%)		
Zhang 2020	Traditional bronchoscopy not feasible	Yes	100.0% (80.0% to 100.0%)		80.0% (55.7% to 93.4%)		
Zheng 2021*	Traditional bronchoscopy not feasible	Yes		100.0% (92.5% to 100.0%)			
Zheng 2021*	Traditional bronchoscopy not feasible	Yes		100.0% (92.5% to 100.0%)			
Cone-Beam CT							
Casal 2018	No information on TTNA/B or bronchoscopy feasibility	Yes		70.0% (45.7% to 87.2%)			
Verhoeven 2021	Traditional bronchoscopy not feasible	Yes	95.3% (90.3% to 97.9%)		78.7% (71.1% to 84.8%)		
Yu 2021	Traditional bronchoscopy not feasible	Yes		86.8% (74.0% to 94.1%)	83.0% (69.7% to 91.5%)	94.4% (80.0% to 99.0%)	83.3% (50.9% to 97.1%)
Electromagnetic navigation and virtual bronchoscopy							
Karnak 2013	Traditional bronchoscopy not feasible	No		91.4% (75.8% to 97.8%)			
Ost 2016	No information on TTNA/B or bronchoscopy feasibility	Mixture		45.9% (39.8% to 52.1%)			

Reference	Population	Index test add on	Navigation success (95% CI)	Yield (95% CI)	Accurate diagnoses (95% CI)	Sensitivity (95% CI)	Negative predictive value (95% CI)
Steinfort 2016	No information on TTNA/B or bronchoscopy feasibility	Yes	76.7% (70.8% to 81.8%)	58.4% (51.9% to 64.6%)			
Electromagnetic navigation and cone-beam CT							
Kheir 2021	No information on TTNA/B or bronchoscopy feasibility	Yes			74.2% (55.1% to 87.5%)		
Pritchett 2018	Traditional bronchoscopy not feasible	Yes		82.8% (73.3% to 89.6%)			
Sobieszczyk 2018	No information on TTNA/B or bronchoscopy feasibility	Yes		77.3% (54.2% to 91.3%)	77.3% (54.2% to 91.3%)		
Verhoeven 2020	Traditional bronchoscopy not feasible	Yes	84.5% (72.1% to 92.2%)		70.7% (57.1% to 81.5%)		
Virtual bronchoscopy and cone-beam CT							
Ali 2019	No information on TTNA/B or bronchoscopy feasibility	No	100.0% (89.1% to 100.0%)	95.0% (81.8% to 99.1%)	90.0% (75.4% to 96.7%)	92.0% (72.5% to 98.6%)	86.7% (58.4% to 97.7%)
Kawakita 2021	No information on TTNA/B or bronchoscopy feasibility	Yes		65.8% (54.2% to 75.9%)	65.8% (54.2% to 75.9%)		

*Two study arms: virtual bronchoscopy with rEBUS and virtual bronchoscopy with rEBUS and fluoroscopy

6B: Complicaties

PICOT 1

Reference	Population	Complication	Number of events	Number of participants	Incidence
Electromagnetic navigation bronchoscopy					
Andersen 2020	Both traditional bronchoscopy and TTNA/B not feasible	Pneumothorax	3	100	3%
Cheng 2019	Both traditional bronchoscopy and TTNA/B not feasible	Bleeding	1	99	1%
		Pneumothorax	1	99	1%
		Respiratory failure	1	99	1%
Mahajan 2011	Both traditional bronchoscopy and TTNA/B not feasible	Pneumothorax not requiring intervention	3	49	6%
		Pneumothorax requiring chest tube insertion	2	49	4%
Oh 2021		Bleeding - any	13	100	13%

	Both traditional bronchoscopy and TTNA/B not feasible	Bleeding - major	0	100	0%
		Bleeding - minor	9	100	9%
		Bleeding - moderate	4	100	4%
		Need for chest tube insertion	1	100	1%
		Death	0	100	0%
		Overall	16	100	16%
		Pneumothorax	3	100	3%
		Respiratory failure	1	100	1%
Pearlstein 2012	Both traditional bronchoscopy and TTNA/B not feasible	Death	0	104	0%
		Pneumothorax requiring chest tube insertion	6	104	6%
Seijo 2010	Both traditional bronchoscopy and TTNA/B not feasible	Bleeding	0	51	0%
		Pneumothorax	0	51	0%
		Mild hypoxemia, not requiring termination of the procedure	4	51	0%
Wilson 2007	Both traditional bronchoscopy and TTNA/B not feasible	Bleeding - moderate	3	248	1%
		Hematoma, not requiring intervention	1	248	0%
		Pneumonia treated with oral antibiotics	1	248	0%
		Pneumothorax not requiring intervention	3	248	1%
Cone-Beam CT					
Hohenforst-Schmidt 2014	Both traditional bronchoscopy and TTNA/B not feasible	Pneumothorax	2	33	6%
		Life threatening major adverse effects	0	33	0%
		Non-life threatening bradycardia and hypotension	1	33	3%

PICOT 2

Reference	Population	Complication	Number of events	Number of participants	Incidence
Electromagnetic navigation bronchoscopy					
Al-Jaghbeer 2016	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	6	92	0.4%
Bellinger 2021		Bleeding, moderate to severe	1	270	1%

Reference	Population	Complication	Number of events	Number of participants	Incidence
	No information on TTNA/B or bronchoscopy feasibility	Ed visit for hemoptysis (without hospital admission)	2	270	2%
		Bronchospasm or hypoxia requiring admission	5	270	1%
		Other without admission	2	270	1%
		Pneumonia or copd exacerbation within one week	3	270	3%
		Pneumothorax	8	270	2%
Bertoletti 2009	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax not requiring intervention	1	54	2%
		Pneumothorax requiring intervention: chest drainage	1	54	1%
Bowling 2015	No information on TTNA/B or bronchoscopy feasibility	Bradycardia, symptomatic	1	107	1%
Bowling 2015		Reintubation following general anesthesia	1	107	3%
Bowling 2015		Iatrogenic pneumothoraces	3	107	0%
Chee 2013	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	0	15	4%
Eberhardt 2010a	No information on TTNA/B or bronchoscopy feasibility	Death during follow-up	2	53	1%
Eberhardt 2007a	No information on TTNA/B or bronchoscopy feasibility	Hypercapnic respiratory failure	1	89	1%
Eberhardt 2007a	No information on TTNA/B or bronchoscopy feasibility	Perforated EWC	1	89	2%
Eberhardt 2007a	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	2	89	5%
Eberhardt 2007b	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	2	39	8%
Eberhardt 2007b	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	3	40	2%
Eberhardt 2010a	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax not requiring intervention	1	53	0%
Flenaugh 2016	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	0	41	2%
		Repeat biopsy	1	41	4%
Garwood 2016	No information on TTNA/B or bronchoscopy feasibility	Bleeding (minor)	4	90	1%
		Death before final diagnosis	1	90	1%

Reference	Population	Complication	Number of events	Number of participants	Incidence
		Pneumothorax not requiring intervention	1	90	6%
		Pneumothorax requiring intervention (small bore chest tube)	5	90	9%
Gildea 2006	Traditional bronchoscopy not feasible	Chest pain	5	56	2%
		Death (beofre any additional procedures could be performed)	1	57	7%
		Emesis	4	56	5%
		Fever	3	56	5%
		Hemoptysis - insignificant	3	56	13%
		Sore throat	7	56	4%
		Pneumothorax, requiring intervention (small chest tube)	2	56	1%
Gu 2017	No information on TTNA/B or bronchoscopy feasibility	Bleeding	1	78	1%
		Pneumothorax	1	78	0%
Hautmann 2005	No information on TTNA/B or bronchoscopy feasibility	No complications: "no complications occurred during bronchoscopy."	0	16	1%
Jensen 2012	No information on TTNA/B or bronchoscopy feasibility	Bleeding	1	92	0%
		Hospitalization	0	92	3%
		Pneumothorax	3	92	6%
Kheir 2021	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	2	31	2%
Lamprecht 2012	Traditional bronchoscopy not feasible	Pneumothorax	2	112	0%
Loo 2014	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	0	40	8%
Ma 2020	No information on TTNA/B or bronchoscopy feasibility	Hemoptysis	7	83	4%
		Hemoptysis	1	26	0%
		Pneumothorax	0	83	4%
		Pneumothorax	1	26	5%
Makris 2007	Traditional bronchoscopy not feasible	Pneumothorax not requiring intervention	2	40	3%
		Pneumothorax requiring intervention: chest tube insertion	1	40	0%

Reference	Population	Complication	Number of events	Number of participants	Incidence
Mukherjee 2017	Traditional bronchoscopy not feasible	Bleeding (major)	0	31	6%
		Pneumothorax	2	31	5%
Odronic 2014	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	5	91	2%
		Repeat biopsy	2	91	0%
Patrucco 2018	Traditional bronchoscopy not feasible	Haemoptysis	0	113	0%
		Pneumothorax	0	113	0%
Raval 2016	No information on TTNA/B or bronchoscopy feasibility	Additional complications	0	48	2%
		Pneumothorax	1	48	3%
Sato 2018	No information on TTNA/B or bronchoscopy feasibility	Fever	1	35	3%
		Hemopneumothorax requiring non-elective thoracotomy and wedge resection	1	35	3%
		Pneumothorax requiring intervention: chest drainage	1	35	8%
Stenger 2020	Traditional bronchoscopy not feasible	Pneumothorax	0	81	0,0%
Sun 2017	Traditional bronchoscopy not feasible	Bleeding	0	40	0%
		Pneumothorax	0	40	34%
Taton 2018	No information on TTNA/B or bronchoscopy feasibility	Bleeding grade 1 (bleeding stopped within fve minutes either spontaneously or by infation of the fogarty balloon)	11	32	13%
		Bleeding grade 2 (bleeding was prolonged for more than fve minutes or needed cold saline instillation)	4	32	3%
		Pneumothorax requiring intervention: chest drainage	1	32	3%
Wang 2021	Traditional bronchoscopy not feasible	Pneumothorax	1	37	0.4%
Virtual bronchoscopy					
Asahina 2005	No information on TTNA/B or bronchoscopy feasibility	Bleeding major	0	29	0%
		Pneumonia	0	29	0%
		Pneumothorax	0	29	0%
Asano 2013	Traditional bronchoscopy not feasible	Bleeding	2	167	1%
Asano 2008	Traditional bronchoscopy not feasible	No complications	0	32	0%

Reference	Population	Complication	Number of events	Number of participants	Incidence
Asano 2006	No information on TTNA/B or bronchoscopy feasibility	No complications	0	37	0%
Asano 2013	Traditional bronchoscopy not feasible	Bradycardia, transient	1	167	1%
		Pneumothorax not requiring drainag	1	167	1%
Bae 2020	Traditional bronchoscopy not feasible	Blood-tinged sputum	0	64	0%
		Pneumothorax minor; improved without chest tube insertion	2	64	3%
Bo 2019	No information on TTNA/B or bronchoscopy feasibility	Bleeding	3	334	1%
		Bleeding requiring interventional therapy	0	334	0%
		Death	0	334	0%
		Pneumothorax	5	334	1%
		Pneumothorax requiring intervention	3	334	1%
Eberhardt 2010b	No information on TTNA/B or bronchoscopy feasibility	Bleeding, self-limiting	1	25	4%
		Pneumothorax, but no intervention was necessary	1	25	4%
Haidong 2017	No information on TTNA/B or bronchoscopy feasibility	Hemoptysis	2	94	2%
		Pneumothorax	0	94	0%
Ikezawa 2017	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	2	169	1%
Ishida 2011	Traditional bronchoscopy not feasible	Severe or moderate adverse events	0	102	0%
		Pneumothorax not requiring drainage	1	102	1%
Kato 2018	Traditional bronchoscopy not feasible	Bleeding, moderate (bleeding had flowed into the other side of the bronchus)	6	50	12%
Kawakita 2021	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	2	93	2%
		Respiratory failure	0	93	0%
Li 2020	Traditional bronchoscopy not feasible	Bleeding	1	109	1%
		Hemoptysis (mild)	67	109	61%
		Infections	0	109	0%
		Pneumothorax	0	109	0%
Maekura 2017	No information on TTNA/B or bronchoscopy feasibility	Bleeding	2	45	4%

Reference	Population	Complication	Number of events	Number of participants	Incidence
Matsumoto 2017	No information on TTNA/B or bronchoscopy feasibility	Pneumothorax	2	121	2%
Oki 2019	No information on TTNA/B or bronchoscopy feasibility	Bleeding	1	177	1%
		Bleeding	2	179	1%
		Vomiting	1	179	1%
		Myocardial infarction	1	179	1%
		Nausea	1	179	1%
		Pneumonia	1	179	1%
		Pneumonia (with new pulmonary infiltrates as revealed by chest radiographs, accompanied by symptoms of respiratory infection and requiring antibiotic therapy)	2	177	1%
		Pneumothorax (neither required chest tube insertion)	2	179	1%
		Pneumothorax (one of which required chest tube insertion)	2	177	1%
Oki 2015	No information on TTNA/B or bronchoscopy feasibility	Bleeding	2	305	1%
		Chest pain	1	305	0%
		Pneumonia	1	305	0%
		Pneumothorax	8	305	3%
Oshige 2011	traditional bronchoscopy not feasible	Bleeding major	0	57	0%
		Pneumothorax	0	57	0%
Shinagawa 2007	no information on TTNA/B or bronchoscopy feasibility	Pneumothorax	1	69	1%
Tachihara 2017	no information on TTNA/B or bronchoscopy feasibility	Pneumothorax - mild in patient in the non-X-ray group who had consequent TBB under fluoroscopy.	1	31	3%
Wong 2014	no information on TTNA/B or bronchoscopy feasibility	No complication was observed	0	16	0%
Xu 2019	no information on TTNA/B or bronchoscopy feasibility	Pneumothorax	1	55	2%
Zhang 2020	traditional bronchoscopy not feasible	Other complications	0	20	0%
		Hemoptysis	0	20	0%

Reference	Population	Complication	Number of events	Number of participants	Incidence
		Pneumothorax	0	20	0%
Zheng 2021	traditional bronchoscopy not feasible	Bleeding	0	120	0%
		Other serious adverse events	0	120	0%
		Arrhythmia	0	120	0%
		Hypoxemia	0	120	0%
		Lidocaine intoxication	0	120	0%
		Pneumonia	0	120	0%
		Pneumothorax	0	120	0%
Cone beam CT					
Casal 2018	no information on TTNA/B or bronchoscopy feasibility	Pneumothorax	1	20	5%
Yu 2021	traditional bronchoscopy not feasible	Bleeding	2	53	4%
		Pneumothorax	0	53	0%
Electromagnetic navigation and virtual bronchoscopy					
Karnak 2013	traditional bronchoscopy not feasible	Pneumothorax	3	76	4%
Ost 2016	no information on TTNA/B or bronchoscopy feasibility	Bleeding	1	581	0.2%
		Refractory hypoxemia	1	581	0%
		Pneumothorax	10	581	2%
		Respiratory failure	1	581	0.2%
Electromagnetic navigation and cone beam CT					
Kheir 2021	no information on TTNA/B or bronchoscopy feasibility	Pneumothorax	2	31	6%
Pritchett 2018	traditional bronchoscopy not feasible	Bronchopulmonary hemorrhage	0	75	0%
		Pneumothorax	3	75	4%
		Respiratory failure	0	75	0%
Sobieszczyk 2018	no information on TTNA/B or bronchoscopy feasibility	Bleeding	0	22	0,0%
		Infections	0	22	0%
		Pneumothorax	0	22	0%

Reference	Population	Complication	Number of events	Number of participants	Incidence
Verhoeven 2020	traditional bronchoscopy not feasible	Bleeding, moderate, intraprocedurally following cryobiopsy	1	87	1%
		Fever, minor(<4 h)	1	87	1%
		Copd exacerbation	1	87	1%
		Pneumothorax	3	87	3%
Virtual bronchoscopy and cone beam CT					
Ali 2019	no information on TTNA/B or bronchoscopy feasibility	Pneumothorax	1	40	3%
Kawakita 2021	no information on TTNA/B or bronchoscopy feasibility	Pneumothorax	1	79	1%
		Respiratory failure	1	79	1%

Referenties

1. Ali EAA, Takizawa H, Kawakita N, Sawada T, Tsuboi M, 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(4):321-328.
2. Al-Jaghbeer M, Marcus M, Durkin M, McGuire FR, Iftikhar IH. Diagnostic yield of electromagnetic navigational bronchoscopy. Therapeutic Advances in Respiratory Disease. 2016;10(4):295-299.
3. Andersen FD, Degn KB, Riis R. Electromagnetic navigation bronchoscopy for lung nodule evaluation. Patient selection, diagnostic variables and safety. The clinical respiratory journal. 2020;14(6):557-563.
4. Asahina H, Yamazaki K, Onodera Y, Kikuchi E, Shinagawa N, et al. Transbronchial biopsy using endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation. Chest. 2005;128(3):1761-1765.
5. Asano F, Matsuno Y, Shinagawa N, Yamazaki K, Suzuki T, et al. A virtual bronchoscopic navigation system for pulmonary peripheral lesions. Chest. 2006;130(2):559-566.
6. Asano F, Matsuno Y, Tsuzuku A, Anzai M, Shinagawa N, et al. Diagnosis of peripheral pulmonary lesions using a bronchoscope insertion guidance system combined with endobronchial ultrasonography with a guide sheath. Lung Cancer. 2008;60(3):366-373.
7. Asano F, Shinagawa N, Ishida T, Shindoh J, Anzai M, et al. Virtual bronchoscopic navigation combined with ultrathin bronchoscopy. A randomized clinical trial. American Journal of Respiratory & Critical Care Medicine. 2013;188(3):327-333.
8. Asano F, Shinagawa N, Ishida T, Tsuzuku A, Tachihara M, et al. Virtual bronchoscopic navigation improves the diagnostic yield of radial-endobronchial ultrasound for peripheral pulmonary lesions with involved bronchi on CT. Internal Medicine. 2015;54(9):1021-1025.

9. Bae S, Lim S, Ahn JJ, Jegal Y, Seo KW, et al. Diagnosing peripheral lung lesions using endobronchial ultrasonography with guide sheath: A prospective registry study to assess the effect of virtual bronchoscopic navigation using a computed tomography workstation. Medicine. 2020;99(17):e19870.
10. Bellinger C, Poon R, Dotson T, Sharma D. Lesion characteristics affecting yield of electromagnetic navigational bronchoscopy. Respiratory Medicine. 2021;180:106357.
11. Bertoletti L, Robert A, Cottier M, Chambonniere ML, Vergnon JM. Accuracy and feasibility of electromagnetic navigated bronchoscopy under nitrous oxide sedation for pulmonary peripheral opacities: an outpatient study. Respiration. 2009;78(3):293-300.
12. Bo L, Li C, Pan L, Wang H, Li S, et al. Diagnosing a solitary pulmonary nodule using multiple bronchoscopic guided technologies: A prospective randomized study. Lung Cancer. 2019;129:48-54.
13. Bowling MR, Brown C, Anciano CJ. Feasibility and Safety of the Transbronchial Access Tool for Peripheral Pulmonary Nodule and Mass. Annals of Thoracic Surgery. 2017;104(2):443-449.
14. Bowling MR, Kohan MW, Walker P, Efird J, Ben O. The effect of general anesthesia versus intravenous sedation on diagnostic yield and success in electromagnetic navigation bronchoscopy. Journal of Bronchology & Interventional Pulmonology. 2015;22(1):5-13.
15. Casal RF, Sarkiss M, Jones AK, Stewart J, Tam A, et al. Cone beam computed tomography-guided thin/ultrathin bronchoscopy for diagnosis of peripheral lung nodules: a prospective pilot study. Journal of Thoracic Disease. 2018;10(12):6950-6959.
16. Chee A, Stather DR, Maceachern P, Martel S, Delage A, et al. Diagnostic utility of peripheral endobronchial ultrasound with electromagnetic navigation bronchoscopy in peripheral lung nodules. Respirology. 2013;18(5):784-789.
17. Cheng SL, Chu CM. Electromagnetic navigation bronchoscopy: the initial experience in Hong Kong. Journal of Thoracic Disease. 2019;11(4):1697-1704.
18. Diez-Ferrer M, Morales A, Tebé C, Cubero N, López-Lisbona R, et al. Ultrathin Bronchoscopy with and without Virtual Bronchoscopic Navigation: Influence of Segmentation on Diagnostic Yield. Respiration. 2019;97(3):252-258.
19. Eberhardt R, Anantham D, Ernst A, Feller-Kopman D, Herth F. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. American Journal of Respiratory & Critical Care Medicine. 2007;176(1):36-41. *[Eberhardt 2007b]*
20. Eberhardt R, Anantham D, Herth F, Feller-Kopman D, Ernst A. Electromagnetic navigation diagnostic bronchoscopy in peripheral lung lesions. Chest. 2007;131(6):1800-1805. *[Eberhardt 2007a]*
21. Eberhardt R, Kahn N, Gompelmann D, Schumann M, Heussel CP, Herth FJ. LungPoint--a new approach to peripheral lesions. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2010;5(10):1559-1563. *[Eberhardt 2010b]*
22. Eberhardt R, Morgan RK, Ernst A, Beyer T, Herth FJ. Comparison of suction catheter versus forceps biopsy for sampling of solitary pulmonary nodules guided by electromagnetic navigational bronchoscopy. Respiration. 2010;79(1):54-60. *[Eberhardt 2010a]*
23. Garwood SK, ClenDening P, Hevelone ND, Hood KL, Pidgeon S, et al. Navigational bronchoscopy at a community hospital: clinical and economic outcomes. Lung Cancer Management. 2016;5(3):131-140.

24. Gildea TR, Mazzone PJ, Karnak D, Meziane M, Mehta AC. Electromagnetic navigation diagnostic bronchoscopy: a prospective study. American Journal of Respiratory & Critical Care Medicine. 2006;174(9):982-989.
25. Gu Y, Chen S, Shi J, Wu C, Wen Z, et al. The introduction of electromagnetic navigation bronchoscopy for the diagnosis of small pulmonary peripheral lesions in an Asian population. Journal of Thoracic Disease. 2017;9(9):2959-2965.
26. Haidong H, Yunye N, Wei Z, Zarogoulidis P, Hohenforst-Schmidt W, et al. Multiple guided technologies based on radial probe endobronchial ultrasound for the diagnosis of solitary peripheral pulmonary lesions: a single-center study. Journal of Cancer. 2017;8(17):3514-3521.
27. Hautmann H, Schneider A, Pinkau T, Peltz F, Feussner H. Electromagnetic catheter navigation during bronchoscopy: validation of a novel method by conventional fluoroscopy. Chest. 2005;128(1):382-387.
28. Hohenforst-Schmidt W, Zarogoulidis P, Vogl T, Turner JF, Browning R, et al. Cone Beam Computertomography (CBCT) in Interventional Chest Medicine - High Feasibility for Endobronchial Realtime Navigation. Journal of Cancer. 2014;5(3):231-241.
29. Ikezawa Y, Shinagawa N, Sukoh N, Morimoto M, Kikuchi H, et al. Usefulness of Endobronchial Ultrasonography With a Guide Sheath and Virtual Bronchoscopic Navigation for Ground-Glass Opacity Lesions. Annals of Thoracic Surgery. 2017;103(2):470-475.
30. Ishida T, Asano F, Yamazaki K, Shinagawa N, Oizumi S, et al. Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: A randomised trial. Thorax. 2011;66(12):1072-1077.
31. Iwano S, Imaizumi K, Okada T, Hasegawa Y, Naganawa S. Virtual bronchoscopy-guided transbronchial biopsy for aiding the diagnosis of peripheral lung cancer. European Journal of Radiology. 2011;79(1):155-159.
32. Jensen KW, Hsia DW, Seijo LM, Feller-Kopman DJ, Lamb C, et al. Multicenter experience with electromagnetic navigation bronchoscopy for the diagnosis of pulmonary nodules. Journal of Bronchology & Interventional Pulmonology. 2012;19(3):195-199.
33. Karnak D, Ciledag A, Ceyhan K, Atasoy C, Akyar S, Kayacan O. Rapid on-site evaluation and low registration error enhance the success of electromagnetic navigation bronchoscopy. Annals of Thoracic Medicine. 2013;8(1):28-32.
34. Kato A, Yasuo M, Tokoro Y, Kobayashi T, Ichiyama T, et al. Virtual bronchoscopic navigation as an aid to CT-guided transbronchial biopsy improves the diagnostic yield for small peripheral pulmonary lesions. Respirology. 2018;23(11):1049-1054.
35. Kawakita N, Takizawa H, Toba H, Sakamoto S, Miyamoto N, et al. Cone-beam computed tomography versus computed tomography-guided ultrathin bronchoscopic diagnosis for peripheral pulmonary lesions: A propensity score-matched analysis. Respirology. 2021;26(5):477-484.
36. Kheir F, Thakore SR, Uribe B, J P, Tahboub M, et al. Cone-Beam Computed Tomography-Guided Electromagnetic Navigation for Peripheral Lung Nodules. Respiration. 2021;100(1):44-51.
37. Lamprecht B, Porsch P, Wegleitner B, Strasser G, Kaiser B, Studnicka M. Electromagnetic navigation bronchoscopy (ENB): Increasing diagnostic yield. Respiratory Medicine. 2012;106(5):710-715.
38. Li S, Yan W, Chen M, Li Z, Zhu Y, Wu Q. Virtual bronchoscopic navigation without fluoroscopy guidance for peripheral pulmonary lesions in inexperienced pulmonologist. Chinese Journal of Cancer Research. 2020;32(4):530-539.

39. Loo FL, Halligan AM, Port JL, Hoda RS. The emerging technique of electromagnetic navigation bronchoscopy-guided fine-needle aspiration of peripheral lung lesions: promising results in 50 lesions. Cancer Cytopathology. 2014;122(3):191-199.
40. Ma L, Fang Y, Zhang T, Xue P, Bo L, et al. Comparison in efficacy and safety of forceps biopsy for peripheral lung lesions guided by endobronchial ultrasound-guided sheath (EBUS-GS) and electromagnetic navigation bronchoscopy combined with EBUS (ENB-EBUS). American Journal Of Translational Research. 2020;12(8):4604-4611.
41. Maekura T, Sugimoto C, Tamiya A, Saijo N, Naoki Y, et al. Combination of virtual bronchoscopic navigation, endobronchial ultrasound, and rapid on-site evaluation for diagnosing small peripheral pulmonary lesions: a prospective phase II study. Journal of Thoracic Disease. 2017;9(7):1930-1936.
42. Mahajan AK, Patel S, Hogarth DK, Wightman R. Electromagnetic navigational bronchoscopy: an effective and safe approach to diagnose peripheral lung lesions unreachable by conventional bronchoscopy in high-risk patients. Journal of Bronchology & Interventional Pulmonology. 2011;18(2):133-137.
43. Makris D, Scherpereel A, Leroy S, Bouchindhomme B, Faivre JB, et al. Electromagnetic navigation diagnostic bronchoscopy for small peripheral lung lesions. European Respiratory Journal. 2007;29(6):1187-1192.
44. Matsumoto Y, Izumo T, Sasada S, Tsuchida T, Ohe Y. Diagnostic utility of endobronchial ultrasound with a guide sheath under the computed tomography workstation (ziostation) for small peripheral pulmonary lesions. The clinical respiratory journal. 2017;11(2):185-192.
45. Miyoshi S, Isobe K, Shimizu H, Sunakawa M, Suzuki A, et al. The utility of virtual bronchoscopy using a computed tomography workstation for conducting conventional bronchoscopy: A retrospective analysis of clinical practice. Respiration. 2018;97(1):52-59.
46. Mukherjee S, Chacey M. Diagnostic Yield of Electromagnetic Navigation Bronchoscopy Using a Curved-tip Catheter to Aid in the Diagnosis of Pulmonary Lesions. Journal of Bronchology & Interventional Pulmonology. 2017;24(1):35-39.
47. Odronic SI, Gildea TR, Chute DJ. Electromagnetic navigation bronchoscopy-guided fine needle aspiration for the diagnosis of lung lesions. Diagnostic Cytopathology. 2014;42(12):1045-1050.
48. Oh JH, Choi CM, Kim S, Kim WS, Hwang HS, et al. Diagnostic yield and safety of biopsy guided by electromagnetic navigation bronchoscopy for high-risk pulmonary nodules. Thoracic Cancer. 2021;12(10):1503-1510.
49. Oki M, Saka H, Ando M, Asano F, Kurimoto N, et al. Ultrathin Bronchoscopy with Multimodal Devices for Peripheral Pulmonary Lesions. A Randomized Trial. American Journal of Respiratory & Critical Care Medicine. 2015;192(4):468-476.
50. Oki M, Saka H, Asano F, Kitagawa C, Kogure Y, et al. Use of an Ultrathin vs Thin Bronchoscope for Peripheral Pulmonary Lesions: A Randomized Trial. Chest. 2019;156(5):954-964.
51. Oshige M, Shirakawa T, Nakamura M, Mineshita M, Kurimoto N, et al. Clinical application of virtual bronchoscopic navigation system for peripheral lung lesions. Journal of Bronchology & Interventional Pulmonology. 2011;18(2):196-202.
52. Ost DE, Ernst A, Lei X, Kovitz KL, Benzaquen S, et al. Diagnostic Yield and Complications of Bronchoscopy for Peripheral Lung Lesions. Results of the AQuIRE Registry. American Journal of Respiratory & Critical Care Medicine. 2016;193(1):68-77.

53. Patrucco F, Gavelli F, Daverio M, Antonini C, Boldorini R, et al. Electromagnetic Navigation Bronchoscopy: Where Are We Now? Five Years of a Single-Center Experience. Lung. 2018;196(6):721-727.
54. Pearlstein DP, Quinn CC, Burtis CC, Ahn KW, Katch AJ. Electromagnetic navigation bronchoscopy performed by thoracic surgeons: one center's early success. Annals of Thoracic Surgery. 2012;93(3):944-949; discussion 949.
55. Pritchett MA, Schampaert S, de Groot JAH, Schirmer CC, van der Bom I. Cone-Beam CT With Augmented Fluoroscopy Combined With Electromagnetic Navigation Bronchoscopy for Biopsy of Pulmonary Nodules. Journal of Bronchology & Interventional Pulmonology. 2018;25(4):274-282.
56. Raval AA, Amir L. Community hospital experience using electromagnetic navigation bronchoscopy system integrating tidal volume computed tomography mapping. Lung Cancer Management. 2016;5(1):9-19.
57. Sato T, Yutaka Y, Ueda Y, Hamaji M, Motoyama H, et al. Diagnostic yield of electromagnetic navigational bronchoscopy: results of initial 35 cases in a Japanese institute. Journal of Thoracic Disease. 2018;10(Suppl 14):S1615-S1619.
58. Seijo LM, de Torres JP, Lozano MD, Bastarrika G, Alcaide AB, et al. Diagnostic yield of electromagnetic navigation bronchoscopy is highly dependent on the presence of a Bronchus sign on CT imaging: results from a prospective study. Chest. 2010;138(6):1316-1321.
59. Shinagawa N, Yamazaki K, Onodera Y, Asahina H, Kikuchi E, et al. Factors related to diagnostic sensitivity using an ultrathin bronchoscope under CT guidance. Chest. 2007;131(2):549-553.
60. Shinagawa N, Yamazaki K, Onodera Y, Asano F, Ishida T, et al. Virtual bronchoscopic navigation system shortens the examination time--feasibility study of virtual bronchoscopic navigation system. Lung Cancer. 2007;56(2):201-206.
61. Shinagawa N, Yamazaki K, Onodera Y, Miyasaka K, Kikuchi E, et al. CT-guided transbronchial biopsy using an ultrathin bronchoscope with virtual bronchoscopic navigation. Chest. 2004;125(3):1138-1143.
62. Sobieszczyk MJ, Yuan Z, Li W, Krimsky W. Biopsy of peripheral lung nodules utilizing cone beam computer tomography with and without trans bronchial access tool: a retrospective analysis. J Thorac Dis. 2018;10(10):5953-5959.
63. Steinfort DP, Bonney A, See K, Irving LB. Sequential multimodality bronchoscopic investigation of peripheral pulmonary lesions. Eur Respir J. 2016;47(2):607-614.
64. Stenger M, Zoorob S, Hussein AA, Eckardt J. Electromagnetic navigation bronchoscopy as an adjunct diagnostic tool in the Danish lung cancer diagnostic pathway: an initial retrospective single centre series. Journal of Thoracic Disease. 2020;12(9):4762-4770.
65. Sun J, Xie F, Zheng X, Jiang Y, Zhu L, et al. Learning curve of electromagnetic navigation bronchoscopy for diagnosing peripheral pulmonary nodules in a single institution. Translational Cancer Research. 2017;6(3):541-551.
66. Tachihara M, Tamura D, Kiriu T, Tokunaga S, Hatakeyama Y, et al. Sbronchoscopy using virtual navigation and endobronchial ultrasonography with a guide sheath (EBUS-GS) with or without fluoroscopy for peripheral pulmonary lesions. Kobe Journal of Medical Sciences. 2017;63(4):E99-E104.
67. Tamiya M, Okamoto N, Sasada S, Shiroyama T, Morishita N, et al. Diagnostic yield of combined bronchoscopy and endobronchial ultrasonography, under LungPoint guidance for small peripheral pulmonary lesions. Respirology. 2013;18(5):834-839.

68. Taton O, Bondue B, Gevenois PA, Remmelink M, Leduc D. Diagnostic Yield of Combined Pulmonary Cryobiopsies and Electromagnetic Navigation in Small Pulmonary Nodules. Pulmonary Medicine. 2018;2018:6032974.
69. Verhoeven RLJ, Futterer JJ, Hoefsloot W, van der Heijden E. Cone-Beam CT Image Guidance With and Without Electromagnetic Navigation Bronchoscopy for Biopsy of Peripheral Pulmonary Lesions. Journal of Bronchology & Interventional Pulmonology. 2020:60-69.
70. Verhoeven RLJ, van der Sterren W, Kong W, Langereis S, van der Tol P, van der Heijden E. Cone-beam CT and Augmented Fluoroscopy-guided Navigation Bronchoscopy: Radiation Exposure and Diagnostic Accuracy Learning Curves. Journal of Bronchology & Interventional Pulmonology. 2021;23:23.
71. Wang N, Ma H, Huang H, Feng Y. Electromagnetic Navigation Bronchoscopy Combined Endobronchial Ultrasound in the Diagnosis of Lung Nodules. Medicine. 2021;100(3):e23979.
72. Wilson DS, Bartlett RJ. Improved diagnostic yield of bronchoscopy in a community practice: Combination of electromagnetic navigation system and rapid on-site evaluation. Journal of Bronchology. 2007;14(4):227-232.
73. Wong KY, Tse HN, Pak KK, Wong CC, Lok PS, et al. Integrated use of virtual bronchoscopy and endobronchial ultrasonography on the diagnosis of peripheral lung lesions. Journal of Bronchology & Interventional Pulmonology. 2014;21(1):14-20.
74. Xu C, Yuan Q, Wang Y, Wang W, Chi C, et al. Usefulness of virtual bronchoscopic navigation combined with endobronchial ultrasound guided transbronchial lung biopsy for solitary pulmonary nodules. Medicine. 2019;98(7):e14248.
75. Yu KL, Yang SM, Ko HJ, Tsai HY, Ko JC, et al. Efficacy and safety of cone-beam computed tomography-derived augmented fluoroscopy combined with endobronchial ultrasound in peripheral pulmonary lesions. Respiration. 2021;100(6):538-546.
76. Zhang H, Wang C, Zhang Y, Xu S, Wang Y, Wang W. Diagnostic value of endobronchial ultrasonography with a guide sheath combined with virtual bronchoscopic biopsy for pulmonary peripheral lesions. Iranian Journal of Radiology. 2020;17(1).
77. Zheng X, Xie F, Li Y, Chen J, Jiang Y, Sun J. Ultrathin bronchoscope combined with virtual bronchoscopic navigation and endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions with or without fluoroscopy: A randomized trial. Thoracic Cancer. 2021;12(12):1864-1872.

Bijlage 7: Overzicht resultaten navigatiesucces, diagnostische opbrengst, percentage accurate diagnoses en sensitiviteit, inclusief subgroepen

7A: PICOT 1

	Total number of studies	Navigational success		Diagnostic yield		Accurate diagnoses		Sensitivity	
		n studies	median (IQR)	n studies	median (IQR)	n studies	accurate diagnoses (95%CI)	n studies	sensitivity (95%CI)
EMN	**7**	**4**	**97.7% (94.9% to 100.0%)**	**7**	**71.7% (67.5% to 94.0%)**	**7**	**69.9% (55.3% to 81.3%)**	**3**	**71.7% (33.0% to 92.8%)**
no addition to navigation	4	2	96.7% (95.1% to 98.4%)	4	78.2% (67.8% to 91.1%)	4	68.4% (40.6% to 87.3%)	2	70.1% (0.1% to 100.0%)
addition to navigation	3	2	97.7% (96.5% to 98.8%)	3	71.7% (65.4% to 85.9%)	3	72.0% (28.5% to 94.3%)	1	74.6% (62.3% to 84.1%)
VB	**0**	**0**	-		-		-		-
CBCT	**1**								
no addition to navigation	1	1	90.9% (95% CI 74.5% to 97.6%)	1	69.7% (95% CI 51.1% to 83.8%		-		-
addition to navigation	0	0							

7B: PICOT 2

	Total number of studies	Navigational success		Diagnostic yield		Accurate diagnoses		Sensitivity	
		n studies	median (IQR)	n studies	median (IQR)	n studies	accurate diagnoses (95%CI)	n studies	sensitivity (95%CI)
EMN	**31**	**17**	**100.0% (93.8% to 100.0%)**	**26**	**78.6% (69.0% to 96.7%)**	**21**	**74.6% (68.7% to 79.7%)**	**9**	**70.5% (57.3% to 81.0%)**
no addition to navigation; conventional bronchoscopy not feasible	4	2	95.1% (92.6% to 97.5%)	4	77.7% (69.2% to 88.0%)	2	70.1% (5.0% to 99.1%)	1	51.2% (35.4% to 66.8%)

	Total number of studies	Navigational success		Diagnostic yield		Accurate diagnoses		Sensitivity	
		n studies	median (IQR)	n studies	median (IQR)	n studies	accurate diagnoses (95%CI)	n studies	sensitivity (95%CI)
no addition to navigation; no information on conventional bronchoscopy feasibility	11	5	100.0% (100.0% to 100.0%)	8	78.6% (70.4% to 98.5%)	7	74.1% (64.8% to 81.7%)	3	63.9% (42.4% to 81.0%)
addition to navigation; conventional bronchoscopy not feasible	4	4	100.0% (100.0% to 100.0%)	4	89.6% (79.1% to 97.6%)	4	75.3% (53.0% to 89.1%)	1	60.9% (38.8% to 79.5%)
addition to navigation; no information on conventional bronchoscopy feasibility	11	6	96.1% (91.4% to 100.0%)	9	75.5% (69.0% to 93.2%)	8	76.4% (60.3% to 87.3%)	4	83.3% (64.9% to 93.0%)
mixture of addition and no addition to navigation; no information on conventional bronchoscopy feasibility	1	0	-	1	59.1% (95% CI 43.3% to 73.3%)	0	-	0	-
VB	**34**	**17**	**94.7% (92.3% to 100.0%)**	**27**	**77.8% (67.9% to 84.1%)**	**18**	**71.1% (65.1% to 76.5%)**	**3**	**75.0% (33.0% to 94.8%)**
no addition to navigation; conventional bronchoscopy not feasible	0	0	-	0	-	0	-	0	-
no addition to navigation; no information on conventional bronchoscopy feasibility	1	1	100.0% (95%CI 83.4% to 100.0%)	1	80.0% (95%CI 58.7% to 92.4%)	0	-	0	-
addition to navigation; conventional bronchoscopy not feasible	10	5	93.0% (92.0% to 93.8%)	8	87.6% (84.2% to 97.7%)	8	76.0% (68.6% to 82.2%)	1	63.4% (46.9% to 77.4%)
addition to navigation; no information on conventional bronchoscopy feasibility	23	11	100.0% (93.4% to 100.0%)	18	74.1% (64.0% to 80.4%)	10	66.9% (57.6% to 75.1%)	2	80.7% (0.5% to 100.0%)
CBCT	**3**	**1**	**95.3% (90.3% to 97.9%)**	**2**	**78.4% (74.2% to 82.6%)**	**2***	**78.7% (71.1% to 84.8%); 83.0% (69.7% to 91.5%)**	**1**	**94.4% (80.0% to 99.0%)**

*meta-analysis not possible

Bijlage 8. GRADE evidence profielen

8A: PICOT 1

Overall

Outcome	Number of studies	Number of lesions	Result	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Certainty
Navigation success median (IQR)	5	568	95.3% (93.5% to 100.0%)	not serious	not serious	not serious			
Diagnostic yield median (IQR)	8	827	70.7% (67.8% to 91.1%)	not serious	not serious	serious[a]			
Accurate diagnoses pooled (95% CI)	7	794	69.9% (55.3% to 81.3%)	not serious	not serious	serious[b]	serious[c]	not serious	**Low**
Sensitivity pooled (95% CI)	3	198	71.7% (33.0% to 92.8%)	not serious	not serious	serious[d]	very serious[e]	not serious	**Very low**
Negative predictive value median (IQR)	3[f]	152	65.3% (60.6% to 66.7%)	not serious	not serious	not serious			

a: Non-overlapping 95% confidence intervals, diagnostic yield ranges from 59% to 100%
b: Non-overlapping 95% confidence intervals, percentage accurate diagnoses ranges from 50% to 83%
c: Wide (width within range 10%-39%) 95% confidence interval
d: Non-overlapping 95% confidence intervals, sensitivity ranges from 55% to 82%
e: Very wide (width ≥40%) 95% confidence interval
f: Studies with at least 12 months follow-up of negative test results

Electromagnetic navigation bronchoscopy

Outcome	Number of studies	Number of lesions	Result	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Certainty
Navigation success median (IQR)	4	535	97.7% (94.9% to 100.0%)	not serious	not serious	not serious			
Diagnostic yield median (IQR)	7	794	71.7% (67.5% to 94.0%)	not serious	not serious	serious[a]			
Accurate diagnoses pooled (95% CI)	7	794	69.9% (55.3% to 81.3%)	not serious	not serious	serious[b]	serious[c]	not serious	**Low**

Sensitivity pooled (95% CI)	3	198	71.7% (33.0% to 92.8%)	not serious	not serious	serious[d]	very serious[e]	not serious	**Very low**
Complications: bleeding	4	498	Median incidence of reported types of bleeding events <3%, except for minor bleeding (9%)	serious[f]	not serious	not serious			
Complications: pneumothorax	7	800	Median incidence from 2% (unspecified) to 4% (pneumothorax requiring intervention)	serious[g]	not serious	not serious			

a: Non-overlapping 95% confidence intervals, diagnostic yield ranges from 59% to 100%

b: Non-overlapping 95% confidence intervals, percentage accurate diagnoses ranges from 50% to 83%; sensitivity ranges from 55% to 82%)

c: (Very) wide 95% confidence interval

d: Unclear risk of bias for flow and timing domain in all studies

g: High risk of selection bias in 2 studies and all but one study have unclear risk of bias for flow and timing domain

Virtual bronchoscopy

No evidence identified.

Cone beam CT

Outcome	Number of studies	Number of lesions	Result	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Certainty
Navigation success (95% CI)	1	33	90.9% (74.5% to 97.6%)	serious[a]	not serious	not serious			
Diagnostic yield (95% CI)	1	33	69.7% (51.1% to 83.8%)	serious[a]	not serious	not serious			
Accurate diagnoses pooled, (95% CI)	0	0	-	-	-	-	-	-	-
Sensitivity pooled, (95% CI)	0	0	-	-	-	-	-	-	-
Complications: bleeding	0	0	-	-	-	-			
Complications: pneumothorax	1	33	6%	serious[a]	not serious	not serious			

a: Unclear risk of bias for patient selection, unclear risk of bias for flow and timing domain

8B: PICOT 2

Overall

Outcome	Number of studies	Number of lesions	Result	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Certainty
Navigation success median (IQR)	37	2903	100% (92.3% to 100.0%)	serious[a]	not serious	serious[b]			
Diagnostic yield median (IQR)	62	4788	78.7% (67.7% to 89.8%)	serious[a]	not serious	serious[c]			
Accurate diagnoses pooled (95% CI)	45	3519	73.4% (69.9% to 76.6%)	serious[a]	not serious	serious[d]	not serious	not serious	**Low**
Sensitivity pooled (95% CI)	14	572	74.9% (64.6% to 83.0%)	serious[a]	not serious	serious[e]	serious[f]	not serious	**Very low**
Negative predictive value median (IQR)	6[g]	196	70.1% (52.3% to 83.3%)	serious[a]	not serious	serious[h]			

a: Considerable number of studies with high or unclear risk of bias for patient selection and flow and timing domains
b: Non-overlapping confidence intervals, navigation success ranges from 71% to 100%
c: Non-overlapping confidence intervals, diagnostic yield ranges from 34% to 100%
d: Non-overlapping confidence intervals, percentage accurate diagnoses ranges from 48% to 97%
e: Non-overlapping confidence intervals, sensitivity ranges from 51% to 94%
f: Wide (width within range 10%-39%) 95% confidence interval
g: Studies with at least 12 months follow-up of negative test results
h: Non-overlapping confidence intervals, negative predictive value ranges from 40% to 89%

Electromagnetic navigation bronchoscopy

Outcome	Number of studies	Number of lesions	Result	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Certainty
Navigation success median (IQR)	17	990	100.0% (93.8% to 100.0%)	serious[a]	not serious	not serious			
Diagnostic yield median (IQR)	26	1511	78.6% (69.0% to 96.7%)	serious[a]	not serious	serious[b]			
Accurate diagnoses pooled, (95% CI)	21	1428	74.6% (68.7% to 79.7%)	serious[a]	not serious	serious[c]	serious[d]	not serious	**Very low**
Sensitivity	9	295	70.5% (57.3% to 81.0%)	not serious	not serious	serious[e]	serious[d]	not serious	**Low**

pooled, (95% CI)									
Complications: bleeding	8	633	13-34% bleeding incidence in one study (n=32); other incidences 4% (minor bleeding) or below (major; moderate/severe; and unspecified bleeding)	not serious	not serious	not serious			
Complications: pneumothorax	27	1873	Median incidences 2% (pneumothorax not requiring intervention) or 3% (requiring intervention or unspecified).	not serious	not serious	not serious			

a: Unclear/high risk of selection bias in about half of the studies and several studies with unclear/high risk of bias for flow and timing domain
b: Non-overlapping 95% confidence intervals, diagnostic yield ranges from 34% to 100%
c: Non-overlapping 95% confidence intervals, percentage accurate diagnoses ranges from 52% to 97%
d: Wide 95% confidence interval (width within range 10%-39%)
e: Non-overlapping 95% confidence intervals, sensitivity ranges from 51% to 90%

Virtual bronchoscopy

Outcome	Number of studies	Number of lesions	Result	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Certainty
Navigation success median (IQR)	17	1420	94.7% (92.3% to 100.0%)	serious[a]	serious[b]	not serious			
Diagnostic yield median (IQR)	27	2424	77.8% (67.9% to 84.1%)	serious[a]	not serious	serious[c]			
Accurate diagnoses pooled, (95% CI)	18	1658	71.1% (65.1% to 76.5%)	serious[a]	serious[b]	serious[d]	serious[e]	not serious	**Very low**
Sensitivity pooled, (95% CI)	3	216	75.0% (33.0% to 94.8%)	serious[f]	not serious	serious[g]	very serious[h]	not serious	**Very low**
Complications: bleeding	13	1700	12% moderate bleeding in 1 study (n=50); all other (median)incidences are 4% or below	serious[i]	not serious	not serious			
Complications: pneumothorax	20	2320	Median incidences 1% (pneumothorax requiring intervention and unspecified pneumothorax)	serious[i]	not serious	not serious			

			to 2% (not requiring intervention)						

a: Unclear/high risk of selection bias in over half of the studies and several studies with unclear risk of bias for flow and timing domain
b: 7 studies with applicability concerns for patient selection;
c: Non-overlapping 95% confidence intervals, diagnostic yield ranges from 50% to 100%
d: Non-overlapping 95% confidence intervals, percentage accurate diagnoses ranges from 48% to 84%;
e: Wide (width within range 10%-39%) 95% confidence interval
f: Unclear/high risk of selection bias in all 3 studies and unclear risk of bias for flow and timing domain in 1 study
g: Non-overlapping 95% confidence intervals, sensitivity ranges from 63% to 86%
h: Very wide (width ≥40%) 95% confidence interval
i: High risk of selection bias in majority of studies and most studies with unclear risk of bias for flow and timing domain

Cone beam CT

Outcome	Number of studies	Number of lesions	Result	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Certainty
Navigation success (95% CI)	1	150	95.3% (90.3% to 97.9)	not serious	not serious	not serious			
Diagnostic yield (95% CI)	2	73	78.4% (74.2 to 82.6%)	serious[a]	not serious	not serious			
Accurate diagnoses (95% CI)	2	203	78.7% (71.1% to 84.8%) 83.0% (69.7% to 91.5%)	serious[b]	not serious	not serious	serious[c]	not serious	**Low**
Sensitivity (95% CI)	1	39	94.4% (80.0% to 99.0%)	serious[b]	not serious	not serious	serious[c]	not serious	**Low**
Complications: bleeding	1	53	4%	serious[d]	not serious	not serious			
Complications: pneumothorax	2	73	0% in one study, 5% in the other study (20 participants)	serious[d]	not serious	not serious			

a: Both studies unclear risk of selection bias, 1 study unclear risk of bias for reference standard and flow and timing domains
b: Unclear risk of selection bias in one study, high risk of bias for flow and timing domain in other study
c: Only one or two studies identified, meta-analysis not possible, wide 95% confidence interval(s)
d: Unclear risk of selection bias and unclear risk of bias for flow and timing domain

Combination of navigation bronchoscopy techniques

Outcome	Number of studies	Number of lesions	Result	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Certainty
Electromagnetic navigation bronchoscopy and virtual bronchoscopy									
Navigation success (95% CI)	1	57	76.7% (70.8% to 81.8%)	serious[a]	not serious	not serious			
Diagnostic yield (95% CI)	3	358	91.4% (75.8% to 97.8%) 45.9% (39.8% to 52.1%) 58.4% (51.9% to 64.6%)	serious[b]	not serious	very serious[c]			
Accurate diagnoses (95% CI)	0	0	-	-	-	-	-	-	-
Sensitivity (95% CI)	0	0	-	-	-	-	-	-	-
Complications: bleeding	1	581	0.2%	serious[d]	not serious	not serious			
Complications: pneumothorax	2	657	2% in one study, 4% in the other study	serious[d]	not serious	not serious			
Electromagnetic navigation bronchoscopy and cone beam CT									
Navigation success (95% CI)	1	58	84.5% (72.1% to 92.2%)	not serious	not serious	not serious			
Diagnostic yield (95% CI)	2	115	82.8% (73.3% to 89.6%) 77.3% (54.2% to 91.3%)	serious[e]	not serious	not serious			
Accurate diagnoses (95% CI)	3	182	74.2% (55.1% to 87.5%) 77.3% (54.2% to 91.3%) 70.7% (57.1% to 81.5%)	serious[f]	not serious	not serious	serious[g]	not serious	**Low**
Sensitivity (95% CI)	0	0	-	-	-	-	-	-	-
Complications: bleeding	3	184	0% in two studies, 1% in the other study	serious[h]	not serious	not serious			
Complications: pneumothorax	4	215	Range 0% to 6%	serious[i]	not serious	not serious			
Virtual bronchoscopy and cone beam CT									
Navigation success (95% CI)	1	40	100.0% (89.1% to 100.0%)	serious[j]	not serious	not serious			
Diagnostic yield (95% CI)	2	119	95.0% (81.8% to 99.1%) 65.8% (54.2% to 75.9%)	serious[j]	not serious	serious[k]			
Accurate diagnoses (95% CI)	2	119	90.0% (75.4% to 96.7%) 65.8% (54.2% to 75.9%)	serious[j]	not serious	serious[k]	serious[g]	not serious	**Very low**

Sensitivity (95% CI)	1	40	92.0% (72.5% to 98.6%)	serious[j]	not serious	not serious	serious[g]	not serious	**Low**
Complications: bleeding	0	0	-	-	-	-			
Complications: pneumothorax	2	119	1% in one study, 3% in the other	serious[l]	not serious	not serious			

a: Unclear risk of selection bias, high risk of bias for flow and timing domain
b: One study at unclear risk of selection bias, two studies at high risk of bias for flow and timing domain
c: Wide range of diagnostic yields, non-overlapping 95% confidence intervals
d: Unclear risk of bias for flow and timing domain
e: Unclear and high risk of selection bias, unclear risk fo bias for reference standard domain in one study, high risk of bias for flow and timing domain in one study
f: High risk of selection bias in two studies, unclear risk of selection bias in other study, one study at high risk of bias for flow and timing domain
g: Only one or two studies identified, meta-analysis not possible, wide 95% confidence interval(s)
h: In one study high risk of selection bias, in two other studies unclear; two studies unclear risk of bias for flow and timing domain
i: High risk of selection bias in two studies, unclear in other two; three studies unclear risk of bias for flow and timing domain
j: High risk of selection bias
k: Wide range between results from the two studies
l: High risk of selection bias, unclear risk for flow and timing domain