CT-controlled advanced navigation techniques for transbronchial pulmonary lesion access; evaluation of augmented fluoroscopy bronchoscopic navigation based diagnostic yield.

Published: 20-12-2017
Last updated: 12-04-2024

Diagnostic yield and navigation accuracy of a combination of commercially available endobronchial navigation and imaging techniques will be evaluated in patients with peripheral pulmonary lesions. Cost-effectiveness and safety will be modelled on...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON44276

Source
ToetsingOnline

Brief title
CONTROL-A

Condition

- Respiratory tract neoplasms

Synonym
early stage lung cancer, peripheral pulmonary nodules

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Pentax Medical,Philips,Radboudumc afdeling Longziekten en MITeC

Intervention

Keyword: Cancer, Interventional pulmonology, Lung diseases, peripheral nodule

Outcome measures

Primary outcome

The first objective is to exploratively study diagnostic yield and navigational accuracy of the studied combination of imaging and navigational modalities. For studying navigational accuracy we will evaluate if the combination of the studied modalities is able to navigate to the peripheral lung lesion in all cases. If not and/or an unrepresentative diagnosis is found, an exploratory analysis will be performed to correlate lesion characteristics to study procedure performance.

Secondary outcome

The secondary objective is to study safety and cost-effectiveness of the diagnostic procedures. To be able to analyse cost-effectiveness and workflow integration of the combined modalities, the study procedures will be compared against the conventional diagnostic TBB work-up (rEBUS and fluoroscopy guided followed by CT guided TTNA and prevented surgical biopsies) by historic database research. Comparison is performed by modelling the study procedures and the conventional work-up. For doing so, multiple parameters will be recorded in a quantitative way (also see the study protocol). In case of partially missing data in these continuous variables, missing data will be

extrapolated from other recorded procedures. Standard deviations and means will be used for developing a mathematical cost-effectiveness model. The conventional procedure cost-effectiveness will be extrapolated from Radboudumc database and reported literature research.

Study description

Background summary

Rationale: Lung cancer is one of the leading most frequent types of cancer and is the most lethal malignancy in the Netherlands. Mortality is high due to its advanced stage disease at diagnosis. To improve survival current guidelines are moving towards CT-screening of the high risk population (U.S. Preventive Services Task Force, 2014). In the American National Lung Screening Trial (NLST), a 20% decrease mortality was found. Herein, 39.1% of the participants of the NLST were found to have at least one peripheral pulmonary lesion (PPL) of more than 4mm in diameter, and of those, 72.1% underwent additional diagnostics procedures (The National Lung Screening Trial Research Team, 2011). These CT-scans thus detect numerous nodules and rapidly increase the demand for minimal invasive accurate and safe diagnostic and therapeutic procedures.
The historically available and current first diagnostic procedure in the work-up of PPLs is fluoroscopy guided Trans Bronchial Biopsy (TBB) despite its low pooled yield of 31.1% (Gould et al., 2013). Several new modalities have recently become available in specialized centers. These endobronchial modalities include endobronchial ultrasound radial mini-probe guided biopsy (rEBUS), ultrathin bronchoscopy (UB), virtual navigation bronchoscopy (VNB), and electromagnetic navigation bronchoscopy (EMN). A meta-analysis by Wang et al. (2012) showed that the individual diagnostic yield of these techniques ranged from 67% to 73.2%, and an overall pooled diagnostic yield was approximately 70% (Wang Memoli, Nietert, & Silvestri, 2012). Although this offers a big improvement in performance when compared to the conventional TBB, a diagnostic yield of approximately 70% still demands further improvement given the clinical need.
When the above transbronchial techniques do not provide an unambiguous outcome, an additional and more invasive diagnostic work-up remains indicated. To exclude the possibility of missing malignancies, trans thoracic needle aspiration is first indicated (TTNA; pooled sensitivity 90%, specificity 96-98%, false positive rate 22% (Rivera, Mehta, & Wahidi, 2013)). If deemed inaccessible, surgical biopsy may be alternatively indicated depending on patient risk of malignancy. With a reported pneumothorax rate of 25% in the Radboudumc and UMC Groningen combined, TTNA complication rates are high when

compared with endobronchial techniques (1.5%) (Wang Memoli et al., 2012; Wiener, Schwartz, Woloshin, & Gilbert Welch, 2011). Surgical biopsy is an even more invasive modality, and a 4.2% 90-day mortality has been reported (British Thoracic Society Pulmonary Nodule Guideline Development Group, 2015).
Once a diagnosis has been made, surgical excision of a pulmonary nodule by VATS or thoracotomy can be used to perform either wedge resection, segmentectomy or lobectomy. Morbidity rates following VATS and thoracotomy have been reported to range from 0-9.6% (British Thoracic Society Pulmonary Nodule Guideline Development Group, 2015).
Ideally, a transbronchial approach having high diagnostic accuracy would overcome the need of this sequential increasingly invasive diagnostic and consecutive treatment approach. Newer pilot studies now show that combining multiple new endobronchial modalities might provide a solution in preventing more invasive additional diagnostic staging, reporting diagnostic yields exceeding 80% (Eberhardt, Anantham, Ernst, Feller-Kopman, & Herth, 2007; Lamprecht et al., 2012; Loo, Halligan, Port, & Hoda, 2014). When an accurate and certain transbronchial diagnosis by combining multiple techniques can indeed be provided, a next step would be to enable immediate transbronchial treatment.

Study objective

Diagnostic yield and navigation accuracy of a combination of commercially available endobronchial navigation and imaging techniques will be evaluated in patients with peripheral pulmonary lesions. Cost-effectiveness and safety will be modelled on basis of collected study performance. The aim of this study is to determine diagnostic yield, navigation accuracy, safety, and, to collect data for developing diagnostic algorithms to further cost-effectively increase yield, reduce complication rate and determine technical needs of future technological platforms that are not only able to diagnose, but also simultaneously treat.

Study design

In this adaptive clinical trial we will investigate the diagnostic yield of a combination of commercially available imaging and navigation techniques for reaching peripheral lung lesions. The two investigated techniques will herein be the rEBUS imaging modality combined with augmented fluoroscopy based virtual bronchoscopy navigation. Confirmation of reaching the lung lesion will be by means of CT (fluoroscopic) imaging. Rapid On-Site Evaluation (ROSE) of cytopathology will be used for obtaing a per-procedural outcome on tissue biopsy representativeness. The study will replace the current conventional standard TBB procedure (fluoroscopy and rEBUS guided bronchoscopy) in the endoscopy suite. Consecutive patients will be included on the the department of radiology (needed to monitor patient safety and CT availability). All data will be prospectively collected. In case tissue biopsy is found to be malignant or

benign, it will be termed representative. In case tissue biopsy is found to be non-representative (=blood, anatomical lung tissue, unreachable), conventional follow-up of CT guided TTNA, follow-up monitoring and/or surgical biopsy will serve as golden standard for obtaining tissue diagnosis. For verification of reaching the target lesion, another study parameter of interest, (cb)CT imaging will be performed for verification that instruments are within the nodule (per-procedurally available).

Intervention

Not applicable, In this diagnostic study a new combination of currently commercially available techniques is evaluated. See the research protocol for more details.

Study burden and risks

The burden and risks associated with participation are considered lower or equal to the combined burden and risks associated to the current daily practice since essentially the same procedures are performed when current clinical standards are followed. rEBUS and virtual navigation bronchoscopy (VBN) based techniques such as AFBN have been studied in clinical studies for several years. rEBUS has herein had a formal recommendation of use for peripheral pulmonary lesion diagnosis in recent guidelines (Rivera et al., 2013). VBN is furthermore suggested also to be used in combination with available technology when sampling nodules, with a pooled yield approximately equal to that of EMN and rEBUS when used as individual modality (Gould et al., 2013; Rivera et al., 2013).

In patients who would conventionally receive TBB (fluoroscopy and rEBUS guided), the following advantages apply:
- An increase in diagnostic yield, without increasing the complication risks as compared to the currently used TBB procedure. The pooled diagnostic yield of newer individual modalities is approximately 70% when compared to the approximate 30% yield of the conventional TBB procedure (Gould et al., 2013; Wang Memoli et al., 2012). Combining modalities has been reported to increase yield further. Complication risks of TBB and these newer diagnostic modalities are both 1.5%, mainly attributable to pneumothoraxes (Wang Memoli et al., 2012).
- The two conventionally temporally separate procedures (TBB & consecutive TTNA if no adequate sample is obtained) are combined into one session in this study when technically possible, as technology for immediate TTNA conversion is available in the study setting. The total patient burden by having to undergo two temporally separate procedures with additional approximately 2-3 weeks waiting time (at current at the Radboudumc) as in the conventional work-up is thus reduced into a single session.
- The necessity of cross-over to CT-guided TTNA is lower, as there is an

expected increased yield by transbronchial diagnosis through the here studied combination of techniques (Gould et al., 2013; Wang Memoli et al., 2012). The pooled risk of pneumothorax requiring chest tube drainage by TTNA was found 25% in the Radboudumc and UMC Groningen combined, and in 10% of cases hemorrhages occurred [unpublished data, submitted to RSNA 2017]. Again, complication risks of TBB and these newer diagnostic modalities are both ~1.5%, mainly attributable to pneumothoraxes (Wang Memoli et al., 2012). The total risk of complications for the majority of patients included in this study is thus lower.

In patients who would conventionally receive TBB (fluoroscopy and rEBUS guided), the following potential burden and risks apply:
- Radiation exposure in the study procedure is higher when compared with the conventional TBB procedure due to the use of CT for navigation calibration and positioning confirmation, and, CT fluoroscopic guidance and positioning confirmation as opposed to C-arm fluoroscopy guidance and confirmation alone in conventional TBB. The added radiation exposure is based upon the need of a navigation system calibration low dose CT (2.4 mSv) and in elective cases where fluoroscopy does not provide sufficient detail, a target lesion confirmation low dose CT (2.4mSv) at the end of the procedure. Because of a study procedure yield increase, conventionally often needed additional procedures due to a lack of diagnostic yield, such as CT guided TTNA and/or surgical biopsy, may be prevented (whereas CT guided TTNA requires multiple low dose CT scans as well). The majority of subjects is >50 years old, and if these study techniques are able to diagnose with high accuracy, yield increase importance in terms of life expectancy greatly outweighs additional radiation exposure risk.
- When participating in this study, all patients will be deeply sedated. In our current local protocol, all patients indicated for fluoroscopy guided TBB are planned for procedural sedation with propofol sedation. The sedation level at current for this procedure is mild in approximately 60% of the cases and deep in 40% in the remaining group following the standard operating procedure. With deeper sedation, a laryngeal mask or endotracheal tube is used to allow a safe ventilation and optimal means for monitoring of the patient. For this reason we will use deep sedation for all patients in this study, improving imaging quality and also allowing for TTNA in breath-hold when a conversion is indicated. Side effects of using a mask are mild pain of the throat and hoarseness in rare cases. Side effects of the deeper sedation are equal as in the conventional work-up, yet chances upon these side effects are higher because of increased procedure duration and deeper sedation.Side effects of the deeper sedation include sleep apnea and muscle dystonia.
- Due to the additional navigation techniques, catheter manipulation time and potential need for additional TTNA the procedure taking place in the interventional radiology in this study setting, the added procedure time is approximately 30 minutes (the current standard of care average procedure time is 75 minutes; approximately 45 minutes for bronchoscopy and 30 minutes for TTNA).

The subgroup of patients initially (conventionally) referred for upfront surgical biopsy may benefit significantly when participating in this study. When a diagnosis can be obtained using this study protocol, a thoracoscopic or open surgical procedure may be prevented or simplified. Currently, when a diagnosis cannot be obtained preceding to the surgical procedure, a CT guided marker and onsite pathology are needed, and, the risk of conversion from VATS to open surgery is higher.

The procedures will take place in an environment optimally suited for finding and treating complications. Subjects will not receive any compensation for study participation other than the here above mentioned benefits.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
* ASA physical status 1-3.
* Age 18 years or older.
* A pulmonary lesion (i.e. a focal, rounded opacity mostly surrounded by aerated lung or a ground glass opacity or part- or sub-solid lesion) with an indication for diagnostic evaluation following current clinical guidelines and/or as decided by multi-disciplinary team consultation.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
* Bleeding disorders.
* Less than 18 years old.
* Contra-indication for temporary interruption of the use of anticoagulant therapy (acenocoumarol, warfarin, therapeutic dose of low molecular weight heparines, clopidrogel or analogs, or, NOAC*s).
* Known allergy for lidocaine.
* Uncontrolled pulmonary hypertension.
* Recent and/or uncontrolled cardiac disease.
* Compromised upper airway (e.g. concomitant head and neck cancer or central airway stenosis for any reason such that endobronchial access is considered unsafe).
* ASA classification greater than or equal to 4 (unfit for performing non-surgical biopsy).
* Pregnancy.
* Inability to consent.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-03-2018
Enrollment:	40
Type:	Actual

Medical products/devices used

Generic name:	augmented fluoroscopy guided virtual bronchoscopy navigation;radial endobronchial ultrasound mini pr
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	20-12-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT03274609
CCMO	NL63109.091.17