Contemporary Clinical Trials 71 (2018) 88–95

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Study Design and Rationale: A Multicenter, Prospective Trial of Electromagnetic Bronchoscopic and Electromagnetic Transthoracic Navigational Approaches for the Biopsy of Peripheral Pulmonary Nodules (ALL IN ONE Trial)

Jeffrey Thiboutot[a,*], Hans J. Lee[a], Gerard A. Silvestri[b], Alex Chen[c], Momen M. Wahidi[d], Christopher R. Gilbert[e], Nicholas J. Pastis[b], Jenna Los[a], Alexa M. Barriere[a], Christopher Mallow[a], Benjamin Salwen[a], Marcus J. Dinga[a], Eric L. Flenaugh[f], Jason A. Akulian[g], Roy Semaan[h], Lonny B. Yarmus[a]

[a] Johns Hopkins University Department of Medicine, Division of Pulmonary and Critical Care Medicine, Baltimore, MD, United States
[b] Medical University of South Carolina Department of Medicine, Division of Pulmonary and Critical Care Medicine, Charleston, SC, United States
[c] Washington University in St. Louis, St. Louis, MO, United States
[d] Duke University Department of Medicine, Division of Pulmonary and Critical Care Medicine, Durham, NC, United States
[e] Swedish Medical Center Department of Medicine, Division of Pulmonary and Critical Care Medicine, Seattle, WA, United States
[f] Morehouse School of Medicine Department of Medicine, Division of Pulmonary and Critical Care Medicine, Atlanta, GA, United States
[g] University of North Carolina School of Medicine Department of Medicine, Division of Pulmonary and Critical Care Medicine, Chapel Hill, NC, United States
[h] University of Pittsburgh Department of Medicine, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Pittsburg, PA, United States

ARTICLE INFO

Keywords:
Electromagnetic navigation
Bronchoscopy
Pulmonary nodule
Transthoracic biopsy

ABSTRACT

Background: Pulmonary nodules are a common but difficult issue for physicians as most identified on imaging are benign but those identified early that are cancerous are potentially curable. Multiple diagnostic options are available, ranging from radiographic surveillance, minimally invasive biopsy (bronchoscopy or transthoracic biopsy) to more invasive surgical biopsy/resection. Each technique has differences in diagnostic yield and complication rates with no established gold standard. Currently, the safest approach is bronchoscopic but it is limited by variable diagnostic yields. Percutaneous approaches are limited by nodule location and complications. With the recent advent of electromagnetic navigation (EMN), a combined bronchoscopic and transthoracic approach is now feasible in a single, staged procedure. Here, we present the study design and rationale for a single-arm trial evaluating a staged approach for the diagnosis of pulmonary nodules.

Methods: Participants with 1–3 cm, intermediate to high-risk pulmonary nodules will undergo a staged approach with endobronchial ultrasound (EBUS) followed by EMN-bronchoscopy (ENB), then EMN-transthoracic biopsy (EMN-TTNA) with the procedure terminated at any stage after a diagnosis is made via rapid onsite cytopathology. We aim to recruit 150 EMN participants from eight academic and community settings to show significant improvements over other historic bronchoscopic guided techniques. The primary outcome is overall diagnostic yield of the staged approach.

Conclusion: This is the first study designed to evaluate the diagnostic yield of a staged procedure using EBUS,

Abbreviations: ACCP, American College of Chest Physicians; AE, adverse event; ALL IN ONE, A Multicenter, Prospective Trial of Electromagnetic Bronchoscopic and Electromagnetic Transthoracic Navigational Approaches for the Biopsy of Peripheral Pulmonary Nodules; BAL, bronchoalveolar lavage; CXR, chest x-ray; CT, computed tomography; CT-TTNA, computed tomography guided percutaneous transthoracic needle aspiration; CTCAE, Common Terminology Criteria for Adverse Events; EBUS, endobronchial ultrasound; EMN, electromagnetic navigation; EMN-TTNA, electromagnetic guided percutaneous transthoracic needle aspiration; ENB, electromagnetic navigation bronchoscopy; FB, flexible bronchoscopy; FDA, U.S. Food and Drug Agency; FNA, fine needle aspiration; GEE, generalized estimating equations; GPS, global positioning system; IFU, instructions for use; NCCN, National Comprehensive Cancer Network; PET, positron emission tomography; PI, primary investigator; PPN, peripheral pulmonary nodule; R-EBUS, radial endobronchial ultrasound; ROSE, rapid on-site evaluation; SAE, serious adverse event; SBRT, stereotactic body radiation therapy; TBBx, transbronchial biopsy; TTNA, transthoracic needle biopsy; VATS, video-assisted thoracoscopic surgery

* Corresponding author at: Johns Hopkins University Department of Medicine, Division of Pulmonary and Critical Care Medicine, 1830 E Monument Street/5th Floor, Baltimore, MD 21287, United States.

E-mail addresses: jthibou1@jhmi.edu (J. Thiboutot), hlee171@jhmi.edu (H.J. Lee), silvestr@musc.edu (G.A. Silvestri), ACHEN@DOM.wustl.edu (A. Chen), momen.wahidi@duke.edu (M.M. Wahidi), Christopher.Gilbert@swedish.org (C.R. Gilbert), pastisn@musc.edu (N.J. Pastis), jlos1@jhmi.edu (J. Los), abarrie2@jhmi.edu (A.M. Barriere), cmallow1@jhmi.edu (C. Mallow), bsalwen1@jhmi.edu (B. Salwen), mdinga1@jhmi.edu (M.J. Dinga), eflenaugh@msm.edu (E.L. Flenaugh), jason_akulian@med.unc.edu (J.A. Akulian), Semaanrw2@upmc.edu (R. Semaan), lyarmus@jhmi.edu (L.B. Yarmus).

https://doi.org/10.1016/j.cct.2018.06.007
Received 14 May 2018; Received in revised form 4 June 2018; Accepted 5 June 2018
Available online 07 June 2018

ENB and EMN-TTNA for the diagnosis of pulmonary nodules. If effective, the staged procedure will increase minimally invasive procedural diagnostic yield for pulmonary nodules.

1. Introduction

Pulmonary nodules are a common but difficult issue for physicians [1]. With the results of the National Lung Cancer Screening Trial demonstrating a reduction in lung cancer mortality with screening of patients with low dose CT, it is expected that the number of nodules detected requiring follow up is likely to increase [2]. In studies of incidentally detected nodules, the prevalence of malignancy ranges from 2 to 82% [3], the dilemma for clinicians is deciding on the management and further diagnostic modalities to pursue to optimize yield, minimize complications and reduce benign surgical resections rates. This study aims to explore the efficacy of a staged procedure for the diagnosis of pulmonary nodules using multiple approaches to perform an electromagnetic (EMN) guided lung biopsy.

The American College of Chest Physicians (ACCP) guidelines for the management of pulmonary nodules state that if a nodule does not have stable or benign features, management decisions are based on surgical risk and the clinical probability that the nodule is malignant [1, 4]. For patients with nodules of intermediate probability for malignancy (5–65%), the various recommended procedures for obtaining tissue diagnosis include transthoracic needle biopsy (TTNA), surgery, and flexible bronchoscopy (FB). The diagnostic yield with FB varies with nodule size and location. Based on a review of 10 studies using FB for diagnosing peripheral pulmonary nodules (PPN), the sensitivity is only 34% for nodules < 2 cm and has been found to be as low as 14% [5, 6]. The sensitivity increases to 63% when nodules are > 2 cm in size, but decreases as the distance from the hilum increases.

Procedural guidance technologies such as EMN and radial endobronchial ultrasound (R-EBUS) have been integrated into bronchoscopic guidelines. Recently, a large retrospective study investigating the yield of bronchoscopy, reported a yield of only 38.5% when an older generation of EMN was used and 47.1% when EMN was combined with R-EBUS [7]. A meta-analysis found a pooled diagnostic yield of 70% for guided bronchoscopy using EMN, EMN bronchoscopy (ENB) or R-EBUS [8]. These studies were performed prior to the introduction of the combined ENB and EMN guided percutaneous transthoracic needle aspiration (EMN-TTNA) system (Veran Inc., St. Louis MO). The novel system allows EMN guidance for a transthoracic approach for the sampling of pulmonary nodules that can be performed during the same procedure as an ENB in a staged procedure.

In a prospective pilot study evaluating the safety, feasibility, and diagnostic yield of this staged approach in patients who underwent endobronchial ultrasound (EBUS), followed by ENB, and EMN-TTNA, the diagnostic yield of EMN-TTNA alone was found to be 83%, and when combined with ENB was 87% [9]. The diagnostic yield increased to 92% when combined with EBUS. The results demonstrated an acceptable safety and feasibility profile, however, due to its small sample size and single center design, a larger, multi-center study is warranted.

We undertake this prospective, single-arm study to assess the benefits of a staged procedure on diagnostic yield, the ability to decrease the need for independent procedures performed, and the time to diagnosis.

2. Methods

2.1. Target population

In this study, we aim to target these patients with indeterminate or high risk nodules in whom a tissue diagnosis via flexible bronchoscopy and/or TTNA would alter management. The ACCP characterizes pulmonary nodules based off their pre-test probability of malignancy. Those at high risk (estimated probability of malignancy > 65%) are generally older, have larger nodules, a smoking history, irregular margins and upper lobe predominance. Intermediate risk nodules (estimate probability of malignancy of 5–65%) have a mixture of high and low probability features. Low risk nodules (< 5%) are typically seen in younger patients who have smaller nodules with minimal smoking history and benign features appearance on CT. Although many clinicians estimate the probability of malignancy intuitively, to aid in determining the pre-test probability of malignancy, multiple risk calculators have been developed [10–12]. One of the most widely used and validated calculator is the Mayo Clinic model which takes into account six independent demographic and imaging predictors of mortality [13]. For inclusion and patient selection in this study, we will utilize the Mayo Clinic model to aid in the estimation of malignancy.

To optimally mimic the real-world application and performance of EMN, nodule size and location need be accounted for in a multicenter trial. Prior data supports smaller nodules and those further from the hilum are significantly more difficult to access [5, 6]. Thus it is reasonable to expect EMN to offer the greatest benefit to those nodules with smaller size which are most difficult to access. For these reasons, we will limit inclusion in this study to nodules < 3 cm with a balance of central and peripheral location.

In an effort to expand external validity, this trial will include eight centers throughout the United States with a balance of practices in academic and community settings. The coordinating center will be Johns Hopkins Hospital (Baltimore, MD), with participating sites including Duke University (Durham, NC), University of North Carolina (Chapel Hill, NC), University of Pittsburgh (Pittsburgh, PA), Washington University in St. Louis (St. Louis, MO), Swedish Medical Center (Seattle, WA), Grady Memorial Hospital (Atlanta, GA), and Banner Health (Phoenix, AZ).

Patient screening and informed consent will follow each participating institution's standard of care. Inclusion and exclusion criteria are listed in Table 1. Subjects will be approached at their standard of care clinic appointment or prior to their scheduled bronchoscopy and will explain the study to qualified subjects prior to obtaining consent. Each patient's participation in this study is expected to be approximately 1 year from the index procedure to study exit.

2.2. Device description

The EMN system (SPiN Thoracic Navigation System™ and SPiNPerc™ Kit, Veran Inc., St. Louis MO) was cleared to market by the U.S. Food and Drug Agency (FDA) under 510(k).

The EMN system is designed to help guide the physician with electromagnetic navigation while using either a bronchoscope and/or a transthoracic needle to reach peripheral nodules in a single procedure setting. The concept has been likened to a global positioning system (GPS) for bronchoscopy and transthoracic biopsy. EMN system components include an electromagnetic field generator, a locatable sensor probe that allows navigation through the bronchi/chest wall and computer software that creates virtual images for procedural guidance [14].

In this study, the EMN system and sampling instruments will be used according to the associated instructions for use (IFU). The EMN system utilized in this study will have SPiN Drive and SPiN Planning software version 4.0 or higher (Veran Inc., St. Louis MO). Minor software updates are allowed if performed at all study sites within a reasonable timeframe; however, new software versions will not be

Table 1
Participant Inclusion/Exclusion Criteria.

Inclusion criteria:

1) The patient is ≥21 years old,
2) The patient has a lung nodule identified on chest CT and is a candidate for elective ENB evaluation as determined by the treating pulmonologist,
3) The size of the target nodule, as measured at its greatest diameter, is between 1 and 3 cm,
4) Staging at the time of enrollment indicates N0/N1 (does not involve lymph nodes or includes nodes within the ipsilateral hilum),
5) The patient has an intermediate risk of malignancy (5–65% per the Mayo Model) and is in need of diagnosis for alternative treatment

OR

The patient has a high probability of cancer (> 65%) and will be referred for surgical evaluation or stereotactic body radiation therapy (SBRT). Note: If the patient refuses surgery or if the surgeon requests a definitive diagnosis prior to surgery the patient will have the option to be included in this study,

6) The patient has a lack of bleeding disorders, and
7) The patient is willing and able to provide informed consent.

Exclusion criteria:

1) The patient is pregnant as confirmed by urine or serum pregnancy testing,
2) The patients has a body mass index (BMI) > 40,
3) There is a predetermined plan to pursue stereotactic body radiation therapy (SBRT) in the event of a nondiagnostic study procedure in patients with a nodule in the outer 1/3 lung zone (i.e. The patient would not go on for a CT guided TTNA),

OR

There is a predetermined plan to pursue stereotactic body radiation therapy (SBRT) in the event of a nondiagnostic study procedure in patients where the target nodule is within a region considered to be not accessible to a percutaneous approach as determined by the radiology core lab and thus would prevent a confirmatory tissue diagnosis before SBRT.

installed over the course of the study.

2.3. Study design

This is a multi-center, non-randomized, single-arm, prospective trial designed to evaluate a staged sampling methodology designed to maximize the diagnostic yield of lung biopsy in a single procedure setting. Participants with a peripheral pulmonary nodule with an intermediate pre-biopsy probability of malignancy will be recruited to undergo a staged approach to diagnosis. In a single procedural setting, those enrolled will first undergo EBUS, if rapid on-site evaluation (ROSE) via cytopathology is negative, they will undergo ENB, if ROSE is again negative following ENB the participant will undergo EMN-TTNA if the nodule is amenable to percutaneous biopsy. Fig. 1 outlines the overall study flow.

An EMN system protocol non-contrast chest CT scan will be performed on the same day as the procedure as a clinically indicated procedural planning tool. Patients will undergo the procedure under moderate or deep sedation with an artificial airway (endotracheal tube, laryngeal mask airway or tracheostomy) in place as appropriate. Moderate or deep sedation medications and route of administration are at the discretion of the sedating physician. When sufficient sedation has been given, topical anesthesia with 1% lidocaine will be administered to the airway tree.

2.3.1. Determination of lung zone

After informed consent is obtained, the patient's most recent chest CT scan will be de-identified and securely downloaded onto the Johns Hopkins secure radiology imaging system (Johns Hopkins Imageshare). If subjects have multiple pulmonary nodules, the site primary investigator (PI) will identify the target nodule. A member of the Johns Hopkins Department of Radiology Core Laboratory will independently review the CT imaging.

To determine if a nodule falls into the outer 1/3 of the lung parenchyma, proprietary software with be utilized to map zones of the lung. “CT Pulmo 3D” workflow using Siemens Syngo which automatically analyzes the lung parenchyma and defines the contours of both lungs. If a nodule is within the outer 1/3 of the lung parenchyma or the nodule touches the border of the outer 1/3 of the lung parenchyma the nodule will be considered amenable to an EMN-TTNA approach. Each site will be provided with the zone of the nodule (outer 1/3 or inner 2/3) and an image of the lung zones and nodule prior to

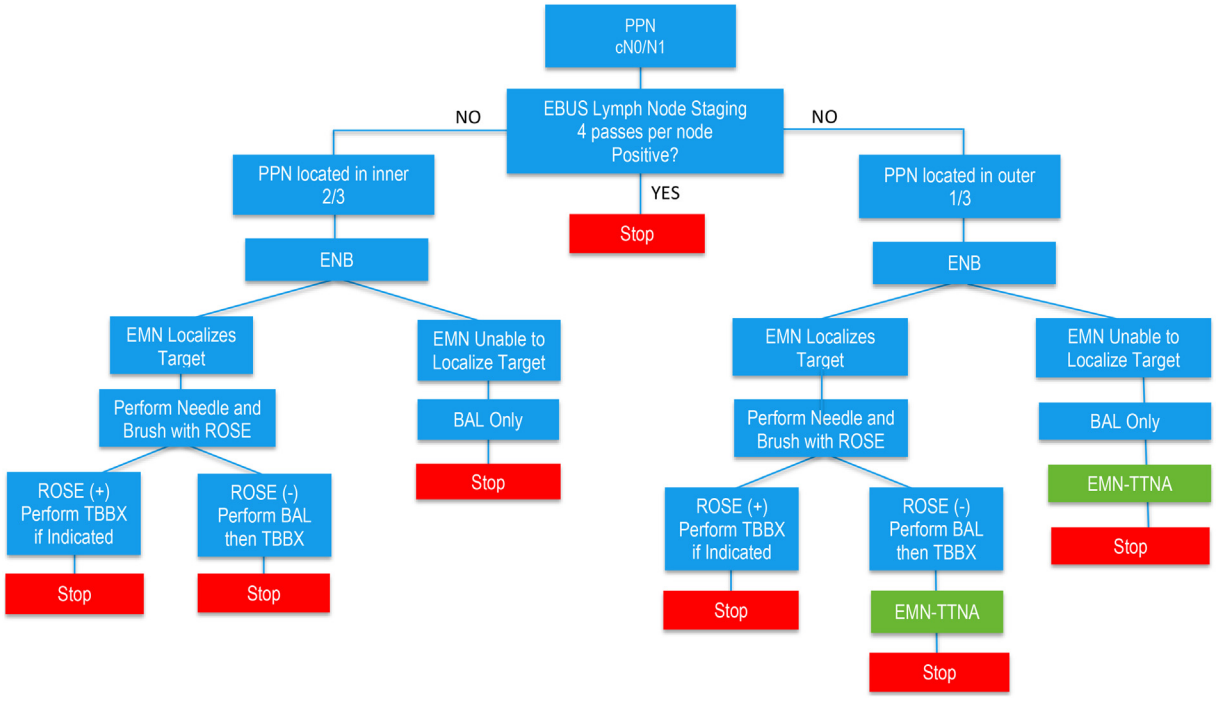

Fig. 1. Study flow of the ALL IN ONE trial. BAL: bronchoalveolar lavage, cN0/N1: clinical N0/N1 disease, EBUS: endobronchial ultrasound, EMN: electromagnetic navigation, EMN-TTNA: electromagnetic navigation guided transthoracic needle biopsy, PPN: peripheral pulmonary nodule, ROSE: rapid onsite evaluation, TBBx: transbronchial biopsy.

the procedure. Fig. 2 depicts example lung zones generated using CT Pulmo 3D.

2.4. Staged diagnostic procedure

As an overview, all patients will undergo bronchoscopy with convex EBUS for mediastinal and hilar lymph node staging. If lymph node staging is negative and the nodule is located within the inner 2/3 of the lung, ENB will be performed. If lymph node staging is negative and the nodule is located in the outer 1/3 of the lung, ENB with possible EMN-TTNA will be performed.

1) At bronchoscopy with EBUS.

The EBUS bronchoscope will be introduced and full mediastinal and hilar staging will be performed as per National Comprehensive Cancer Network (NCCN) and ACCP guidelines for all lymph nodes greater than or equal to 5 mm [3, 15, 16]. If any lymph node is positive per ROSE and ample tissue is collected, the procedure is considered complete. If ROSE does not yield a diagnosis, then the EBUS scope is removed and the bronchoscope (Olympus MP-160 or BF-P190) will be introduced into the airway.

2) For nodules located within the inner 2/3 of the lung and successfully targeted by the ENB system.

The bronchoscope (Olympus MP-160 or BF-P190) will be introduced into the airway. An EMN tip tracked needle will then be introduced into the working channel of the bronchoscope and utilizing standard ENB and EMN-TTNA system navigation-matching protocols, the main and secondary carinas are identified using the tip tracked needle and adjusted accordingly.

The bronchoscope will then be advanced as distally as possible under direct visualization with EMN guidance and the target identified. The ability for EMN guidance to successfully navigate to the nodule will be recorded (defined as instrument within the target nodule and the nodule turning green). The EMN tip tracked needle will then be guided to the nodule and tissue samples will be taken under EMN guidance with a minimum of two separate passes. If ROSE yields a diagnosis on any pass with the needle then the procedure is complete, additional samples with any EMN guided instrument and/or a bronchoalveolar lavage (BAL) can be taken at the discretion of the performing provider.

In the event the nodule is localized as defined above but ROSE does not yield a diagnosis with the needle, a minimum of two passes with a tip tracked Brush with ROSE evaluation is performed. If ROSE yields a diagnosis on any pass with the brush, additional samples with any EMN guided instrument and/or a BAL can be taken at the discretion of the performing provider and the procedure is completed.

In the event the nodule is localized as defined above but ROSE does not yield a diagnosis with the needle and/or brush, a BAL for cytology and microbiology samples is taken followed by at least 5 tip tracked transbronchial biopsy samples to obtain pathologic specimens under direct EMN guidance should be taken and the procedure is completed.

3) For nodules located within the inner 2/3 of the lung and Unsuccessfully targeted by the ENB System.

In the event the nodule is not localized a BAL sent for cytology and microbiology in the most specific lung segment only may be performed and the procedure is completed.

4) For nodules located within the outer 1/3 of the lung and successfully targeted by the ENB System.

The same ENB will be performed in nodules located within the inner 2/3 of the lung and successfully targeted. However, if ROSE does not yield a diagnosis after needle, brush or forceps biopsy, procedural conversion to EMN-TTNA (Fig. 3) is performed as below.

Prior to removing the bronchoscope, the tip tracked transbronchial biopsy forceps are used to reconfirm that the EMN system is properly matched to the airway defined by accurate matching of the main and secondary carina. The clinician will then rule out the presence of a pneumothorax following endobronchial biopsy using ultrasound, fluoroscopy or chest x-ray as clinically indicated. Following this, a sterile field is created on the chest wall as identified by the EMN-TTNA planning software and the area is prepped and draped. Utilizing the EMN tip tracked EMN-TTNA needle introducer, the nodule is localized. The introducer needle is then advanced into the nodule under EMN guidance. A minimum of two fine needle aspiration (FNA) samples are obtained followed by at least 5 core biopsy samples. Prior to removal of the introducer needle, 1–3 cm^3 sterile saline should be injected as the introducer needle is removed and the procedure is then completed [17]. The use of ROSE during this phase is recommended to ensure that the target nodule has been sampled.

5) For nodules located within the outer 1/3 of the lung and Unsuccessfully targeted by ENB.

In the event the nodule is not localized during the ENB phase, a BAL sent for cytology and microbiology in the most specific lung segment only will be performed. Following this, procedural conversion to EMN-TTNA is performed. Prior to removing the bronchoscope, the tip tracked

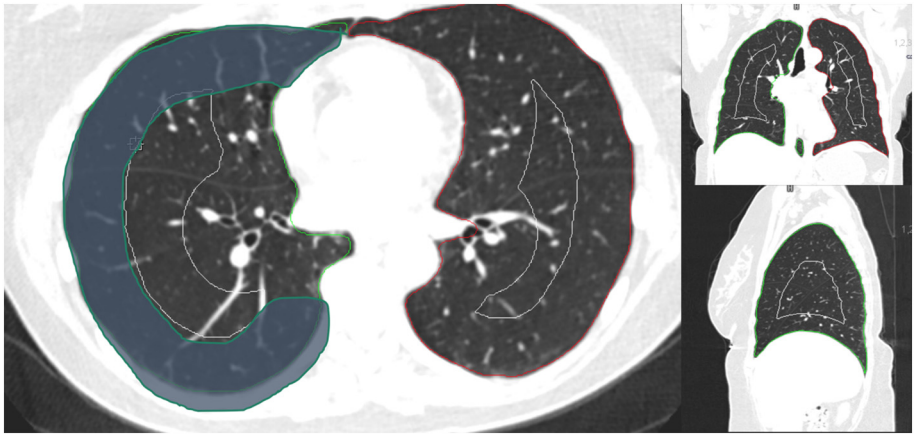

Fig. 2. Sample image from CT Pulmo 3D software depicting lung zones. Outer 1/3 lung zone is shaded in blue. Any lesion within or touching the blue zone is considered approachable via EMN-TTNA.

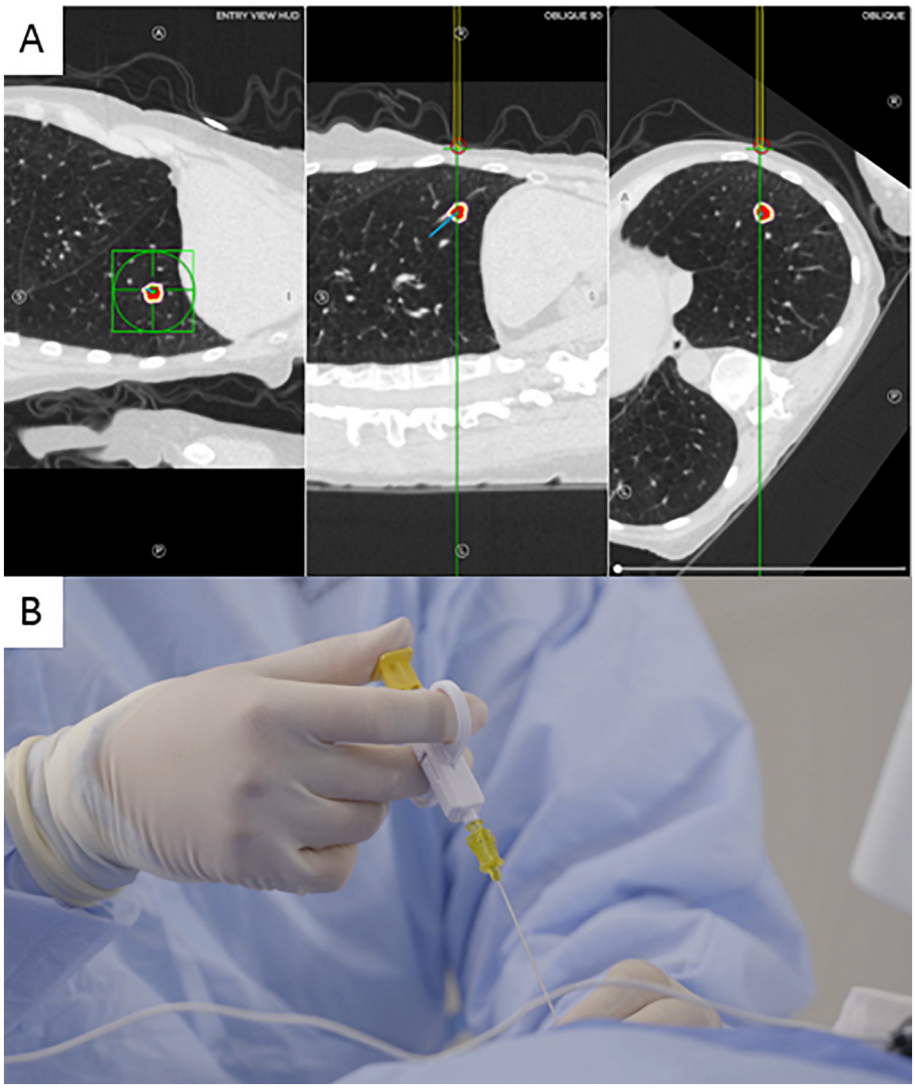

Fig. 3. Electromagnetically guided TTNA needle placement. Electromagnetic guidance planning CT views (A) with needle insertion on the chest wall (B).

transbronchial biopsy forceps are used to reconfirm that the EMN system is properly matched to the airway defined by accurate matching of the main and secondary carina. Following this, a sterile field is created on the chest wall. Utilizing the EMN tip tracked EMN-TTNA needle introducer, the nodule is localized. The introducer needle is then advanced into the nodule under EMN guidance. A minimum of two fine needle aspiration (FNA) samples are obtained followed by at least 5 core biopsy samples. Prior to removal of the introducer needle, 1–3 cm^3 sterile saline should be injected as the introducer needle is removed and the procedure is then completed [17]. The use of ROSE during this phase is recommended to ensure that the target nodule has been sampled.

6) For nodules located within the outer 1/3 of the lung and Unsuccessfully targeted by ENB OR EMN-TTNA.

In the event the nodule is not localized during the ENB phase, a BAL sent for cytology and microbiology in the most specific lung segment only will be performed. Following this, procedural conversion to EMN-TTNA is performed. Prior to removing the bronchoscope, the tip tracked transbronchial biopsy forceps are used to reconfirm that the EMN system is properly matched to the airway defined by accurate matching of the main and secondary carina. Following this, a sterile field is created on the chest wall as identified by the EMN-TTNA planning software and the area is prepped and draped. Utilizing the EMN tip tracked EMN-TTNA needle introducer, if the nodule cannot be targeted with EMN-TTNA, no FNA or biopsies are taken and the patient is referred to interventional radiology for a CT guided TTNA or thoracic surgery for consideration of surgical resection.

2.5. Post-procedure management

Following all procedures, a portable chest X-ray will be performed to rule out pneumothorax. All patients who have a nondiagnostic EMN guided procedure who have a nodule that falls within EMN-TTNA range and plan to undergo SBRT MUST undergo a CT guided TTNA prior to SBRT. In these cases, the investigator will confirm with the interventional radiologist that the nodule is reachable via CT guided TTNA. Diagnostic tissue from all patients with a nondiagnostic study procedure who proceed with surgical resection will be recorded. The treating physician will make further recommendations regarding treatment (i.e. follow-up CT chest, CT guided transthoracic needle aspiration, or surgery) and all decisions will be recorded. All nondiagnostic and benign study cases will be reviewed by an independent pathology core lab. Atypia or lung parenchyma without pathologic finding are considered nondiagnostic. Further subject follow up will be at the discretion of each site as clinically indicated.

2.6. Data collection/adverse events

2.6.1. Radiographic characteristics

The location of the target nodule (side, lobe and segment, i.e. right upper lobe anterior segment, etc.) will be determined and recorded. The radiographic information collected will include size of the nodule (longest axis), distance from a visible bronchus, whether there is a positive bronchus sign and distance from the pleural surface perpendicular to the nodule. If the patient has undergone a positron emission tomography (PET) scan, the metabolic activity (measured SUV) will be recorded.

2.6.2. Procedural characteristics

Collected procedural information will include the number of biopsy passes, types of biopsy performed (TBBx, TBNA, Brush, BAL), distance of target from airway, pleura, and hilum, nodule statistics (volume, RESIST diameter, maximum, minimum, and effective diameter), and target motion. The duration of the procedure, type and amount of sedation administered as well as, artificial airway selection will also be recorded.

2.6.3. Diagnostic yield

Primary outcome of diagnostic yield will be determined from the results of ENB and/or EMN-TTNA. A biopsy that results in a specific diagnosis, either malignant or benign (granuloma, inflammation, fibrosis, infection) will be assumed to be a true positive with appropriate follow up as indicated for up to one year. Atypia or lung parenchyma without pathologic findings on final pathology reads are considered nondiagnostic.

2.6.4. Crossover to other procedures

Procedures performed to aid in the diagnostic management of patients with a non-diagnostic biopsy will be captured (e.g. CT-guided TTNA, R-EBUS). In these cases, the attending physician will determine the patient's diagnostic care plan.

2.6.5. Confirmation of diagnosis

An independent pathology core lab will review all nondiagnostic study cases. Confirmation of the diagnosis by surgery, CT guided TTNA or repeat imaging will be recorded for those patients who have nondiagnostic results from the study procedures. If the patient is referred for surgery, the surgical pathology will be considered the final diagnosis. If the patient has follow-up imaging that shows a decrease in size or resolution of the nodule, the nodule will be determined to be of benign etiology if the study pathology yields a benign diagnosis (granuloma, inflammation, fibrosis, infection). To verify final diagnosis, a copy of the final pathology report from bronchoscopy and any pathology reports from subsequent surgical resection, will be de-identified and provided by the site to the Coordinating Center.

2.6.6. Adverse events

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. All device and/or procedure related adverse events will be recorded. Events will be collected at the initiation of the index procedure (EBUS), intra-EMN procedures, and for a period of 30 days post-procedure.

Serious Adverse Events (SAE) are those that lead to death or lead to serious deterioration in the health of the subject (i.e. life threatening injury/illness, permanent impairment of a body structure, leading to prolonged hospitalization). The PI will assess if there is a relationship of an adverse event to the procedure, as related or not related, and categorized as resolved or continuing. Severity of the common complications of pneumothorax and hemorrhage (including hemoptysis) will be classified according to Common Terminology Criteria for Adverse Events (CTCAE). All SAEs are to be reported to the sponsor within 24-h of the aware date.

2.7. Study outcomes

2.7.1. Primary outcome

The objectives of this study are to evaluate diagnostic yield following biopsy of peripheral pulmonary nodules as identified on chest CT utilizing ENB and/or EMN-TTNA. The primary efficacy endpoint of diagnostic yield associated with a staged approach will be defined as the proportion of subjects with a diagnostic sample after undergoing EBUS and/or ENB and/or EMN-TTNA. All participants that undergo EBUS, the index procedure, will be included. The primary safety endpoint will be rates of SAEs defined as those attributed to device and/or procedural related complications.

2.7.2. Secondary outcomes

The diagnostic yield of each of the components of the staged approach will also be evaluated as part of a secondary analysis. Diagnostic yield again will be defined as the proportion of subject with a diagnostic result. The diagnostic yields will be calculated for: (1) BAL cytology, (2) EBUS, (3) ENB, (4) EMN-TTNA. Additionally, the proportion of cases that are cancelled due to regression of the lesion on the same-day CT will be evaluated. Procedural factors that impact diagnostic yield will be assessed – number of procedures performed, type of specimen obtained (brush, peripheral needle, forceps biopsy, transthoracic core biopsy or transthoracic needle), site of biopsy (within vs. adjacent to nodule). The radiographic characteristics that influence diagnostic yield will be evaluated, these include the size and location of the nodule, the distance from the main carina, presence of and distance from visible bronchus, and PET characteristics.

2.8. Statistical analysis

2.8.1. Sample size

We are interested in estimating the sample size for a clinical trial comparing a new biopsy protocol for lung nodules with historical controls. The primary outcome of the trial is diagnostic yield of a staged approach to 1–3 cm pulmonary nodules using ENB and/or EMN-TTNA.

To calculate sample size, we used a two-sided Z test of difference in proportions with unpooled variance under the null hypothesis that the diagnostic yield of staged approach using to lung biopsy using EMN will be equal historical diagnostic yield of advanced bronchoscopic techniques. Based on our pilot data [9] and review of the literature we hypothesize a conservative diagnostic yield of 70% in the staged approach. After review of current published diagnostic yields of 1–3 cm nodules [14, 18–26], the estimated diagnostic yield of historical controls is 59% (historical data on 665 patients out of which 385 had a successful biopsy). To achieve 80% power to detect a difference between the group proportions of 11% (70% versus 59%), a sample size of 149 will be needed in this single-arm trial. The significance level of the test was targeted at 0.05.

2.8.2. Statistical analysis plan

The primary outcome of diagnostic yield using a staged approach using EMN will be calculated as a simple proportion of those whom have a diagnostic procedure after undergoing the staged approach. All participants who complete the EBUS procedure will be included in the analysis (EBUS is considered the index procedure). Secondary analysis of the diagnostic yields of BAL cytology, EBUS, ENB and EMN-TTNA will be calculated as the proportion of participants with a diagnostic result including on those whom underwent the given procedure. As part of a secondary analysis of procedural and radiographical factors that may impact diagnostic yield, we will examine their effects on diagnostic yields using a logistic regression model which will be estimated using the generalized estimating equations (GEE) approach of Zeger and

Liang (1986) [27].

2.9. Ethical aspects

The study has been approved by the Institutional Review Board of Johns Hopkins University (IRB00150177). All participants will undergo written informed consent prior to enrollment. The study has been registered with the National Institute of Health – United States National Library of Medicine (clinicaltrials.gov Identifier: NCT03338049, 09 Nov 2017).

3. Discussion

The management of intermediate risk pulmonary nodules continues to present a clinical dilemma. With no single approach proven superior to another, clinicians and their patients are left to decide between surveillance and the multiple forms of biopsy including: surgical biopsy, flexible bronchoscopy and TTNA. Ideally, to guide further management, a minimally invasive approach to obtaining a tissue diagnosis would be preferred. However, at this time, no perfect approach exists. Simple surveillance often leaves patients with anxiety with regards to the possibility of malignancy and carries a risk (albeit small) of disease progression. The most aggressive and decisive approach is surgical biopsy; however, this comes with added risk and in the case of potentially benign disease, the patient may have been subjected to harm that may have been avoidable. At this time, there are two main options for obtaining a minimally invasive biopsy, via flexible bronchoscopy or percutaneous (transthoracic) needle biopsy. Both of these approaches have limitations and when considering the risk and benefit profiles of these procedures neither has been definitively proven superior to another. This study aims to evaluate the efficacy of a staged, combined approach using both flexible bronchoscopy and transthoracic needle biopsy using EMN, hypothesizing that there will be an increase in diagnostic yield with a significant decrease in complications, in comparison to historic controls. This staged approach has potential to position itself as the preferred method of minimally invasive biopsy.

4. Limitations

One of the limitations of this study is the lack of a comparator arm. At this time, there is no single procedure that could equivocally be compared to a combined approach. Comparisons could be made to CT guided TTNA; however, this comparison would be biased as classically central lesions are not accessible to CT guided TTNA, which would limit a direct comparison to pulmonary nodules across all lung zones. A direct comparison of a combined EMN approach to CT guided TTNA would also potentially subject patients to added procedures if either procedure were nondiagnostic. Another potential limitation is a lack of a mortality analysis. We feel it would be inappropriate to comment on mortality given there will be wide variation of the underlying diagnosis' that would certainly bias any mortality assessment.

4.1. Strengths

With the advent of EMN-TTNA, pulmonologists now have the ability to perform guided TTNA. This enables multiple procedures to be performed in a single setting, not only mitigating anesthesia risk but expediting diagnosis and ultimately definitive treatment. To our knowledge, this will be the first trial to evaluate a combined approach using both flexible bronchoscopy and TTNA during a single procedure. In the design of this trial we generate a definitive prospective diagnostic yield for this approach, opening more (and potentially superior) options for the diagnosis of pulmonary nodules. This will aid and assist clinicians in decision making regarding the management of intermediate pulmonary nodules.

This trial is strengthened by its external validity to real-world practice by including 1–3 cm nodules with procedures performed in diverse clinical practices. Additionally, this study will not only display the efficacy but also highlight the safety profile of EMN guided procedures. Data will be generated that will enable direct comparison (efficacy and safety) of CT guided TTNA to EMN-TTNA. Furthermore, it will be possible to evaluate of the efficacy of the various instruments used to obtain tissue diagnosis via flexible bronchoscopy (needle, brush, forceps and BAL) that will guide future procedural technique.

5. Conclusion

This single-arm trial of a combined, staged approach to the diagnosis of pulmonary nodules using ENB and TTNA is well positioned to generate impactful data to guide clinician decision making for the management of intermediate pulmonary nodules.

Acknowledgements

None.

Funding

This study is sponsored by Veran, Inc. (St. Louis, MO). Veran, Inc. played no role in the design of this study, data collection, analysis, interpretation of data or in writing of this manuscript. This study was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number T32HL007534. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing interests

GAS, AC, MMW, CG, JAA, RS, LBY hold investigator-initiated research grants for this study from Veran, Inc. The other authors declare they have no conflicts of interest.

References

[1] M.K. Gould, J. Donington, W.R. Lynch, P.J. Mazzone, D.E. Midthun, D.P. Naidich, R.S. Wiener, Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest 143 (5 Suppl) (2013) e93S–120S.

[2] D.R. Aberle, A.M. Adams, C.D. Berg, W.C. Black, J.D. Clapp, R.M. Fagerstrom, I.F. Gareen, C. Gatsonis, P.M. Marcus, J.D. Sicks, Reduced lung-cancer mortality with low-dose computed tomographic screening, N. Engl. J. Med. 365 (5) (2011) 395–409.

[3] M.M. Wahidi, J.A. Govert, R.K. Goudar, M.K. Gould, D.C. McCrory, Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition), Chest 132 (3 Suppl) (2007) 94S–107S.

[4] D. Ost, A.M. Fein, S.H. Feinsilver, Clinical practice. The solitary pulmonary nodule, N. Engl. J. Med. 348 (25) (2003) 2535–2542.

[5] W.A. Baaklini, M.A. Reinoso, A.B. Gorin, A. Sharafkaneh, P. Manian, Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules, Chest 117 (4) (2000) 1049–1054.

[6] M.P. Rivera, A.C. Mehta, M.M. Wahidi, Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest 143 (5 Suppl) (2013) e142S–165S.

[7] D.E. Ost, A. Ernst, X. Lei, K.L. Kovitz, S. Benzaquen, J. Diaz-Mendoza, S. Greenhill, J. Toth, D. Feller-Kopman, J. Puchalski, et al., Diagnostic yield and complications of bronchoscopy for peripheral lung lesions. Results of the AQuIRE registry, Am. J. Respir. Crit. Care Med. 193 (1) (2016) 68–77.

[8] J.S. Wang Memoli, P.J. Nietert, G.A. Silvestri, Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule, Chest 142 (2) (2012) 385–393.

[9] L.B. Yarmus, S. Arias, D. Feller-Kopman, R. Semaan, K.P. Wang, B. Frimpong, K. Oakjones Burgess, R. Thompson, A. Chen, R. Ortiz, et al., Electromagnetic navigation transthoracic needle aspiration for the diagnosis of pulmonary nodules: a safety and feasibility pilot study, J. Thorac. Dis. 8 (1) (2016) 186–194.

[10] M.K. Gould, L. Ananth, P.G. Barnett, A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules, Chest 131 (2) (2007) 383–388.

[11] E.M. Schultz, G.D. Sanders, P.R. Trotter, E.F. Patz Jr., G.A. Silvestri, D.K. Owens,

M.K. Gould, Validation of two models to estimate the probability of malignancy in patients with solitary pulmonary nodules, Thorax 63 (4) (2008) 335–341.
[12] K. Yonemori, U. Tateishi, H. Uno, Y. Yonemori, K. Tsuta, M. Takeuchi, Y. Matsuno, Y. Fujiwara, H. Asamura, M. Kusumoto, Development and validation of diagnostic prediction model for solitary pulmonary nodules, Respirology (Carlton, Vic) 12 (6) (2007) 856–862.
[13] S.J. Swensen, M.D. Silverstein, D.M. Ilstrup, C.D. Schleck, E.S. Edell, The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules, Arch. Intern. Med. 157 (8) (1997) 849–855.
[14] R. Eberhardt, D. Anantham, F. Herth, D. Feller-Kopman, A. Ernst, Electromagnetic navigation diagnostic bronchoscopy in peripheral lung lesions, Chest 131 (6) (2007) 1800–1805.
[15] D.S. Ettinger, D.E. Wood, D.L. Aisner, W. Akerley, J. Bauman, L.R. Chirieac, T.A. D'Amico, M.M. DeCamp, T.J. Dilling, M. Dobelbower, et al., Non-small cell lung Cancer, version 5.2017, NCCN clinical practice guidelines in oncology, J. Natl. Compr. Cancer Netw. 15 (4) (2017) 504–535.
[16] G.A. Silvestri, A. Vachani, D. Whitney, M. Elashoff, K. Porta Smith, J.S. Ferguson, E. Parsons, N. Mitra, J. Brody, M.E. Lenburg, et al., A bronchial genomic classifier for the diagnostic evaluation of lung cancer, N. Engl. J. Med. 373 (3) (2015) 243–251.
[17] Y. Li, Y. Du, T.Y. Luo, H.F. Yang, J.H. Yu, X.X. Xu, H.J. Zheng, B. Li, Usefulness of normal saline for sealing the needle track after CT-guided lung biopsy, Clin. Radiol. 70 (11) (2015) 1192–1197.
[18] D. Makris, A. Scherpereel, S. Leroy, B. Bouchindhomme, J.B. Faivre, J. Remy, P. Ramon, C.H. Marquette, Electromagnetic navigation diagnostic bronchoscopy for small peripheral lung lesions, Eur. Respir. J. 29 (6) (2007) 1187–1192.
[19] A. Sanchez-Font, L. Giralt, I. Vollmer, L. Pijuan, J. Gea, V. Curull, Endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions. A controlled study with fluoroscopy, Arch. Bronconeumol. 50 (5) (2014) 166–171.
[20] C.H. Kuo, S.M. Lin, F.T. Chung, K.Y. Lee, Y.L. Ni, Y.L. Lo, H.C. Chen, H.P. Kuo, Echoic features as predictors of diagnostic yield of endobronchial ultrasound-guided transbronchial lung biopsy in peripheral pulmonary lesions, Ultrasound Med. Biol. 37 (11) (2011) 1755–1761.
[21] C.H. Kuo, S.M. Lin, K.Y. Lee, F.T. Chung, Y.L. Lo, T.C. Hsiung, C.Y. Liu, H.P. Kuo, Endobronchial ultrasound-guided transbronchial biopsy and brushing: a comparative evaluation for the diagnosis of peripheral pulmonary lesions, Eur. J. Cardiothorac. Surg. 45 (5) (2014) 894–898.
[22] I. Kokkonouzis, I. Lampaditis, A. Charpidou, E. Kainis, K. Syrigos, Usefulness of endobronchial ultrasound (EBUS) in the diagnosis of peripheral pulmonary lesions in a general hospital, In vivo (Athens, Greece) 27 (5) (2013) 655–660.
[23] N. Shinagawa, K. Nakano, H. Asahina, E. Kikuchi, T. Ito, Y. Matsuno, S. Oizumi, Y. Nasuhara, M. Nishimura, Endobronchial ultrasonography with a guide sheath in the diagnosis of benign peripheral diseases, Ann. Thorac. Surg. 93 (3) (2012) 951–957.
[24] K. Roth, T.M. Eagan, A.H. Andreassen, F. Leh, J.A. Hardie, A randomised trial of endobronchial ultrasound guided sampling in peripheral lung lesions, Lung Cancer 74 (2) (2011) 219–225.
[25] S. Disayabutr, J. Tscheikuna, A. Nana, The endobronchial ultrasound-guided transbronchial lung biopsy in peripheral pulmonary lesions, J. Med. Assoc. Thailand 93 (Suppl. 1) (2010) S94–101.
[26] F.J. Herth, A. Ernst, H.D. Becker, Endobronchial ultrasound-guided transbronchial lung biopsy in solitary pulmonary nodules and peripheral lesions, Eur. Respir. J. 20 (4) (2002) 972–974.
[27] S.L. Zeger, K.Y. Liang, Longitudinal data analysis for discrete and continuous outcomes, Biometrics 42 (1) (1986) 121–130.