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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)

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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

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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