DF/HCC Protocol #: 20-580

TITLE: Cone Beam Computed Tomography - Guided Navigational Bronchoscopy for Peripheral Pulmonary Nodules: A Randomized Trial

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NCI-Supplied Agent(s): N/A
Other Agent(s): Philips - Image Guided Therapy Systems

Study Exempt from IND Requirements per 21 CFR 312.2(b).

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ABBREVIATIONS

NB - Navigational Bronchoscopy
ENB – Electromagnetic Navigational Bronchoscopy
CBCT – Cone Beam Computed Tomography
EBUS – Endobronchial Ultrasound
TBBX – Transbronchial Biopsy
ROSE – Rapid Onsite Evaluation
BAL – Bronchoalveolar Lavage
AF – Augmented Fluoroscopy
APL – Adjustable Pressure Limiting
TTNA – Transthoracic Needle Aspiration
SBRT - Stereotactic Body Radiation Therapy

1. OBJECTIVES

In this study, we hypothesize that CBCT-guided NB would improve diagnostic yield for peripheral lung nodules as compared to NB alone. We aim to find the difference in the diagnostic yield between both groups (Percentage of lesions tested positive).

$\mu 0$= Diagnostic yield NB-alone = Diagnostic yield CBCT-guided NB $\mu 1$= Diagnostic yield CBCT-guided NB > Diagnostic yield NB-alone

$\mu 0$= Null Hypothesis
$\mu 1$= Alternate Hypothesis

1.1 Study Design

- We propose a prospective, randomized, two- arm, single-center nonblinded, controlled clinical trial to evaluate the diagnostic yield of lung biopsy in NB-alone and CBCT-guided NB.
- Randomization schedule will be determined in advance by computer with the intent of a 1:1 randomization scheme.
- For randomization, Block randomization will be used. The block randomization method is designed to randomize subjects into groups that result in equal sample sizes. This method is used to ensure a balance in sample size across groups over time. This was decided based on the limited access to the Cone Beam room, which is available exclusively once a month (the first Friday of each month).
- All bronchoscopies will be performed under general anesthesia and ROSE will be available upon physician request/preference.
- Radial probe-EBUS and fluoroscopy will be utilized in all cases.
- Tissue samples will be obtained using multimodality tools, including cytology brush, fine needle for aspiration, biopsy forceps, and bronchoalveolar lavage.
- NB procedure will be performed per product instructions and the institution's standard practice.

<u>CBCT-guided NB procedure arm:</u>
Following intubation, an inspiratory breath-hold maneuver with the adjustable pressure limiting (APL) valve set at 20 cm H2O will be performed by the anesthesiology provider. This mimic the inspiratory

breath hold done during a CT scan. During the breath-hold maneuver, CBCT will be performed. A dedicated arm attached to the bronchoscopy cart will be utilized to hold the bronchoscope in position so that the operators can leave the room during CBCT scan. Lung nodules will be highlighted using available software (OncoSuite; Philips) during a process known as segmentation. A bronchoscope will be introduced into the airway and then using NB to navigate to the lesion. Nodule segmentation will be visualized in an overlay with live fluoroscopy. Geometric correspondence of augmented fluoroscopy (AF) will be maintained throughout the case while manipulating C-arm angulation, table position, and image-zoom settings. Final catheter position will then be verified in multiple planes with AF. Additional CBCT scans will be acquired when deemed necessary.

If a non-diagnostic lesion resolved, stayed stable or decreased in size on follow-up CT for at least 6 months after the index procedure then this will be as presumed benign and classified as a true negative for the purposes of calculating sensitivity and prevalence of malignancy, as well as for diagnostic accuracy.

1.2 Primary Objectives

- To compare overall diagnostic yield following biopsy of peripheral pulmonary nodules in the NB alone group versus the CBCT-guided NB group.

1.3 Secondary Objectives

- To compare the need of additional diagnostic procedures in both groups.
- To compare navigation success in the CBCT-guided NB group.
- To compare complications between groups

2. BACKGROUND

2.1 Study Disease

Diagnostic sampling of suspicious peripheral lung nodules has become increasingly important, as early diagnosis of malignancy can provide an opportunity for potentially curative resection and improved survival. Traditionally, CT-guided transthoracic needle aspiration (TTNA) was the most accepted modality to obtain tissue diagnosis of suspicious peripheral lung nodules, with a diagnostic yield reported in the literature ranging from 77 to 98% (1–4). However, despite the high diagnostic yield, pneumothorax can occur in up to 35% of patients, with up to 15% requiring chest tube placement, increasing hospital stays and overall healthcare costs (5,6). In contrast, the transbronchial approach the risk of pneumothorax is only around 0.02% to 4.9% (7–10). Furthermore, CT-guided TTNA might be associated with a higher incidence of local recurrence with pleural dissemination when compared with transbronchial or open lung biopsy (11).

Transbronchial biopsy is a safe diagnostic tool recommended for patients with peripheral lung nodules with the limitation of a lower diagnostic yield compared with CT-guided TTNA. The diagnostic yield of transbronchial biopsy guided by fluoroscopy is widely variable, ranging from 18 to 80%, and is strongly dependent on the lesion size (12,13). In order to increase the diagnostic yield of the transbronchial

approach, techniques and devices such as the ultrathin bronchoscope, radial endobronchial ultrasonography with guided sheath (EBUS-GS), electromagnetic navigation bronchoscopy and cone beam CT (CBCT) are becoming widely utilized (11).

ENB allows bronchoscopists to safely navigate to and sample peripheral lung lesions minimally invasively with an acceptable safety profile. Furthermore, the ability to provide concurrent lymph node staging with linear endobronchial ultrasound (EBUS) or assist in nodule localization via pleural dye or fiducial marking in a single procedure could potentially decrease health care costs and improve patient satisfaction (10). However, due to CT to body divergence and atelectasis, increasing diagnostic yield has been an ongoing challenge. Recently, cone beam CT (CBCT) has emerged as a promising adjunct to navigational bronchoscopy, allowing real-time "needle in lesion" static confirmation, with a potential increase in diagnostic yield (14).

2.2 IND Agent(s)

N/A

2.3 Other Agent(s)

N/A

2.4 Rationale

Pulmonary nodules are a common diagnostic problem in daily clinical practice. The results of the National Lung Cancer Screening Trial demonstrated a reduction in lung cancer mortality with screening of patients with low dose CT (15). This has led to an increase in the number of nodules detected requiring appropriate follow up (16). The challenge in the management of pulmonary nodules lies in the necessity to identify the few lung cancers within the vast majority of benign nodules. This created a dilemma for clinicians to decide about further diagnostic modalities to pursue for optimizing yield, minimizing complications while reducing unnecessary benign surgical resections rates. Thus, there is an urgent need for minimally invasive diagnostic techniques with both excellent performance and safety for evaluation of lung nodules. The overall diagnostic yield of currently available electromagnetic navigation bronchoscopy (ENB) technique is 67% based on meta-analysis of 11 studies (17). However, when analyzed more closely, the diagnostic yield appears to be influenced by nodule size and presence of a bronchus sign and it appears to be much lower approaching 47% (7). However, a major limitation of all ENB platforms is the reliance on preoperative CT for planning and navigation as opposed to real-time image guidance. This commonly results in CT body divergence leading to disappointing yields on navigational bronchoscopy. Cone beam computed tomography (CBCT) is a newer modality that emerged as a promising adjunct to navigational bronchoscopy that might mitigate CT to body divergence allowing near real-time confirmatory imaging, with a potential impact on diagnostic yield. However, data on the use of this technology in combination with bronchoscopy is very scant and mostly based on non-randomized studies (18–20).

2.5 Correlative Studies Background

N/A

3. SUBJECT SELECTION

Adult patients who will be referred to our clinic (Interventional Pulmonology) for diagnosis of lung nodules of 1–3 cm identified on chest CT scan obtained within the previous 3 months.

3.1 Subject Screening and Recruitment

The subjects for this study will be recruited consecutively from the investigators' clinical practices. The screening requirements are all standard of care for bronchoscopy procedures. No pre-procedure test or examinations outside of standard of care are required for this study.

All subjects who are eligible based on the inclusion and exclusion criteria will be asked to participate in this study. Subjects will then sign an IRB-approved consent form.

A subject will be considered enrolled when the following occurs:

1. Subject provides consent for participation by signing the current, IRB approved study informed consent form
2. Subject meets all eligibility criteria

3.2 Informed Consent

The principal investigator (PI) or Co-Investigator will conduct the informed-consent process. The PI/Co-Investigator will explain the nature and scope of the trial and potential risks and benefits of participation and will answer any questions from the subjects. If the subject agrees to participate, the informed-consent form must be signed and dated by the subject and the PI/Co-Investigator prior to enrollment in the study..

3.3 Eligibility Criteria

1) Patients ≥18 years old.
2) Patients with lesions having an intermediate pre-test probability of malignancy (pCA, 0.05 to 0.65) as determined by Swensen-Mayo nodule risk calculator and in whom bronchoscopic biopsy was determined to be the next best treatment step by the treating pulmonologists
3) Patients with higher risk lesions (pCA > 0.65) in need of a diagnosis for nonsurgical treatment or prior to surgery.
4) Patients are willing and able to provide informed consent.

3.4 Exclusion Criteria

1) 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).
3) Lacked fitness according to physician judgement to undergo bronchoscopy.
4) Contraindication for temporary interruption of the use of anticoagulant therapy. 5) Uncontrolled or irreversible coagulopathy.

6) Known allergy for lidocaine.
7) Uncontrolled pulmonary hypertension.
8) Recent (< 4 weeks) and/or uncontrolled cardiac disease.
9) Compromised upper airway (eg concomitant head and neck cancer or central airway stenosis such that endobronchial access is considered unsafe).
10) ASA classification ≥ 4
11) COVID-19 positive patient at the time of procedure.

3.5 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. Except for pregnant women as CT scan is generally contraindicated during pregnancy.

3.6 Subject Study Assessments

Pre-procedure Assessment
A pre-procedure assessment will be performed for each subject enrolled in the study in accordance with standard of care for bronchoscopy procedures. Trained study staff will review the data from available or indicated diagnostic tests confirming the subject's eligibility for study, (i.e. pre- procedure CT scan and laboratory tests), inclusion-exclusion criteria review, and perform an assessment of their medical history. For subjects of child bearing potential, a biochemical (blood or urine) pregnancy test must be obtained prior to the study procedure, per standard practice. If a subject's pre-procedure CT scan was obtained more than 21 days prior to the expected procedure date, a more recent CT scan should be obtained.

Intra-procedure Assessment
Procedure details, including the ability of the investigator to reach a pre-planned target location and obtain a tissue sample will be collected. Procedure durations, such as the total procedure time, anesthesia time, fluoroscopy time and navigation time are among those that will be collected. In addition, the ability to facilitate sampling through the catheter instrument, need for conversion to an alternative biopsy approach or surgery, Rapid On-site Evaluation (ROSE) results and intra- procedural complications (i.e. pneumothorax, bleeding, estimated blood loss and airway damage) will be obtained.

Post-procedure (prior to discharge) Assessment
The following outcomes will be collected: length of stay (bronchoscopy suite or hospitalization) and procedure related complications. Of note, per standard practice, subjects will be required to undergo a chest x- ray at least 1-hour post-procedure but prior to discharge to assess for pneumothorax.

Post-procedure (10 ± 4 days) Assessment
For patients that continue in the study due to a benign or non-diagnostic biopsy. This visit may be completed as a hospital visit, virtual visit or telephone contact. Any potential procedure-related complications will be recorded; in addition, the diagnostic characteristics of the obtained sample, initial pathology result and disease assessment will be obtained. If a subject has undergone any additional diagnostic interventions or treatment related to their pulmonary nodule, data regarding their interventions will be collected for the study but information related to complications will not be collected.

Post-procedure (30 ± 7 days) Assessment
For patients that continue in the study due to a benign or non-diagnostic biopsy, information related to any additional procedural complications (i.e. pneumothorax or pneumonia) will be collected.

Post-procedure (up to 180 days) Assessment
For patients that continue in the study due to a benign or non-diagnostic biopsy. Pathology and disease information will be obtained from any additional diagnostic assessments, interventions or treatments associated with the study related nodule(s).

4. REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Chest Disease Center will register eligible subjects in the Clinical Trials Management System (CTMS) OnCore. Registrations will occur prior to the initiation of any protocol-specific therapy or intervention. Any subject not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, subjects may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI).

If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

N/A

4.3 General Guidelines for Other Investigative Sites

N/A

4.4 Registration Process for Other Investigative Sites

N/A

5. TREATMENT AND/OR IMAGING PLAN

5.1. Treatment Regimen

N/A

5.2. Pre-Treatment Criteria

N/A

5.3. Agent Administration

5.3.1. *CTEP and/or CIP IND Agent(s), or other IND agent*

N/A

5.3.2 *Other Agent(s)*

N/A

5.3.3 *Other Modality(ies) or Procedures*

N/A

5.3.4 *Investigational Imaging Agent Administration*

Image Acquisition Details:

SuperDimension:
The SuperDimension navigation system version 7.2 with fluoroscopic navigation technology (Medtronic, Minneapolis, MN) is a minimally invasive approach to guide endoscopic tools to difficult to reach lung nodules or masses. The fluoroscopic navigation module incorporates a proprietary advanced algorithm that uses tomosynthesis to reconstruct a 3-dimensional model from multiple 2-dimensional C-arm fluoroscopic images taken at various angles around the patient. Operators are also able to scroll through multiple fluoroscopic slices from different angles, minimizing the impact of any visual obstructions. This method provides enhanced visualization of nodules that might not have been visible on standard fluoroscopy. A local registration feature updates the relationship between the catheter tip and the target intra-procedurally, thus helping to correct CT-to-body divergence.

Ion Endoluminal System:
The Ion™ Endoluminal System assists the user in navigating a catheter and endoscopic tools in the pulmonary tract using endoscopic visualization of the tracheobronchial tree for diagnostic and therapeutic procedures. The Ion™ Endoluminal System enables fiducial marker placement. It does not make a diagnosis and is not for pediatric use. The Ion™ Endoluminal System, Model IF1000, is a software-controlled, electro-mechanical system designed to assist qualified physicians to navigate a catheter and endoscopic tools in the pulmonary tract using endoscopic visualization of the tracheobronchial tree for diagnostic and therapeutic procedures.

The cone beam CT (CBCT) is a high-resolution 2D detector adapted for use with a C-arm. During the procedure, imaging will be performed using angiographic system (XperCT Dual P- Cone beam CT tool, Philips) equipped with a 40×30 cm detector. The CBCT imaging protocol (DynaCT) will be characterized by the following parameters: 8 s rotation time, 200° gantry rotation, 0.5°/projection, 396 total projections, and a detector dose of 0.36 μGy/frame. Using 3D cross section images, the target will be identified and manually contoured on workstation in multiple orthogonal planes using dedicated software (OncoSuite; Philips), and then superimposed on live fluoroscopy to provide real time imaging. Two dedicated holders attached to the bronchoscopy will be utilized to hold the bronchoscope in position so that the operators can leave the room during CBCT scan.

5.4. Definition of Dose-Limiting Toxicity (DLT)

N/A

5.5 General Concomitant Medication and Supportive Care Guidelines

N/A

5.6 Duration of Follow Up

Subjects with a benign / non-diagnostic biopsy may be followed for 24 weeks after the procedure. Subjects removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event

5.7 Criteria for Taking a Subject Off Study

Subjects will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- If there is a predetermined plan to pursue stereotactic body radiation therapy (SBRT) in the event of a non-diagnostic 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.
- If there is a predetermined plan to pursue SBRT in the event of a non-diagnostic 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.

The reason for taking a subject off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the subject's status is updated in OnCore.

6 DOSING DELAYS/DOSE MODIFICATIONS

N/A

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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).

8 PHARMACEUTICAL AND/OR IMAGING AGENT INFORMATION

N/A

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

N/A

9.2 Investigational Device Information

N/A

9.3 Laboratory Correlative Studies

Pulmonary Nodule Biopsy

Collection of Specimen(s)
Tissue samples will be obtained using multimodality tools, including cytology brush, fine needle for aspiration, biopsy forceps, and bronchoalveolar lavage at the discretion of the performing provider.

Historically, 4 specimens or passes have been shown to be adequate for optimal diagnostic yield in central lesions (22,23). When the tumor is located on the lateral wall of the airway, biopsy specimens are difficult to obtain using standard forceps. To optimize specimens, use of a spear forceps that has a small needle between the biopsy jaws to anchor into the airway wall is recommended. Additional malignant cells are obtained when bronchial wash is performed after bronchial brushing and bronchial biopsy (24). Most bronchoscopists perform bronchial brushing, biopsy, and washing in that order.

Although, in most cases 4 specimens/passes may be enough to make a diagnosis of lung cancer, they may not provide enough tissue to perform a more detailed molecular analysis. In patients with suspected non-small cell lung cancer (NSCLC), 4 passes may not be enough. Thus, with the use of multiple needle passes and ROSE by proficient endoscopists enough tissue can be aspirated to obtain material suitable for both cytologic diagnosis as well as additional immunohistochemical and molecular testing for EGFR and ALK mutations. Consideration should be given to obtaining up to 6 specimens/passes.

Handling of Specimens(s)
Handling of specimens will be done as stated by the Pathology-laboratory guidelines for ROSE and for further examination.

Shipping of Specimen(s)

N/A

Site(s) Performing Correlative Study
Beth Israel Deaconess Medical Center.

9.4 Special Studies

N/A

10 STUDY CALENDAR

Baseline evaluations (Standard of Care for Bronchoscopy procedures) are to be conducted within 1 week prior to the procedure. Scans and x-rays are usually done ≤3 months prior to the start of procedure, this timeframe will be at the discretion of the PI. If the participant's condition is deteriorating, laboratory evaluations should be repeated within 24 hours prior to initiation of the procedure at the discretion of the PI.

Lab tests taken before the procedure are part of the standard of care. Blood collection will not differ from the usual amounts required for conducting the preanesthetic consultation. A negative blood or urine pregnancy test is required prior to performing the procedure as it involves low dose radiation.

Typical follow-up consultations for standard bronchoscopy procedures are done 1 week. If biopsy is benign or non-diagnostic then the patients will be followed at 4 weeks, and 24 weeks after the procedure but may vary depending on the subject's final diagnosis, underline conditions, further treatment, and PI/Investigator preference.

During the follow-up time, subjects will receive phone calls from the study team to check on the subjects well-being and to remind him/her of any future appointments.

11 MEASUREMENT OF EFFECT

N/A

12 DATA REPORTING / REGULATORY REQUIREMENTS

12.1 Data Reporting

To ensure subject privacy, all data collection will be performed in the Chest Disease Center research office. Only authorized BIDMC employees have access to this office. The data collected electronically will be held securely on a secure network drive (RedCap®). No PHI will be used in the analysis or publishing of the data.

12.2 Data Safety Monitoring

Local data and safety monitoring will be conducted in accordance with Beth Israel Deaconess data safety monitoring plan and policies.

12.3 Multi-Center Guidelines

N/A

12.4 Collaborative Agreements Language

N/A

13 STATISTICAL CONSIDERATIONS

Previous studies have shown variable CBCT diagnostic yields, but prospective evidence remains poor. Sobieszczyk et al. published retrospective case series of 22 patients with combination of ENB, R-EBUS, CBCT and TBAT reporting a diagnostic yield of 77.2%. However, authors have not clarified how such yield was calculated. Ali et al. reported prospective case series of 40 patients with combination of ultrathin bronchoscope, ENB and CBCT achieving diagnostic yield of 90% (11). However, the likely explanation for such high yield is inclusion of nodules with bronchus sign only, and inclusion of non-specific inflammation in diagnostic yield calculation. Casal et al. combined thin/ultrathin bronchoscope, R-EBUS and CBCT in a prospective series of 20 patients (19). The median size of the nodules in the series was 21 mm, and diagnostic yield was 70%. In their series non-specific inflammation were considered diagnostic if confirmed by surgical pathology or resolved or improved during follow-up period. Hofenforst-Schmidt et al. published one of the earliest series on CBCT and peripheral pulmonary nodules (25). It was a prospective series of 33 patients divided into subgroups bases on nodule size $\leq$ 20 mm, and > 20 mm. The reported diagnostic yield was 75% in subgroup of nodules $\leq$ 20 mm (mean size 15 mm) and was 67% in subgroup of nodules > 20 mm (mean size 30mm). In 2018, Pritchett et al. published one of the larger retrospective series of 74 patients with 92 nodules combining ENB and CBCT-AF (20). The median lesion size was 16 mm in their series and diagnostic yield of 83.7%.

The overall diagnostic yield of currently available ENB alone is 67% based on meta-analysis of 11 studies (17). We aim to detect an absolute 20% difference between CBCT+NB and NB alone

13.1 Study Design/Endpoints

Primary outcome of diagnostic yield will be determined from the results of NB as compared with CBCT-guided NB. A biopsy that results in a specific diagnosis, either malignant or benign (i.e. granuloma, inflammation, fibrosis, infection) will be assumed to be a true positive with appropriate follow up as indicated for up to 6 months. Atypia or lung parenchyma without pathologic findings on final pathology reads will be considered non-diagnostic. If a nondiagnostic lesion resolved, stayed stable or decreased in size on follow-up CT for at least 6 months after the index procedure then this will be presumed benign and classified as a true negative for the purposes of calculating sensitivity and prevalence of malignancy, as well as for diagnostic accuracy.

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 subject is referred for surgery, the surgical pathology will be considered the final diagnosis.

If the subject 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).

13.2 Sample Size, Accrual Rate and Study Duration

The study is designed with 80% power and confidence level of 95% to detect an absolute 20% difference between diagnostic procedure arms in diagnostic yield with two-sided hypothesis testing. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis.
Total patient cohort will be 136; sixty-eight in each arm with a ratio of control to experimental subjects of 1:1. We expect to enroll the patients in a 2-year span as our center has a volume of approximately 3 patients per week

13.3 Stratification Factors

Stratification factors for the study will be:

- Nodule size (< 20 mm vs ≥20 mm)
- Distance to the pleura (< 10 mm vs ≥10 mm)
- Presence of bronchus sign (Binomial: Yes vs No)

13.4 Interim Monitoring Plan

Data reporting and monitoring plan can be found in Section 12.

13.5 Analysis of Primary Endpoints

The overall diagnostic yield will be calculated by adding the number of true positives (TP) for both malignancy and benign disease in the numerator and dividing by the total number of procedures performed for each arm of the study.
Proportions will be compared with the Chi-Square Test as this test is equivalent to the z-test of two proportions (26). A p-value <0.05 will be considered as statistically significant.

13.6 Analysis of Secondary Endpoints

Secondary analysis of the diagnostic yields of BAL cytology, EBUS, NB 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.

Data regarding procedural complications, radiation exposure, and need of further diagnostic procedures will be prospectively recorded.

13.7 Reporting and Exclusions

N/A

13.7.1 Evaluation of Toxicity

N/A

13.7.2 Evaluation of the Primary Efficacy Endpoint

N/A

14 PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

N/A

APPENDIX B MULTI-CENTER GUIDELINES

N/A

APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

N/A

APPENDIX D BIOASSAY TEMPLATES

N/A