A Study to Evaluate the Feasibility of Robotic Bronchoscopy-guided Miniature Cryoprobe Biopsy of Peripheral Pulmonary Lesions

NCT05399082

December 15, 2021

A study to evaluate the feasibility robotic bronchoscopy guided miniature cryoprobe biopsy of peripheral pulmonary lesions

Principal Investigator: Ryan Kern MD

Site(s) where study will be performed:

Mayo Clinic, Rochester, MN

1 Objectives

1.1 Primary Objective:

This is a prospective randomized control study to evaluate the feasibility of using a miniature (1.1 mm) cryoprobe to perform biopsy of peripheral pulmonary lesions using robotic bronchoscopy

1.2 Secondary Objective:

1. To assess safety of cryobiopsy through a robotic bronchoscope
2. Comparison of sample size acquired via cryobiopsy to routine forceps biopsy.
3. Comparison of quality of sample for histologic diagnosis of malignant lung lesions between cryobiopsy to routine forceps biopsy.

2 Background

Lung nodules and masses may represent primary lung cancer, metastatic disease, infection, or more benign findings such as granuloma. Often, lung nodules require biopsy to confirm a diagnosis. Computerized tomography (CT) guided lung biopsy is the gold standard technique. Diagnostic rates are 90% or greater with excellent pathologic quality core biopsies. However, CT guided core lung biopsy is associated with a high pneumothorax rate that may be as high as 20%(1). Because of this, there has been intense interest in bronchoscopic alternatives to obtain biopsies while minimizing the risk of pneumothorax. Patients suspected of having lung cancer undergo bronchoscopy for mediastinal staging with lymph node sampling. Mayo Clinic has acquired the Ion Robot bronchoscopy system (Intuitive Surgical, Sunnyvale, CA, USA). This system uses a robotically driven 3.5 mm steerable catheter to navigate into the periphery of the lung. A 2.0 mm working channel allows the passage of needles, up to

19 gauge, and forceps to obtain biopsy specimens. Using this method, diagnostic yields are comparable to CT biopsy with a pneumothorax rate less than 2%. However, these biopsy specimens often lack adequate tissue for both diagnosis and molecular adequacy that can be obtained with CT biopsy using core needles.

Cryobiopsies are obtained with cryoprobes which are flexible catheters that can be passed through the channel of a bronchoscope. Rapid cooling of tissue results from the Joule-Thomson effect which cases tissue to freeze and adhere to the probe. The biopsy is obtained by subsequently avulsing small fragments of tissue. This results in larger specimens with less crush artifact. This is a common technique used at centers around the world to obtain lung biopsies. Mayo Clinic has significant published experience with this technique (1-3). This technique has not been combined with robotic bronchoscopy due to size (both length and diameter) of older generation cryoprobes.

Erbe Medical, (Marietta, GA, USA) recently received FDA approval for a 1.1mm disposable cryoprobe, which will pass through the working channel of the Ion Robotic bronchoscope. The goal of this study is to assess the feasibility of using that probe with the Ion Robot and evaluate biopsy quality.

3 Research plan and method

Study design: This will be a prospective pilot study.
We will include patients who undergo robotic bronchoscopy with cryobiopsy at Mayo Clinic, Rochester, MN who meet the below inclusion/exclusion criteria.

4 Inclusion Criteria/exclusion criteria

4.1 Inclusion criteria:

1. Male and female patients age $\geq$18 at the time of informed consent
2. Patients clinically meets indication for peripheral lung nodule biopsy and has been scheduled for robotic bronchoscopy

Lesion Criteria:
Inclusion:

1. Pulmonary nodules of 8-50mm in largest dimension

4.2 Exclusion Criteria:

1. Patients with known bleeding diathesis
2. Platelet count <50,000 per µL
3. Current use of systemic anticoagulation or antiplatelet therapy without the ability to hold therapy for the recommended amount of time prior to an invasive procedure (aspirin monotherapy is acceptable)
4. Inability or unwillingness to give informed consent
5. Pregnant or nursing females, or females of child-bearing potential who decline a pregnancy test prior to enrollment
6. Pulmonary hypertension, defined as a right ventricular systolic pressure > 50 mmHg
7. Individuals with current or recent systematic conditions, such as, acute kidney injury, or conditions that would mandate anticoagulation, such as a recent coronary stent.
8. International Normalized Ratio (INR) <1.5
9. Do Not Resuscitate (DNR) status
10. Do Not Intubate (DNI) status

5 Specific aims:

Primary Objective:

This is a prospective randomized control study to evaluate the feasibility of using a miniature (1.1 mm) cryoprobe to perform biopsy of peripheral pulmonary lesions using robotic bronchoscopy

Secondary Objectives:

1. To assess safety of cryobiopsy through a robotic bronchoscope
2. Comparison of sample size acquired via cryobiopsy to routine forceps biopsy.
3. Comparison of quality of sample for histologic diagnosis of malignant lung lesions between cryobiopsy to routine forceps biopsy.

6 Study Endpoints:

6.1 Primary Endpoint:

Feasibility of obtaining biopsy will be assessed as the ability to insert the cryoprobe into the robotic working channel and retrieve at least one tissue sample per patient that is considered by the bronchoscopist as adequate for further pathological analysis.

6.2 Secondary Endpoints:

Procedural:

1. Duration of each individual biopsy procedure from first insertion of probe into robotic sheath to removal of specimen. Duration of full procedure from first insertion of probe into robotic sheath to last removal of specimen.
2. Freezing time (seconds) for cryoprobe biopsies
3. Number of "successful" and "unsuccessful" biopsy attempts.
   One attempt is defined as insertion of the biopsy probe into the robotic sheath, activation/employment of the biopsy mechanism at the target site and retrieval via the robotic sheath. A biopsy attempt is successful if a tissue sample that is considered by the bronchoscopist to be adequate for further pathological analysis can be retrieved. In the case of unsuccessful cryobiopsy attempts, it should be recorded whether tissue sampling was successful but the tissue sample was "lost" i.e. if a successful "bite" took place as indicated by freezing activation and adhesion, but the sample detached from the cryoprobe tip on its way out of the body and could not be recovered (e.g. because it was too big to fit thorough the over sheath or tissue channel or freezing was deactivated too soon).

Histological:

4. Histological accessibility grade
   Assessed by pathologist according the following scale:

Grade	Pathological Description
1	Insufficient tissue
2	Sizable tissue sample but no diagnostic material (likely indicating the lesion was missed but a reasonable amount of tissue was sampled)
3	Lesional tissue present but considerable artifact clearly hampering the morphologic evaluation of the lesion (diffuse crush artifact, procedure-related hemorrhage, large amount of necrosis)
4	Diagnostic material

5. Histological diagnostic yield
   Defined as the ability of the pathologist to make a diagnostic statement based on the histological analysis of the obtained tissue samples.
6. Total histological area (mm^2)
7. Crush artifacts (% total area)
8. Fresh hemorrhage (procedural related) (% total area)
9. Other artifacts that obscure pathological assessment (% total area, artifacts will be listed)
10. Different tissue types in the tissue specimen (e.g. alveoli, bronchus, mucus, blood, target tissue; % total area) .

Safety:

11. Occurrence and grading of bleeding according to CTCAE (version 5) following each individual biopsy and overall for each procedure.
12. Occurrence and grading of the following related adverse events according to CTCAE (version 5):
    a. Pneumothorax, as determine by post procedural chest x-ray, which is standard of care after robotic bronchoscopy, or any intraprocedural imaging such as cone beam CT or fluoroscopy.
    b. Respiratory failure
13. Occurrence of all related adverse events Grade 3-4 (according to CTCAE) during or directly following the biopsy procedure.

7 DSMB

The Department of Surgery DSMB will provide interim reviews and serve as in internal safety control.

8 Early Stopping Rules

If any patient is permanently disabled, has life threatening consequences (defined as Grade 3 bleeding episode or Grade 4 adverse event by CTCAE Version 5.0) the study will be temporarily halted until the DSMB has reviewed the Adverse Events. The study will be continued if the event is demonstrably unrelated to the procedure or was a reasonable adverse event in relation to the research study procedure. The trial will be permanently halted for a grade 5 event (death) if attributable to the cryobiopsy procedure. The study will be continued if the event is demonstrably unrelated to the procedure or was a reasonable adverse event in relation to the research study procedure.

9 Study Plan:

The proposed study will prospectively enroll patients being evaluated for robotic bronchoscopic lung nodule/mass biopsy which will be done as **part of their standard medical care**.

1. Patients who present for robotic navigational bronchoscopy with planned biopsy of lung nodule or mass will be eligible to consent to be included in prospective study.
2. Patients will be screened for inclusion and exclusion criteria via review of medical history and standard of care pre-procedure examinations.
3. Robotic assisted bronchoscopy will be performed as per institutional standard of care. In addition to robotic shape sensing technology, radial probe ultrasound, fluoroscopy, and cone beam CT may be used for navigation.
4. The position of the navigation catheter relative to the nodule or mass will be confirmed via radial EBUS and cone beam CT.
5. The lung nodule or mass will be biopsied using standard biopsy needles, ranging from 19-23 gauge. Rapid onsite evaluation of the needle biopsy will be performed according to standard of care.

6. Per clinical practice, after the needle biopsy we will also take tissue biopsies. We will take 3 biopsies using the 1.1 mm Erbe cryoprobe and 3 biopsies using forceps. The order in which the biopsy methods are employed will be randomized 1:1. In 50% of the patients, forceps will be

followed by cryoprobe. In 50% of the patients cryoprobe will be followed by forceps biopsy. Randomization will take place after needle biopsy, prior to tissue biopsy. Only patients for which further tissue biopsy is deemed necessary following needle biopsy will be randomized. Remaining patients will be excluded from the study and will be treated according to the standard of care. See randomization procedure for details.

7. Cryoprobe and forceps biopsy will be performed according to standard of care and the device instructions for use. The initial freeze time for the cryobiopsy is 3 seconds as measured on the device timer. If inadequate tissue is obtained due to incomplete freeze, the freeze time can be extended by 1 second on each consecutive attempt (to a maximum of 8 seconds) at the discretion of the bronchoscopist.

8. Samples retrieved via forceps and cryoprobe biopsy will be placed into separate formalin containers and forwarded to pathology for sample processing and further pathological analysis as per standard practice.

9. Patients will be followed up for adverse events until completion of the standard of care post-procedure follow-up within 2 weeks of the procedure. The follow up may occur as a in person visit, video visit or telephone call. Adverse events will be graded using CTCAE Version 5.0 and will be attributed using the following scale:

Adverse Event Attribution Categories:

Attribution	**Description**
Unrelated	The AE *is clearly NOT related* to the intervention
Unlikely	The AE *is doubtfully related* to the intervention
Possible	The AE *may be related* to the intervention
Probable	The AE *is likely related* to the intervention
Definite	The AE *is clearly related* to the intervention

10 Randomization and Blinding

All patients will first receive needle biopsy and rapid onsite evaluation followed by tissue biopsy (forceps and cryo-biopsy). The order in which the forceps and cryo-biopsy methods are employed will be randomized 1:1. In 50% of the patients, forceps will be followed by cryoprobe. In 50% of the patients

cryoprobe will be followed by forceps biopsy. Randomization will take place inter-procedurally; after needle biopsy and prior to tissue biopsy. Only patients for whom, in the opinion of the investigator, further tissue biopsy is medically advisable, will be randomized. Remaining patients will be excluded from the study and will be treated according to the standard of care. See Figure 1 for the randomization schema.

Sealed envelopes will be prepared at the beginning of the study using an independently managed (a research professional that is not a member of the study team) double-blinded envelope system. The double-blinded envelope will be opened at the randomization timepoint (intra-procedurally after needle biopsy and just prior to the tissue-biopsy) to revel the order of methods (forceps/cryobiopsy). If a further biopsy is not deemed necessary or medically advisable, the patient will be excluded from the study. The unopened randomization envelop will be replaced, and will be used for the next eligible participant.

Allocation will be double blinded to patient and bronchoscopist until the intra-procedural randomization timepoint after which blinding of the bronchoscopist is not possible due to the nature of the procedure. Pathologists interpreting the biopsy samples will be blinded to the biopsy device used although, due to the expected differences in biopsy size and appearance, the allocation of the biopsy method may be apparent. Unblinding will be performed in case of medical need or if required by regulatory or legal authorities.

11 Devices and Equipment

The following devices will be used to perform the transbronchial biopsy procedure.

- Intuitive Ion Robot platform (Sunnyvale, CA)
- Bronchoscope: Olympus P190 bronchoscope (Olympus, USA).
- Biopsy Needle: 23-gauge Flexision Biopsy Needle (Intuitive, USA)
- Biopsy forceps: Olympus disposable EndoJaw (FB-211), Olympus, USA)
- Cryoprobe: Flexible cryoprobe, single-use, ø 1.1 mm (Erbe Elektromedizin GmbH, 20402-401) used with ERBECRYO 2 (Erbe Elektromedizin GmbH, 10402-000)
- Radial probe ultrasound: (Olympus, USA)
- Cone beam CT and fluoroscopy (Cios C-spin, Siemens)

All other procedural devices and equipment will be used according to institutional availability and standard of care.

12 Schedule of Events

	Screening max. 30d prior to procedure	**Procedure**	**Follow Up**
Informed consent	X		
Review of inclusion and exclusion criteria	X	X	
Medical chart review and medical history	X		X
Review concomitant medication	X	X	
Clinical assessment/physical exam	X	X	
Urine pregnancy test (for women of child bearing potential as standard of care)	X**	X**	
Robotic-assisted bronchoscopy procedure		X	
Randomization		X	
Follow-up Chest X-ray		X*	
Adverse events	X	X	X***

*Post-procedure standard of care x-ray is done prior to discharge.

** Standard of care pre-procedure pregnancy test, on the day of the procedure if not done 30-days prior.

*** In person, video, or telephone

13 Specimen processing

For specimen processing, cryobiopsy and forceps specimens will be placed in separate formalin containers and evaluated by a dedicated pulmonary pathologist.

14 Data Collection and Confidentiality Procedures:

The following data will be collected from the patient's medical record:

1. Demographic data (such as age, gender, BMI, and other non-identifiable demographics)
2. Past medical history
3. Nodule characteristic (size, location, presence of bronchus sign, PET avidity, central lucency, distance to the pleural surface, distance to the nearest visible bronchus)
4. History of prior treatments
5. Indication for procedure
6. Radiologic data
7. Preliminary ROSE assessment (Rapid On-Site Evaluation) and final histopathology result

The following technical procedural data will be collected:

1. Position of the robotic catheter relative to the nodule prior to biopsy sampling as assessed via rEBUS ("concentric", "eccentric" or "adjacent" orientation) and/or cone beam CT.
2. Procedural details such as number of biopsies performed, duration of procedure, freezing time for cryoprobe

Study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap (www.project-redcap.org) is a secure, web-based application, with controlled access designed to support data capture for research studies. It provides: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources.

Access to the data will include the study PI and research team personnel. All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis.

Study data will be archived indefinitely in REDCap following publication. This will allow the data to be used in future research studies performed under separate IRB approved protocols. REDCap is a secure electronic database with controlled access, and because patient identifiers may be needed to link study data to data from other sources under future IRB approved protocols, thus patient identifying information will be retained in the archived database.

15 Statistical analysis

All statistical analyses will be performed in collaboration with the Mayo Clinic Department of Biostatistics.

A descriptive analysis will be done first. Descriptive statistics (e.g., frequencies, ranges, means, medians, proportions, and standard deviations [SDs]) along with 95% confidence intervals (CIs) for the means or proportions will be computed for the measures of interest described in primary and secondary objectives.

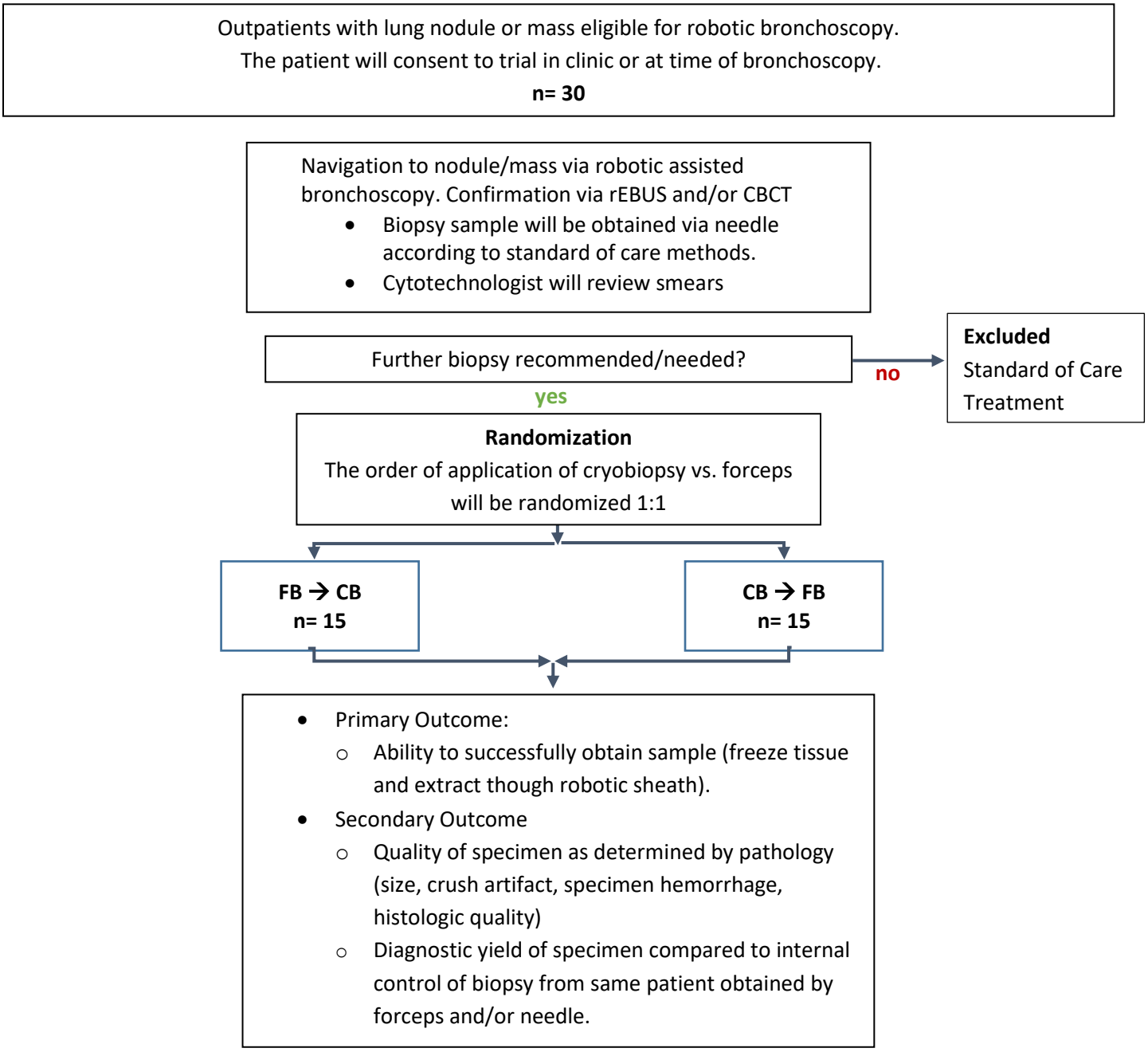
15.1 Sample Size

A total sample size of 30 patients will be enrolled in this pilot, feasibility study. The study will be divided into two phases. Phase one will include 10 cases. Following the first 10 cases, an interim safety review will be performed by a DSMB from the Department of Surgery. If the risk to the study patients is deemed acceptable the study will progress to Phase two. Phase two will include another 20 patients with the aim of assessing biopsy size and diagnostic yield. The pilot study will not be powered to make a statistical conclusion but will instead provide information on the primary objective of feasibility and data on secondary objective to inform future studies.

16 Informed Consent/Authorization

We will obtain written patient consent for this prospective pilot study.

Figure 1. Study flow chart



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