Assessing the ability to obtain a core biopsy from peripheral lung lesions (PPL) using the novel Gen Cut tool with Radial EBUS.
 (R-CORE)

MULTI CENTRE PROSPECTIVE INTERVENTIONAL PILOT STUDY WITH THE VIEW OF PROGRESSING TO A MULTI-CENTRE RANDOMISED CONTROL TRIAL

Abstract

Lung cancer is the commonest cause of cancer death worldwide. Peripheral Pulmonary Lesions (PPL) suspected of lung cancer requires biopsy at the earliest possible opportunity to improve survival. Radial EBUS is now an established method of obtaining biopsies from PPL suspected of cancer as an alternative to CT guided biopsy due to the highly favorable safety profile of Radial EBUS. Despite the lower adverse effect rates of Radial EBUS, this method has still not been utilised to perform a “core biopsy” in the lungs. As the progressive development of novel immunotherapies, including immunotherapy targeted for PD L1, a “core biopsy” that can be processed as a histology sample, becomes mandatory to perform multiple testing. This study aims to investigate the possibility of obtaining a core biopsy from PPL using the novel “Gen Cut” core biopsy tool in conjunction with radial EBUS.

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**CONTENTS**

1. Study Synopsis ………………………………………………………3
2. Protocol…………………………………………………………….….5
	1. Rationale & background information……………………………...5
	2. Study goals and objectives………………………………………....6
	3. Methodology ……………………………………………….……...7
		1. Study Design ………………………………………….…...7
		2. Participants …………………………………………...……7
		3. Inclusion criteria ……………………………………..…….7
		4. Exclusion criteria……………………………………..…….7
3. Description of procedure ………………………………………………7
4. Data collection sheets used …………………………………………….8
5. Safety Considerations ………………………………………………….8
6. Training and support …………………………………………………...9
7. Follow-Up ……………………………………………………………...9
8. Data Management and Statistical Analysis …………………………….9
9. Quality Assurance ……………………………………………………...9
10. Expected Outcomes of the Study ………………………………………9
11. Dissemination of Results and Publication Policy ……………………...9
12. Project time line and duration ………………………………………….9
13. Project Management …………………………………………………..10
14. Ethics ………………………………………………………………….10
15. Budget …………………………………………………………………10
16. Collaboration with other scientists or research institutions……………10
17. Financing and Insurance ………………………………………………11
18. Reference ………………………………………………………………11
19. Images ………………………………………………………………….13
	1. Image 1 …………………………………………………………13
	2. Image 2 …………………………………………………………13
20. **STUDY SYNOPSIS**

Assessing the diagnostic ability and safety in obtaining a core biopsy from peripheral lung lesions (PPL) using the novel Gen Cut tool with Radial EBUS. (R-CORE)

Multi Centre Prospective Interventional Pilot Study with the view of progressing to a Multi-Centre Randomised Control Trial

Rationale: Lung cancer is the commonest cause of cancer death worldwide. Peripheral Pulmonary Lesions (PPL) suspected of lung cancer requires biopsy at the earliest possible opportunity to improve survival. Radial EBUS is now an established method of obtaining biopsies from PPL suspected of cancer due to the very low adverse events in comparison to CT guided biopsy. Despite the remarkable safety profile this method has still not been utilised to perform a core biopsy in the lungs. As the progressive development of novel immunotherapies, including targeted agents for PD L1, a core biopsy that can be processed as a histology sample becomes mandatory to perform multiple testing. This study aims to investigate the possibility of obtaining a core biopsy from PPL using the novel “Gen Cut” core biopsy tool in conjunction with radial EBUS.

Co-Primary End Points

1. Ability to obtain a core biopsy sample that would be suitable for PDL-1 testing
2. Adverse events of the procedure

Methods: Multi centre prospective interventional pilot study of 20 patients

Procedure: Informed consent will be taken for the procedure. Procedure will be performed under conscious sedation or general anaesthesia as per the protocol used for Radial EBUS for that institution.

Once the patient is sedated, the bronchoscope is introduced via the mouth/nose to the required location. The Radial EBUS with the large guide sheath (GS) will be introduced to locate the lesion. Once this is located, the GS will be left in situ as an extended working channel.

Following this the Gen cut biopsy tools will be introduced through the GS as the first mode of biopsy. Once in the lesion, suction will be applied using the provided lockable syringe of 20ml. The tool is then rotated clockwise 45 degrees at a time, mounting to at least 5 rotations, to complete a 360-degree rotation. The suction will be removed and the tool withdrawn.

The first drop of the specimen will be placed in a slide to assess for ROSE. The remaining specimen will be placed in Hanks solution. The specimen will be pushed out of the tool using air via a 10-ml syringe. The residual specimen will be pushed out using a cytology brush which is included in the tool kit. Saline 10 ml will be used finally to rinse off the remaining sample. Once all the specimen is placed in Hanks solution, a pipette is used to gently suction out the “micro-core’ samples and place them directly in formalin. (Video of this process will be provided for all participating sites)

Following a wait time of 5 minutes an USS examination will be performed on the 2nd intercostal space on the side where the biopsy was taken to assess for pneumothorax, whilst the patient is in supine position. Following this, conventional Radial EBUS biopsies will be performed as per the routine practice of the institution and the diagnostic yield and complications will be compared.

Populations: All patients diagnosed with a peripheral lung mass suspected of cancer and requires a biopsy to diagnose the aetiology, will be offered this new biopsy technique in addition to the conventional radial EBUS biopsies. Inclusion: Lesions >1.5 cm in size that are in the outer half of the lung parenchyma. Exclusion: Not suitable for flexible bronchoscopy and biopsy including anticoagulation that cannot be stopped for the procedure, recent MI within the last 6 weeks and known pulmonary hypertension with PASP>40mmHg Time frame: 6 months. Expected outcomes: 1. Ability to obtain a core biopsy that can be used for immunohistochemistry and molecular testing including PD-L1 testing. 2. Safety of this novel biopsy method in comparison to the conventional Radial EBUS biopsy methods that are currently in use.

General information

Name of sponsor: Department of Respiratory and Sleep Medicine, Westmead Hospital

* Name and title of the investigator responsible for conducting the research:
* Dr. Samantha Herath, Respiratory and Sleep Physician.
* Responsibility:
* 1. Chief Investigator of the project
* 2. Co-ordination of multicentre study
* 3. Data collection and analysis.
* 4. Write up and publication of the results
* Names and addresses of the other medical departments and institutions involved in the

research

* 1. A/Prof. Alvin Ing Macquarie university Hospital, Sydney, Australia.
* 2. Dr. Elaine Yap, Middlemore Hospital, Auckland, New Zealand.
* 3. Dr. David Fielding, Royal Brisbane Hospital, Queensland, Australia.
* 4. Dr. Farzad Bashirzadeh, Royal Brisbane Hospital, Queensland, Australia.

**2. STUDY PROTOCOL**

2.1 Rationale & background information

Lung cancer is the leading cause of cancer death worldwide. Death due to lung cancer is greater than the combined death rate from breast, prostate and colon cancer (1-5). Once an abnormal area in the lung is discovered during a Chest X-ray or CT scan it is of paramount importance to obtain a lung biopsy to diagnose if this is of cancerous origin, as research had shown that every centimetre of growth can dramatically reduce prognosis (5).

The gold standard in obtaining a tissue sample in peripheral lung masses had been CT guided biopsy for many years. Although the diagnostic yield was satisfactory, this method carries a high risk of side effects. The occurrence of pneumothorax can be as high as 40% in some reported series (6-11). Lung Haemorrhage is another recognised complication that occurs up to 5% patients (6-11). Another disadvantage of CT-guided biopsy is having many patients that are unsuitable for CT guided biopsy, due to the location of the abnormal lesion or due to patient factors. For example, if the peripheral pulmonary lesion (PPL) in question, is closer to large blood vessels or near the heart, it becomes riskier to have a CT guided biopsy due to the exceptionally high risk of bleeding. With regards to patient factors, in CT guided biopsy patients are instructed to hold a position that would enable good access to the lesion and most elderly patients are unable to maintain the position required for CT guided biopsy due to arthritis of shoulder joints or general immobility. In patients with psychiatric issues it is difficult to perform a CT guided biopsy as they are unable to hold the breath for a period, that is required for CT guided biopsy.

Radial EBUS was initially introduced to the armoury of lung biopsy in 2002. This is an endobronchial biopsy method using a flexible bronchoscope. Radial EBUS is now an established method of obtaining biopsies from peripheral lung lesions. It has recently been popularised as a safer lung biopsy method to overcome the above-mentioned problems, so that more patients can benefit from a diagnostic biopsy. In a meta-analysis of 1400 patients in 14 studies Radial EBUS had demonstrated a diagnostic success rate of 73%. The pneumothorax rate was less than 1%. The bleeding risk was <1% (12). The safety of the radial EBUS lies in the guide sheath (GS) (12). When biopsies are taken from radial EBUS the GS which covers the ultra sound is left in situ as an extended working channel and this GS works as a tamponade and prevents bleeding (13).

The disadvantage of Radial EBUS is that despite the remarkable safety profile, this method still lacks the ability to perform a core biopsy in the lungs. Core biopsies are increasingly becoming an essential requirement in the diagnosis of lung cancer and in examine for molecular markers including PD L 1 testing. Most trials that had tested these molecular markers had used CT guided core biopsies, and therefore to qualify for some trials, the tissue specimen should be processed as a core histology biopsy sample. As the development of novel immunotherapies increases, a core biopsy is now required for multiple immunohistochemistry as well as molecular tests.

Therefore, there is a need to find a new biopsy technique that could be used via the GS, thereby preserving safety aspect, but enabling a core biopsy. This study aims to investigate use of the novel “Gen Cut” core biopsy tool in conjunction with radial EBUS to obtain a core biopsy of PPL.

The Gen cut core biopsy tool is a thin small wire like equipment that can be introduced via the GS to the desired location. Fluoroscopy, if available and is in routine use at the institution can be used to confirm the position. This biopsy tool is blunt but has an internal sharp edge (Image 2). With rotatory movement of the tool small thin slices of the tumour will be shaved off which can be suctioned in to the biopsy tool with the use of a suction syringe connected at the distal end of the Gen cut tool, that can be used for histology.

Studies on Gen cut biopsy so far are very favourable. A porcine study performed with 6 animals and performing 60 biopsies, using the same tools used in conventional Radial EBUS i.e. forceps and aspiration needle, in comparison to Gen cut tool were investigated. In this study, the Gen Cut tool had 30/60 biopsies done. There was no bleeding with the Gen Cut tool (0/30), and pneumothorax was 2/30. In comparison, the bleeding was 2/15 for the aspiration needle (14). Gen Cut tool was TGA approved to be used as a biopsy tool for electromagnetic navigation bronchoscopy since 2015. There are two case reports demonstrating the ability to obtain a core biopsy sample with good success rates and the bleeding or pneumothorax was not noted (15). However, there are no studies published on the ability of Gen cut biopsy tool to obtain core biopsy samples that can be used for PD L1 testing.

Gen Cut tool was designed initially for the use with navigation bronchoscopy as mentioned above, via a guide sheath. This GS is very similar, but approximately five-fold more expensive than the standard radial EBUS GS. Using this Gen cut tool through radial EBUS, we anticipate would give similar results at a much lower cost.

Navigation bronchoscopy is costly and would only be available in few centres, whereas Radial EBUS is low cost and will be available for many centres.

2.2 Study goals and objectives

Study Goals: This study aims to investigate if Gen cut biopsy tool used via Radial EBUS (as a low-cost alternative to electromagnetic navigation) can be utilised to obtain a core biopsy from peripheral lung masses in patients who are referred for Radial EBUS biopsy.

Co-Primary objectives

1. Ability to obtain a core biopsy sample that would be suitable for PDL-1 testing
2. Safety

2.3 Methodology:

 2.3.1Study Design: This is a multi-centre prospective phase 2, interventional, open label pilot study. Sample size 20 as calculated for a pilot study.

2.3.2 Participants: All patients referred for Radial EBUS

2.3.3 Inclusion criteria:

1. Age 18 or older
2. Able to give consent
3. Has a Peripheral lung lesions noted on CT chest/Chest X ray that require a biopsy
4. Lung lesions should be >1.5 cm
5. Lung lesion should be in the outer half of the lung parenchyma

2.3.4 Exclusion criteria:

1. Not suitable for flexible bronchoscopy
2. Coagulopathy with INR>1.5 or platelets <100
3. Known pulmonary hypertension with RVSP >40
4. Recent myocardial infarction (within 6 weeks)
5. On anticoagulation or anti-platelets other than aspirin that cannot be stopped for the procedure
6. Description of procedure:

Informed consent will be taken from all patients for the procedure. Procedure will be performed under conscious sedation or general anaesthetic as per the protocol used for radial EBUS for that institution.

Once the patient is sedated the bronchoscope (minimum working channel diameter of 2.8mm) is introduced via the mouth/nose to the required location. The Radial EBUS (20R Olympus) with the large guide sheath (K 203 GS) will be introduced to locate the lesion. Once this is located, (+/- use of fluoroscopy as per routine practice of the institution), the GS will be left in situ as an extended working channel.

Following this the Gen cut biopsy tools (Medtronic’s Super dimension) will be introduced through the GS as the first mode of biopsy. Once in the lesion, suction will be applied using the provided lockable syringe of 20ml. The Gen cut tool is then rotated clockwise 45 degrees at a time mounting to at least 5 rotations. The suction will be removed and the tool withdrawn.

Once the biopsy tool is taken out from the bronchoscope a single drop of the sample will be placed in a slide for Rapid Onsite Cytology (ROSE) assessment. Following this the remaining specimen will be placed in Hanks solution. Once all the specimen is placed in Hanks solution, a pipette is used to gently suction out the “micro-core’ samples and place them directly in formalin. (Video of this process will be provided for all participating sites)

Following 5 minutes’ wait time after the last Gen Cut biopsy an USS will be performed to assess for pneumothorax by a Respiratory Physician accredited in chest USS procedure. Two ultrasonic determinants of pneumothorax will be assessed, namely: 1. loss of sliding sign and 2. appearing of bar code in M band to confirm pneumothorax. The USS will be performed on the 2nd intercostal space, at mid clavicular line when patient is supine on the side of biopsy.

If there is detection of a pneumothorax or any doubt about a pneumothorax the procedure will be terminated and a routine CXR will be performed to determine the occurrence of a pneumothorax.

Once the Gen cut biopsies are taken, routine Radial EBUS biopsies are performed as per routine practice of the respective institutions.

Samples from different biopsy tools will be labelled separately as 1. Gen cut core biopsy (placed in formalin) 2. Needle aspiration sample (placed in Hanks solution) 3. Cytology brush sample (placed in Cytolyt solution) and 4. Forceps’ biopsy samples (placed in formalin solution). The conventional radial EBUS sampling modalities and number of passes used will be up to the discretion of the proceduralist as per the institutional routine practice.

One hour post procedure, the patient is asked to complete the comfort score from 1-10.

Post procedure CXR will be performed 1 hour post procedure to assess for pneumothorax.

Each procedure will be recorded in a bronchoscopy record form as usual practice.

Following each procedure, if an adverse event were to occur, the adverse event record will be filled and any adverse event will be reported to the ethics committee and data safety monitoring board.

4. Data collection sheets used:

1. Bronchoscopy procedure record form (This is the routine form used in bronchoscopy to record the detailed procedure, sedation used and side effects)
2. Side effects recording form for pneumothorax and bleeding
3. Pathology assessment form of the ability to perform PD-L1 testing in the Gen cut sample.
4. Patient comfort questionnaire of the procedure (with 1-10 pain chart)

5.Safety Considerations

This protocol was discussed and peer reviewed by the Australia New Zealand Interventional Pulmonary Group meeting in June 2017. All the samples, will be collected via the GS and the GS acts as a tamponade, therefore the risk of bleeding was considered minimal. An endobronchial balloon was not deemed necessary following review of this protocol.

The sedation will be provided by a second Respiratory Physician or an anaesthetist to enable the proceduralist to focus on the task.

6. Training:

Each bronchoscopic procedure will be performed by a Respiratory physician trained in Radial EBUS and who has performed at least 50 Radial EBUS procedures and does procedures on regular basis.

Medtronic’s team will provide training and technical support at each procedure (to assist with specimen retrieval from the tool and using the needle safely) for the duration of the pilot study in all institutions, to maximise training in preparation for the larger RCT.

This is an easy to use technique with a blunt ended instrument. To increase uniform approach to the procedure, a training video will be made and will be available online for all proceduralists to follow with a step by step guide to ensure safety and efficacy.

1. Follow-Up

The patient will be observed in the bronchoscopy unit for 2 hours as per routine practice. This is a one-time procedure and does not require follow up for this study.

The patient will be followed up as per routine practice by the referring physician.

1. Data Management and Statistical Analysis

At the time of consent the patient will be allocated to a study number with four letter and 2 digits. The data will be collected under this study ID (de-identified) and kept in the research office of the Respiratory Medicine Department at Westmead Hospital in a password protected computer. The data will be collected by the primary study investigator for that site. SPSS will be used for data analysis. A sample size of 20 was calculated to be adequate by the biostatistician of the study.

1. Quality Assurance

The study will be followed up by a Data Safety Monitoring Committee (DSMC) and at each 5 patient recruitment data will be analysed for safety.

The DSMC will consist of a Respiratory Physician (not involved in the study), the study statistician and a study pathologist (who is not involved with patient care).

1. Expected Outcomes of the Study

This study will introduce a new biopsy tool that can be used via the Radial EBUS procedure to obtain core biopsies from the lung tissue with abnormalities. This introduces a safer method in obtaining a core biopsy in the lungs enabling PDL1 testing, which will be a mandatory requirement for molecular testing in the very near future.

1. Dissemination of Results and Publication Policy

This study would result in a publication of novel procedural knowledge and will be another link in the advancing minimally invasive bronchoscopic lung biopsy techniques.

Publication is aimed at The American Association of Interventional Bronchoscopy and planned presentation at the European Respiratory Society meeting in 2018 September.

1. Project time line and duration

This project is planned for 6 months

|  |  |  |
| --- | --- | --- |
| Time line | Date | Planned outcomes |
| Ethics application | September 2017 |  |
| Ethics approval | Mid Oct 2017 |  |
| Training of proceduralists and completion of training | November 2017 |  |
| Distribution of Medtronic’s navigation systems to the participating centres | November 2017 |  |
| Delivery of Gen cut tools to participating Centres | November 2017 |  |
| Commencement of Recruitment | Late November 2017 |  |
| Competition of Recruitment | March 2018 | Planned abstract presentation at ERS 2018 |
| Write up and publication | April 2018 |  |

1. Project Management

Dr. Herath is responsible for overall project management

1. Ethics

Ethics consent will be applied through Westmead Hospital as the leading site for this trial

1. Budget

This is an investigator initiated non-funded project

Funding support for equipment has been applied to Medtronic’s which produces Gen Cut tools

1. Collaboration with other scientists or research institutions

This is a multi-centre Pilot study involving 4 major centres that perform Radial EBUS including Westmead Hospital

As listed below.

* 1. A/Prof. Alvin Ing Macquarie university Hospital, Sydney, Australia.
* 2. Dr. Elaine Yap, Middlemore Hospital, Auckland, New Zealand.
* 3. Dr. David Fielding, Royal Brisbane Hospital, Queensland, Australia.
* 4. Dr.Farzad Bashirzadeh, Royal Brisbane Hospital, Queensland, Australia.
1. Financing and Insurance

15.1 Equipment support:

This study has generous support from Medtronic’s supplying a planning lap top on loan for four participating sites.

Grant support had been applied via Medtronics investigator initiated grant scheme for supply of 20 Medtronic Gen cut “core biopsy” needles.

Grant support had been applied for Australian Lung Foundation Pilot Project for research nurse support and consumables.

15.2 Insurance: The University of Sydney will be issuing an insurance certificate as Dr. Herath is performing this study as part of her PhD studies at the University of Sydney.

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19. Images

 19.2. Image 1: The Novel Gen Cut Biopsy tool

