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Radial Endobronchial Ultrasound guided biopsy for lung lesions: Evaluating the role of the guide sheath size, addition of needle aspirate and multi-modal sampling, in improving the diagnostic yield : An Exploratory randomized study.

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Abstract

Introduction:

Radial EBUS (R-EBUS) biopsy for lung lesions has a marked safety profile with less than 1.5% pneumothorax in comparison to CT-guided transthoracic biopsy of 20 %. However, the diagnostic yield of R-EBUS remains suboptimal at 73 % in comparison to CT -TTB at 92 %. The size of the Guide Sheath (GS), the addition of aspiration needle biopsy and multi-modal sampling may improve the diagnostic yield.

Methodology:

This is a multi-center randomized controlled study. All patients referred to R-EBUS for a biopsy were offered the study and randomized to large or small GS arms. An aspiration needle is added to the large GS arm to assess the additional diagnostic yield. Each patient had 1-3 biopsies of forceps and brush (+ needle aspirate in large GS arm). All procedures were done under sedation. CXR has taken 1-hour post-procedure. The study was terminated due to slow recruitment at 42 patients planned interim analysis.

Results:

The large GS tended to provide a better diagnostic yield (72 %) in comparison with small GS (60 %) OR 1.77 (95 % CI 0.44- 7.17), this was improved further with an addition of aspiration needle (86 %) in the large GS arm. Aspiration needle was the sole diagnostic specimen 13 % and able to provide EGFR analysis similar to forceps biopsy. Multimodal biopsies seem to improve diagnostic yield. No pneumothorax or bleeding was recorded.

Conclusion:

Despite the type 2 error and small sample size, the large GS seem to provide better results. We suggest utilising an aspiration needle to improve the diagnostic yield. A multimodal biopsy is encouraging with better diagnostic yield, EGFR capability without additional side effects.

Keywords: Cryo-biopsy, radial EBUS, CT-Guided transthoracic biopsy, Diagnostic yield, EGFR, Bleeding, pneumothorax, Biopsy technique.

Introduction

Peripheral pulmonary Lesions (PPL) suspected of lung cancer requires a safe and effective biopsy. Radial Endobronchial ultrasound (R-EBUS) is a widely used guided bronchoscopy method **[1,2]** for diagnosis of PPL, with marked safety profile. In five meta-analyses of over 50 studies with 7000 patients on R-EBUS, the overall side effect rate was 1.5 % with 0.7 % requiring a chest drain insertion **[1-5]**. This is in comparison to the "gold standard" CT-guided transthoracic (CT-TTB) biopsy, which has a pneumothorax rate of 20 % with a chest drain rate of 7.3 % in a meta-analysis of 48 papers consisting of 10.383 biopsies.**[6]**. Yet, the diagnostic yield of R-EBUS is suboptimal (69 %-73 %) **[4,7-9]**, in comparison to the"gold standard" CT-guided transthoracic biopsy yield of 92 % **[10,11]**. Despite being recommended by the American College of Chest Physicians (ACCP) clinical guidelines as a mainstream diagnostic method of PPL, this lower diagnostic yield hinders R - EBUS being a more widely used biopsy technique in PPL **[12]**.

R-EBUS is a flexible wire-like ultrasound probe that gives a 360-degree radial view of the airway. It can be used via the working channel of the bronchoscope and advances to the bronchial subsegments beyond the bronchoscopy vision. This R-EBUS is

introduced using a guide sheath (GS), which houses the ultrasound and has a snug fit to it. Once the PPL is located using the ultrasound, the ultrasound is withdrawn leaving the GS in situ which then acts as an extended working channel. Biopsy tools are introduced via this GS. There are two commercially available GS sizes. The small GS (K 201-Olympus) houses small instruments and accommodates biopsy equipment up to a diameter of 1.4 mm and the large GS (K203-Olympus) houses all conventional bronchoscopy biopsy equipment up to a diameter of 1.91 mm.

Despite the radial, ultrasound being able to visualise or "see" the PPL the diagnostic yield seemed to lag by 10-20 %. This was first reported by Herth et al in 2006 with a visualisation success of 89 % yet the diagnostic yield was only 70 % **[13]**. Nearly all studies published since then had continued to report this gap between visualisation and diagnosis. **[14-18]**. One reason for this gap and a lower diagnostic yield, maybe the size of the GS used, that then determines the size of the biopsy tool utilised. If the biopsy tools used are too small, the resultant small biopsy samples may get destroyed whilst being processed.

The two sizes of the GS had been head-to-head compared only in a single study **[19]**. This limited data demonstrated overall diagnostic yield was no different (77 % for large GS and 83 % for the small GS), but the small GS was better at diagnosis of left upper lobar PPL due to the better reach (40 % for the large GS and 88 % for the small GS) **[19]**. Despite this lack of data, the small GS had been preferentially used in published studies, with only 2/14 studies in a review study using the large GS (2.6 mm outer diameter, Olympus K 203) **[20]**.

Another reason for the lower diagnostic yield of R-EBUS maybe not customising the biopsy tool to suit the PPL location in relation to the bronchi. Whilst some PPL are located within or "end on" in the bronchi, some are located adjacent to the bronchus. Forceps biopsy can obtain samples effectively from PPL "end on" to the bronchi, however, the forceps cannot pierce the bronchial wall hence a PPL situated adjacent to a bronchus will get a negative result. An excellent solution to this would be an aspiration needle biopsy that would pierce the bronchial wall and can obtain tissue from a PPL located adjacent to the bronchi.

There is marked underutilisation of aspiration needles. The AQIRE Registry (ACCP Quality Improvement Registry, Evaluation, and Education) data demonstrate the use of aspiration needles is only 16.4 % **[21]**. At the time of this study, all available aspiration needles came in with a diameter of 1.8mm and could be used only via the large GS, hence the reluctance to use the large GS may be one reason for the low uptake of the aspiration needle as well.

Another reason for the low diagnostic yield of R-EBUS may be the reliance on a single type of biopsy mainly forceps biopsy for sampling. Using multiple biopsy tools in combination (multi-modal biopsy) may produce a better result due to the ability to biopsy both adjacent and "end on" PPL has not being explored. In a meta-analysis of 57 studies all 57 used forceps biopsies, 29/57 (51 %) used dual biopsies with forceps and cytology and only 5/57 had used aspiration needle together with forceps or brush as multi-modal biopsy **[2]**. Due to the reluctance of performing multi-modal biopsies in the literature, the safety profile in performing multiple biopsies in PPL is not well known.

In the era of personalised medicine for lung cancer, the ability to perform molecular testing including EGFR (Epidermal Growth Factor Receptor) status becomes important. In these small biopsy samples from R-EBUS, 80 % were suitable for EGFR analysis **[22]**. However, the available data is mostly with forceps biopsies. There are limited data demonstrating the ability of cytology brush to provide EGFR analysis **[23]**. There are no data on the ability of aspiration needles to perform EFGFR analysis nor comparison of aspiration needle to forceps biopsy in this regard.

Therefore, the impact of various biopsy tools on the diagnostic yield nor the impact of the size of the GS that then determines the size of the biopsy tools have not been well explored.

This randomized exploratory study was designed with the primary objective of comparing the diagnostic yield between the large and small-GS from all modalities of sampling tools used in R-EBUS. The secondary objective was assessing the side effect profile and the ability to perform EGFR testing.

Methodology

This is a single-blind, randomized, multicentre, interventional exploratory study.

Ethics approval: Australia (HREC 2019/ETH02599) and New Zealand (15/STH/3).

Patients over 18y, referred for R-EBUS were recruited. Pregnant and lactating patients, patients on anti-coagulation that cannot be stopped for medical reasons were excluded. Aspirin was permitted. Informed consent was taken from all patients and randomized to the large-GS (K -203 Olympus-outer diameter 2.6mm and the largest diameter of biopsy tool that can be accommodated 1.91mm) or small-GS (K-201 Olympus-Outer diameter 2mm and the largest diameter of biopsy tool that can be accommodated 1.4mm) arms. A planning CT scan of the chest within one month of the procedure was needed with the slice thickness of at least 1mm for the bronchoscopist to perform a manual pathway to the segmental bronchi.

Patients in the large-GS arm was sampled with forceps, brush, and aspiration needle (either Exelon 21G;13 mm length or Medtronic's 21G: 8mm length); while patients in the small-GS arm were sampled with forceps and brush only as a small-sized aspiration needle was not available. For each sampling method, 1-3 samples were taken at the discretion of the proceduralist. For each GS type, the sequence of the sampling method was randomized. The small USS probe 1.7mm

Olympus UM-S20-17S was used for all procedures.

The type of needle aspirate used was not randomized and determined by availability. If both needle aspirates were available the Medtronic 8mm needle was selected over the 15 mm Boston scientific needle, due to the ease of use in the upper lobes.

All procedures were performed under conscious sedation. Once the PPL was detected on radial ultrasound, the ultrasound probe was removed leaving the GS in situ and sampling instruments were introduced via the GS. Fluoroscopy was not used. The GS position within the PPL was checked with an ultrasound between each sampling instrument. Rapid Onsite Cytology Examination (ROSE) was used at the proceduralists' request.

The sample size was calculated with a Type 1 error of 5 %, and power of 80 %, requiring a sample size of 58 subjects to detect a minimum difference of 25 % in yield between the arms and 88 patients to determine a difference between upper and lower lobar location. A planned analysis was carried out at 25 % recruitment to confirm the sample size, due to the above data being limited to s a single published study. At this 25 % analysis point, the study was terminated due to a perceived clinical benefit with the large-GS and slow recruitment resulting from this referrer bias. The data were analysed using Stata Version 17.

Results

42 patients from two tertiary hospitals were recruited from January 2015 to December 2017. 24 were assigned to the large GS and 18 to the small GS. There were no statistically significant differences between the two groups in any of these baseline parameters **(Table 1)**.

Table 1: Comparing the patient demography and CT characteristics between the Large GS and small GS arms.

Comparison	Large-GS arm	Small-GS arm	P value
Mean age (years)	64.3 (SD14.18)	66.9 (14.02)	P<0.05
Mean FEV 1	2.04 L (74.7%)	1.92 L (77.8%),	P<0.05
Gender - Female	15/24 (62.5%)	9/18 (50%)	P<0.05
Lesion size	4.2 cm (SD 1.8)	Vs 3.7 cm (SD 2.3)	P<0.05
Lobar distribution	17/24 (70%)	14/18 (77%)	P<0.05

Two subjects in the small-GS arm and two in the large-GS arm had a diagnosis via Linear-EBUS prior to the R-EBUS procedure, performed as per institutional guidelines. One lesion in the thin-GS arm was not visible on ultrasound. After these three patients were excluded, a total of 22 patients from the large-GS group and 15 from the small GS group underwent R-EBUS. In the large-GS arm, 19/22 (86 %) had a diagnosis made on R-EBUS. (16 malignant, three benign). Of the three who were non-diagnostic, two proceeded with CT-guided biopsy which confirmed malignancy and one received radiotherapy based on high clinical probability of malignancy. In the small-GS arm, R-EBUS was diagnostic in 9/15 (60 %). (Five malignancies, four benign). Of the six who were non-diagnostic, four were confirmed malignancy (one lobectomy, three CT-guided biopsy), one was benign on follow-up, and one was lost to follow-up. The overall diagnostic yield, with only the forceps and brush, as sampling methods was 16/22 (72 %) in the large- GS arm and 9/15 (60 %) in the small-GS arm. OR 1.77 (95 % CI 0.44- 7.17). When the aspiration needle was added to the large-GS arm, the diagnostic yield improved to 19/22 (86 %) Vs 9/15 (60 %) OR 4.2 (95 CI 0.85-20), P =0.118. 3/22 (13.6 %) were diagnosed only from the aspiration needle. In the large-GS arm, a diagnosis was made solely from forceps in 18.1 %, needle aspirate in 13.6 % and brush in 4.5 %.

In terms of ability to perform EGFR testing,12/16 (75 %) had EGFR status diagnosed in the large-GS. The number of malignancies diagnosed and ability to perform EGFR were analysed: with the aspiration needle there were 13/16 (81 %) malignancies, with 62 % suitable for EGFR, Cytology brush had 11/16(69 %) malignancies with 54 % suitable for EGFR and Forceps had 9/16 (56 %) malignancies with 66 % suitable for EGFR.

In the small-GS, a diagnosis was made solely on forceps in 7 % and brush in 7 %. 40 % of the small-GS samples were suitable for EGFR.

All patients had a chest-X ray one-hour post-procedure. No bleeding or pneumothorax was reported in both arms.

Discussion

Both large and small-GS arms had similar baseline patient demographics and lesion size.

In comparing the use of small biopsy forceps and brush through the small-GS, the larger biopsy forceps and brush, via the large-GS demonstrated a tendency for a better diagnostic yield and better suitability for EGFR testing. This may be due to the larger samples obtained from the large biopsy tools that would survive the processing better. It may also be possible that the large GS arm had more

malignancies than the small GS producing better diagnostic yield. However, these results were not statistically significant in keeping with the only previously published study by Kurimato et al **[19]**.

The addition of an aspiration needle improved the diagnostic yield of the large GS further. This may be due to the ability of the aspiration needle to sample PPL placed adjacent to bronchi as well as inside the bronchi. 13.6 % of patients had a diagnosis made solely from the aspiration needle. There is limited retrospective analysis published by Chen et al that had compared the aspiration needle against forceps biopsy with R-EBUS and demonstrated 80 % diagnostic yield with aspiration needle in comparison to 77 % with forceps biopsy **[8]**. Our data is also supported by the ACQUIRE registry data that demonstrate aspiration needle was able to provide a diagnosis 9.5 % of the time when forceps biopsy was negative **[21]**. The aspiration needle increased the diagnostic yield as the sole diagnostic sample and also complement the procedure by improving the overall diagnostic yield in our study and reported by previous limited studies as well **[24-26]**.

The ability of aspiration needle sample to be examined at ROSE for immediate results and manoeuvre the GS to a better location, if needed, and the ability to perform the procedure under sedation are additional advantages **[27]**.

Whilst the ability to perform EGFR had been reported to be 80 % for forceps biopsy with R-EBUS **[22]**, studies have demonstrated cytology brush to be able to provide EGFR as well but less (66 %) than that of forceps biopsy **[23]**, however in cytology samples with malignant cells, a 100 % ability for the cytology brush to provide EGFR analyse on the malignant samples had been demonstrated **[28]**. Studies have not prospectively compared the ability to perform EGFR in aspiration needles nor compared it with forceps biopsy in radial EBUS. In this study, aspiration needle was suitable for EGFR analysis similar to the forceps biopsy; adding further value to the already improved diagnostic yield.

The addition of the aspiration needle to the large-GS, improved the diagnostic yield further, without an increase in complications, especially pneumothorax, this has been confirmed by one other study demonstrating no increase in adverse events with the use of needles aspirate even when the PPL was not visible on ultrasound **[24]**.

Multi-modal biopsy techniques have not been well considered as a measure of improving diagnostic yield. The tendency has been on high reliance on forceps biopsy alone and addition of cytology brush on a few studies with a very limited combination of aspiration needle as a multi-modal biopsy tool[2]. Although studies in R-EBUS had demonstrated that the addition of cytology brush had improved the diagnostic yield compared to forceps alone, the concept of multimodal biopsy was not well explored. In this study, using multi-modal sampling (forceps, brush +/- aspiration needle) has resulted in an improved overall diagnostic yield in both arms.

With the multimodal biopsy techniques, the patients in the large GS arm received a maximal of 3 types (Forceps biopsy, cytology brush and aspiration needle) of biopsies with a maximum of three passes in each biopsy leading to nine biopsies per patient, yet there were no reported pneumothorax and bleeding, and all patients were discharged home as planned. Whilst this is in keeping with the overall safety of the R-EBUS procedure, as well as the haemostasis achieved by using a GS, this may also be due to the larger (mean 3.7-4.2cm) PPL size in this cohort as well. Multi-modal biopsy needed to be performed in smaller PPL with further studies to confirm safety. Using the GS consistently may have led to better haemostasis and higher diagnosis in both arms as acknowledged by the previous meta-analysis. **[3]**.

Limitations

The main limitation of this study is the early termination due to lack of recruitment. These results are not statistically significant due to the small sample size with the resultant type 2 error. In this study all procedures were performed using the GS therefore, appreciating that some centres do not use the GS due to the extra expense or the inability to reach certain locations, the result of this study is not applicable when a GS is not used.

We were not able to perform a needle aspirate in the small GS arm due to the lack of availability of a small needle which is a future development requirement. We are unable to provide guidance on the best needle aspirate to use as there was no randomisation of the different types of needle aspirate and further studies are needed.

Conclusion

We suggest including an aspiration needle and using multi-modal biopsy tools with R-EBUS via a large GS to improve the diagnostic yield of R-EBUS. The ability to perform EGFR testing with aspiration needle samples further strengthens the argument. We noted utilising a GS consistently improved the side effect profile and the diagnostic yield as noted in the previous meta-analysis.

Multi-modal sampling is able to provide better diagnostic results and the tools used need to be tailored to PPL characteristics for the optimum results. Despite the higher number of biopsies performed the safety profile of R-EBUS was well preserved.

The R-EBUS procedure can be performed under sedation and doesn't require fluoroscopy. If biopsy tools can be improved to provide better diagnostic yield, this extremely safe method would be widely utilised and form an integral pathway of a lung cancer diagnosis.

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Abbreviations List:

R-EBUS: Radial Endobronchial Ultrasound-guided biopsy CT: Computed Tomography

EGFR: Epidermal Growth Factor Receptor GS: Guide Sheath

Guarantor: Dr. Samantha Herath is the Guarantor of the content of the manuscript including the data and analysis.

Author contribution

1. Dr. Samantha Herath (Respiratory Physician) is the principal investigator and designed the study protocol, designed consent forms, and data entry forms, obtained ethics approval for ethics committees in Australia and New Zealand. Dr. Herath applied and secured grant funding and equipment funding for the Cryo-Radial procedure. Dr. Herath performed the Cryo-Radial procedure and collected data. She was responsible for patient follow-up, data entry, and data analysis as well as the write-up of this paper.

2. Dr. Alvin Ing (Respiratory Physician) is a co-investigator and assisted with designing the study protocol, performed the Cryo-Radial procedure, and collected data. He was responsible for patient follow-up and the write-up of this paper.

3. Dr. Elaine Yap (Respiratory Physician) assisted with designing the study protocol, assisted in obtaining ethics approval for ethics committees in New Zealand. She performed the Cryo-Radial procedure and collected the data. She was responsible for patient follow-up, data entry, and analysis. She assisted in the write-up of this paper.

4. Dr. Hema Mahajan (Pathologist) is a co-investigator. She assisted in the design of the study protocol and assisted in the analysis of pathological specimens.

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