Does AQuIRE challenge the role of navigational bronchoscopy for peripheral pulmonary lesions?

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The rise of navigational or guided bronchoscopic techniques over the last 15 years has changed our approach to the diagnosis of suspicious peripheral pulmonary lesions (PPL). PPL are described as focal radiographic lesions ≤3 cm diameter surrounded by normal lung parenchyma that are not visible beyond segmental bronchi and are without evidence of endobronchial abnormalities (1-5). Diagnostic yields for these lesions with standard flexible bronchoscopy are generally lower than those achieved with central lesions (5,6). The use of computer tomography guided transthoracic needle/core biopsy (CT-TTNA) has frequently been the method of choice and has higher diagnostic yields than standard bronchoscopy. However, it is associated with significant risks of bleeding and pneumothorax with ~5–7% of all biopsies requiring chest tube insertion (5-7). Bronchoscopy has the advantage that staging can be performed at the same time and is the lower risk procedure.

Technological advances in flexible bronchoscopy have produced ultrathin bronchoscopes that enable the bronchoscopist to navigate closer to peripheral lesions (7-11). However, finding the correct route and confirming the target lesion remain challenging (7,8). The development of multi-detector row CT scanners, thin slice CT and better image reconstruction technology has produced CT images with excellent resolution thereby improving procedural planning. Planning has been further enhanced by the subsequent production of 3D virtual maps that can be constructed with CT image data illustrating the path leading to the lung lesion and displayed as virtual bronchoscopy maps (2,4,8-10). This 'virtual bronchoscopic navigation' (VBN) has been shown to improve the diagnostic yield of bronchoscopy for peripheral lung lesions (2,4,8,10). Systems are now available that can synchronise the virtual map with *in vivo* bronchoscopic images to guide the bronchoscopist in realtime (12). There has been simultaneous development of other tools, such as radial endobronchial ultrasound (radial EBUS) and electromagnetic navigation (EMN) that may be used to improve localization of the lesion during bronchoscopy and increase diagnostic yield (5,7).

Radial ultrasound utilizes miniature flexible radial ultrasound probes with/without guide sheaths through the working channel of a flexible bronchoscope (13-15). The latest generation of probes with a diameter of 1.4 mm can be used with guide sheaths via thin bronchoscopes enabling access to all sub-segmental branches of the lung. Radial EBUS confirms localisation of the pulmonary lesion prior to attempting specimen collection. Radial-EBUS can localize lesions that are not visible on fluoroscopy (16). The use of a guide sheath (radial EBUS-GS) acts as an extension to the working channel of the bronchoscope and ensures that specimens are taken at the confirmed lesion site once the radial probe is removed (1).

Published reports of the performance of radial EBUS-GS for PPLs show diagnostic yields between 46–88% (1,2,4,15-22). The reported adverse events including bleeding and/or pneumothorax rates were 1–5%. Failure to locate the lesion has been reported as a significant issue and occurs in ~8–27% cases. The other important factor influencing diagnostic yield was the ability to position the probe within the lesion (15,18). A meta-analysis of radial EBUS with and without use of a guide sheath showed an

overall diagnostic yield of 73% (3).

Two randomized studies have directly compared radial EBUS-GS with CT-TTNA (21,22). In these studies, participants were not selected based on size or location of the peripheral lesion. These studies did not utilize virtual bronchoscopy maps for procedural planning. There was no significant difference in overall diagnostic yield between radial EBUS-GS and CT-TTNA and diagnostic yields were reported as 68–88% for radial EBUS-GS between the two studies. The complication rates were lower with radial EBUS-GS compared to CT-TTNA (21,22).

Another navigational method that is currently being utilised is EMN bronchoscopy. This is a technique that utilizes a steerable sensor probe in an extended working channel that can be tracked by an external electromagnetic device. This is similar in concept to a global positioning system. A single breath hold chest CT is used to create a three-dimensional virtual bronchoscopy map prior to the procedure. The use of the trackable probe/catheter with the map gives real-time guidance to the bronchoscopist. Prospective, published series have reported diagnostic yields of 57–89% (2,23-31). The reported pneumothorax rates were 1–4%. Its performance has been limited by navigation errors and its inability to directly confirm the target prior to biopsy. A recent meta-analysis reported an overall diagnostic yield of 65% with a 3% pneumothorax rate although some studies included in the analysis used other techniques such as fluoroscopy, radial EBUS and rapid on site cytological evaluation (ROSE) rather than EMN alone (32).

The populations evaluated with these navigational techniques had well defined peripheral lesions and a high prevalence of malignant disease. This has been reported as influencing the diagnostic yield (3,18). A meta-analysis of all navigational techniques, with inclusion of 39 prospective and retrospective studies, showed that navigational techniques had greater diagnostic yield (~70%) than reported rates of standard flexible bronchoscopy (7). However, each technique used alone has limitations and a combination of complementary technologies is likely to yield the best results. This has subsequently been demonstrated in two randomized studies. Ishida *et al.* showed that combination of VBN with radial EBUS-GS improved diagnostic yield to 88% from 67% with radial EBUS-GS alone (4). Eberhardt *et al.* also reported that diagnostic yields were highest with a combination of EMN and radial EBUS-GS reaching 88% compared with either technique alone (EMN 59%, radial EBUS 69%) in a randomized study (2).

The aim of the report from the AQuIRE Registry (ACCP Quality Improvement Registry, Evaluation and Education) was to evaluate the diagnostic performance of navigational bronchoscopy techniques for PPLs in a broader field (33). Fifteen participating institutions with 22 physicians prospectively entered 581 consecutive patients with PPLs into the web-based registry between 2009–2013. Peripheral lesions were defined as lesions at the segmental bronchus or beyond that required transbronchial rather than endobronchial biopsy. The primary outcome was diagnostic yield of bronchoscopy. Secondary outcomes included diagnostic yield of different sampling techniques, complications and practice pattern variations. A procedure was considered diagnostic if a specific malignant or benign diagnosis was made. Inflammatory tissue or lymphocytes only was considered non-diagnostic.

The overall diagnostic yield for flexible bronchoscopy was 54% but the rate varied widely between centers from 33–73%. Standard bronchoscopy had a diagnostic yield of 64%, radial EBUS alone was 57%, EMN alone 39% and EMN + radial EBUS was 47%. Standard bronchoscopy alone was performed in 27% cases, radial EBUS was used in 66% cases and EMN, VBN or CT fluoroscopy was used in 46% cases. In addition, the majority used fluoroscopy. Specimens collected included transbronchial biopsy (100%), brushings (79%), washings (56%), lavage (44%) and transbronchial needle aspiration (TBNA) (16%). The diagnostic yield was highest with TBNA (47%) followed by transbronchial biopsy (43%), brushings (38%) and lavage (19%). The yield of washings was not reported.

The authors concluded that navigational bronchoscopy with radial EBUS and EMN were associated with a lower diagnostic yield than standard flexible bronchoscopy for PPLs. They also concluded that peripheral TBNA improved diagnostic yield for peripheral lesions but was underutilized. Complications were rare at 2.2%. This conclusion conflicts with previously published work within the field. However, this is not a randomized study of comparison of techniques but is an evaluation of a clinical cohort across multiple centers. Interpretation of these results needs to take into account the limitations of the dataset and the likely clinical differences to published studies.

Firstly, case selection may have played a role in the differences in diagnostic performance. The seemingly lower diagnostic yield of navigational techniques compared to standard bronchoscopy may reflect the technical difficulty of the cases rather than the performance of the technique i.e., more advanced techniques would be chosen for the more difficult cases. There is no information as to whether

any of the subjects had undergone a prior non-diagnostic standard bronchoscopy. Subjects were not randomized to one technique or another but the technique used was based on clinician's choice and availability of technology. We have no ability to evaluate the selection of bronchoscopic technique for each subject. It is also not known how many of the radial EBUS cases used the guide sheath technique and this could also influence yields. The authors describe that in centers with EMN, this technique was more frequently used for smaller lesions revealing that this technique was likely used in more technically challenging cases. Of the 15 registry centers, only 11 had access to radial EBUS, 10 had access to EMN and 2 centers had access to neither radial EBUS nor EMN. Although not described in the Methods, it appears that other techniques such as VBN and/or CT fluoroscopy have been included in the EMN subset, although the majority was EMN. This definition of EMN differs from the established use of the term and technique in the literature.

Secondly, another limitation is the lack of follow-up data and final diagnosis for all subjects included in this analysis. There were 269 subjects with a non-diagnostic bronchoscopy included in the analysis and their final results are unknown. Follow-up data was not part of the standard dataset of AQuIRE. The report does describe a subset analysis of 4 of the 15 centers that collected follow-up data for 336 subjects (58% of total cohort) but 13% of these subjects were also lost to follow-up. The prevalence of malignancy in this subset was estimated at 58%, lower than reported datasets of navigational bronchoscopy of >70–80%. The overall prevalence of malignancy in the AQuIRE cohort is unknown and the true performance of the bronchoscopic techniques could only be estimated. Lower prevalence of malignancy in the AQuIRE cohort is likely to influence results as diagnostic yields are often higher in malignant compared to benign disease (3,5).

Thirdly, although this analysis was of peripheral lesions, a large proportion of the lesions (41%) were centrally located on chest CT. Furthermore, linear EBUS was used to assist in 23% cases that used TBNA to sample peripheral lung lesions raising the possibility that these lesions may not have been truly peripheral in location. The linear EBUS bronchoscope is too large to be inserted peripherally in the lung. Central lung lesions have higher diagnostic yields with bronchoscopy and linear EBUS is not considered a standard bronchoscopic tool for a peripheral lung lesion. The possible inclusion of central lesions and use of linear EBUS-TBNA may have increased the diagnostic yield for standard bronchoscopy and TBNA in this report.

The authors discussed that only a small proportion (16%) of cases used TBNA and concluded that it is underutilized. One of the limitations of TBNA for PPLs is that the currently available TBNA needles are too large to be inserted into a guide sheath or catheter following localization with radial EBUS. Many small peripheral nodules are also not visible on fluoroscopy making real-time visualization/confirmation of the lesion location and positioning of the TBNA needle difficult. These factors will likely influence the current use of TBNA for small lesions with navigational bronchoscopy. The development of a smaller, flexible TBNA needle that could be used via a small guide sheath following confirmed localization of a PPL would be a welcome addition to the bronchoscopist's toolkit and would likely increase utilization of this valuable technique.

Previously published reports of navigational bronchoscopic techniques reveal that they perform well compared to standard bronchoscopy and CT-TTNA when used for diagnosis of PPL in groups with high prevalence rates of malignancy. In the AQuIRE cohort, the use of some form of navigational bronchoscopy yielded a diagnosis in ~40–60% cases which is close to the range in published series although not as high as has been reported. The combination of EMN with radial EBUS yielded higher diagnostic yields than with EMN alone that has also been previously reported (2). The AQuIRE data reported, however, that lower diagnostic rates were achieved with navigational techniques compared to standard bronchoscopy, particularly EMN. This is not completely surprising considering the factors that have been discussed. The large, prospective, multicenter NAVIGATE study that is currently underway may help in clarifying the role and success of EMN in clinical practice (34).

The results of the AQuIRE registry report do not refute the findings of other published studies of navigational bronchoscopy but do prompt reflection of the performance of these techniques in the broader medical community and the most cost-effective algorithm for diagnosis of PPLs. One clear message is that flexible bronchoscopy, with or without the use of modern navigational tools, is a reassuringly low risk procedure. Flexible bronchoscopy has the advantage of providing diagnostic and staging information in one day-case procedure. In addition, it can provide tissue for genomic analysis that will guide lung cancer treatment. Navigational bronchoscopy, utilizing a combination of complementary methods, has

an important role to play in the management of patients with suspicious PPL. This is particularly relevant as the target lesion has reduced in size with the technological improvements in chest CT and the advent of low dose CT screening. Continued development of navigational tools and techniques, combined with ongoing clarification of case selection, will lead to further improvements in patient care.

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Footnote

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