Integration of robotic bronchoscopy and cone beam computed tomography: a narrative review

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Background and Objective: The last decade has seen a rapid increase in technology available for the biopsy of pulmonary nodules. Historically, the diagnostic yield (DY) by conventional bronchoscopic navigation had varying results with DY close to 50%. This has led to the advent of newer technologies designed to increase yield. Initial technologies included bronchoscopy with fluoroscopy as a guide to radiographically visible lesions. Radial-endobronchial ultrasound (r-EBUS) was created, and a modest increase in diagnostic accuracy (DA) followed. Since that time, a number of novel technologies to aid in the diagnosis of pulmonary nodules have been introduced. Most recently, cone beam computed tomography (CBCT) with or without augmented fluoroscopy (AF), as well as robot assisted navigational bronchoscopy (RANB) have emerged. The objective of this review is to consider the DY of these most promising tools, how to optimize DY, and best practice into the future.

Methods: A literature review was conducted using online database resources, searching from 2010 to 2023 for published peer review studies that evaluated the DY of various bronchoscopic technologies.

Key Content and Findings: This review found that the use of CBCT and RANB have increased DA of bronchoscopy for the diagnosis of pulmonary nodules to as high as 90% and 86% respectively. However, the range of DY by modality varies considerably, and very few controlled, prospective studies exist. Even less common are studies comparing these interventions.

Conclusions: While these new technologies potentially improve DY, further research is needed to directly compare these modalities in a controlled manner to guide best practice. Despite the limitations of available data, we propose a suggested workflow when using CBCT and RANB aimed at optimizing DY.

Keywords: Pulmonary nodule; bronchoscopy; interventional pulmonology; cone beam computed tomography (CBCT); augmented fluoroscopy (AF)

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Introduction

The last decade in medicine has seen a revolution in technology available for the diagnostic evaluation of pulmonary nodules. Historically, nodules less than 2 cm or in the outer third of the lung parenchyma have been difficult to reach by conventional bronchoscopy even with the use of technologies such as radial-endobronchial ultrasound (r-EBUS), thin and ultrathin bronchoscopes (1-4). What used to be a field dominated by fluoroscopy-guided bronchoscopy for large central lesions and the use of transthoracic needle biopsy (TTNB) for peripheral nodules, has seen the advent of both hardware improvements and advanced imaging integration. Robotic technology combined with electromagnetic or shape-sensing navigation aims to provide stability, precise control, and more distal airway cannulation. Cone beam computed tomography (CBCT) during bronchoscopy allows for tool-in-lesion confirmation using three-dimensional (3D) reconstruction and/or CBCT derived augmented fluoroscopy (AF). There are other computer-based systems that allow for standalone AF technology utilizing traditional C-arms. These advanced imaging techniques provide superimposed guidance on live fluoroscopy to steer biopsy tools towards the target.

Both CBCT and robot-assisted navigational bronchoscopy (RANB) allow for navigation to and biopsy of smaller, more peripheral nodules bronchoscopically (5). While TTNB has reported diagnostic yield (DY) reaching 91%, it has also been associated with a 10% risk of pneumothorax (6). More recent literature suggests that patients undergoing TTNB for cancer diagnosis are at increased risk for ipsilateral pleural recurrence due to tumor seeding of the biopsy track (7). Furthermore, TTNB in the traditional radiology setting does not allow for invasive mediastinal staging at the time of initial pulmonary nodule sampling as is often indicated (8). This has set the stage for innovation as we look toward minimally invasive technologies that have fewer adverse events, improve DY closer to that of TTNB, and allow for simultaneous lymph node staging.

Increasing effectiveness of minimally invasive nodule diagnosis has become all the more important as more patients are identified with pulmonary nodules through guideline recommended lung cancer screening (9). The goal of newer technology is 2-fold. First, increased precision theoretically offers improved DY; correctly identifying the true positive and true negative cases (10). Second—as diagnostic methods continue to evolve, increased precision in navigation will provide for a possible therapeutic application of navigational bronchoscopy such that lung cancer treatment itself could include the use of these technologies to provide tumor directed therapeutics that reduce lung cancer morbidity and mortality (11). However, DY varies amongst these technologies and minimal large prospective data exists to support the effectiveness of these newer methods. The objective of this review is to discuss the current body of evidence for these new technologies in diagnostic bronchoscopy, and highlight how a combination of these technologies could provide an increased DY of navigational bronchoscopy. We present this article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-23-96/rc).

Methods

The authors conducted a literature review using online database resources, primarily PubMed, searching from 2010 to 2023. We reviewed all peer reviewed studies published with the search criteria listed in *Table 1*. Descriptive epidemiology studies (i.e., case series), randomized clinical trials, structured reviews, and meta-analyses were considered for inclusion. All studies included in this review article had to provide their study DY and their DY definition.

Diagnostic accuracy (DA) versus DY

DY, the commonly used term in interventional bronchoscopy literature, refers to the rate of a positive or clinically definitive finding for a given test. Whereas, a less commonly used term, the DA, uses the sensitivity and specificity of a test within a study population, and evaluates the proportion of correctly classified results for a given disease (i.e., lung cancer). Therefore, DA has a standardized definition and permits the calculation of sensitivity, specificity, positive predictive value, and negative predictive value. DY, on the other hand, has a wide range of definitions and introduces the idea of integrating follow up testing into the definition of a true negative result (12). The existing literature on bronchoscopy for the diagnosis of a pulmonary nodule has a wide range of DA and DY reported with many versions of DY used. This leads to significant variation in the DY of bronchoscopy according to the definition used, and the inclusion of follow up information into the DY calculation (10). The DY can be altered based on how often benign, non-specific, or non-diagnostic biopsy results are categorized as true negatives, and how

Table 1 The search strategy summary

Items	Specification
Date of search	04/01/2023
Databases and other sources searched	PubMed, Ovid Medline, GoogleScholar
Search terms used	Electromagnetic navigational bronchoscopy, cone beam CT and bronchoscopy, robot assisted bronchoscopy, augmented fluoroscopy and bronchoscopy, shape sensing robotic navigation, trans-thoracic needle aspiration, radial endobronchial ultrasound
Timeframe	2010-2023
Inclusion and exclusion criteria	All case series, retrospective, prospective, and metanalysis were considered; exclusion was follow-up of long-term data of previously conducted study; studies were excluded if they did not report a diagnostic yield or their methods for calculating a diagnostic yield
Selection process	Review was conducted by three authors independently with consensus reached for inclusion if two authors felt a study was appropriate

CT, computed tomography.

patients lost to follow up are handled. For this review, we have categorized the included studies by DY methodology (*Table 2*) as described below.

A strict categorization of DY only includes data available at the time of bronchoscopy, meaning only specific diagnoses made via bronchoscopy can be categorized as diagnostically successful. Using this strict definition of DY, there is no role for adjudicating non-specific or non-diagnostic biopsies as true negatives using follow up data. An intermediate category allows for the inclusion of follow up data only for non-specific benign biopsy results, and allows for categorization of nonmalignant diagnoses as true negatives if confirmed by a subsequent biopsy or the evolution of follow up imaging. A liberal category allows for follow up of all biopsies initially negative for malignancy, including non-diagnostic samples showing normal pulmonary elements, and categorizes them as true negatives if a subsequent biopsy confirms nonmalignant diagnosis or imaging evidence of benign disease. In the intermediate and liberal categories, patients with non-malignant biopsy results who are lost to follow up can be either excluded from the analysis, counted as true negatives, or counted as false negatives.

Discussion

Bronchoscopy literature variation

Evaluation of new technology has been plagued by many factors. As most data comes from single arm prospective or retrospective cohorts, these studies are prone to bias.

Two of the most prominent biases are selection bias and measurement bias. Selection bias in these studies is driven by patient selection for ideal candidates for emerging diagnostic tools (13). Frequently, patients are not enrolled consecutively and those not deemed good candidates for new technology are excluded from studies (14). As mentioned previously, the definition of DY used by studies varies widely as well, which can exaggerate or underestimate study results, causing measurement bias. An example can be found in the two largest data sets in the diagnosis of peripheral pulmonary nodules (PPNs) that have evaluated electromagnetic navigation (EMN) technology. In 2016, the AQuIRE registry published observational comparisons of EMN to bronchoscopy with and without r-EBUS. They found a DY of 63.7% when bronchoscopy alone was used compared to a DY of 57% for bronchoscopy with r-EBUS and a DY of 38.5% when EMN was used (15). More recently the NAVIGATE study demonstrated a DY of 73% for EMN in a prospective cohort of 1,215 patients (5). The AQuIRE registry used a strict DY definition where only categorization of pathology at the time of the biopsy was included in determining DY, whereas in NAVIGATE a more liberal definition of DY was used that allowed for the recategorization of non-diagnostic samples. The previously mentioned biases are two main issues with both multi and single arm studies in diagnostic bronchoscopy. Multi-arm observational studies also have issues with another bias, confounding by indication. Confounding by indication is when the cases with the most difficult navigation are selected into the arm with the technology that has the perception of the highest probability of success

Table 2 Comparison of available robotic platforms

Device	Outer sheath diameter	Data supporting use	Disposables	Navigation system	Technology highlights	Potential cons to technology
Monarch	Outer sheath: 6 mm; inner scope: 4.2 mm	Multiple single-arm studies in humans, including multicenter studies	Compatible with tools via 2.0 mm working channel	EMN augmented by robotic data and computer vision	Vision is maintained, mother-daughter scope design	Large outer diameter, known limitations to EMN
Galaxy	4.0 mm	Porcine study only	Compatible with tools via 2.0 mm working channel	EMN plus proprietary digital tomosynthesis (TiLT Technology)	Integrated augmented fluoro and RAB system with real time update in nodule location, vision is maintained, disposable single use bronchoscope	Limits to tomogram-derived imaging and EMN, limited in-human peer-reviewed data
Ion	3.5 mm	Multiple single-arm studies in humans, including multicenter studies	Built to use with proprietary TBNA needles made by Intuitive, compatible with tools via 2.0 mm working channel	Shape sensing technology	Small outer diameter 3.5 mm, shape sensing not affected by C-arm interference	Vision is lost when using biopsy tools, unique scope reprocessing takes place on site which can create a burden for staff

EMN, electromagnetic navigation; RAB, robotic assisted bronchoscopy; TBNA, transbronchial needle aspiration.

and therefore the DY of that arm could be artificially low compared to older technology. More recent literature has attempted to evaluate the overall effectiveness of diagnostic bronchoscopy and comparative effectiveness of diagnostic bronchoscopy technology, attempting to overcome the variation historically seen in the literature.

Two systematic review and meta-analyses have been published on this topic. Nadig *et al.* found an overall DY for guided bronchoscopy of pulmonary lesions to be 69.4%. They found no difference in DY in studies prior to 2012 compared to after 2012, suggesting no improvement in DY with advances in technology (16). In subgroup analysis, there was no difference in DY when newer technology was added, though the limitation of this study is that all new technologies such as CBCT, RANB, and AF were grouped into a single category in subgroup analysis. Kops *et al.* published a similar meta-analysis using different study selection criteria, and found an overall DY of 70.9%. This study did do subgroup analysis of technologies used and found that newer techniques, including CBCT, RANB, and tomosynthesis based EMN have a statistically higher DY than older techniques, suggesting that there has been some improvement in DY when evaluating the newest technology (17). Kops *et al.* also categorized studies by the definition used by Vachani *et al.* (10) but found no statistical difference in DY

when comparing studies that used a liberal definition of DY to those that used a strict definition. However, both of these studies comment on the significant study heterogeneity, which is primarily due to the variation in study design and DY definition.

Another area of variation in bronchoscopic literature has been the type of biopsy tool used in diagnosing PPNs. The AQuIRE registry showed the marginal benefit of peripheral transbronchial needle aspiration (TBNA) when added to transbronchial biopsy with forceps, bronchoalveolar lavage, and brushings to be 6.3%, but that must be weighed against the marginal risk incurred by performing needle aspiration (18). The added benefit of TBNA remains to be studied in a prospective randomized fashion. The author in this response notes a significant amount of resources would have to be used to answer this question appropriately. More recently, cryobiopsy is being considered for the diagnosis of PPNs. It has not been prospectively evaluated, however, ongoing clinical trials should help clarify the utility of this emerging technology (NCT05751278).

Traditional navigational bronchoscopy

EMN bronchoscopy and virtual bronchoscopic navigation (VBN) have been used in combination with r-EBUS to reach more PPNs. These modalities use the same basic

concept: generate a 3D roadmap of the bronchial tree and provide directionality to the bronchoscopist to enhance biopsy accuracy and precision. These modalities use software to analyze computed tomography images obtained prior to bronchoscopy. This guidance ranges from VBN where a simulated airway path to the nodule of interest is created; to EMN where an electromagnetic signal from instruments placed inside the lung provide 3D spatial information about the instrument's relationship to the lesion. Initial results of navigational software for the diagnosis of pulmonary nodules demonstrated positive results. A meta-analysis by Jiang *et al.* (3) supported the use of navigational bronchoscopy as it increased DY by an odds ratio (OR) of 1.69 [confidence interval (CI): 1.32–2.18, P<0.001] for pulmonary nodules. The pooled DY of navigational bronchoscopy was 73% compared to 62% for non-navigational bronchoscopy. This meta-analysis supported the use of navigation as a tool to increase DY in more peripheral, smaller lesions, with a bronchus sign. Another meta-analysis published by Giri *et al.* found no difference in DY between VBN compared to non-VBN, 74.17% to 69.51%, however, VBN had superior DY for pulmonary nodules <2 cm with a risk ratio (RR) of 1.18 (95% CI: 1.05–1.32) (19). We must interpret these analyses with caution, as the biases and methodologic issues mentioned above do apply. For example, more recently a prospective study using a strict definition of DY found that EMN alone only had a DY of 53% (20). This study demonstrates possible limitations of EMN using a strict DY definition with prospective, careful data collection in a multi-centered setting.

As the initial navigational technology has emerged, it is worth mentioning that VBN offers a more cost-effective option. VBN does not consume disposables or require the purchase of extensive hardware beyond the traditional guidance of r-EBUS. VBN has performed well when combined with r-EBUS even in the prospective setting (1,21-23). However, this technology, as well as other virtual and EMN based techniques are limited by CT -to-body divergence, differences between the pre-procedure CT mapping and the true anatomy of the PPN during bronchoscopy (24). CT-to-body divergence is affected by factors including atelectasis, lung volume during mechanical ventilation versus awake breath holding during pre-procedure imaging studies, nodule movement during respiration, and anatomic changes in the time from the planning CT to the procedure (25,26). Specifically, in EMN, a study found that on average a pulmonary nodule moved 17.6 mm between end exhalation and full inspiration, and that nodules located in the lower lobes moved more than in upper lobes (26). In an effort to reduce or eliminate CT-to-body divergence, newer technologies discussed below are less dependent on pre-procedural CT scan analysis in an effort to improve accuracy (24).

CBCT and AF

CBCT involves cross sectional imaging intra-procedurally using a capable C arm in the bronchoscopy suite. This is traditionally done in a hybrid OR using fixed CBCT systems. The use of CBCT to increase DA/DY in pulmonary nodule diagnosis is twofold. First, CBCT could demonstrate a biopsy tool within the lung nodule ("tool-in-lesion")—allowing the bronchoscopist to radiographically demonstrate successful navigation and placement of a biopsy instrument into a pulmonary nodule. This may or may not significantly increase DA/DY despite the obvious plausible benefit. Casal *et al.* studied the concept of CBCT tool-in-lesion in a prospective analysis of 20 patients and demonstrated a DY of 70%, similar to that provided by EMN or VBN alone (27). However, Casal *et al.* and other CBCT literature has shown a navigational yield, where the biopsy instrument is demonstrated to be within the nodule, to be up to 91%, suggesting the difference between navigational yield and biopsy yield may be limitations intrinsic to the biopsy instruments available (28). This aspect of navigational yield becomes valuable when considering the therapeutic application of bronchoscopy in the future for the treatment of lung cancer, where accurate placement of an ablative tool within the lesion is critical.

The second important effect of CBCT on DA/DY is the combination of CBCT with AF to improve navigation to pulmonary nodules using an image that is much less susceptible to CT-to-body divergence. AF allows for the overlay of a highlighted, artificial pulmonary nodule target directly onto the real-time fluoroscopy screen during biopsy. This is achieved by utilizing the CBCT imaging obtained intraoperatively along with software that translates the 3D position of the pulmonary nodule onto the 2D image of traditional fluoroscopy. This process is frequently called "segmentation" and allows a computer system to understand the position of a pulmonary nodule by referencing bone landmarks and set references within a hybrid OR (29). This highlighted target image then provides another data point for navigation and localization, decreasing the effects of atelectasis and periprocedural variation in anatomy by relying on a cross sectional image collected just moments

before the biopsy starts. This information is not truly "real-time" in that the overlay is based on the CT scan that was just collected, rather than coaxial imaging happening during the actual biopsy maneuver.

Using either of these benefits of CBCT, or their combination, several single-arm descriptive studies and observational studies have shown impressive results with DY ranging from 70–90% (see *Table 3*) (26,35,37,38,51). A retrospective cohort study comparing CBCT + AF to r-EBUS alone found that CBCT improved DY to 75.5% from 52.8% (32). In another retrospective cohort study of 236 patients the DY of CBCT + AF was not statistically significantly different compared to r-EBUS alone (83.5% in the CBCT group versus 74.4% in the r-EBUS group, P=0.06). However, when considering smaller lesions <20 mm, CBCT with AF had a statistically significant higher DY. The authors attributed this to the improved navigation of CBCT with AF for smaller pulmonary nodules (52). A retrospective comparison study of EMN and CBCT versus EMN found increased DY of 74.2% with EMN + CBCT compared to 51.6% with EMN alone using a strict definition of DY (34). Most recently, using a strict DY definition, DiBardino *et al.* demonstrated a DA of 86.7% with the combination of r-EBUS, ultrathin bronchoscopy, CBCT with AF, and frequent tool-in-lesion confirmation (36). While much of this data has shown that CBCT with AF has improved DY compared to r-EBUS alone or EMN, many of these studies are prone to selection bias, confounding by indication, and lack of generalizability given their single-center, retrospective design.

One of the concerns of CBCT has been added radiation exposure to patients. Various studies have evaluated the dose of radiation exposure using CBCT and the most important factor is the number of image acquisitions. Radiation exposure varies by device and number of images per spin. A phantom study in 2014 demonstrated radiation doses of 0.98–1.15 mSv from CBCT without AF (53). More recent literature has demonstrated the learning effect associated with the use of CBCT with AF. In one study radiation doses decreased from 14.3 mSv per case to 5.8 mSv per case over a 3 year period as bronchoscopists became more adept at using the technology (54). For comparison, the radiation dose for a low dose CT in the National Lung Cancer Screening Trial (NLST) was 1.4 mSv (55). While the radiation exposure of a single CBCT spin is similar to that of a low dose CT, the risk of higher exposure with more image acquisition brings up the importance of having more data to determine if a tool-in-lesion spin increases DY

enough to justify a higher radiation dose.

AF without CBCT

There is also technology that generates AF images without the use of CBCT. In digital tomosynthesis a standard C-arm produces a 3D image using multiple X-rays, that in combination with software, can produce a near co-axial image of the target lesion. An example of this technology is LungVision (Body Vision Medical Inc., Campbell, CA, USA) that utilizes software that can generate AF as well as a navigational pathway, and has shown to have a DY of 78.4% when used in a prospective single arm study. This study calculated the average CT-to-body divergence at 14.5 mm which they could correct for using AF (40). A prospective multicenter study utilizing on-site cytology analysis found the DY of this technology was 75.4%, demonstrating the effectiveness of tomosynthesis-derived AF. A second technology that utilizes AF without CBCT uses similar digital tomosynthesis is Illumisite (Medtronic, Minneapolis, MN, USA). This system uses digital tomosynthesis and combines that with EMN navigation. This system has been shown to mitigate CT-to-body divergence as well (56). A single center study of 100 patients demonstrated a DY of 83% when using Illumisite (42). As stated repeatedly, this set of data suffers from the same host of methodologic issues surrounding most navigational bronchoscopy literature.

Tomosynthesis based 3D imaging alone

Similarly, C-arm technology has evolved to harness the same principles of digital tomosynthesis to provide high quality 3D imaging for the real time evaluation of biopsy tool placement without the use of AF or CBCT (57). These advanced C-arms can obtain co-axial images intraprocedurally without needing the resources of a fixed CBCT hybrid OR. These recently launched C-arms are referred to as 3D C-arms or mobile CBCT C-arms, and generate co-axial images by rotating around the patient by +/– 100 degrees over a period of roughly 30 seconds. By combining this imaging modality with EMN, a small single arm case series demonstrated a DY of 80% (58).

Robotic bronchoscopy

The past five years in interventional pulmonology has seen the Federal Drug Administration (FDA) approval of three robotic bronchoscopy systems. The systems allow for the

Table 3 Bronchoscopic technology literature comparison

Author	Year	Population	Modalities	Overall diagnostic yield	Study definition
EMN/VBN					
Wang Memoli *et al.* (30)	2012	Meta-analysis	"Guided bronchoscopy" included EMN, VNB, r-EBUS, ultrathin bronchoscope	70%	Multiple
Folch *et al.* (NAVIGATE) (31)	2019	Prospective cohort study of 1,215 patients at 29 academic community centers	EMN	73%	Liberal
Yu *et al.* (32)	2021	Retrospective consecutively matched non-randomized 308 patients	r-EBUS + CBCT with AF *vs.* r-EBUS alone	75.5% *vs.* 52.8%	Strict
Thiboutot *et al.* (20)	2023	Prospective cohort study of 160 participants at 8 centers	EMNB *vs.* EMN-TTNA *vs.* EMNB + EMN-TTNA	49% *vs.* 27% *vs.* 53%	Strict
CBCT + AF					
Hohenforst-Schmidt *et al.* (28)	2014	Prospective single arm analysis of 33 patients with incidental solitary pulmonary nodules	EMN, CBCT, AF	70%	Strict
Pritchett *et al.* (33)	2018	Retrospective analysis of 75 patients	EMN, CBCT, AF	83.7%	Strict
Kheir *et al.* (34)	2021	Retrospective two-armed comparison of 62 patients	EMN *vs.* EMN + CBCT	74.2% *vs* 51.6%	Strict
Verhoeven *et al.* (35)	2021	Prospective two-armed comparison of 87 patients	CBCT + AF + r-EBUS *vs.* EMN + r-EBUS + tool in lesion	CBCT AF alone 61.75%, EMN 50%, combined ~70%	Liberal
DiBardino *et al.* (36)	2023	Comparative retrospective cohort study of 116 patients	CBCT + UTB, r-EBUS, AF *vs.* CBCT, r-EBUS, AF *vs.* r-EBUS	86.7% *vs.* 70.4% *vs.* 42.4%	Strict
CBCT alone					
Casal *et al.* (27)	2018	Prospective single arm analysis of 20 patients	r-EBUS, CBCT tool in lesion	70%	Moderate
Ali *et al.* (37)	2019	Prospective single arm analysis of 30 patients	VBN, CBCT with tool in lesion	90.0%	liberal
Kawakita *et al.* (38)	2023	Prospective single arm study of 20 patients	CBCT + UTB + r-EBUS	85%	Strict
AF alone					
Aboudara *et al.* (39)	2020	Retrospective analysis of a single center experience with 101 patients	EMN + AF *vs.* EMN	79% *vs.* 54%	Strict
Pritchett *et al.* (40)	2021	Prospective single arm 51 patients	AF, lung vision	78.40%	Strict
Cicenia *et al.* (41)	2021	Prospective multicenter single arm 55 patients	Lung vision	75.40%	Strict
Avasarala *et al.* (42)	2022	Prospective single center study with 100 patients	Illumisite	79%%	Intermediate

Table 3 (*continued*)

Table 3 (continued)

Author	Year	Population	Modalities	Overall diagnostic yield	Study definition
RANB					
Chaddha et al. (43)	2019	Retrospective review of 165 patients	RANB, EMN, r-EBUS	69.1%	Strict
Fielding et al. (44)	2019	Prospective single-arm analysis of 30 patients	RANB, r-EBUS	79.3%	
Chen et al. (BENEFIT) (45)	2021	Prospective single-arm analysis of 55 patients	RANB, r-EBUS	74.1%	Moderate
Kalchiem-Dekel et al. (46)	2022	Prospective single-arm analysis 131 patients	ssRAB	81.7%	Strict
Khan et al. (47)	2023	Retrospective analysis of 264 patients	RANB	85.2% at index and 79.4% at 12 months follow up	Strict and intermediate
Low et al. (48)	2023	Retrospective analysis of 133 consecutively enrolled patients	ssRAB vs. EMN	77% vs. 80%	Strict
CBCT and RANB					
Benn et al. (49)	2021	Prospective single-arm analysis of 52 patients	RANB, CBCT	86%	Liberal
Styrvoky et al. (50)	2022	Retrospective analysis of 209 pulmonary nodules	ssRAB, CBCT	91%	Intermediate
r-EBUS and TTNA					
DiBardino et al. (6)	2015	Meta-analysis	CT-TTNA	92.1%	
AQuIRe Registry (15)	2016	–	r-EBUS	57%	Strict

EMN, electromagnetic navigation; VBN, virtual bronchoscopy navigation; r-EBUS, radial endobronchial ultrasound; CBCT, cone beam computed tomography; AF, augmented fluoroscopy; TTNA, transthoracic needle aspiration; UTB, ultrathin bronchoscope; RANB, robot assisted navigational bronchoscopy; ssRAB, shape sensing robot assisted bronchoscopy; CT-TTNA, computed tomography guided transthoracic needle aspiration.

integration of novel bronchoscopes designed to reach more peripheral lesions, navigation systems, and a more stable platform when sampling PPN. The first system to market, the Monarch Platform (Auris Health, Inc., Redwood City, CA, USA), utilizes EMN and was retrospectively evaluated with 165 cases and found a DY of 69.1%, with a successful navigation rate of 88.6% (43). A second retrospective study used both a strict and intermediate DY definition and found an impressive DY of 85.2% vs. 79.4%, demonstrating consistency between results (47).

Prospective analysis of an alternative robotic system, Ion Endoluminal Platform (Intuitive Surgical, Sunnyvale, CA, USA), has demonstrated a high DY of 79.3%, in a single center study (44). This system uses novel shape-sensing robotic assisted bronchoscopy (ssRAB) for navigation.

The ssRAB tracks the shape and motion of the airways and provides a complete view of the catheter in the airway while also providing direct visualization of the airway during navigation. Robotic and navigational control are available during biopsy under fluoroscopy. Most recently, a retrospective multicenter single arm study of ION found a DY of 81.7%, and showed that prior indicators of decreased DY (size, location, and bronchus sign) are potentially less important with this technology. They found a DY of lesions <2 cm of 69.6%, a DY of 71.1% for negative bronchus sign lesions, and a DY of 70.9% for lesions in the outer third of lung parenchyma (46). Interestingly, this system has demonstrated similarly high DY when compared to EMN with digital tomosynthesis in a strict definition retrospective study (77% vs. 80%) (48).

The newest technology, Galaxy SystemTM (Noah Medical, San Carlos, CA, USA), uses an integrated tomosynthesis technology to provide intraprocedural imaging to compensate for CT-to-body divergence and create AF. It has demonstrated successful navigation to peripheral nodules in a pig model (59).

RANB has demonstrated consistently impressive DY compared to historical controls. Theoretically, these systems improve navigation accuracy and our ability to reach smaller, more peripheral nodules. However, these forms of navigation can be limited by the same CT-to-body divergence that has been problematic for EMN and VBN modalities. As such, this initial data should be interpreted with similar caution as the bulk of the data described above. Given the further novelty of initial RANB, concerns for selection bias are even higher than average. However, there is no current prospective comparative literature between RANB and CBCT, AF, EMN or a combination of technologies.

Combined advanced imaging and robotic bronchoscopy

The DA/DY of bronchoscopy for the diagnosis of pulmonary nodules has likely improved over time, but it remains unlikely that it approaches the DY seen in TTNB. Little data exists combining the most recent technologic improvements of advanced imaging and RANB. Benn *et al.* prospectively evaluated the combination of ssRAB with CBCT and found a DY of 86% while using a liberal definition (49). In this study, CBCT was used to provide secondary confirmation of tool in lesion rather than using CBCT-derived AF to enhance navigation and reduce real time CT-to-body divergence intraprocedurally. In a retrospective analysis of 209 pulmonary nodules, the combination of ssRAB and CBCT with AF had a DY of 91.4% (50). To date there have been no comparative trials evaluating RANB with and without advanced imaging.

Our hybrid approach

Currently, we are utilizing a hybrid approach, combining the technology of CBCT and RANB to optimize DA/DY and operating room efficiency. The authors have access to both the Monarch and Ion RANB systems that we have combined each with the Phillips Azurion ceiling mounted fixed CBCT system (Philips, Amersterdam, NL, USA). The workflow can be seen in *Figure 1*. The patient is brought into a hybrid OR with a ceiling mounted CBCT that allows

for the use of RANB with CBCT-derived AF. The patient is intubated with an 8.5–9.0 endotracheal tube and the EMN leads are placed on the patient. The endotracheal tube is shortened using scissors to cut the proximal end of the tube roughly in line with the patient's nose. This is to further assist the C-arm clearance with the endotracheal tube during image acquisition, as well as optimize the robotic platform's interface with the patient. The patient is then tightly wrapped with bedding to again facilitate CBCT C-arm clearance during image acquisition. To do this, two operating room staff place the patient's arms against their sides and secure bedding under one arm. Then the staff cross the bedding over the anterior surface of the patient and place the patient in a semi-lateral decubitus position to tightly wrap the bedding under the patient's opposite side. The patient is then returned to the supine position. The patient is ventilated at 8–10 cc/kg ideal body weight, with positive end expiratory pressure (PEEP) of 8–15 cmH$_2$O to reduce atelectasis. The volume and PEEP are increased for obese patients and lesions in the dependent lung zones (60). Ten recruitment breaths are then performed at 30–40 cmH$_2$O pressure after the airway is secured.

The patient is then isocentered by making sure the table height, body position on the bed, and bed position in the room permits full imaging of the region of interest on anterior-posterior and full lateral fluoroscopy imaging. CBCT C-arms utilize standard C-arm programs to check this position before acquisition of co-axial imaging. These programs are accessed via proprietary bedside controls and should be checked before connecting RANB equipment, as the bed cannot be adjusted safely after RANB devices are attached to the patient. The RANB equipment is secured to the endotracheal tube and positioned. The authors then approach the pulmonary nodule with RANB using both robotic navigation and fluoroscopy guidance. Once the nodule is potentially reached, the r-EBUS probe is inserted to further visualize the lesion. When the lesion is either located on r-EBUS, or the navigation pathway has been completed, an initial CBCT is performed. A breath hold maneuver is done during the CBCT. The pressure used for the breath hold is targeted to match the lung volume being achieved during routine ventilation at 8–10 cc/kg. This pressure will vary depending on the patient's lung mechanics, but is generally ~5 cmH$_2$O pressure below their peak airway pressure during ventilation. More care and precision is taken with this step for lower lobe lesions where lung movement is more dramatic (40). The initial CBCT is used to segment the lesion using software associated with
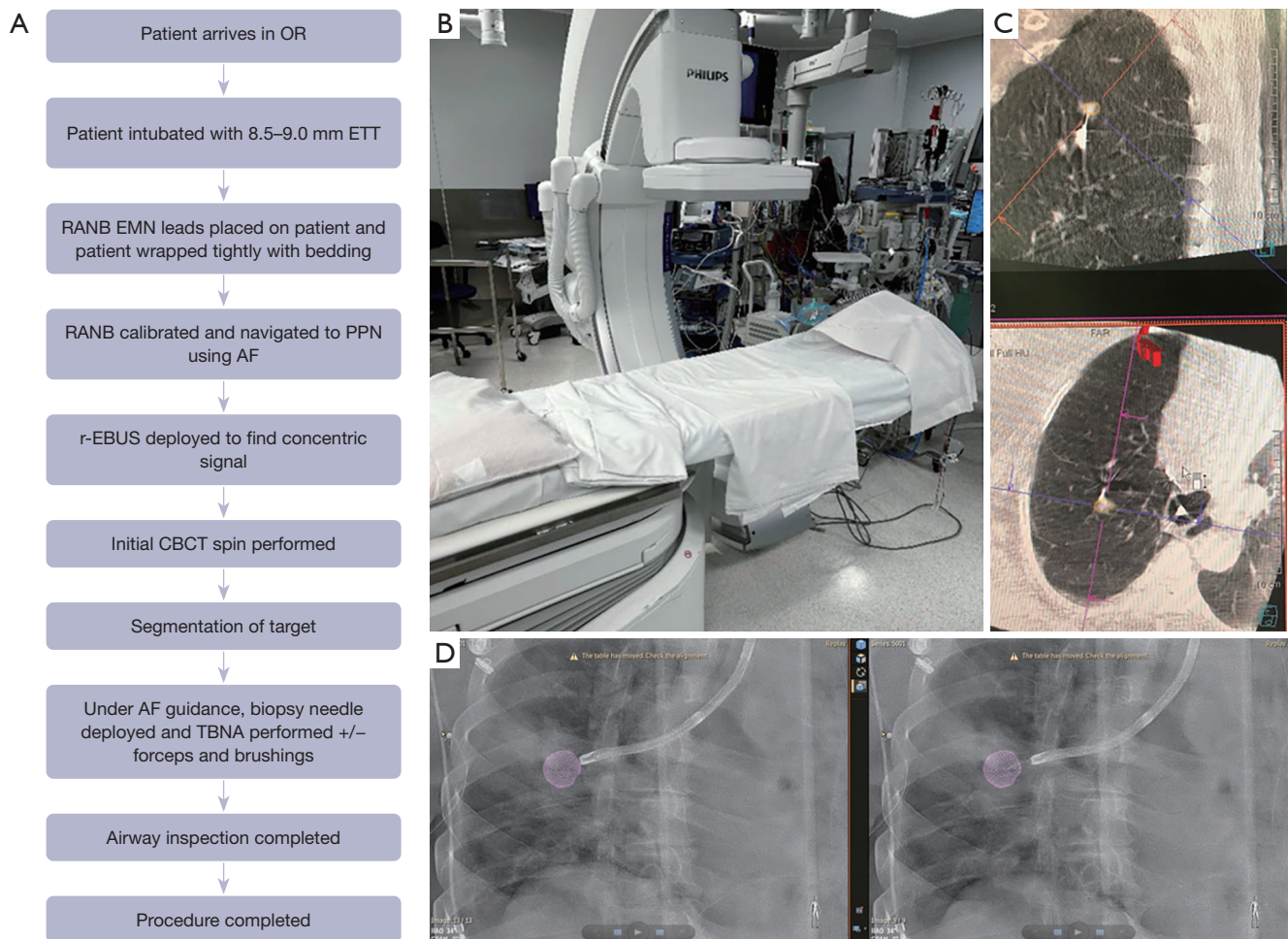
Figure 1 CBCT combined with RANB OR Set Up. (A) Hybrid OR work flow; (B) CBCT set up using Philips Azurion ceiling mounted fixed CBCT system; (C) segmentation of peripheral pulmonary module for augmented fluoroscopy; (D) augmented fluoroscopy overlay in active navigation during the biopsy of a pulmonary nodule. CBCT, cone beam computed tomography; RANB, robot assisted navigational bronchoscopy; OR, operating room; ETT, endotracheal tube; EMN, electromagnetic navigation; PPN, peripheral pulmonary nodule; AF, augmented fluoroscopy; r-EBUS, radial endobronchial ultrasound; TBNA, transbronchial needle aspiration.

the CBCT hybrid room. This allows the CBCT system to understand what target will be highlighted, and its relationship to other fixed landmarks in the patient and in the room. The segmented nodule is then overlaid onto the live fluoroscopy image (i.e., AF). Using this digital overlay, biopsy tools are then guided into the lesion. When that is achieved based on the AF image, additional CBCT spins to confirm tool-in-lesion are optional. If RANB is not available and a nodule is reached using navigational bronchoscopy, a scope holder is utilized during any further CBCT image acquisition to avoid radiation exposure to operators.

This combination of CBCT-derived AF and RANB reduces CT-to-body divergence and provides a target on live fluoroscopy to aim biopsy tools. Biopsy tool position can be checked in multiple fluoroscopy angles including angles recommended by RANB systems. As the AF guidance is not truly real-time, additional CBCT imaging to confirm tool-in-lesion has plausible benefit. If additional CBCT images do not confirm proper biopsy tool placement, the lesion can be re-segmented to create an updated AF target using the most recent CBCT, and the spatial information obtained on the CBCT can be used to reposition the biopsy tool. The use of the RANB in combination with CBCT + AF allows the authors to reach more distal pulmonary nodules and provides for a stable platform to maintain position. Many aspects of the combined procedure need further research

with comparative studies. There may be little benefit in the tool-in-lesion confirmation, AF itself, and combining RANB with CBCT.

Conclusions

The past 10 years have seen a rapid increase in technology available to biopsy pulmonary nodules that has reduced barriers in nodule size and location. Current technology of CBCT and RANB have allowed for the successful navigation to PPNs over 90% of the time. With this improvement in navigation, the DY of a diagnosis for malignancy using these technologies has increased compared to historic controls, and probably ranges from 70–80% with fewer adverse events compared to TTNB. While we have seen a plateau in DY, this is in the context of the literature available. As technology has improved, bronchoscopists may be attempting to biopsy smaller and more peripheral nodules. However, without randomized or consecutive enrollment studies, trends in nodules characteristics for lesions undergoing biopsy have not been captured adequately. Little comparative data of newer bronchoscopy technology exists as most current study designs have been single arm prospective or retrospective studies often without a comparison arm. The comparative studies that do exist have been retrospective. This has provided difficulty in comparing these modalities to recommend a best practice for bronchoscopists, or support the purchase of expensive navigational or robotic systems. Future studies evaluating the cost-effectiveness of these technologies would be beneficial for understanding the impact of these technologies on the healthcare system's costs at large. CBCT in combination with AF and RANB may provide for an appropriate workflow that is both efficient and high yield. While tool-in-lesion has demonstrated successful navigation, the subsequent improvement in DY has not been adequately studied. Any improvement in DY must be balanced by the added radiation exposure from multiple CT spins and requires further investigation. Future research should be aimed at comparative trials to best ascertain what modality or combination of modalities the field should invest in to improve DA and navigational success.

Acknowledgments

Footnote

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