Cone-beam CT in lung biopsy: a clinical practice review on lessons learned and future perspectives

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Abstract: Pulmonary nodules with intermediate to high risk of malignancy should preferably be diagnosed with image guide minimally invasive diagnostics before treatment. Several technological innovations have been developed to endobronchially navigate to these lesions and obtain tissue for diagnosis. This review addresses these technological advancements in navigation bronchoscopy in three basic steps: navigation, position confirmation and acquisition, with a specific focus on cone-beam computed tomography (CBCT). For navigation purposes ultrathin bronchoscopy combined with virtual bronchoscopy navigation, electromagnetic navigation and robotic assisted bronchoscopy all achieve good results as a navigation guidance tool, but cannot confirm location or guide biopsy positioning. Diagnostic yield has seen improvement by combining these techniques with a secondary imaging tool like radial endobronchial ultrasound (rEBUS) and fluoroscopy. For confirmation of lesion access, rEBUS provides local detailed ultrasound-imaging and can be used to confirm lesion access in combination with fluoroscopy, measure nodule-contact area length and determine catheter position for sampling. CBCT is the only technology that can provide precise 3D positioning confirmation. When focusing on tissue acquisition, there is often more than 10% difference between reaching the target and getting a diagnosis. This discrepancy is multifactorial and caused by breathing movements, small samples sizes, instrument tip displacements by tool rigidity and tumour inhomogeneity. Yield can be improved by targeting fluorodeoxyglucose (FDG)-avid regions, immediate feedback of rapid onsite evaluation, choosing sampling tools with different passive stiffnesses, by increasing the number biopsies taken and (future) catheter modifications like (robotic assisted-) active steering. CBCT with augmented fluoroscopy (CBCT-AF) based navigation bronchoscopy combines navigation guidance with 3D-image confirmation of instrument-in-lesion positioning in one device. CBCT-AF allows for overlaying the lesion and navigation pathway and the possibility to outline trans-parenchymal pathways. It can help guide and verify sampling in 3D in near real-time. Disadvantages are the learning curve, the inherent use of radiation and limited availability/access to hybrid theatres. A mobile C-arm can provide 3D imaging, but lower image quality due to lower power and lower contrast-to-noise ratio is a limiting factor. In conclusion, a multi-modality approach in experienced hands seems the best option for achieving a diagnostic accuracy >85%. Either adequate case selection or detailed 3D imaging are essential to obtain high accuracy. For current and future transbronchial treatments, high-resolution (CBCT) 3D-imaging is essential.

Keywords: Pulmonary nodules; cone-beam computed tomography (CBCT); navigation bronchoscopy; lung cancer; early stage

Introduction

The vast majority of screening detected peripheral pulmonary nodules (PN) will raise the question if the nodule is malignant. Once identified, malignancy risk calculators based on imaging and patient characteristics are used to assess the risk of malignancy and guide subsequent steps (1-3). In case of a low risk of malignancy (i.e., <10%) follow-up of PN is indicated. PN with intermediate to high risk of malignancy (i.e., >10%) should preferably be diagnosed with image guided minimally invasive biopsy before treatment (3-5). However, multiple studies show that stereotactic ablative radiotherapy is often considered without pathological confirmation of lung cancer (6,7). Other studies on surgical lung resections without a pre-procedural pathological confirmation of lung cancer furthermore reveal that benign resection rates vary from approximately 10% (8-10) to as much as 86% (3,11). Contrarily, lung cancer patients with an initial calculated low risk of malignancy may unintentionally suffer from a reduced survival outcome, due to the treatment delay caused by watchful waiting, while minimally invasive diagnostics might have provided a diagnosis in an earlier stage. The International Association for the Study of Lung Cancer (IASLC) lung cancer staging project showed that even within stage I disease, survival is significantly related to size (12). Even when there is no evidence of metastatic spread, a tumour of <1 cm size has a 5-year survival of 92% while a single 2–3 cm sized T1c tumour has a 5-year survival of 77%. To improve survival, it is essential to diagnose as early and as safe as possible and with the lowest possible burden for these symptomless patients. Ideally, an approach that is easily accessible and has a high diagnostic accuracy would provide a means for early diagnostics. This approach might become increasingly more important when the number of detected small PN rises as a result of implemented screening programs increasing the burden on diagnostic test availability. However, it must be considered whether the currently available approaches are able to fulfil this emerging demand.

Historically, the gold standard for diagnosing pulmonary lesions has been image guided trans-thoracic needle biopsy (TTNB), with a diagnostic yield of approximately 90% (13). Yet, passing the pleura is associated with a high pneumothorax rate of 18.8–25.3%, of which 6–7% require a chest tube placement (14). However, while it is considered the gold standard, patients are frequently treated without a diagnosis. Possible explanations could be the relatively high complication rates in an often already vulnerable group with comorbidities like chronic obstructive pulmonary disease (COPD) and emphysema, or because of variation in operator skill across centres. Furthermore, two studies recently hypothesized that traversing the thoracic wall may increase ipsilateral disease recurrence through seeding, and may affect overall survival (15,16).

A conventional bronchoscopy where the bronchoscope is led up until the segmental bronchus after which biopsy tools are advanced further under C-arm fluoroscopy has been reported as an alternative to reach small peripheral nodules. This technique showed a 34% sensitivity in a meta-analysis but a sensitivity lower than 14% with a negative predictive value (NPV) of 47% in lesions as found in analysis of a subset of patients identified through the NELSON computed tomography (CT) screening study (3,17). Potential major advantages of an endobronchial approach is the pooled chance of pneumothorax of 1.5% (of which only 0.6% requires chest tube placement) and the possibility to perform the intervention in patients with severe co-morbidities. However, the conventional 'blind' C-arm guided trans-bronchial biopsy certainly does not have the accuracy needed to be a valid alternative to TTNB.

Technological innovations

To address the clinical need for minimal invasive diagnostics, several technological innovations have been developed/implemented that can help the physician to endobronchially navigate more peripheral and more accurate than ever before. The introduction of a radial endobronchial ultrasound (EBUS) mini probe imaging was first reported two decades ago as one of first technologies in this area (18), followed by electromagnetic navigation technology (EMN), virtual bronchoscopy (VB) and ultrathin bronchoscopes (UTB) not many years later. As the landmark meta-analysis of Wang Memoli *et al.* [2011] showed, all of these technologies indeed increased diagnostic yield to the often encountered limit of 70%, although a minority of studies have reported a slightly higher yield (19). In part, based on the same data, guidelines subsequently recommended the use of radial endobronchial ultrasound (rEBUS) mini probe imaging but also EMN if available (3,20).

However, both technology and our routine clinical practice have evolved since then. High-resolution CT has become the standard and the radiologist routinely can define small nodules as suspicious while they previously

would have gone unnoticed. And on top of updates in pre-existing technologies such as EMN, several novel navigation bronchoscopy technologies have been introduced with the potential to further improve diagnostic yield. New kids on the block that aim to help diagnose peripheral pulmonary nodules now include specialized navigation instruments (21), robotics (22-26), cone beam CT (CBCT) (27-30), mobile 3D C-arm imaging (31,32) and hybrid methods that combine modalities for navigation guidance and confirmation (33,34).

Technology implementation

Biopsy of peripheral PN using conventional bronchoscopy has such a low diagnostic accuracy because the samples are taken without clear navigation assistance and because there is a lack of confirmation that the sampling instruments are at the correct target lesion. The navigation bronchoscopy procedure addresses these problems and consists of three basic steps: navigation, positioning confirmation and tissue acquisition.

From this perspective, an optimal navigation bronchoscopy setting that is able to target peripheral pulmonary lesions of all origins must help physicians in all three procedure steps.

A short overview of technology and their clinical outcomes will allow putting these requirements into a more general perspective before we focus on CBCT.

Technology overview

Navigation tools

UTB and virtual bronchoscopy navigation (VBN)
Most familiar to any endoscopist is likely the utility of ultrathin bronchoscopy. It relies on conventional video-endoscopy, but in a smaller package. Therapeutic scopes of >5.0 mm outer diameter often become wedged at the segmental bronchi. The newest scopes now have a 3.0 mm outer diameter whilst facilitating a 1.7 mm working channel that can be used in combination with the smallest of rEBUS mini probes and sampling instruments (for example: Olympus BF-MP190F and UM-S20-17S). Consequently, it can be navigated 3–4 bronchial generations further than conventional bronchoscopes. In selected patients, this is sufficient to directly visualize the lesion. Oki *et al.* [2019] showed that the ultrathin bronchoscope in combination with tools such as rEBUS, VBN and fluoroscopy had

an excellent diagnostic yield of 70.1% in a group of 177 patients with a median largest tumor diameter of only 18.9 mm (35).

While UTB facilitates visualization of the navigation pathway and lesion and can help guide tissue acquisition, there is no meta-analysis or systematic review available on the applicability as a stand-alone device for navigation bronchoscopy. Surely, this modality will evolve and will foremostly be used as means of navigation to the lesion. Combining UTB with rEBUS seems logical, as rEBUS facilitates visualization beyond the bronchial wall and once vision has become obscured due to i.e., mucus or bleeding after the first biopsy. A rEBUS mini probe, with an outer diameter of 1.4 mm, is also able to advance more peripherally once the UTB becomes wedged.

When navigating the UTB through the small peripheral airways, that differ per patient, VBN software is a valuable addition. VBN utilizes a preprocedural CT to segment and plan a path towards the lesion based on the bronchial anatomy which is correlated per-procedurally with the live video-bronchoscope imaging. To help reconstruct the smaller airways for VBN software, CT quality should have slices with a maximum of 1.0 mm thickness. A major limitation of VBN/UTB is that in a significant portion of cases there will not be a bronchus leading to the lesion at all. As the study by Oki *et al.* showed in their multi-modal approach, a lack of bronchus sign (on 0.5 mm CT-slices) had significant impact on diagnostic yield (74.6% *vs.* 57.4%) (35). A randomized trial by Ishida *et al.* [2011] showed that diagnostic yield was higher in cases where VBN was used (80%) than where it did not (67%). However, the added value of VBN goes beyond only increasing diagnostic yield (DY), as they also showed that procedure time was significantly shorter (36).

In the near future, we will likely see redesigned UTB's that are smaller and facilitate more tools, while simultaneously improving reconstruction of the bronchial tree by VBN to include smaller, more distal airways. An important aspect in that quest is the trade-off between going further out and/or reducing sampling instrument diameter. What Gildea for example already mentioned in 2016 but remains apparent is that all studies report a discrepancy between getting there and getting a diagnosis (37). Theoretically, this could be caused by mispositioning (38), yet on the other hand, it could also be caused by a lack of sufficient volume of tissue for analysis. A means for the UTB to facilitate accurate trans-parenchymal navigation in cases without a bronchus sign is another design challenge.

EMN

EMN technology guides the physician to the target location by electromagnetic sensors on- and within the patient, based on a pre-procedural CT scan. A weak electromagnetic field in the vicinity of the patient allows tracking of the sensors on the patient (for reference position) and the sensor within the special extended working channel or tools that go through the bronchoscope. The catheter used for navigation in combination with the sensor is torsional stiff and pre-angulated at the distal tip. These properties allow navigation through the bronchial tree beyond what is feasible with the conventional bronchoscope, into the most distal segments of the airways. It has been extensively studied and recent data shows that it is often used in combination with imaging confirmation modalities such as rEBUS and fluoroscopy (39). While a systematic review and meta-analysis by Folch *et al.* [2020] showed EMN had a pooled sensitivity of 77% and specificity of 100% in 3,342 study patients with an average lesion size of 23.2 mm (40), a recent update of the NAVIGATE trial's (n=1,388) reported a diagnostic yield of 67.8% overall and 62% for <20 mm nodules (41).

Over the years, it became apparent that EMN in clinical practice was often influenced by significant CT to body divergence. CT to body divergence is a definition used to describe the difference between pre-procedural and intra-procedural lesion positioning, which is multi-factorial (42). It is caused by breathing movement (43,44), instrument and bronchoscope movement (45), atelectasis (42,46,47), cardiovascular motion (48) and system measurement error (49). These errors are most outspoken in the lower lobes. Breathing motion alone has shown to cause a divergence of up to 17.6 mm on average (43,44) while system registration error can also be several millimetres (49). As a result, more recent updates of EMN systems are primarily aimed at reducing or compensating for this problem. To reduce CT to body divergence, updates of commercial EMN systems have led to the introduction of using both in- and expiratory CT scans for planning the procedure (43,44) as well as implementing a custom digital tomosynthesis algorithm that can be used in combination with C-arm fluoroscopy (34).

Considering the intuitive means with which the commercial EMN platforms guide the physician toward the target lesion, it is a great help for every physician in need for navigation guidance. EMN is a navigation guidance tool, but cannot confirm location positioning in real-time. Bigger and solid lesions might be targeted in combination with fluoroscopy or with artificial tomosynthesis such as provided by the platforms while smaller lesions with bronchus sign might be viable options when further assisted by rEBUS. If no bronchus sign is present based on high resolution CT, or if precise positioning is necessary, EMN is best used in combination with a system allowing detailed 3D visualization and confirmation of the catheter position (such as CBCT). CBCT allows precise intra-procedural 3D assessment of catheter position in relation to the target lesion and can be used to determine the optimal trans-parenchymal route, if needed (45,50).

Advanced multi-modality reconstruction

Novel hybrid technological systems such as Lung Vision (Body Vision Medical) but in-part also the tomosynthesis feature of the Illumisite™ EMN platform integrate multiple information sources for reconstructing and/or confirming a navigation pathway and lesion position (33,34,51). These systems rely on using advanced image processing that integrates fluoroscopy along with additional information (i.e., a pre-procedural CT-scan) for providing a coarse 3D tomographic image or augmented fluoroscopy image. Being compatible with most other technologies and available with specialistic tools, these systems can be a valuable addition to the toolbox of the physician. As Pritchett showed with Lung Vision technology in combination with a bronchoscope and pre-angulated catheters for navigation, this technique can help guide experienced physicians to the lesion in 96% of cases and can reduce CT to body divergence to as little as 5.9 mm (range, 2.1–10.0 mm) in a cohort of 51 patients (51). CBCT verification allowed Pritchett to obtain a diagnostic accuracy as high as 88.2%. As technology and the navigation bronchoscopy procedure evolves, it becomes increasingly clear that not one technique will be a do-it-all. These multi-modality reconstruction technologies that are compatible and integrate with other methodologies are surely here to stay. While they currently do not provide millimetre accuracy by themselves, they are sufficiently accurate and easily combined with secondary technologies to help obtain diagnoses for all peripheral lesions referred for diagnostic biopsy. A second example showing the added value of this multi-modality approach is the study by Aboudara *et al.* [2020]. Using the Illumisite™ EMN platform and it's digital tomography algorithm that reconstructs 3D imaging information out of conventional C-arm fluoroscopy showed to significantly improve diagnostic yield from 59% when using EMN alone to 79% when used in combination (34).
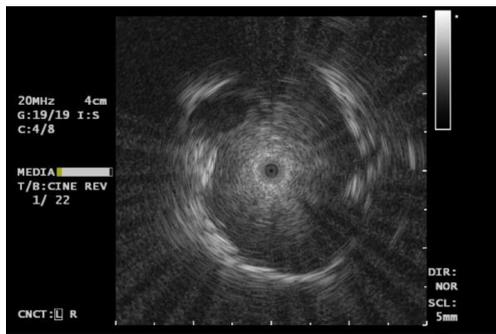
Figure 1 Example of rEBUS miniprobe imaging of a peripheral pulmonary nodule with a central position of the probe, and a vessel structure which was found to be pulsating on live imaging in the left upper quadrant. rEBUS, radial endobronchial ultrasound.

Robotic endoscopy

Robotic assisted bronchoscopy (RAB) is a technology that has gained much attention since the introduction of the first system in the US in 2018. However, since robotics is the subject of a dedicated issue of this series we would like to recommend readers towards this article. In brief, there are currently two systems available in the US market: the Auris Monarch® system (52) and Intuitive Surgical's Ion® system (53). A third company called Noah medical is developing a platform called the Galaxy system (26). Currently, studies using the two commercially available robotic systems (with or without using additional technology) have shown diagnostic yields of 69–82% (22-25,54). Their major advantage when compared to other technologies is their integrative design; combining multiple technologies into a singular easy-and-intuitive platform. The steady distal tip furthermore allows the advantage of active steering and a stable repeatable exit point for sampling tools which might close the gap between getting there and getting a diagnosis. However, the robotic aspect does show to be in need of secondary imaging confirmation; RAB is therefore routinely combined with rEBUS and fluoroscopic imaging techniques (23,32,55).

Confirmation tools: rEBUS

rEBUS miniprobe

rEBUS has been around for more than two decades and has been a valuable tool for the endoscopist as method for position confirmation. It does not however, provide any navigation support nor real-time tissue acquisition guidance. The currently available commercial systems are sideways looking ultrasound systems with a maximum depth of around 15–20 mm. Wang-Memoli [2011] and more recently Ali [2018] have shown that the diagnostic yield of rEBUS in navigation bronchoscopy is approximately 71%. As not much has changed in its design over time, these numbers are most likely still accurate (19,56). Considering that it is a relatively low-cost device that can be re-used some 40–100 times before it breaks, rEBUS is a cost-effective addition in navigation bronchoscopy. The limited range of application needs to be accounted for when selecting a nodule or using additional tools. Lesions with a lack of bronchus-sign on high resolution CT, or ground glass opacities are best not targeted by rEBUS alone. In the remainder of cases, it is however a useful instrument in confirming correct positioning and gives good indication about chances of adequate tissue sampling. Since it provides local and detailed imaging, it can additionally be used to (repeatedly) measure contact area length and positioning to guide subsequent sampling tool positioning after rEBUS removal. rEBUS can also provide information on pulsating structures that require caution such as in *Figure 1*. But, interpretation of the rEBUS image can be difficult. Bleeding caused by prior biopsy, remaining fluid after a lavage, or atelectasis (especially in posterior lung fields) will give a similar image as the targeted lesion on rEBUS-imaging. Increased heterogeneity of the rEBUS image might allow differentiation of false positive imaging versus the image as obtained in a solid tumor, but this is not always easy to distinguish.

Nakai *et al.* (57) and Ikezawa *et al.* (58,59) showed that rEBUS can be used in ground glass opacities (GGO) and part solid lesions, as these lesions provide a relative increase in echogeneity when compared to the surrounding lung parenchyma. This is also our experience, but similarly, we also have experienced that putting the rEBUS under friction or minor bleedings may result in ostensible GGO or part solid lesion imaging.

Tissue sampling

Ultimately, getting the correct diagnosis is the goal. And while navigation success is often around ~90%, the diagnostic accuracy remains at 70–75% in the majority of studies (19,23,33,40,56), although some centres do seem to have closed the gap [i.e., 82–95% (24,29,32,51,60)]. As mentioned before, navigation bronchoscopy procedure can be divided into three different steps. The third step—tissue acquisition—seems to be the area with the highest need for

improvement as there often is more than a 10% difference between getting there (e.g., navigation success) and getting a diagnosis (e.g., diagnostic accuracy). The limited literature on tool efficacy shows that a set of sampling tools combined with technology that helps position these tools is likely needed. Even with 3D-imaging confirmed correct positioning, a diagnosis sometimes remains uncertain (37,61) and this is most likely multifactorial. First: precise position is essential in obtaining representative samples, for which real-time 3D-guidance is an important asset. When using navigation tools such as robot bronchoscopy or EMN without additional guidance, it can be difficult to precisely determine where to biopsy in small lesions. Second: when using increasingly smaller sampling tools, the biopsy samples can become too small for optimal evaluation. Third: when using pre-angulated catheters without distal tip manipulation, (as commonly used in EMN and CBCT guided navigation) the rigidity of the sampling tools will change the angulation of the catheter which increases uncertainty. Oki *et al.* and de Ruiter *et al.* both showed that the angulation of catheter/bronchoscope can alter significantly based on instruments used and material interaction (62,63). Lastly: even biopsies of endobronchially visible tumours do not always result in a diagnosis if non-vital tissue is sampled (64). When a fluorodeoxyglucose (FDG)-PET-scan is available, diagnostic yield could be optimized by aiming for regions with a high FDG-avidity.

There is no uniform way to overcome all above mentioned hurdles, but as we recently reported, taking more (multimodality) samples than is thought necessary for a diagnosis, might close the gap between getting there ('navigation success') and getting a diagnosis ('diagnostic accuracy') (29,61). This is corroborated by the in-depth analysis of the NAVIGATE trial which showed that a multi-modal approach for sampling increases yield (65).

Cone-beam CT and augmented fluoroscopy in pulmonary nodule biopsy

Conventional transbronchial biopsy is often performed under guidance of mobile or fixed C-arm fluoroscopy. In larger lesions, fluoroscopy offers gross lesion positioning and provides coarse guidance and confirmation. Smaller PN however are often not visible on fluoroscopy. To allow for real-time guidance during navigation and biopsy, more detailed and precise 3D-imaging such as provided by cone beam CT imaging systems is essential. It is further relevant when looking at future developments of endobronchial treatments.

CBCT and augmented fluoroscopy (CBCT-AF) have long been implemented in almost every hospital's interventional radiology or cardiology suites and is found in the newly implemented hybrid operating room (OR) environment. It has however only recently become of more interest to the field of interventional pulmonology (27,28). The CBCT system knows the exact patient-table positioning and it can obtain a 3D scan of patient anatomy with high (soft-tissue) contrast within 3 to 8 seconds. Such a high-powered and calibrated system is not just an improved version of a mobile (3D) C-arm. With a reconstructed 3D CBCT scan under breath-hold, the physician obtains slice reconstructions of around 0.65 mm thickness that allow for detailed evaluation of navigation pathways and instrument to lesion positioning. Complementary software can subsequently be used to outline the lesion and navigation pathway intra-procedurally (*Figure 2*). In cases where sampling very near the pleura is required, it can be useful to outline the pleural edges as well as margin reference. Based on the availability of the software, the delineated pathway and segmented lesion can be projected over the fluoroscopy images under different angles to support real-time augmented fluoroscopy in the hybrid OR.

The overlays on fluoroscopy help the physician to determine navigation progress, where every bifurcation of a bronchus can be found, or, the position at which one needs to create a trans-parenchymal pathway. Without software, these overlays are not possible and its use is limited to reviewing obtained 3D imaging and normal fluoroscopy images. Repeated CBCT scanning allows for detailed confirmation that the target has been reached (or the need for repositioning). If needed, segmentation of the lesion can be performed again to overlay new pathways or provide positioning updates. The CBCT system and augmented fluoroscopy can also provide 3D confirmation of instrument positioning (for biopsy), which is closest to real-time guidance when no endobronchial visualization can be provided.

In summary, CBCT- and AF-imaging systems combine navigation and confirmation of instrument positioning. The entire workflow of a patient undergoing a CBCT guided navigation bronchoscopy is visualized and explained in *Figure 3*. When compared to the mentioned navigation tools, CBCT-AF provides the essential aspects of intra-procedural and (near-) real-time image guidance needed by the physician. Since it provides this information from a global perspective rather than a local perspective
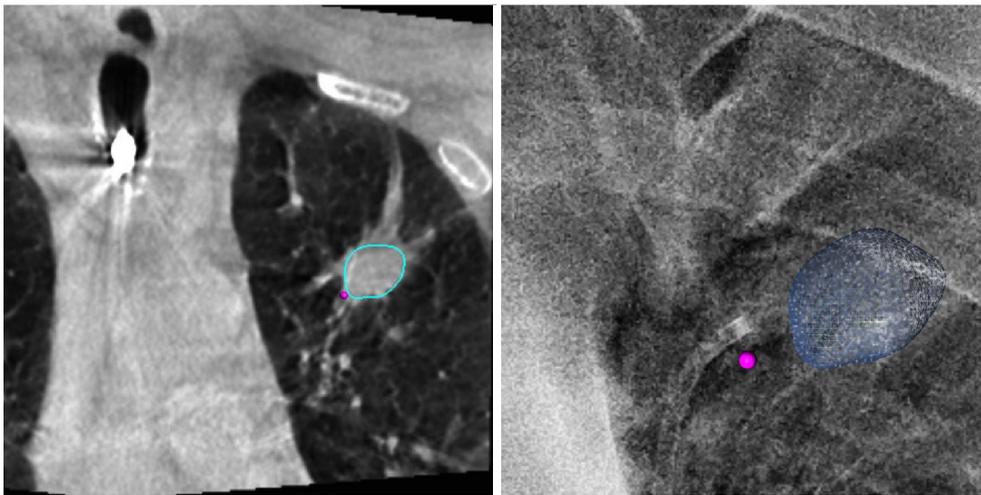
Figure 2 CBCT images with augmented fluoroscopy. The left panel shows a coronal reconstruction of a CBCT image with a segmented nodule in the left upper lobe, a (purple) marker is placed to correlate the catheter position during breath-hold for the CT acquisition with real-time augmented fluoroscopy. The right-hand panel shows augmented fluoroscopy image of the nodule in the left upper lobe. The slight real-time displacement of the catheter compared to the marker in breath-hold position can be seen in this overlay. This is explained by breathing (CBCT acquired in breath-hold and AF performed under continuous breathing) and the stress imposed on lung tissue by the catheter and sampling tools. CBCT, cone-beam computed tomography; AF, augmented fluoroscopy.

(such as rEBUS/video-endoscopy) it has advantages as well as disadvantages. The major advantage of having a complete and actual 3D-image of the patient compared to technology such as EMN is that it addresses the CT-to-body divergence concerns, and thus allows for a more accurate trans-parenchymal navigation, and allows creating a pathway when there is no bronchus sign. This is a valuable addition in patients with nodules smaller than 20 mm or nodules without a bronchus sign and thus for approximately 40–60% of patient cohort. Especially in these small nodules, CT-to-body divergences can be larger than the maximal diameter of the target nodules (29,42-44,60). Relating 3D-positioning to previous PET/CT-scans also allows the physician to target and verify the most FDG-avid region of a lesion has been reached, increasing the chance of obtaining vital tissue. Having intra- and post-procedural proof of adequate positioning can also help in the in-room decision-making process with the pathologist for the rapid on-site cytology evaluation (ROSE). The 3D-imaging capability is furthermore an essential component in future endobronchial treatments like transbronchial microwave ablation that requires precise catheter positioning confirmation as well as the need to determine the ablation zone to fully cover the tumour in three dimensions with an additional safety margin of 5 to 10 mm.

A major disadvantage of current CBCT-AF systems is the learning curve that must be overcome to be able to interpret and translate the global perspective into local navigation, that results in suboptimal results during this learning process (29). This translation is often of lesser concern in lesions of >2 cm size with a central bronchus sign. Small PN's however, require refined movements and have a small margin of error for biopsy-instrument positioning. Combining CBCT-AF with an additional navigation technique such as EMN or robotic bronchoscopy may reduce this problem, but increases the financial burden of the procedure. A second often discussed disadvantage of CBCT over other navigation methods is the inherent use of radiation (66). The entire team should rigorously adhere to the As Low As Reasonably Achievable (ALARA) principle and thus use shielding and aggressively collimate. While applying ALARA, continuously monitoring dose and adjusting imaging settings, we have been able to significantly reduce radiation dose from a dose area product (DAP) of 47.5 to 28.4 Gy·cm^2, which translated to an estimated effective dose of 5.8 mSv (29). While there has been variation in procedural dosing estimates as well as different reconstruction calculation parameters (29,66), even the worst estimations seem to not exceed a dose obtained by a whole body PET/CT-scan. The vast majority
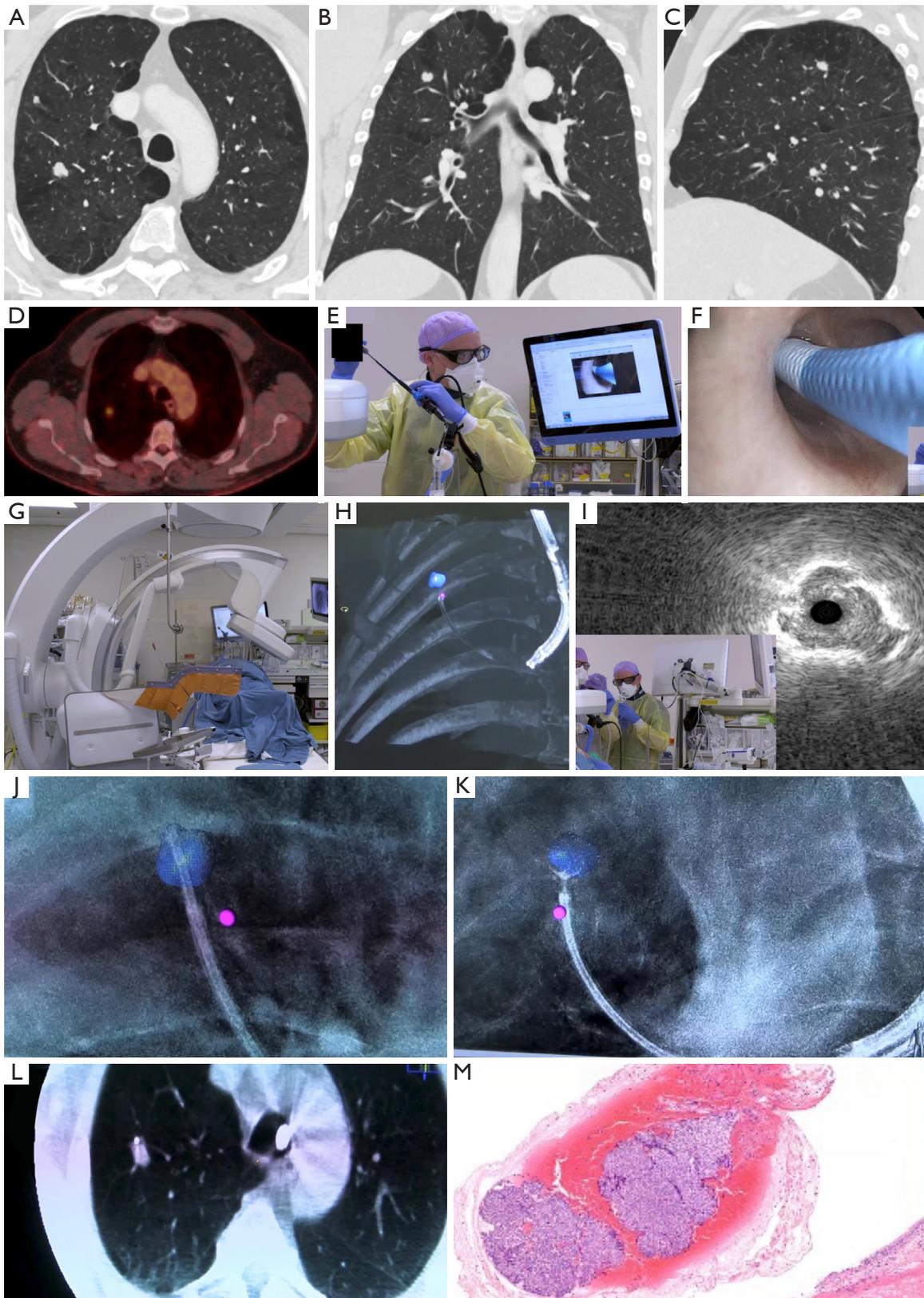
Figure 3 CBCT based navigation bronchoscopy (see Appendix 1 for details). These images are published with the patient's/participant's consent. CBCT, cone-beam computed tomography.

of dose herein comes from the CBCT, which is performed while the staff has left the room.

A potential disadvantage of CBCT-AF for navigation bronchoscopy guided biopsy can be the lack of (allowed) access for the interventional pulmonologist to a hybrid OR, or an interventional radiology room. This requires collaboration with fellow specialties, as purchasing a CBCT only for performing navigation bronchoscopy procedures will be a significant investment. When putting different systems side by side, some aspects might be mentioned. For navigation bronchoscopy, ceiling mounted systems are generally easier to use than floor mounted systems, as these leave more room at the head of the patient and provide a more predictable rotation during CBCT scanning (less likely to hit the endoscope). The user interface of the workstations also slightly differ per vendor, in particular when it comes to delineating the lesion and navigation pathway. Whereas one system for example allows lesion delineation by clicking and pulling a region of interest within the nodule in only one orientation, the other requires defining the lesion in two directions and a paint brush technique. There is furthermore a potential difference in spin time, but this will greatly depend on the imaging protocol that the system has installed and if it is optimized for navigation bronchoscopy. In systems where no specific navigation bronchoscopy protocols have been installed, we recommend consulting to your clinical physicist or system representative as they may be able to allow for an optimization of the system protocol to reduce radiation dose and optimize image quality by tailoring the filtering, hardness and contrast.

When there is no access to a hybrid OR with a fixed CBCT-AF system, a possible alternative solutions might be the integration of mobile 3D imaging systems or tomosynthesis-based software programs. Similar to CBCT, these systems allow intraprocedural determination of lesion-to-instrument positioning. Mobile 3D-imaging systems can—as with CBCT—additionally be used at different locations and across specialities (24). A major limitation is the lower imaging quality obtained with these systems due to system power/sensitivity and resulting higher scan time. Latest technologies have already improved image distortion, spatial resolution and noise of mobile 3D-imaging systems (67), but image quality is still not comparable to CBCT imaging. Images are considered of less quality due to poorer contrast-to-noise ratio (CNR) and therewith also a lesser ability for soft tissue imaging. When looking at the average radiation dose of mobile 3D

imaging systems, the currently reported average radiation dose (DAP 37.1–50.3 Gy·cm²) is comparable or exceeds the radiation dose of CBCT (24,32). This might however decrease over time, as learning curves and radiation safety improve. Another barrier in mobile system application is the lacking software tools for outlining the lesion and navigation trajectory intra-procedurally as well as the overlay during navigation, as are available in CBCT systems. Furthermore, because of longer scan times also longer inspiratory breath-holds are required. Currently, one rotation of the gantry takes 30 seconds (CIOS 3D Spin Mobile, Siemens Healthineers), compared to 3–8 seconds with routine CBCT systems. This might however be a smaller problem in procedures under general anaesthesia with inspiratory breath-hold during scanning. Alternatively to dedicated 3D mobile C-arms, tomosynthesis-based software algorithms (i.e., the Lung Vision platform) used in conjunction with existing mobile 2D C-arms can be used. Emerging robotic innovations are also being developed to integrate these tomosynthesis-based imaging techniques (68). Major advantage of this technology is the lower cost and higher availability of C-arms (31). However, the low CNR of the C-arm based tomography produces images of lower quality than conventional (CB)CT, which could remain a major disadvantage. This reduced image quality in both mobile 3D-imaging and tomosynthesis-based software systems can be problematic in cases with small lesions, ground glass opacities, atelectasis and local bleeding. Small GGO's will be barely visible on 3D-images produced by a mobile C-arm, while they will be more easily visualized in CBCT imaging (31). Both mobile 3D-imaging and tomosynthesis-based software systems also experience smaller 3D volume recordings that require extra attention on focusing the centre of the C-arm rotation on the lung nodule. It also remains to be seen if the lower image quality is sufficient enough to be utilized in endobronchial treatments such as microwave ablation (31).

Future perspectives

As physicians we tend to rely on decade's old data, but technology is constantly updated and improved. The outcomes and usability of technology are valid for a limited time. For example, commercially available EMN systems have different technological features across systems and have now been integrated with mobile c-arms for generating tomosynthesis images to compensate for CT-to-body divergence. Whereas we tend to look and discuss a specific

technique such as EMN, we are increasingly moving to multi-modality approaches and integrations where one specific system might have a significantly different approach than another.

There is a growing body of literature on navigation bronchoscopy for lung biopsy, but one modality does not seem to achieve the same diagnostic accuracy in every study. At current, we have to acknowledge it is very difficult to compare technologies head-to-head based on reported study outcomes. Most, if not all—studies have at least some sort of selection bias. Every physician will refer the patient for navigation bronchoscopy using slightly different inclusion criteria. To date, for small peripheral pulmonary nodules, the highest results in terms of diagnostic accuracy (defined as the total of true positive and true negative results with adequately long follow-up time for non-malignant lesions, divided by the total number of procedures) is CBCT-AF. Robotic assisted bronchoscopy is runner up, but also here, position confirmation seems to become an integral part to meet the high standards of diagnostic yield/accuracy we want to achieve. No single device seems to perform best and a multi-modality approach combined with experience seems to be the only option for achieving a diagnostic accuracy of >85% at current.

In experienced centers, coarse navigation guidance seems of lesser concern and fine positioning and optimal tissue sampling are the biggest problems to be overcome. One should therefore look beyond the reported diagnostic yields when deciding on choosing for a specific technology. Not only does the definition seem different per report, it is also highly affected by inclusion criteria such as size and bronchus sign. In a multi-modality diagnostic approach, we should look for techniques that are most complementary and within cost-effective range. When considering moving to locally applied, minimal invasive therapies, it will become essential to integrate detailed imaging into the workflow.

The WHO predicts the global lung cancer incidence to double in the next 20 years, and with screening programs being implemented, the demand for minimal invasive, safe biopsy procedures will likely increase exponentially. These patients, when diagnosed with early-stage lung cancer, will most likely be referred for minimal invasive treatment options. To improve diagnostic and treatment procedures, this could even be directed into a one-stop-shop setting. However, when considering local curative treatment, we must address potential local spread in order to make curation feasible. Current combined EBUS/EUS staging procedures cannot evaluate any lymph nodes beyond station 12, while in reality the pathologist will routinely report finding additional lymph nodes in the further peripherals. In breast cancer and melanoma, this is currently tackled by performing a sentinel lymph node (SLN) procedure, where these lymph nodes are imaged, biopsied and pathologically assessed as part of routine workup. In lung cancer we have recently seen that more than 23.1% of clinical N0 patients are upstaged to N1 or N2 disease after surgical resection and pathological evaluation (69). SLN evaluation in lung cancer has been attempted over the last decades, but has shown difficult to implement in routine clinical practice (70,71). Further development in this field will be necessary to help improve survival of early-stage lung cancer.

When looking at local treatment options, microwave ablation seems to be most advanced in its scientific evaluation and is therefore subject of a dedicated manuscript in this series. For current and future treatment options, high-resolution 3D-imaging for precise positioning seems essential and at current CBCT is the best available technology in this area.

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Appendix 1 How we do it: practical step-by-step considerations for new CBCT-AF users

Figure 3 represents the entire workflow of a patient undergoing a CBCT guided navigation bronchoscopy (CBCT-NB).

Step 1: preprocedural planning: *Figure 3A-3D* show a peripheral pulmonary nodule in the right upper lobe on a preprocedural CT and PET-CT scan. The first (preprocedural) step is to determine and memorize the optimal path through the airways towards the nodule based on the preprocedural CT, preferably on the axial slices. If no bronchus sign is present, it is advisable to try to determine your exit point for a trans-parenchymal approach as well. The eventual navigation path might differ from the preprocedural mental plan made, but a memorized preprocedural plan significantly helps navigating on 2D imaging (augmented fluoroscopy) in 3D lungs and decreases navigation time needed.

Step 2: General inspection: After the patient is sedated, the first step is a general inspection bronchoscopy with a normal flexible bronchoscope. Any endobronchial abnormalities can be sampled.

Step 3: Course navigation: After general inspection, the pre-angulated extended working channel (EWC) is inserted through the bronchoscope. The bronchoscope is wedged in the subsegment of the target nodule (predetermined on preprocedural CT) and the extended working channel is guided through as can be seen on *Figure 3E,3F*. Based on your predetermined memorized path initial course navigation in the direction of the nodule can be performed.

Step 4: CBCT spin and segmentation: After the EWC is inserted, the first CBCT spin is performed (*Figure 3G*) on (inspiratory) breath-hold. The target nodule and pathway are segmented on your workstation, where optimal viewing angles for fluoroscopy can be determined. When the extended working channel is in close proximity to the target nodule, mark the distal tip of the EWC. This mark helps correlate the projected image from the 3D CBCT with the real-life position on 2D fluoroscopy (*Figure 3H*) as there will be a discrepancy between a breath-hold scan, and fluoroscopy of the breathing patient. The mark can be correlated with the visible distal tip of the catheter and helps place the segmented nodule in perspective with the live imaging.

Step 5: When the catheter is at the target nodule, position confirmation is important for optimal sampling. rEBUS can provide confirmation; *Figure 3I* shows central positioning of the rEBUS probe in the lesion. In absence of rEBUS confirmation or when in doubt of positioning, an additional CBCT scan can help confirm the position and assist in repositioning if the extended working channel or sampling instrument need readjusting. *Figure 3L* shows a needle in the target lesion, confirming that the sample taken is from the lesion. The CBCT scan furthermore gives information on the optimal fluoroscopy angles for a progression and angulation view for optimal sampling.

Step 6: Tissue acquisition: After position confirmation sufficient samples need to be taken (*Figure 3J-3M*). Even when there is a clear rEBUS image, it is advisable to obtain multiple samples with both transbronchial needle and forceps biopsy device. Aim to sample in multiple sections of the nodule. When there is doubt of optimal positioning (both on rEBUS and CBCT) obtain multiple samples not only of the segmented lesion but also of the direct vicinity of the lesion to increase the chance of a diagnostic sample. Rapid OnSite Evaluation (ROSE) can help to determine if the target lesion is sampled successfully, especially when positioning of the sampling instrument has been confirmed with CBCT.

General considerations

Ventilation: An optimized ventilation protocol and collaboration with the anesthesia are important. CBCT scanning is performed under breath-hold and should only be performed 5–7 seconds after initiating breath-hold due to initial lung movement. See Bhadra *et al.* (2022) for a ventilation protocol that can help optimize the navigation bronchoscopy procedure. Especially obesity and lesions in the posterior lung fields might be troubled by atelectasis (42,46,47).

Learning curve: CBCT-NB is a navigation technique with a long learning curve. An additional navigation modality such as

EMN can help fasten this process.

Radiation: Monitor procedural radiation dose closely, collimate as much as possible and communicate with your radiology technician on when to radiate.

Interfering objects: Take care to place objects such as the metal components of a blood pressure cuff as far from the radiation field as possible. Even if not visible on the reconstructed slices of your 3D scan; CBCT scanning is based on a cone beam and as such they can negatively influence the image quality.

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