Chapter 2
Review on Image Guided Lung Biopsy

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Abstract Lung biopsy is an established field. Throughout years physician and scientist have been exploring the field, from technical and clinical point of view. Mainly there are three types of lung biopsy, open, bronchoscopic, and fine needle aspiration biopsy. Open biopsy is essentially a surgery, thus not really dependent on image guiding system. On the other hand, bronchoscopic and fine needle aspiration biopsy relay heavily in image guiding system. Curiously, it is rare to find both biopsy types talked side by side. In this paper, both biopsy types explored and compared from technical and clinical point of view. Technical wise, bronchoscopic biopsy trend is toward path finding algorithm, while fine needle aspiration biopsy trend is toward breathing compensation algorithm and automatization. Clinical wise, there is no evidence that one type hold better diagnostic value than the other.

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2.1 Introduction

According to WHO mention that Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths (around 13 % of all deaths) in 2008 [1]. Among them, lung cancer contributed around 1.37 million deaths [2]. Some statistic from National Cancer Council of Malaysia (MAKNA), lung cancer is one of the most deadly cancer, 95 % of patients dead within 5 years of diagnosis. Cigarette smoking is one of the main cause of lung cancer, smoking pipe or cigar have even higher risk of lung cancer [3].

Lung cancer is a disease where lung cell growth uncontrolled, these cell will eventually disturb lung function. Lung cancer symptoms usually take years to emerge, and only emerge while the cancer already advanced, because of this, some of physicians recommend people with high risk of lung cancer (i.e. people who smoke a lot) to do an early screening in order to check wether they have lung cancer or not. If screening results show something suspicious, such as an unidentified nodule inside lung, physicians will recommend biopsy procedure [4].

Unidentified nodules could be proven as cancerous or not. In 2012, Xueqian Xie et al. conducted a research on the sensitivity and accuracy of volumetry of pulmonary nodules [5]. They found out that in anthropomorphic study, the sensitivity of detection is 100 % for nodules of greater than 5 mm in diameter. But, the sizes between the 3 and 5 mm in diameter are needed that present as the limitations which actual it found for early stage of suspicious lung nodules, mostly small nodules presents.

On the other hand, in 2010, Marios A. Gavrielides et al. showed the lung nodules consisted of sizes 5, 8, 10, 12, 20, 40 mm, shape with spherical, elliptical, speculated and irregular and varying of density −800, −630, −300, −10, +20 and +100 HU [6]. It found that it is well suited for the development and assessment of lung nodules size and shape estimation. But, the study includes of the lack of complexity in the lung field and nodules shape. The simplicity of the human anatomy sometimes in gives inefficiency of the evaluation.

Biopsy is a medical diagnosis technique involving removal and examination of cells from various part of human body in order to detect presence or extend of disease. Lung biopsy is biopsy done in order to help diagnose lung disease, including lung cancer and tumor. There are three type of lung biopsy, bronchoscopic biopsy, needle biospy, and open biopsy.

Bronchoscopic biopsy is biopsy technique using a bronchoscopic tool inserted into thoraxic air pathway. A needle for biopsy is mounted on the top of this tool. Some kind of position tracker will be employed to track the immediate position of the needle, or physician doing lung biopsy can just recognize the path toward biopsy target by seeing the inside of thoraxic air pathway using camera also mounted on the top of the tool.

Fine needle aspiration biopsy, recognized as the standard method of biopsy, is a simple biopsy technique involving thrusting a special needle to human body for taking sample from suspected target. Position and elevation angle hold great value in this technique. Nowadays, some physician use a special laser guide to help them measure angle of elevation of the needle.

Open biopsy can be considered as last resort, since this biopsy basically is a mini surgery. Physician will open the suspected area, and take sample from there.

2.2 Image Guided Biopsy

2.2.1 Image Guided Biopsy System

Biopsy is an invasive procedure, just like any other invasive procedure, there are a lot of risk involved. In order to minimize the risk, physician employ various technique to make the invasion as small as possible. Image guided biopsy is biopsy procedure performed under the guidance of imaging system such as, CT, fluoroscopy, or ultrasound. Image-guided system has been widely developed in intervention and surgery. In lung cancer imaging, image-guided system is mostly applied in minimally invasive staging, such as image-guided transthoracic tissue acquisition, thoracoscopic diagnosis and staging, and nodal assessments. This technology allows for a more accurate pathologic staging to guide surgical interventions, multimodality treatment approaches, and sequencing of systemic management. A large number of imaging modalities, e.g. X-rays, CT, Magnetic Resonance Imaging (MRI), Ultrasound, Positron Emission Tomography (PET), and many others, have been involved in lung cancer management.

According to the James G. Ravanel from Imaging Lung Cancer book [7], the improvements in minimally invasive staging especially in image-guided transthoracic tissue acquisition, thoracoscopic diagnosis and staging, and esophageal or endobronchial ultrasound assessments of nodal involvement, have allowed more accurate pathologic staging to guide surgical interventions, multimodality treatment approaches, and sequencing of systemic management. There was reported that the first clinical experience of biopsy by radiofrequency ablation (RFA) of tumors in the lung. The needle electrode is advanced through the chest wall and into the lung. Although ultrasound may be used for imaging guidance of RFA of a peripheral lung mass, usually CT is chosen as the imaging modality. Placement of the needle electrode must pass to the deep edge of the tumor, or slightly beyond, and must be positioned in the tumor

The choice of proper imaging modality depends on the type of abnormality and the procedure. However, the limitation of lung cancer imaging is that it only visualizes and quantifies the abnormal regions. Malignancy confirmation can only be performed through biopsy. The biopsy is recommended for small pulmonary nodules with size of greater than 8 mm. During the biopsy procedure where images provide guidance, image-guided biopsy system requires the surgeon’s hand as the

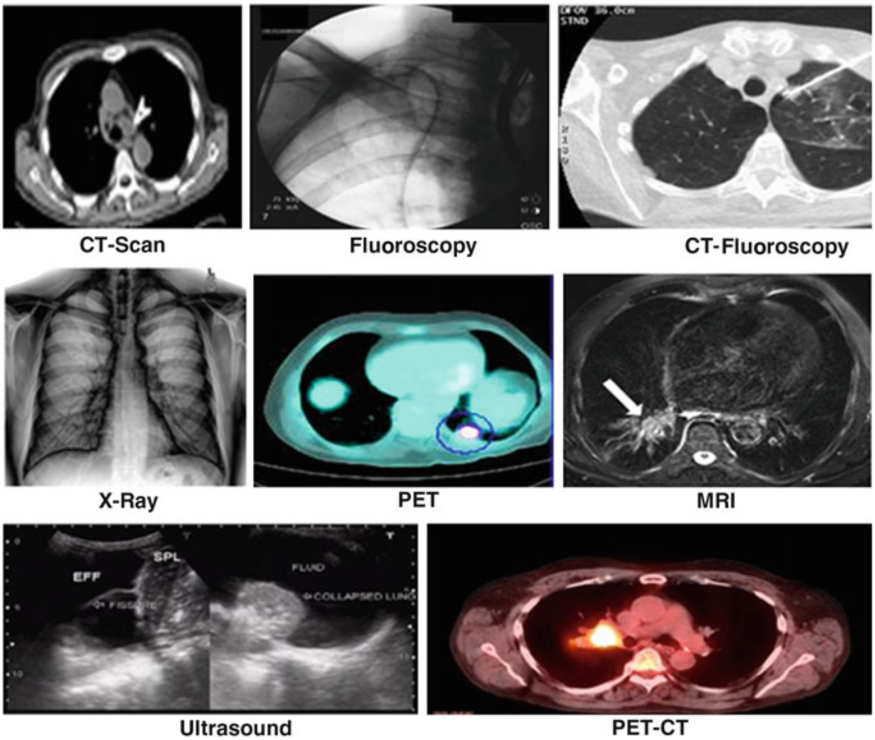

Fig. 2.1 Lung imaging using various modalities

effector. Some research on intervention effectors have involved robotic-based remote effectors that can be controlled in a distance (Fig. 2.1).

2.2.2 Image Guided Biopsy Testing

Before the developed image guided system can be used on patient, there should be a test to confirm the accuracy and safety of the system. In order to test the developed image guided system, a phantom of patient body should be employed, in case of image guided biopsy system for lung, lung phantom along with its nodules will be used. The fabrication of lung phantom was based on similarities as human features. Usually, the material selection was based on two main goals which are the material selection must have similar physical properties to human tissue such as density and attenuation coefficient. Besides, the phantom must be easier of manufacturing that result in economical price. According the research in 2009, James F. Winslow et al. [8] three material that have mimic human tissue diagnostic photon energies which are soft tissue-equivalent (STES), lung tissue-equivalent (LTES) and bone tissue-equivalent (BTES). The formulation for BTES was epoxy resin compound while

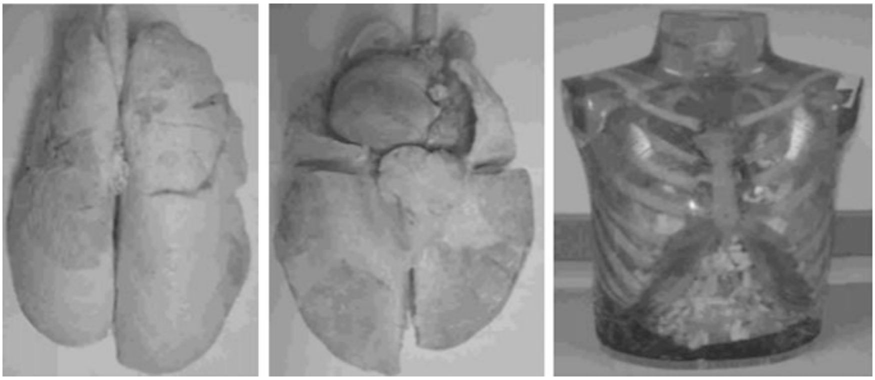

Fig. 2.2 Plastinated anthropomorphic lung phantom external and sample chest cavity with ribs that can be used in conjunction with the phantom to generate more realistic data [13]

STES and LTES were designed based on the urethane-based compound. These urethane-based materials were chosen in part for improved phantom durability and easier accommodation of real-time dosimeters [8]. Another research also mentions the same material substitute of polyurethane foam and epoxy resin that select to represent lung tissue and bone respectively [9–11].

In year 2008, Sungwon Yoon et al. from their researched [12] was found that a novel anthropomorphic lung phantom was develop by plastination of an actual pig lung. The plastinated is characterized and compared with references to in vivo image of the same tissue prior to plastination using high resolution 3D CT. The phantom is stable over time and preserves the anatomical features and relative locations of the in vivo sample. A 42 kg female Yorkshire pig was obtained through lab animal facility's procurement office. After 1 week acclimation, the animal was fasted 18 h prior to the study. The pig was administered a single intramuscular injection of Telazol for sedation and Atropine. It also found that in year 2009, Jiali Wang etc. al. from their studies [3] was using Styrofoam beads or air to stimulate lung tissue density that can give anthropomorphic lung phantom. A hollow sphere filled with FDG was used to stimulate lung tumors as shown in Fig. 2.2.

2.3 Bronchoscopy Based Method

2.3.1 Procedure

Bronchoscopy is a procedure used to look inside the lungs' airways, called the bronchi and bronchioles. The airways carry air from the trachea or windpipe, to the lungs. During the procedure, physician passes a thin, flexible tube called a bronchoscope through nose (or sometimes mouth), down the throat, and into the airways. If the patients have a breathing tube, the bronchoscope can be passed through the tube to your airways. The bronchoscope has a light and small camera that allow physician to see the inside of windpipe and airways and take pictures. The procedure can be performed without anesthesia, but in most cases, conscious sedation is utilized. If there's a lot of bleeding in the lungs or a large object stuck in the throat, physician may use a bronchoscope with a rigid tube. The rigid tube, which is passed through the mouth, is wider. This allows physician to see inside it more easily, treat bleeding, and remove stuck objects. A rigid bronchoscopy usually is done in a hospital operating room using general anesthesia.

2.3.2 Technologies and Methods

During the last decade, the development of image guided system using bronchoscopy method are focused on development and enhancement of virtual navigation system. Virtual navigation system in lung bronchoscopy case is a system that virtualize lung anatomies that can help physician to figure the best path toward the targeted nodules.

In 2001, Helferty et al. [5] began to develop image-guided endoscopy for assessment of lung cancer. An assessment system for medical image 3D virtual endoscopy and endoscopic follow-on life are described. The Focus of the development and the results are a 3D CT images of the chest and lung-cancer assessment. Two stages are involved in the assessment. In stage 1, the doctor uses a series of tools for visualization and analysis of 3D center-axis to establish guidance plan (a "case study"). Furthermore, during the phase-2 endoscopy, the doctor connects computer systems and case studies for endoscopy. Video endoscopy registered virtual 3D image data to provide physicians "augmented reality" for more information endoscopy. The results illustrate the utility systems for animal and human cases.

In 2004, Shinagawa et al. [14], evaluate virtual navigation system for bronchoscopic biopsy using ultrathin bronchoscopy equipment. Lung virtual model had been developed using autosegmentation and volume-rendering algorithm. Experiment shows that the view of virtual lung is relatively same with the view from bronchoscopic camera. Ultrathin bronchoscopy used to explore deeper part of lung, where the path of airways smaller. CT system utilized to track the position of bronchoscopy equipment while virtual navigation system guide the operator toward targeted nodules. This study give results about diagnostic sensitivity of the technique, which is 65.4 %, among test subject no one get complications problems except for small bleeding issue. Time used to finish the procedure varied between 5 and 30 min depend on the location of the lesions.

Reasoning that a live guidance is necessary, in 2006 and 2007, Helferty et al. [5] and Higgins et al. [6], respectively expand the idea of virtual navigation system and develop a system that fuse the lung virtual model with video stream from mounted camera in bronchoscopy equipment. It is found that breathing phase do not affect bronchoscopy significantly.

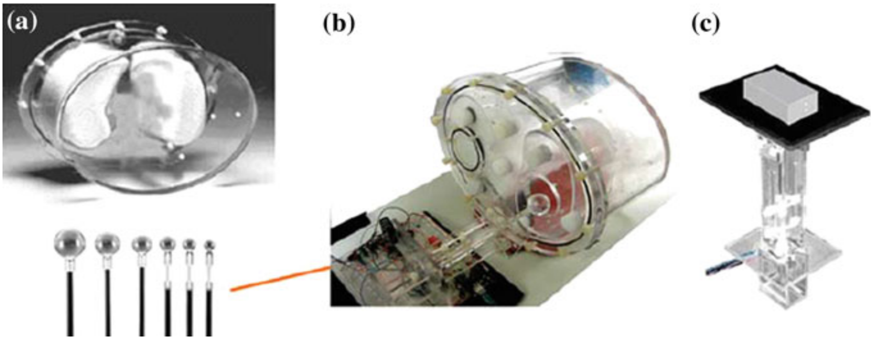

Fig. 2.3 **a** Static physical phantom and spheres, **b** the static phantom is converted to a dynamic phantom with the addition of a stepper motor connected to the spheres (*arrow*), **c** another stepper motor assembly used to simulate the movement of the chest [12]

In 2010 Xu et al. [11] proposed a method that fuses pre-operative 3D CT images with real-time fluoroscopy images. The result shows that this method has an accuracy around 2–4 mm. The single-view 2D/3D registration algorithm is feasible for X-ray guided bronchoscopy. The proposed algorithm shows good robustness for in-plane parameters (Rz, Tx and Ty). The performance of the algorithm is inferior for the three through-plane parameters (Rx, Ry and Tz). This result is expected Because only a single view is used in the registration. Another source of errors Might Be the different intrinsic binary patterns that virtual images and real X-ray images have. Therefore, feature points difference might have detected, hence some errors might be involved. Since the registration is designed for interventional use, it needs to be sufficiently fast so that the procedure will not be significantly prolonged. Their experiments show that the algorithm is much faster than both of intensity-based algorithms by splatting and ray-casting DRR generation. The proposed algorithm is faster and has a large capture range, though it sacrifices some through-plane accuracy in the process. This trade-off was motivated by the observation that in the X-ray guided bronchoscopy, a rough alignment between the CT can X-ray images may already provide sufficient information for the pulmonologist to choose the correct respiratory airway branch for inserting the surgical devices. This is in contrast to today's standard practice, in the which no CT overlay is used, Reviews such that the physician has no visual feedback of the airways (see Fig. 2.3a). Therefore, they believe that their work can improve the clinical outcome of the X-ray guided bronchoscopy by showing the patient's airways corresponding to the X-ray image.

In the virtual bronchoscopy, the airway should be Recognized path, in 2010 Graham et al. [15], proposed a novel algorithm for airway segmentation. Image-based planning and guidance of peripheral bronchoscopy requires the robust reconstruction of the peripheral airways visible in a patient's chest MDCT scan. Their proposed method is computationally efficient, requiring under 3 min on average to complete, has Essentially no parameter values to select, and consistently extracts far more peripheral airways than three companies competing methods. In addition, they have successfully applied the method to related problems in central-station chest lymph nodes and lymph-node definition extraction. It is, however, notable that in their ground truth study, no method was Able to extract 100 % of the airways that two expert observers were able to identify. Along in this line, they point out that they do not claim that their proposed method outperforms all existing methods for all cases. Furthermore, past research has shown a trend toward not-similar having a proposed method is "always" outperform another. This is a credit to Reviews These Researchers and reveals the difficulty of the fundamental problem. However, one of the other existing methods could serve as an alternative to their conservative region-growing approach for producing in stage 1 (provided leakage does not occur!). They believe this flexibility is a strength of their method. Furthermore, no existing method attempts to exploit both local and global information, both in the form of intensity and shape characteristics, as their method attempts to do. In particular, their algorithms for locating candidate airway cross sections and combining them into a tubular airway segments are novel for later counterbalancing the global benefit versus the cost of retaining an individual branch segments. Regarding the segmentation of small

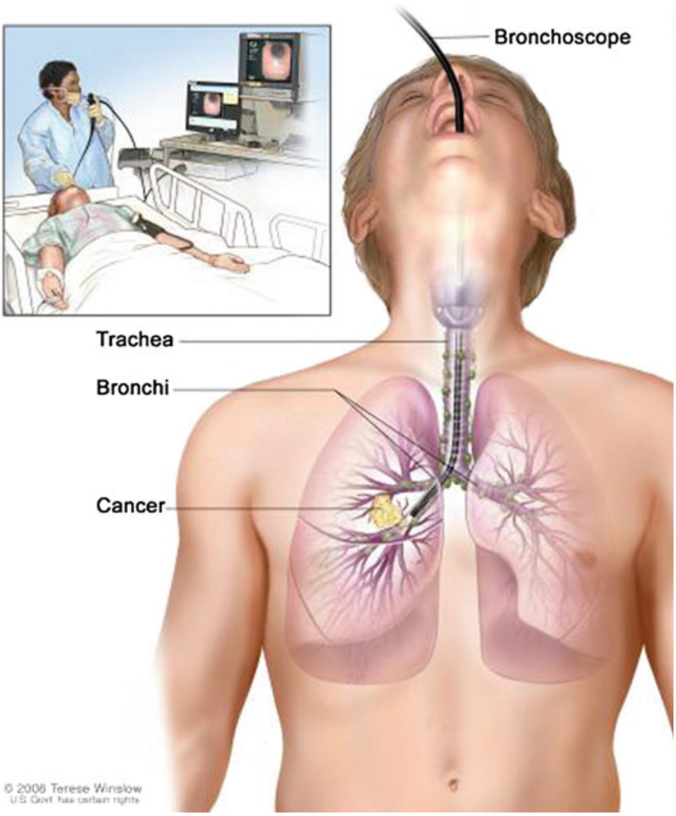

Fig. 2.4 Bronchoscopy procedure (*Source* emedicine.medscape.com/article/280104-overview)

peripheral airways, the choice of image-reconstruction kernels can have a substantial effect. Soft kernels (e.g., Siemens B31) have a smoothing effect and growing niche to blur the small airways, while sharp kernels (e.g., Siemens B50) can highlight the small airways, but amplify high-frequency noise. Patient motion can also adversely Affect a Reconstructed scan, as incorrect abrupt discontinuities can occur between adjacent 2-D sections. Finally, reviews of those employing thick-slice scans (3–10 mm-thick) sections and still commonly used clinically-are unsuitable for robust definition of peripheral airways (Figs. 2.4, 2.5).

In 2012 Rosell et al. [16] proposed a haptic interface for virtual bronchoscope. This interface help physician during planning phase to decide the best course for bronchoscope. This interface also open possibilities for training and simulation before attempting real procedures.

In 2013 Leong et al. [17] made a review about bronchoscopy technology and methods. Existing bronchoscopy methods such as Electromagnetic Navigation, Virtual Navigation, and Endobrochial ultrasound. Electromagnetic Navigation

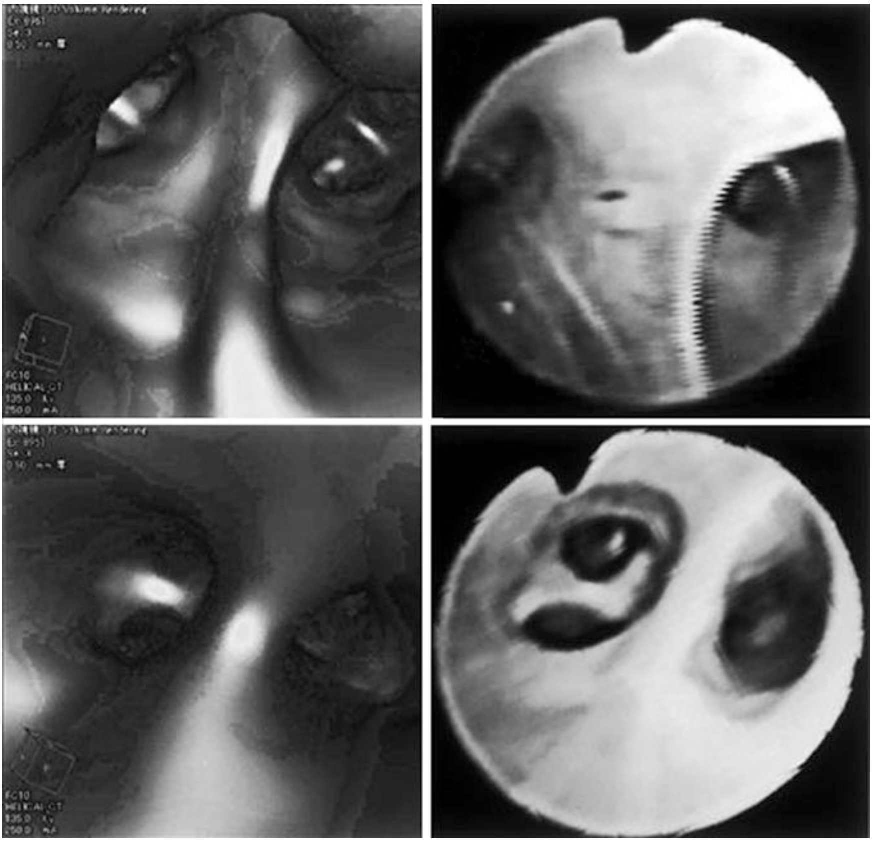

Fig. 2.5 Comparison of shinagawa's virtual lung airway and real lung airway [14]

Bronchoscopy is a bronchoscopy system where the position of bronchoscopy equipment is tracked using an electromagnetic sensor. There are 2 phases of Electromagnetic Navigation Bronchoscopy, planing phase, and execution phase. Electromagnetic Navigation Bronchoscopy has an elegant navigation and easy control, but had longer processing time, moreover, the system still cannot adapt to human breathing motions. Virtual Navigation Bronchoscopy is similar to Electromagnetic Navigation Bronchoscopy, because both of them used a virtual generated lung model for navigate inside lung. Virtual Navigation Bronchoscopy use real time CT imaging to track the position of bronchoscopy equipment. Endobrochial ultrasound is a minimaly invasive system combine endoschopy and bronchoscopy with mini ultrasound imaging system. Endobrochial ultrasound system mount mini ultrasound probe in the head of bronchoscopy equipment. Operator of this system need to be trained in order to recognize resulted ultrasound images.

Another facet of research in bronchoscopy is the development of the flexible bronchoscope, in 2014, Surakusumah et al. [18], apply soft-actuator as possible method to develop a more flexible bronchoscope. Flexible bronchoscope (FOB) is commonly used nowadays for airway observation in lung diagnosis because of its easier, safer, and good tolerant technique. However, during intubation, FOB may lead to get jammed due to unpassed size. Rino et al., develop a novel soft-tip FOB development using soft actuator mechanism to solve the jamming problem. Their study is focused on the design, fabrication, and implementation stages. The FOB design utilized a molding system that was drawn using SolidWorks and printed using 3D printer. The FOB fabrication used the printed mold to create the soft-tip by pouring the silicon rubber and mixing the inner and outer layers into the mold and solidifying them. The FOB initial implementation was performed by using tube and air pressure generator. By fabricating two types of soft actuator, combining twisting as well as bending movement actuator, a half-sphere movement actuator was developed. The result is that the proposed soft-tip could move close to half-sphere bending motion after standard pressure driving experiment was executed.

2.3.3 Clinical Value

In 2009 Iwano et al. [19] grouped pulmonary lesion based on size and position in pulmonary segment. Their research shows diagnostic sensitivity for peripheral pulmonary lesions <20 mm in diameter using virtual bronchoscopic was 71 % while using traditional method was only 33 %. Iwano et al. also concluded that lesion is the most significant factor for diagnostic rate.

One of the best advantage of bronchoscopic biopsy is, together with virtual bronchoscopy guidedance system, it has capabilities to take a sample from really small lesions, hence the capabilities to be used in pediatric patient cases. In 2010, Soo et al., describe a case, where 3d virtual bronchoscopy employed to remove bronchial foreign bodies from children.

Matsuno et al. (2011) try to measure diagnostic value of CT-guided ultrathin bronchoscopy. The diagnostic yield according to lesion size was 53.3 % for diameters ≤10 mm, 78.3 % for >10–15 mm, 96.4 % for >15–20 mm, and 72.7 % for >20 mm.

2.4 Needle Based Method

2.4.1 Procedure

CT-guided fine needle aspiration biopsy procedure starts with CT image acquisition. Physician then will detect the position of targeted nodules. Biopsy procedures should be executed without any delay after CT-Image acquisition. Further CT acquisition must be done before biopsy execution, in order to avoid the growth of the targeted nodule. As for any other intervention procedure, physicians should wear protective clothes and gloves. Based on acquired CT images, the physician determines the best point to insert the needle. Then the patient is required to stay in position to facilitate the procedure for physician to reach that point. The physician will find the most suitable needle entry point by analyzing data from the acquired CT image data set. The physician will mark the target and other important features, such as pulmonary blood vessels, which must be avoided by the needle. The skin entry point should be sterilised, a local anesthesia can also be delivered. During insertion of the needle, the patient will be asked to control his breathing, the technique to do this should be teached and practised before needle insertion. The patient should completely suspend his breathing when the needle is advanced or withdrawn (Fig. 2.6).

2.4.2 Technologies and Methods

Contrast with lung bronchoscopy biopsy methods, the research for image guided lung fine needle aspiration biopsy methods do not focused on the navigation systems, rather the trend of research is how to develop systems that can assist the procedure or even execute the procedure automatically.

In 2005 Hagman et al. [20] develop a haptic interface for fine needle aspiration biopsy guidance, according to Hagmann, there are several types of guidance system, robots, navigation and measurement tools, and tele-operated system. Robots mean automatization, physician let robot do the entire biopsy process with little to none intervention. Navigation and measurement tools is used by the physician to find the targeted lesions, but the execution of the procedure still done by the

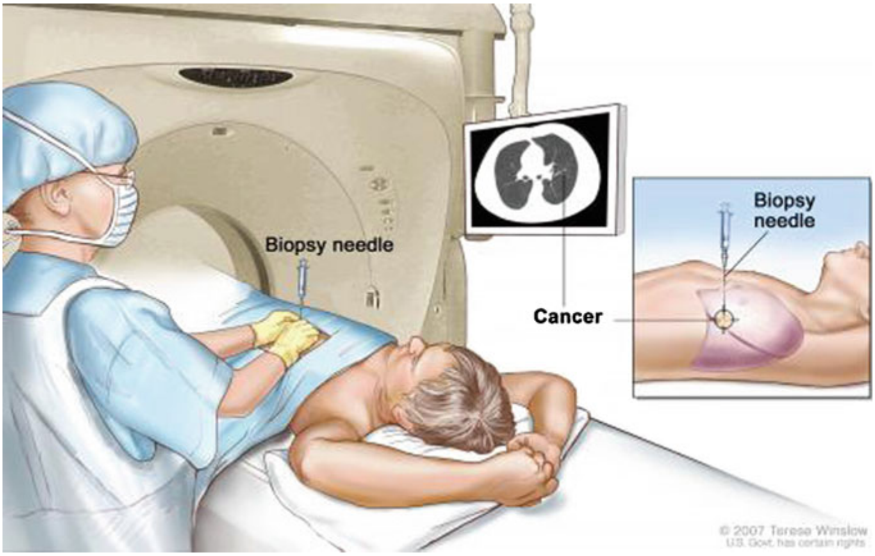

Fig. 2.6 Fine needle aspiration biopsy

physician. Tele-operated system give the physician control over a remote system, this system can move and hold a position accurately, but all of the procedure is controlled by the physician. Hagmann proposed a shared control approach, system can guide the needle into approximately correct position, but the physician will decide whether to execute the needle insertion or not. In the event the position is slightly incorrect, physician can also force the system to change needle position.

Also in 2005, Fichtinger et al. [21], developed an image overlay guidance for fine needle aspiration biopsy. The device consist of a display and semi-transparent mirror put in front of a CT-gantry. The display will show real time slice image from the CT, due to the arrangement of the semi transparent mirror, physician looking through the mirror will see the image overlay patient body. This system allow physician to measure and find lesion position and insert the needle simultaneously.

In 2007, Hanumara et al. [22] develop a remote controlled robotic for fine needle aspiration biopsy assistant, focused in user interface to increase learning curve of physician that use this robot. The procedure was not different from the usual fine needle aspiration biopsy procedure, but using robot as assistant the writers claim that could improve the procedure (i.e. faster, more accurate, etc.).

In 2009 Yaniv et al. [23], develop image guided navigation system for needle intervention using an open source C++ framework, called Image Guided Surgery Toolkit. According to them, an image guided navigation system had threefold effect, which are, shorten time for minimal invasive procedures, allowed for new procedures to emerge (i.e. the procedure that used to deemed as too dangerous), and transform qualitative evaluation into quantitative one. In their Image guided navigation system for lung, they address several problem, including how the imaging

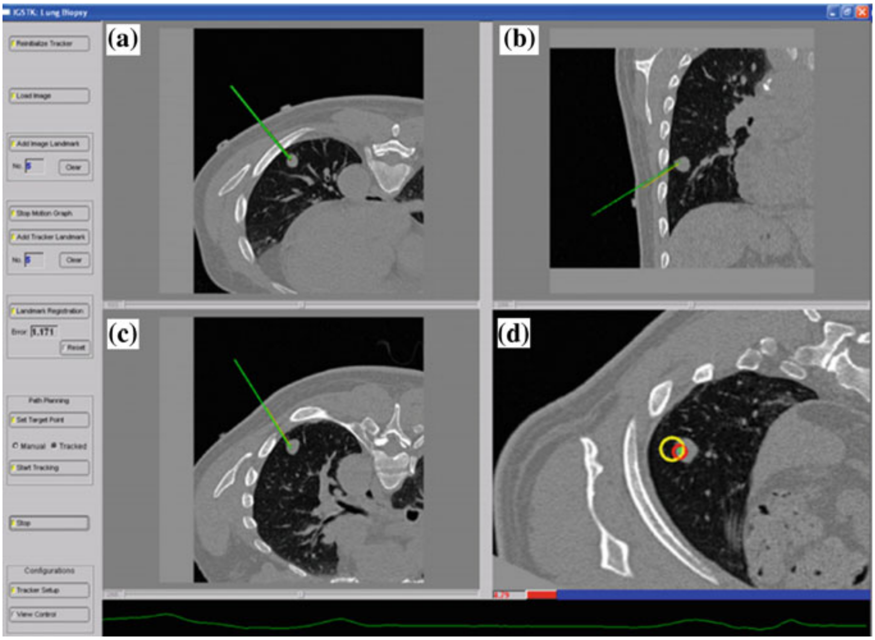

Fig. 2.7 Yaniv's image guided needle navigation system [23]

modality (CT) only provide single tomography thus limit the trajectory view, and about ionizing radiation for physician and patient. Their solution was to use pre-operative imaging combined with magnetic tracker device, thus allow for oblique trajectory examination as well as, minimize radiation (Fig. 2.7).

In 2011, Zhou et al. [9], develop a robotic biopsy system that adapt to patient motion pattern while breathing. They acquire several image of patient lung in their breathing cycle, these image then combined with camera that record patient skin surface to recognize breathing phase.

In 2013 Su et al. [24] proposed a fast CT and CT-fluoroscopy data fusion with respiratory motion compensation, while not specifically designed for fine needle aspiration biopsy, it is mentioned that this method can be used for percutaneous lung intervention.

2.4.3 Clinical Value

In 2010, Wu et al. [25] evaluating the procedures for percutaneous fine needle aspiration biopsy. According to them the most optimal technique for fine needle aspiration biopsy is composed of, conscious sedation, CT as imaging guidance, patient positioning in supine or prone position, as well as careful choosing of access route.

In 2010 Hiroki et al. [26] concluded that use of CT-fluoroscopy do not lessen risk of pneumothorax compared to conventional CT guided biopsy, however it is indeed reduce time needed for the procedure. On the same year, Kim et al. [27] also published a research report that confirm that use of CT-fluoroscopy reduce time of procedure, however, CT-fluoroscopy expose the patient to more radiation compared with conventional CT.

Comparison

In 2011, steinfort et al. [28] try to compare diagnostic value of EBUS-Bronchoscopy and Fine needle aspiration biopsy for peripheral lung lesions, they conclude that there are no significant difference in diagnostic value between EBUS-Bronchoscopy and Fine needle aspiration biopsy for peripheral lung lesions with size <3 cm.

2.5 Conclusion

Both of bronchoscopy and fine needle aspiration biopsy nowadays make use of image guiding systems. It seems like, bronchoscopy biopsy research trend was toward getting a better lesions detection and path finding, while fine needle aspiration biopsy research trend more focused on automatic systems. Bronchoscopy biopsy mostly use pre-operative image from CT-modalities combined with some form of position tracker, some of them is another imaging modalities such as bronchoscopy video and EBUS system, while fine needle aspiration biopsy nowadays use CT-Fluoroscopy or combination of pre-operative image from CT-modalities and real time image of CT-Fluoroscopy. Most of research report claim image guiding system promote less time procedure and more accuracy. No significant difference between the two method, however there is claim that while fine needle aspiration biopsy has slightly more accuracy, bronchoscopy biopsy has slightly less risk.

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