Peer Review File

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Reviewer A:

Comment 1: Using cone beam CT enhanced fluoroscopy combined with electromagnetic navigation bronchoscopy, Michael et al. Performed biopsy of pulmonary nodules with a median size of 16.0 mm (range: 7-55 mm). The diagnostic accuracy was 93.5% and the safety margin was 4%. However, patients using the technique received an average dose of 2.0 mSv each time. What progress has been made in radiation reduction?

Reply 1: We appreciate such comment. Indeed, how to reduce the radiation dose has always been a concern for doctors and patients, especially for clinicians who work on the front line all the year round. It is more necessary to solve this problem. According to the existing research results and clinical practical application guidance content, we added some data (see Page 7, line 145-153).

Changes in the text: Therefore, reducing the radiation dose is very beneficial to patients and doctors. Because the lung tissue has an air-filled alveolar structure, the natural contrast of the lung tissue structure is higher than that of air. Therefore, to a certain extent, reducing the tube current and tube voltage has no pronounced effect on the display and positioning of lung tissue lesions. Additionally, effectively reducing the repeated guidance and positioning of CT is an auxiliary improvement measure to reduce the radiation dose. These measures have effectively reduced the radiation dose and considerably reduced the loss of the tube and detector.

Comment 2: He Jie et al. showed that the diagnostic rate of enbcb for pulmonary nodules less than 3.0 cm was 89.2%. Unfortunately, the incidence of mild to moderate bleeding was 40.5% due to the use of cryosurgery. How to reduce the complications of cryosurgery?

Reply 2: Thank you for pointing it out. Indeed, with the popularization and

application of cryosurgery, how to effectively reduce bleeding complications is a problem that must be addressed. According to the precautions commonly used in clinical practice, we have modified our text as advised (see Page 8, line 157-165).

Changes in the text: To reduce the occurrence of this complication, the clinic has also made further improvements and provided guidance. First, the freezing time of the probe site must be strictly controlled. Second, cryosurgery should be performed on the lung periphery where the blood vessel density is low. When performing operations on the area close to the hilar where the blood vessel density is high, norepinephrine can be injected into the airway in advance to contract the blood vessels properly. Finally, the balloon can be preinstalled before surgery to prepare for closure. Abundant clinical experience and skilled operation are also important factors in reducing bleeding complications.

Comment 3: Exercise of the heart and aorta can make the left lung more active than the right lung, and the lower and upper lobes are also more active due to respiratory movement. These differences will lead to ENB navigation and positioning errors and affect the diagnostic rate. How to further reduce the error of ENB navigation and positioning?

Reply 3: We appreciate such comment. In fact, the accuracy of ENB navigation is directly related to the quality of imaging data collection. Therefore, ensuring the accuracy of image data can reduce the error rate of ENB navigation. According to some current practices and the latest developments in navigation technology, we have modified our text as advised (see Page 13, line 265-271).

Changes in the text: Of course, research on ENB has also made further improvements to reduce errors in clinical applications. On the one hand, the CT data near the examination date (the same day or day before) are used to reconstruct the lung images accurately. On the other hand, a respiratory gating system is introduced based on ENB to restore the patient's accurate image data through respiratory compensation. However, it remains difficult to completely overcome the positioning errors caused by cardiovascular pulsation and respiratory motion.

Comment 4: The emergence of ENB has greatly improved the diagnostic efficiency of early lung cancer, but compared with the results of 2007-2018, it is not difficult to find that the diagnostic efficiency of ENB alone has not improved significantly in the past 10 years. What are the causes of ENB diagnostic efficiency bottleneck?

Reply 4: Thank you for pointing it out. It is undeniable that the current ENB navigation technology has developed more maturely, and more research has been carried out on the joint use of various technologies. But in our opinion, the bottleneck restricting ENB navigation technology is still the objective and subjective uncertainty in the biopsy process. Based on the above point of view, we have modified our text as advised (see Page 12, line 247-253).

Changes in the text: The bottleneck restricting the further improvement of ENB diagnostic efficiency is largely the uncertainty associated with biopsy. Specifically, the objective factors of the patient's lung lesions (e.g., whether there is tracheal access in the lesion, whether the ENB probe can reach the lesion site, whether the lesion is positioned accurately, and the choice of biopsy method) and the subjective factors of ENB operators (e.g., experience, proficiency, correctness of clinical decision-making) collectively lead to uncertainty.

Comment 5: Studies have shown that two-thirds of the lungs using ENB biopsies are twice as much as one in the peripheral lung, and the detection rates of central, intermediate and peripheral lesions are 82%, 61% and 53%, respectively. Why? How to improve the detection rate of ENB for peripheral lung lesions?

Reply 5: We appreciate such comment. In fact, affected by many objective factors such as respiratory activity, tracheal passage, airway diameter, etc., the diagnostic efficiency of ENB gradually decreases from the hilar to the periphery of the lung. For these reasons, ENB is focusing on the development of transparenchymal nodule access (ENB-TPNA) technology in order to improve the detection rate for peripheral lung lesions. We have modified our text as advised (see Page 13, line 274-284).

Changes in the text: In addition to the lesions near the periphery of the lung being

more affected by respiratory movement, the ability to accurately detect, locate and biopsy the lesions is also an important reason for this phenomenon. In particular, ENB's endoscopic probe cannot reach the airway after level 12 because of its outer diameter and supporting force. Thus, ENB also focuses on developing transparenchymal nodule access (ENB-TPNA) technology in terms of technical exploration. The principle is to make an “artificial tunnel” leading to the lesion in the adjacent airway of the lesion that has no tracheal access or where the probe cannot reach and subsequently biopsy the lesion through this passage. However, the technology is still in the stage of continuous exploration and has not been popularized to date.

Comment 6: The size of SPN is also the main factor affecting the efficacy of ENB. Compared with lesions larger than 20 mm, the diagnostic rate of peripheral lesions smaller than 20 mm is 57% lower, which has become the consensus of ENB application. How to improve the diagnostic rate of ENB for small peripheral lesions?

Reply 6: We appreciate such comment. In our opinion, for nodules with a peripheral lung diameter of less than 20mm, biopsy can be combined with percutaneous lung biopsy technology in some cases, and there are companies currently doing research and development in this area. We have modified our text as advised (see Page 14, line 287-291).

Changes in the text: If ENB positioning technology is combined with percutaneous lung biopsy technology, it can effectively improve the diagnostic performance of lesions with a peripheral diameter of less than 20 mm. Currently, the 4D electromagnetic navigation system developed by related companies is working on this exploration.

Reviewer B:

Comment 1: In Line 31-32, I think this sentence is very confusing. NLST trial showed that a nodule on the screening CT more than 4mm was defined as positive

and about 96% of the lung nodules were false positive, but most of the diagnostic evaluation was done from the further imaging analysis and invasive procedure was rarely performed.

Reply 1: Thank you for pointing it out. We apologize for such mistake. The expression in the original article is like this: “More than 90% of the positive screening tests in the first round of screening (T0) led to a diagnostic evaluation. Lower rates of follow-up were seen at later rounds. The diagnostic evaluation most often consisted of further imaging, and invasive procedures were performed infrequently. Across the three rounds, 96.4% of the positive results in the low-dose CT group and 94.5% of those in the radiography group were false positive results”. It is our incorrect interpretation of the original text that has caused you confusion, we have modified our text as advised (see Page 3, line 54-57).

Changes in the text: Notably, the false-positive rate (FPR) of low-dose spiral CT can be as high as 96.4%. That is to say, 96.4% of the positive screening results in the low-dose CT group were false-positive results.

Comment 2: The paragraph of line 52-63 would be better to move to the main context rather than being in the introduction section. Also, the introduction of the SPiN Thoracic Navigation System that is different from the Super dimension navigation system could be helpful to understand the EMN device more broadly.

Reply 2: We appreciate such comment. Indeed, if you modify it according to your suggestions, it will be more helpful for a systematic statement and a broad understanding of the content of the article. We have modified our text as advised (see Page 4, line 82-88, Page 5, line 89-90, 106-110, Page 6, line 111-117).

Changes in the text: In recent years, a new generation of assisted navigation technology represented by the SPiN Thoracic Navigation System has also gradually emerged. Prior to the CT scan, stickers equipped with electromagnetic sensors were placed on the patient's chest and kept in place during the procedure to help guide navigation and track the patient's breathing [Figure 1 c, d]. Next, a highly accurate 3D map of the lungs that can quickly calculate the shortest path from the lesion and

accurately guide the positioning path was synthesized according to the inspiration/expiration CT scanning protocol, providing more strategies for the diagnosis and treatment of peripheral lung lesions.

The ENB operating system includes the main body of the tracheal mirror magnetic navigation system, electromagnetic board, navigation positioning catheter, tracheal mirror working channel extension catheter and navigation positioning sensor [Figure 1 a, b]. To operate ENB, the prior chest thin layer CT image is used for 3D reconstruction to establish a navigation route, and the guiding catheter is subsequently carried in the bronchoscopy to reach the lesion. Because the guiding catheter tip carries the electromagnetic positioning sensor, the lesion location can be reproduced in real time onto the pre-generated lung 3D roadmap. The patient lies on the magnetic plate such that the whole chest is in a weak magnetic field, and a special curved catheter with a microsensor inserted into the head end extends into the bronchial cavity. Finally, the catheter can be accurately delivered to the site where the lesion is located for a needle biopsy [Figure 2, Figure 3].

Comment 3: Figure 1 suggested the way to perform the EMN procedures, but a little bit insufficient to understand it. I recommend that more detailed pictures about the procedure or related devices would be included regarding the EMN procedures.

Reply 3: Thank you for pointing it out. Indeed, more relevant pictures will be very helpful for deepening the understanding of the EMN procedures. We have modified our text as advised (see Figure 1, Figure 2, Figure 3).

Changes in the text: The specific modifications are shown in Figure 1, Figure 2, and Figure 3.

Comment 4: In the section of pulmonary nodule, “Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions: One-Year Results of the Prospective, Multicenter NAVIGATE Study. J Thorac Oncol. 2019 Mar;14(3):445-458. is also an important article that has to be addressed.

Reply 4: We appreciate such comment. Indeed, NAVIGATE is a large, multicenter

cohort study that prospectively evaluated the diagnostic yield of ENB with rigorous follow-up to ensure that negative or indeterminate results are truly negative. NAVIGATE shows that an ENB-aided diagnosis can be obtained in approximately three-quarters of evaluable patients across a generalizable cohort based on prospective 12-month follow-up in a pragmatic setting with a low procedural complication rate. We have modified our text as advised (see Page 6, line 129-132).

Changes in the text: Another large, multicenter cohort study showed that approximately three-quarters of patients with evaluable lung lesions could be safely diagnosed in all medical institutions and in all challenging areas of the lung.

Comment 5: In the lymph node biopsy section, most of the mediastinal LN biopsy is implemented with EBUS-TBNA. Dose EMN-TBNA have any other advantages compared to the EBUS-TBNA?

Reply 5: Thank you for pointing it out. Indeed, in the lymph node biopsy section, we ignore the application comparison between EMN-TBNA and EBUS-TBNA. In our opinion, in the specific operation of lymph node biopsy, the biggest advantage of EMN-TBNA compared to EBUS-TBNA is that it is less restrictive, especially in some enlarged lymph nodes with special growth properties. We have modified our text as advised (see Page 9, line 178-187).

Changes in the text: Moreover, ENB-TBNA also has a greater advantage than EBUS-TBNA. EBUS-TBNA has relatively strict requirements on the location and growth characteristics of lymph nodes. When enlarged lymph nodes are located close to the hilar and grow outside the trachea, EBUS-TBNA can achieve a higher biopsy success rate. However, once there is a tissue partition between the enlarged lymph node and airway, the ultrasound probe cannot detect the lesion well, resulting in a greatly reduced biopsy success rate. ENB-TBNA is less affected by the above factors. For swollen lymph nodes that are not adjacent to the hilar, biopsy can still be performed under the conditions of no adherent growth and increased tissue separation from the airway.

Comment 6: In line 187-188, the meaning of the sentences is somewhat ambiguous. I suggest this sentence should be written more clearly. And you can introduce another navigation system to overcome the respiratory movement in the both lower lung by adopting the respiratory gating system.

Reply 6: Thank you for pointing it out. Indeed, these few sentences in our article are somewhat ambiguous. At the same time, it is also very meaningful to introduce the content of the respiratory gating system in overcoming the errors caused by the respiratory movement. We have modified our text as advised (see Page 12, line 259-263, Page 13, line 265-271).

Changes in the text: Clinical studies have shown that lesions in the upper and middle lobes of the right lung have higher diagnostic efficiency than other lung lobes using ENB. Being affected by the pulsation of the heart and great blood vessels, the left lung has greater mobility than the right lung. At the same time, being affected by respiratory movement, the lower lobe of the lung has greater mobility than the upper lobe.

Of course, research on ENB has also made further improvements to reduce errors in clinical applications. On the one hand, the CT data near the examination date (the same day or day before) are used to reconstruct the lung images accurately. On the other hand, a respiratory gating system is introduced based on ENB to restore the patient's accurate image data through respiratory compensation. However, it remains difficult to completely overcome the positioning errors caused by cardiovascular pulsation and respiratory motion.

Comment 7: In line 210-211, I couldn’t catch the exact meaning why you think is difficult to diagnose the lesions near the hilum through the navigation system. It would be best for us to explain it in more detail or provide related articles.

Reply 7: Thank you for pointing it out. It may be that our presentation logic is not very clear, which has caused your confusion. In fact, from our point of view, compared with other endoscopy and navigation techniques, ENB has not significantly improved the diagnostic performance of lesions close to the hilar, such as biopsy of

hilar enlarged lymph nodes, lesions in the large airways, and other easier-to-reach lesions. It is possible to use ordinary endoscopy techniques to achieve high-efficiency diagnostic capabilities. The choice of ENB biopsy strategy at this time will undoubtedly increase the burden on patients and the workload of doctors. Therefore, the use of ENB should be considered based on actual conditions. We have modified our text as advised (see Page 14, line 303-308, Page 15, line 309-310).

Changes in the text: Second, compared with other endoscopy and navigation techniques, ENB has not significantly improved the diagnostic performance of lesions close to the hilar, such as biopsy of hilar enlarged lymph nodes, lesions in the large airways, and other easier-to-reach lesions. It is possible to use ordinary endoscopy techniques to achieve high-efficiency diagnostic capabilities. The choice of ENB biopsy strategy at this time will probably increase the burden on patients and the workload of doctors. Therefore, the use of ENB should be considered based on actual conditions.