

# Usefulness of 3D-printed Coplanar Puncture Template Assisted CT- guided Percutaneous Core Needle Biopsy of Small ( $\leq 20\text{mm}$ ) Pulmonary Nodules: 3 Years of Experience

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## Research

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# Abstract

**Background and Objective:** Computed tomography guided percutaneous lung biopsy is a commonly used method for clarifying the nature of pulmonary nodules. However, due to the existence of breathing movement, the lungs have greater mobility, and biopsy of small pulmonary nodules is difficult. In recent years, 3D-printed coplanar templates are gradually used in percutaneous biopsy of small pulmonary nodules. Therefore, this study aimed to evaluate the application value of 3D-printed coplanar puncture template assisted computed tomography guided percutaneous core needle biopsy of small ( $\leq 20\text{mm}$ ) pulmonary nodules.

**Method:** From January 2018 to January 2021 in Taihe Hospital, 210 hospitalized patients with pulmonary nodules underwent percutaneous core needle biopsy for histopathology/cytopathology diagnosis and were included in the study. All patients were randomly allocated into two groups, patients in Free-hand group underwent percutaneous core needle biopsy without 3D-printed coplanar templates, and patients in 3D-PCT group underwent percutaneous core needle biopsy with 3D-printed coplanar templates. The number of needle adjustments, number of CT scans, surgical time-consuming, diagnostic accuracy, and incidence of complications were recorded and compared between the two groups. Rapid on site evaluation was routinely used for guiding specimens' triage. Approval for this trial was obtained from the Ethics Committee of the Taihe hospital.

**Result:** The number of needle adjustments ( $1.41 \pm 0.63$  vs.  $2.23 \pm 0.85$ ), the number of CT scans ( $3.63 \pm 0.73$  vs.  $4.25 \pm 0.81$ ) and the incidence of pneumothorax (9.6% vs. 21.1%) during the procedure were significantly lower in the observation group than the control group ( $P < 0.05$ ), whereas there were no significant differences in the diagnostic accuracy (95.2% vs. 94.3%) and incidence of pulmonary hemorrhage (65.4% vs. 62.3%) between the two groups ( $P > 0.05$ ), however, the surgical time-consuming in 3D-PCT group is significantly more than Free-hand group.

**Conclusions:** These findings indicated that the 3D-printed coplanar puncture template combined with CT guided percutaneous biopsy can relatively fix the target lesion, reduce the number of needle adjustments and number of CT scans, reduce iatrogenic radiation, and reduce the incidence of complications, especially pneumothorax.

## Introduction

Low-dose CT (low dose computed tomography, LDCT) has unique advantages for the detection of small pulmonary nodules<sup>1</sup>, therefore, the detection rate of pulmonary nodules has increased, it's reported to be 8–51%<sup>2,3</sup> according to related studies. Fleischner society defines pulmonary nodules as dense, spherical or irregular, clear or unclear lesions with a diameter of  $\leq 3$  cm scanned by Low-dose CT<sup>3</sup>, CT guided percutaneous core needle biopsy (CNB) can directly obtain lesion tissue, which is an important means for the diagnosis of pulmonary nodules<sup>4</sup>. However, the small pulmonary nodules are small in size and shifted with respiratory movement, thus, traditional CT-guided percutaneous CNB is lack of certain

advantages. Huang MD *et al.*<sup>5</sup> and Kothary N *et al.*<sup>6</sup> reported that the biopsy results of small lesions were less accurate than those of large lesions, and studies reported a diagnostic accuracy of 87–95% during CNBs of nodules smaller than 20mm<sup>7–9</sup>.

Therefore, the accuracy of traditional CT guided percutaneous CNB for small lung nodules is also worth studying. Certainly, a fixed needle is needed to fix the moving nodules, similar to a "moving target" that becomes a "stationary target", which reduces the difficulty of biopsy and obtains the diseased tissue accurately. Recently, the use of the 3D-printed navigational template for localization of small peripheral lung nodules showed good efficacy and safety<sup>10</sup>.

However, there are few reports on 3D-PCT assisting CT guided percutaneous CNBs of pulmonary nodules. Although, Ji Z *et al.*<sup>11</sup> summarized the process and technical characteristics of 3D-PCT assisting CT guided percutaneous CNBs, there is no control group, and no comparative study about the diagnostic accuracy, pathological examination results, and complications. In order to further explore the efficacy and safety of 3D-PCT assisting CT guided percutaneous CNB of pulmonary nodules, we conducted comparative clinical research, all cases were reviewed, and patients were divided into 3D-PCT group and Free-hand group. Based on the diagnostic accuracy of CNB, the incidence of complications, such as pneumothorax, pulmonary hemorrhage and air embolism, as well as the operation time and the number of CT scans, we comprehensively evaluate the utility of 3D-PCT in percutaneous CNB of pulmonary nodule.

## Patients And Methods

### Patients

This is a single center, comparative clinical study. This study has been approved by Taihe hospital ethics committee. Between January 2018 and January 2021, there are 289 patients who are recommended to be hospitalized for diagnosis or treatment due to pulmonary nodules. All patients who are recommended for percutaneous lung puncture need to undergo contrast-enhanced CT (CECT), which is in advance to determine the blood supply of the pulmonary nodule and the blood vessels adjacent to the nodule.

Inclusion criteria: ☑Patients diagnosed for the first time or with a history of tumors, with lung lesions  $\leq 2$  cm in diameter; ☑There is a needle path; ☑Can tolerate puncture surgery. Exclusion criteria: ☑ those with the lesion close to large blood vessels; ☑those with abundant blood donors in the nodules; ☑those with severe emphysema, pulmonary bullous disease, chronic obstructive pulmonary disease (COPD); ☑those with abnormal blood coagulation; ☑those with hemorrhagic diseases; ☑patients with severe infections. Finally, 210 of the 289 patients underwent CT-guided percutaneous CNB, all of whom gave written informed consent before the procedure. 3D-PCT group, 55 males, 49 females, aged 26 to 77 (Mean,  $53.3 \pm 11.1$ ) years; Free-hand group, 54 males, 52 females, aged 22 to 76 (Mean,  $54.7 \pm 10.6$ ) years. Patient's demographics and nodule characteristics of the two groups were recorded and analyzed, including lesion size, pleura-to-lesion distance, lesion location, causes of nodules and specimens obtained. Patient characteristics and lesion parameters are detailed in Table 1.

Table 1  
Patient characteristics and lesion parameters

	<b>3D-PCT (n)</b>	<b>Free-handed (n)</b>	<b>Difference (<math>\chi^2</math> or <i>t</i>)</b>	<b>Significance (<i>P</i> value)</b>
Patients(male/female)	104(55/49)	106(54/52)	0.079*	0.778
Age(range),years	53.3 ± 11.1(26–77)	54.7 ± 10.6(22–76)	-0.93#	0.36
Size ,mm				
1–10	34(32.7%)	29(27.4%)	0.711*	0.399
11–20	70(67.3%)	77(72.6%)		
Pleura-to-lesion, mm				
0–30	32(30.8%)	33(31.1%)	2.139*	0.343
30–60	53(50.9%)	61(57.6%)		
>60	19(18.3%)	12(11.3%)		
Number of fixed needles				
1	77(74.0%)	0		
2	27(26.0%)	0		
Lesion location				
Superior lobe of left lung	22(21.2%)	25(23.6%)		
Inferior lobe of left lung	9(8.7%)	5(4.7%)		
Superior lobe of right lung	32(30.8%)	36(34.0%)		
Middle lobe of right lung	14(13.5%)	14(13.2%)		
Inferior lobe of right lung	27(25.8%)	26(24.5%)		
Causes of nodules				
Physical examination	99(95.2%)	96(90.6%)		
Tumor history	5(4.8%)	10(9.4%)		
Specimen (range) ,n	3.7 ± 1.2(1–6)	3.8 ± 1.1(1–6)	-0.32#	0.75
#represents the <i>t</i> value of Independent-Samples <i>t</i> Test; * represents $\chi^2$ value of Chi-square test.				

## Equipment

16 multislice spiral computed tomography (Philips Co. Ltd.), disposable 17-gauge coaxial biopsy needle (C1816B, BARD Medical Devices Inc, USA), which allows multiple biopsies once the lesion has been targeted. Disposable 18-gauge core biopsy needle (MN1816, BARD Medical Devices Inc, USA) used to collect samples. 3D-printed Coplanar Puncture Template, three-axis coordinate navigation frame, angle-measuring instrument (Tangshan Tongrenhe Technology Co. Ltd), negative pressure position fixing pad (Philips Co. Ltd.) (Figure S1). Disposable 17-gauge coaxial introducer needle (MCXS1820BP, Argon Medical Devices, Inc, USA). BioPince™ full core biopsy instrument (360-2080-01, Argon Medical Devices, Inc, USA). Disposable fixed needle (Argon Medical Devices, Inc, USA).

## Patient position and fixation

Patients were admitted to the interventional radiology department on the same day of the procedure, According to the patient's recent imaging data, draw up the approximate puncture path, and select the appropriate patient position based on facilitating access to the target lesion and avoiding target lesion motion, in addition, Try to keep the patient in a comfortable and relaxed position. For patients in the 3D-PCT group or Free-Hand group, negative pressure vacuum bag need to be used to fix their positions. Place the self-made positioning metal grid (Figure S2) tightly on the body surface of the patient's pre-puncture point.

## Location of puncture point

Patients in both groups need to be scanned the pre-puncture point first, images of 3-mm slice thickness with a standard lung window were acquired during the entire procedure, so that the nodules can be clearly displayed. Generally, the maximum cross-section of the nodule under the CT scan is designed for the puncture path, and the needle path from the pleura to the target lesion was also chosen to be as short as possible. Generally, the maximum cross-section of the nodule under CT scan was selected to design the puncture path, and the needle path from the pleura to the target lesion was also chosen to be as short as possible. The most appropriate needle insertion point is selected according to the cross point formed by the imaging point of the positioning metal grid on the patient's body surface under the CT image and the positioning laser line. Mark the selected intersection point, that is, the pre-puncture needle point, and then record the puncture angle and depth based on the CT image.

## Installation of navigation system and 3D-PCT

The three-axis coordinate navigation frame was installed on the same side of the lesion and connected with the angle-measuring instrument. Then, coplanar puncture template was connected to the navigation frame, and adjusts the template in all directions (X-, Y- and Z-axis) (Figure S3) to match the intersection line and laser positioning line on the patient's body surface (Figure S4). Finally, adjust the template angle to meet our demands<sup>11</sup>. The above operation is only for patients in the 3D-PCT group.

## Computed tomography-guided CNBs procedure

After sterile preparation for all patients, 1% lidocaine was used for local anesthesia. In the 3D-PCT group, 1 or 2 fixed needles are inserted about 0.5 to 1.0 cm from one or both sides of the nodule (Figure S5).

Confirm that the insertion position, depth and direction of fixed needle are consistent with the designed. If there is an angle or depth deviation, adjust the needle to the ideal position. The fixation needle is punctured to a distance of 0.5 to 1.0 cm from the lesion to fix the local lung tissue and the nodule itself. The fixed needle is used as a reference, combined with the CT scan layer and template coordination, the biopsy needle path was accurately designed. Coaxial needle was inserted into the upper edge of lesion (about 0.5 cm away from the lesion) through the selected template holes, CT scan again to confirm that the position is accurate, and then biopsy with biopsy instrument. If the biopsy specimen is not satisfied, adjust the biopsy direction appropriately and re-biopsy. Patients in Free-hand group, the biopsy were performed with coaxial method. A 17-gauge coaxial introducer needle (C1816B, BARD Medical Devices Inc, USA) was introduced to the upper edge of the lesion (about 0.5 cm away from the lesion) from the pre-designed needle path and puncture point. Then perform a CT scan to confirm that the position, depth and angle of the coaxial introducer needle are completely consistent with the pre-designed, if there is a deviation of angle or length, adjust the needle in real time. an 18-gauge core biopsy instrument (MN1816, BARD Medical Devices Inc, USA) was introduced through the central canal of the coaxial biopsy needle, The specimen notch of biopsy was 19 mm or 9.5 mm, according to the lesion size.

Rapid on site evaluation was performed for all biopsies by a presented cytopathologist (Dr.Wang). Biopsied specimens gently rolled onto the slide and stained with Diff-Quik for on-site evaluation and preliminary diagnosis. ROSE results interpreted as malignancy, tuberculosis or granuloma, fungus, and feedback to the interventional radiologist to biopsy at least twice to obtain enough specimens for subsequent immunohistochemistry (IHC) testing, molecular testing, and Ziehl-Neelsen staining or schiff periodic acid shiff (PAS), periodic acid-silver methexamine (PASM) or microbiology culture. Workflow of ROSE in sample triaging for ancillary testing as reported by Jain D *et al.*<sup>12</sup>. Record ROSE results of biopsy specimens in all cases.

The number of samples obtained was based on the cytopathologist's evaluation, the clinical suspicion, and the presence of an acute complication that necessitated the termination of the procedure.

All tissue samples obtained by CNBs were fixed with 10% formalin and embedded in paraffin for routine histopathological examination. The patient's electrocardiogram, vital signs, and blood oxygen saturation are monitored throughout the operation. After the operation is completed, the CT scan is used to observe whether there are complications such as pneumothorax and pulmonary hemorrhage. If the patient felt discomfort or blood oxygen dropped, which occur during a major pneumothorax, a chest tube was inserted into the pleural cavity, if necessary. Then transferred to the recovery room where oxygen (100%) was administered by nasal cannula at a rate of 3 L/min. Record the number of CT scans, the number of needle adjustments, frequency of biopsy, and complications of each patient. All patients were monitored closely for 4 hours after the biopsy procedure.

## **Histopathological diagnosis**

Whether the needle biopsy is successful depends on the pathological examination or microbiology report. The needle biopsy specimens were double-blindly diagnosed by two experienced chest pathologists in the

pathology department. Histopathological findings reported as malignant tumors, sarcomas, atypical hyperplasia, or microbiology diagnosed as tuberculosis and fungal. Non-specific inflammation cases showed no significant changes in the nodules during follow-up, which means that the needle biopsy is successful. The pathological diagnosis report indicates that the specimens with insufficient tissue or cells are considered non-diagnostic cases, and the cases is suspicious or inconclusive and cannot be clearly diagnosed are also regarded as non-diagnostic cases. That is, negative biopsy specimens, meaning that the needle biopsy failed.

## Statistical analysis

SPSS software version 17.0 was used for statistical analysis. Measurement data are expressed as the mean  $\pm$  standard deviation (mean  $\pm$  SD), and *t* test was used; the chi-square test or Fisher's exact test was used to compare categorical data. Probability values  $< 5\%$  ( $p < 0.05$ ) were considered statistically significant

## Results

104 patients were included in 3D-PCT group, 55 males, and 49 females, with a median age of 58.7 years (range, 26–77 years). 106 patients in Free-hand group, 54 males, 52 females, with a median age of 58.7 years (range, 13–84 years). No significant difference was observed between 3D-PCT and Free-hand about age and gender. The number of patients in the 3D-PCT group and the Free-Handed group with pulmonary nodules ranging from 1 to 10 mm is 34(32.7%) and 29(27.4%) respectively, the number of patients with lung nodules ranging from 11 to 20 mm is 70(67.3%) and 79 (72.6%) respectively, and there was no statistical difference in pulmonary nodule size. In present study, the pleura-to-lesion distance is divided into three ranges: 0-30mm, 30-60mm and  $> 60$ mm, the number of patients with pleura-to-lesion of 0-30mm in the 3D-PCT group and Free-hand group is 32(30.8%), 33(31.1%) respectively, 30-60mm is 53(50.9%), 61(57.6%) respectively,  $> 60$ mm is 19(18.3%), 12(11.3%) respectively. No significant difference was observed about pleura-to-lesion distance in the two groups, as shown in Table 1. The patients in the 3D-PCT group who used 1 fixed needle was 77 cases, and who used 2 fixed needles was 27 cases during the puncture procedure. In 3D-PCT group and Free-hand group, there were 22(21.2%) and 25(23.6%) cases of patients with pulmonary nodules in the superior lobe of left lung respectively, 9 (8.7%) and 5 (4.7%) cases in the inferior lobe of left lung respectively, 32 (30.8%) and 36 (34.0%) in the superior lobe of right lung respectively, 14(13.5%) and 14(13.2%) cases in the middle lobe of right lung respectively, and 27 (25.8%) and 26(24.5%) cases in the inferior lobe of right lung respectively. There was no statistical difference about the nodules location between the two groups. The average number of specimens obtained for each patient in the 3D-PCT group and the Free-hand group was  $3.7 \pm 1.2$  (range, 1–6) and  $3.8 \pm 1.1$  (range, 1–6) respectively, no significant differences were observed.

As shown in Table 2, the incidence of pneumothorax in 3D-PCT group was 9.6% (10/104), significantly lower than Free-hand group 21.1% (22/106) ( $p < 0.05$ ). The number of patients with pulmonary hemorrhage in the two groups was 39.6% (41/104), 37.5% (40/106) respectively, and no statistical

difference was observed. hemoptysis occurred in 7.7% (8/104) patients of 3D-PCT group, 8.5% (9/106) in Free-hand group, no significant differences were observed.

Table 2

Comparison of complications, number of needle adjustments, number of CT scans and time calculation between 3D-PCT and Free-hand group during biopsy procedure

	3D-PCT	Free-hand	Difference ( $\chi^2$ or <i>t</i> )	Significance ( <i>P</i> value)
Complications, n				
Pneumothorax	10(9.6%)	22(21.1%)	5.04*	0.025
Hemorrhage	41(39.6%)	40(37.5%)	0.221*	0.638
Hemoptysis	8(7.7%)	9(8.5%)	0.045*	0.832
Air Embolism	0	0		
Needle adjustments (range),n	1.41 ± 0.63(1–3)	2.23 ± 0.85(1–4)	-7.85#	0.00
Number of CT scans (range), n	3.63 ± 0.73(3–5)	4.25 ± 0.81(3–6)	-5.95#	0.00
Time calculation(range), min	61.36 ± 9.96(48– 110)	36.48 ± 6.55(22– 63)	21.34#	0.00
Diagnostic accuracy	95.2%(99/104)	94.3%(100/106)	0.077*	0.782
#represents the <i>t</i> value of Independent-Samples <i>t</i> Test; * represents $\chi^2$ value of Chi-square test.				

No complications of air embolism or death cases. Needle adjustments in 3D-PCT group were significantly lower than those in Free-hand group, during the puncture procedure, the needle adjustments in 3D-PCT group averaged 1.41 ± 0.63 times (range, 1–3) and Free-hand group averaged 2.23 ± 0.85times (range, 1–4). The number of CT scans in 3D-PCT group was 3.63 ± 0.73 (range, 3–5), which was significantly lower than 4.25 ± 0.81 (range, 3–6) in Free-Handed group (*p* < 0.05). The average surgical time of 3D-PCT group was 61.36 ± 9.96 minutes (range, 48–110 minutes), which was significantly longer than Free-hand group, with an average time of 36.48 ± 6.55minutes (range, 22–63 minutes).

Histopathological/Microbiology findings of total 210 biopsied patients were detailed in Table 3. There were 69 (66.4%) and 71 (67.0%) malignant/premalignant cases in 3D-PCT group and Free-Handed group, respectively. Primary adenocarcinoma accounted for the largest proportion of malignant tumor cases in the two groups, 51(49.0%) and 56 (52.8%) cases respectively; Followed by atypical hyperplasia, with 12 (11.54%) and 7 (6.60%) cases respectively; last metastatic AdC, with 4 (3.85%) and 3 (2.83%) cases respectively. There were 30 (28.8%) and 29 (27.4%) benign cases in 3D-PCT group and Free-hand group, respectively. Of the benign cases, tuberculosis in the two groups accounted for 13.5% (14/104), 7.54%

(8/106), respectively. *Cryptococcus neoformans* accounted for 2.88% (3/104), 4.72% (5/106), respectively. And non-specific inflammation accounted for 8.65% (9/104), 6.6% (7 /106). In 3D-PCT group and Free-hand group, there were 5 (4.8%) and 6 (5.7%) cases of non-diagnostic findings, respectively, including inadequate materials, suspicious, and inconclusive. Positive cases in the two groups was 99,100 in all, with a diagnostic accuracy of CNB is 95.2% (99/104), 94.3 % (100/106), respectively. Statistical analysis showed that there was no significant difference in diagnostic accuracy between the two groups, detailed in Table 2.

Table 3  
Histopathology/Microbiology findings of 210 biopsied lesions

<b>Histopathological/Microbiology findings</b>	<b>3D-PCT (104)</b>	<b>Free-hand (106)</b>
Malignant/Premalignant	69(66.4%)	71(67.0%)
Primary AdC	51	56
Primary SqCC	0	2
Metastatic AdC	4	3
Other malignant	1*	2*
AAH	2	3
Atypical hyperplasia	12	7
Benign	30(28.8%)	29(27.3%)
Hamartomas	1	2
Tuberculosis	14	8
Non-necrotic granuloma	2	3
Cryptococcus neoformans	3	5
Aspergillus	0	1
Organizing pneumonia	1	2
Fibrosis	0	1
Non-specific inflammation <sup>#</sup>	9	7
Non-diagnostic	5(4.8%)	6(5.7%)
Inadequate materials	1	2
Suspicious	1	0
Inconclusive	3	4
AAH, Atypical adenomatous hyperplasia		
*Lymphomas, <sup>#</sup> patients has been followed-up for more than 1 year,		

The specimens were triaged based on the preliminary diagnosis of ROSE. Ancillary tests were performed in 153 of 210 (72.85%) cases (Fig. 1). 114 cases underwent subsequent immunohistochemistry (IHC) assessment, like CK7, TTF-1, and Napsin A for adenocarcinoma and p63, p40, and CK5/6 for squamous cell carcinoma. predictive biomarkers (ER, PR, HER2, Ki-67) was routinely performed for all metastatic

breast cancer cases. In addition, of the 114 cases, 33 cases that diagnosed adenocarcinoma carried out molecular tests of EGFR, KRAS and ALK genes simultaneously, 3 cases of specimens that ROSE preliminary diagnosed lymphomas performed flow cytometry. 27 cases of ROSE preliminary diagnosed tuberculosis or granuloma, obtained additional materials for Ziehl-Neelsen staining, molecular testing by polymerase chain reaction (PCR). 9 cases of cryptococcus neoformans or aspergillus diagnosed with PAS, PASM staining or microbiology culture. The typical ROSE cytological (Diff-Quik staining) and histopathological (Hematoxylin-Eosin staining) morphology of adenocarcinoma, cryptococcus neoformans, aspergillus and tuberculosis are shown in Fig. 2.

## Discussion

The lungs swings up and down with breathing, especially the lower lung, and so the location of the pulmonary lesion is not fixed. Therefore, the position of the image marker during positioning may be different from the actual position after needle insertion. In addition, the lung is a loose air-containing organ with abundant internal blood vessels. In biopsy, a puncture needle is generally required to pass through normal lung tissue to reach the lesion. Pneumothorax, pulmonary hemorrhage or even air embolism may occur during repeated passage through the pleura and lung tissue. Based on these characteristics, the needle biopsy for small pulmonary nodules ( $\leq 20\text{mm}$ ) is more difficult and the probability of complications is higher.

Since 2016, Chinese scholars have tried to apply 3D-printed coplanar puncture template and fixed needle technical to CT-guided percutaneous core needle biopsy of pulmonary nodules<sup>11</sup>, but reports on this technology are rarely. Therefore, we conducted a comparative study to explore the clinical application value of 3D-printed coplanar puncture template assisted CT guided percutaneous core needle biopsy of small ( $\leq 20\text{mm}$ ) pulmonary nodules. In present study, we reached an interesting conclusion through comparative analysis, the accuracy of 3D-PCT assisted CT guided percutaneous CNB puncture was 95.2%, which was not significantly higher than 94.3% in Handed-free CNB group ( $p > 0.05$ ). Many researchers have shown that compared with other puncture methods, CT-guided CNB has advantages in terms of accuracy or positive rate. For instance, Choi SH *et al.*<sup>13</sup>, Andrade JR *et al.*<sup>14</sup> reported an overall diagnostic accuracy of 95.0% and 92.3% during CT guided percutaneous CNB of small pulmonary nodules ( $\leq 20\text{ mm}$ ) respectively, concluded that diagnostic accuracy is influenced by the biopsy method, and CT-guided CNB is an excellent diagnostic tool, its accuracy being high. Li Y *et al.*<sup>15</sup> reported an overall diagnostic accuracy of 93.5% during CT-guided percutaneous CNB of small ( $\leq 20\text{ mm}$ ) pulmonary lesions. The diagnostic accuracy and yield in present study are almost similar to reported literature of CT-guided CNB. In present study, 3D-printed coplanar puncture template assisted CT guided percutaneous core needle biopsy of small pulmonary nodules overall diagnostic accuracy was not significantly higher than that of Free-Handed group, which may be due to the use of CT- guided CNB in both 3D-PCT group and Free-hand group, with trained and experienced interventional radiologist for more than 10 years.

Pneumothorax and pulmonary hemorrhage are the most common complications during percutaneous core needle biopsy of the pulmonary lesions. The incidence of pneumothorax in the previous article is

generally between 15% and 62%<sup>6,7,16-20</sup>. previous study reported that risk factors for the development of biopsy-related pneumothorax include the presence of chronic obstructive pulmonary disease (COPD)<sup>21</sup>, small lesion size<sup>22,23</sup>, a long needle path<sup>22,24</sup>, and technical factors like repeated pleural puncture<sup>25</sup> or wider insertion angle of the needle<sup>26</sup>. We excluded COPD patients in our study, thereby avoiding patient-related risk factors for pneumothorax, and considered technical factors for pneumothorax, CNB was completed by two trained and over 10 years of experienced interventional radiologists (Dr. Ren and Dr. Wang). Therefore, compared with the incidence of pneumothorax previously reported in the literature, the overall incidence of pneumothorax in this study is at a relatively low value of 9.6%. According to present research, we believed that the number of needle adjustments significantly decreased, then avoiding pneumothorax related to repeated pleural puncture, which attributed to use 3D-printed coplanar puncture template. This is an important reason why the incidence of pneumothorax in the 3D-PCT group was significantly lower than that in the Free-hand group. Needle adjustments require CT scans to determine whether the angle and depth are adjusted correctly, so the increased number of CT scans was associated with increasing the number of needle adjustments. With the assistance of 3D-printed coplanar puncture template, the number of needle adjustments is significantly reduced, avoiding more number of CT scans of iatrogenic radiation for patients. Therefore, we believe that 3D-printed coplanar puncture template is good auxiliary equipment for CT-guided CNB of small ( $\leq 20\text{mm}$ ) pulmonary nodules. Although the reported incidence of pulmonary hemorrhage ranges from 4–43%<sup>7,23,24,27</sup>, the present study revealed that a 39.6% (41/104), 37.5% (40/106) of intrapulmonary hemorrhage rate for the two groups respectively, and no significant differences were observed. pulmonary haemorrhage were considered as mild based on our data, which benefit from all patients receiving contrast-enhanced CT (CECT) before puncture, experienced interventional radiologist analyze the distribution of pulmonary vessels near pulmonary nodules according to the image of CECT, avoid blood vessels and choose a reasonable puncture path. Other scholars believed that small lesion size and greater lesion depth or long biopsy path are associated with a higher risk of bleeding<sup>23,24</sup>. Interestingly, the risk factors of pulmonary hemorrhage in the two groups mentioned above are no statistical difference. No complications of air embolism and tumor seeding of the pleura or chest wall during percutaneous core needle biopsy of the pulmonary lesions. Average surgical time-consuming in 3D-PCT group is significantly more than Free-hand group, which is due to large time-consuming of 3D-PCT group pre-puncture preparation, including Installation of navigation system and 3D-PCT and fixed needle use.

Use of ROSE for triaging biopsy specimens has been encouraged by many scholars. For example, Collins *et al.*<sup>28</sup> showed that ROSE service can improve cell block quality, thereby providing better utilization for IHC assessment and for IHC testing in positive diagnostic category cases. Fetzner *et al.*<sup>29</sup> concluded that ROSE can prioritize the management of tissue specimens to maximize tissue preservation and minimize wastage. Nasuti JF *et al.*<sup>30</sup> demonstrated that ROSE can be beneficial in facilitating rapid clinical decisions and triaging specimen for ancillary studies. In our institution, ROSE is routinely used in CNB procedures. Interventional radiologists decide to re-biopsy or not according to the interpretation of ROSE, and triage the specimens, especially for preliminary diagnosis of malignant tumors or special infections

(e.g. tuberculosis, Aspergillus, cryptococcus neoformans) specimen by ROSE. Based on our long-term practical experience, we believe that the application of ROSE for triage of CNBs biopsy specimens can take priority of management of tissue materials for patients, minimize specimen storage, and play a role in precise diagnosis.

Nevertheless, our research still has some limitations, Firstly, the number of cases is small, and more samples are needed to confirm our conclusions. Secondly, the risk factors related to puncture complications have not been systematically studied, such as lesion size, lesion depth, and needle path, insertion angle of the needle or repeated pleural puncture. This is also the direction that we need to further study later.

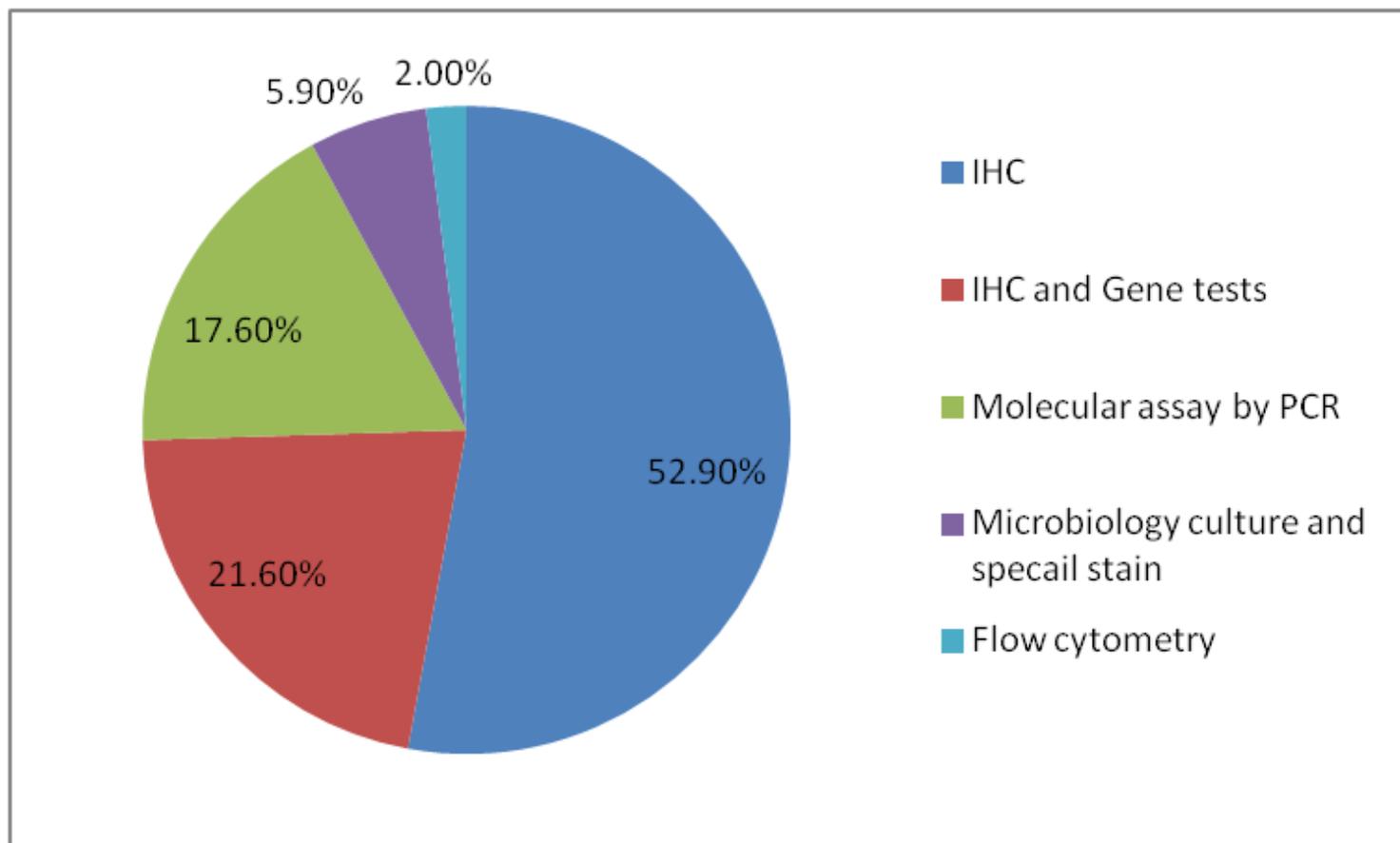
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## Figures



**Figure 1**

Triage of specimens based on preliminary diagnosis of ROSE.

## Diff-Quick

## HE

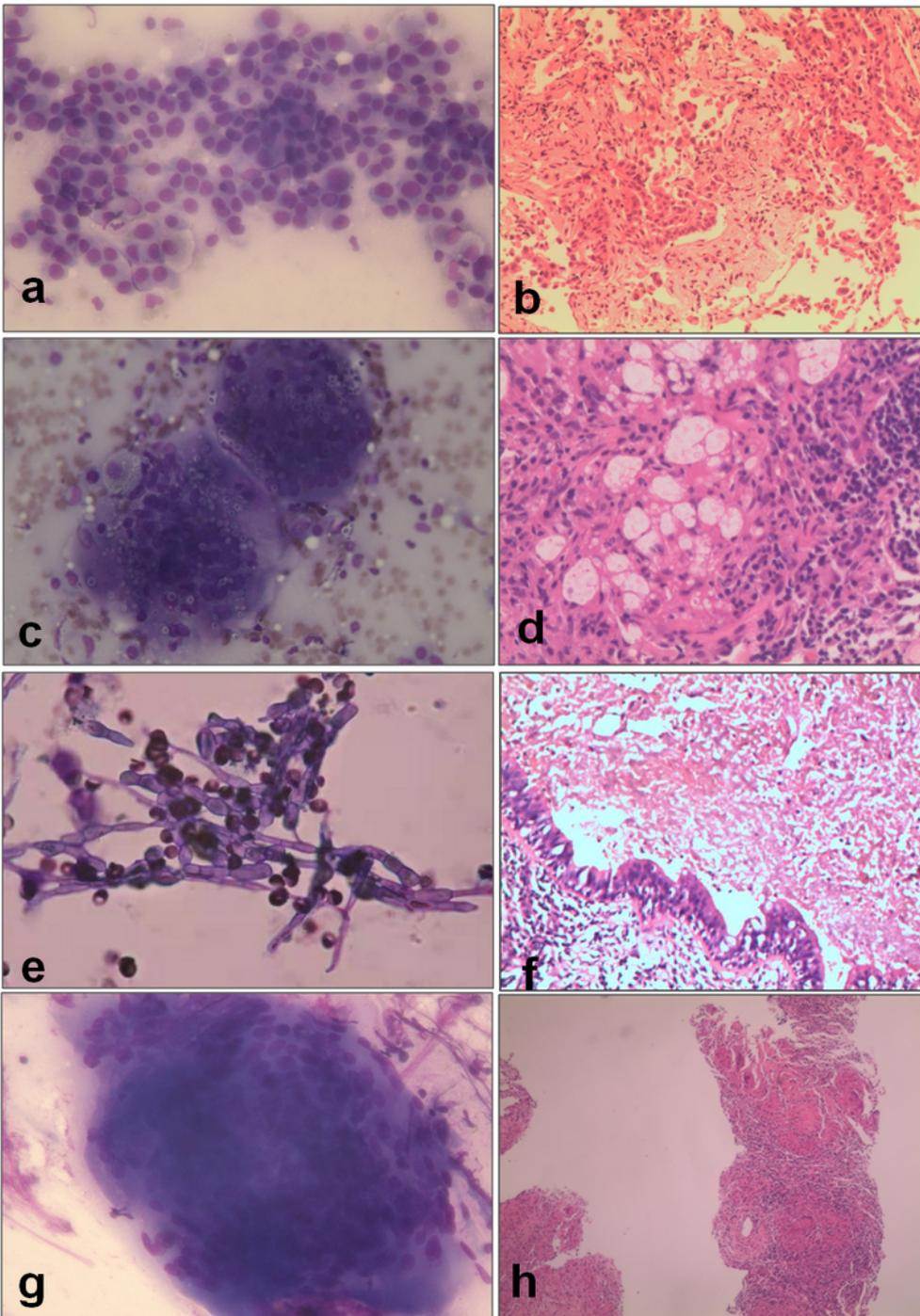


Figure 2

Diff-Quick and histological hematoxylin-eosin (HE) staining for biopsy specimens: (a, b) adenocarcinoma, (c, d) cryptococcus neoformans, (e, f) Aspergillus, (g, h) tuberculosis.

## Supplementary Files

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