

2020 Clinical Practice Guideline for Percutaneous Transthoracic Needle Biopsy of Pulmonary Lesions: A Consensus Statement and Recommendations of the Korean Society of Thoracic Radiology.

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Image-guided percutaneous transthoracic needle biopsy (PTNB) is a minimally invasive tissue sampling procedure for the pathologic diagnosis of peripheral lung lesions. Image-guided PTNB has been performed since the 1960s (1); however, its first modern practice guideline was established by the British Thoracic Society (BTS) in 2003 (2). The introduction of lung cancer screening with low-dose computed tomography (CT) (3 4 5) and the evolving field of precision medicine for lung cancer in the 2010s (6) are expanding the role of PTNB in lung cancer diagnostics. Nevertheless, the 2003 BTS guideline remains the sole guideline dedicated to PTNB. Wide variations in domestic practice patterns of PTNB were reported among surveyed radiologists in Korea (7), the United States (8), and the United Kingdom (9). The lack of an up-to-date guideline for PTNB may be responsible for these variations in practice, potentially hampering the delivery of standardized diagnoses and management of lung cancer. Therefore, we embarked on a project to develop the first evidence-based clinical practice guideline for PTNB in Korea by adapting pre-existing guidelines to improve the quality of PTNB in daily practice and promote standardization of the procedure nationwide.

The working group comprised 14 thoracic radiologists from the Korean Society of Thoracic Radiology (KSTR). The development committee included the working group members, an expert respiratory physician, an oncologist, a thoracic surgeon, and a clinical guideline methodologist who supported the planning of the overall process and guideline methodology. All the working group members participated in the development of the guidelines, in which key questions were assigned (Supplementary Table 1).

Our guidelines development process employed the guideline adaptation methodology of the Korean Society of Radiology and the National Evidence-Based Healthcare Collaborating Agency (10) while following the Reporting Items for Practice Guidelines in Healthcare Statement (11).

The working group had an offline meeting to discuss and list questions that should be addressed in the guidelines. The tentative list of key questions was circulated to working group members after meeting and debated online to prioritize the questions until consensus was reached. The four main

domains for key questions addressed the indications for PTNB, pre-procedural evaluation, procedural technique of PTNB and its accuracy, and management of post-biopsy complications. For each domain, three key questions were specified, as follows:

- 1-1) What are the conventional indications and general factors for considering PTNB?
- 1-2) What are the upcoming indications for PTNB in the era of personalized medicine?
- 1-3) What are the contraindications for PTNB?
- 2-1) What kinds of laboratory tests are required prior to PTNB?
- 2-2) Should a pulmonary function test be performed prior to PTNB?
- 2-3) Which imaging examinations should be performed prior to PTNB?
- 3-2) How should interventionists choose the imaging guidance modality for PTNB?
- 3-3) Which needle size, how many samples, and which technique (biopsy vs. aspiration) should be used for PTNB?
- 4-1) What is the appropriate management of pneumothorax?
- 4-2) What is the appropriate management of hemoptysis?
- 4-3) What is the appropriate management of air embolism and hemothorax?

To identify relevant guidelines, a study coordinator performed systematic literature searches of international databases up to August 2018, including the Ovid-MEDLINE, Ovid-EMBASE, Guidelines International Network, Cochrane Library, and major domestic databases, including KoreaMed, KMBASE, and Korean Medical Guidelines and Information (Supplementary Table 2). The searches were supplemented by screening the bibliographies of retrieved publications.

A total of 910, 1033, 344, and 466 publications were identified in the initial searches for the main domains of key questions 1, 2, 3, and 4, respectively. The appropriateness of the identified publications was assessed by three members per key question: the members independently selected guidelines based on the predefined inclusion and exclusion criteria, followed by establishing a consensus through discussion under the supervision. After excluding duplicates and performing an initial screening of titles and abstracts with a subsequent full-text review, the working group included 29, 4, 15, and 6 guidelines for the evidence synthesis of the four main domains, respectively (Supplementary Fig. 1).

The working group members reviewed the quality of the selected guidelines using the Korean Appraisal of Guidelines for Research and Evaluation II tool. We applied the following criteria for final inclusion: 1) guidelines with a mean overall quality score of 50 or higher by all reviewers; 2) guidelines with a mean recommendation score of 50 or higher by the reviewers assigned to each key question. The median number of participating reviewers for assessing the overall quality was 8 per guideline, and the number of reviewers for key questions 1 to 4 was 4, 3, 4, and 3 members, respectively. After these processes, 11, 7, 1, and 4 guidelines were finally included for key questions 1 to 4, respectively (Supplementary Table 3).

The working group members reviewed the evidence in the literature that supported the recommendations of the included guidelines. The members graded the level of evidence of each guideline based on the evidence level criteria of the Korean Clinical Imaging Guidelines to create an

evidence table (Table 1 , Supplementary Table 4) (10). A draft version of the recommendation document was produced based on the evidence table, then reviewed by the development committee, resulting in 39 recommendations in four key questions. The final level of evidence and grade of recommendation was determined by the consensus of the development committee and working group members.

The two-round Delphi method was used for formal consensus. The recommendation document with supporting materials was circulated to working group members via email. The members independently graded the degree of agreement in each recommendation using a 9-point scale: 1 to 3, inappropriate; 4 to 6, uncertain; 7 to 9, appropriate recommendation. We adopted the recommendations for which more than two-thirds of the members assigned scores of 7 or higher. Among the 39 recommendations, 35 recommendations were adopted in the first round, and the other four recommendations were adopted in the second round after the modification of tone and expression. The appropriateness score for the accepted recommendations was 7.0–9.0 (standard deviation: 0.4–2.1).

The final recommendations were reviewed by the core members of the KSTR and relevant Korean Academic Societies, including the Korean Academy of Tuberculosis and Respiratory Disease, the Korean Association of Lung Cancer, the Korean Society of Medical Oncology, and the Korean Society for Thoracic and Cardiovascular Surgery. Feedbacks from the societies were evaluated and reflected in the practice guidelines as appropriate.

The summary of the recommendations for the key questions is presented in Table 2 .

- We recommend assessing the risk of malignancy of pulmonary lesions before performing a biopsy.

(recommendation grade A, evidence level III)

- We suggest performing a biopsy of pulmonary lesions that show definite growth.

(recommendation grade B, evidence level III)

- We suggest performing a biopsy of multiple nodular lesions of unknown etiology.

(recommendation grade B, evidence level III)

- We suggest performing a biopsy of persistent focal infiltrates of unknown etiology.

(recommendation grade B, evidence level III)

- We recommend assessing the risks and benefits of a biopsy procedure before performing the biopsy.

(recommendation grade A, evidence level II)

- We recommend evaluating the persistence of subsolid lesions by performing a follow-up CT scan 6–12 months later for pure ground-glass lesions, and 3–6 months later for part-solid lesions.

(recommendation grade A, evidence level II)

- We suggest that a biopsy may be considered for persistent or growing part-solid lesions larger than 15 mm overall and for those with a solid portion that is 8 mm or larger in diameter.

(recommendation grade B, evidence level II)

Remark: if a persistent or growing part-solid lesion is strongly suspected to be lung cancer, it is possible to proceed directly to surgical resection without PTNB.

The 2013 American College of Chest Physicians (ACCP) and 2015 BTS guidelines recommended assessing the pretest probability of malignancy when any diagnostic interventions, including PTNB, are applied for an indeterminate pulmonary nodule and when clinicians interpret biopsy results (12 13) (Supplementary Table 4). A few risk prediction models for managing pulmonary nodules have been developed and validated (12 13). Of these models, the Brock model generally provides the highest predictability of malignancy (13 14). The Brock model calculates the estimated probability of malignancy for a pulmonary nodule based on the patient's age, sex, family history of lung cancer, emphysema, nodule size, location of the nodule, nodule type (solid, part-solid, ground-glass nodule), nodule count, and spiculation. A negative biopsy result for malignancy must be cautiously interpreted, given the pretest probability of malignancy. If the biopsy result is negative for malignancy despite a high probability of malignancy (13), a repeated biopsy can be considered.

A growing pulmonary nodular lesion is one of the main indications of PTNB in several guidelines (2 13 15 16). Multiple nodular lesions of unknown etiology are another indication of PTNB (2). PTNB is also applicable to persistent focal infiltrates of unknown etiology when other non-invasive or minimally invasive diagnostic procedures fail to make a diagnosis (2). PTNB is preferentially recommended for peripheral pulmonary lesions, which are likely to be inaccessible with a bronchoscopic approach (2 12 17).

The risk-benefit assessment of PTNB is presented in several guidelines as a fundamental step before performing the procedure (2 12 15 18 19 20). PTNB is regarded to be generally safe, but complications of the procedure may occur. The risk of complications differs across patients, characteristics of the pulmonary lesions, and procedures. Accordingly, the benefits and risks of PTNB are assessed on an individual basis before performing PTNB, along with a consideration of other alternative diagnostic procedures that may be safer than PTNB. Detailed information about specific complications is presented in other parts of the text.

It is recommended to check the persistence of subsolid lesions before considering PTNB (12 16), as a substantial proportion of subsolid lesions are transient (21). If a lesion persists, the 2013 ACCP and 2017 Fleischner guidelines recommend positron emission tomography (PET), nonsurgical biopsy, or surgical biopsy for a part-solid lesion with a solid portion larger than 8 mm (16), or a part-solid lesion larger than 15 mm (12). Persistent subsolid lesions represent a spectrum of disease from atypical adenomatous hyperplasia to invasive lung adenocarcinoma (22). When the PTNB result indicated a preinvasive atypical adenomatous hyperplasia, approximately 90% of the lesions were found to be adenocarcinoma upon resection (23). Furthermore, the diagnostic accuracy of pre-surgical PTNB followed by resection was comparable to that of surgical resection based on CT analysis without PTNB (24). Considering the findings above, subsolid lesions strongly suspected to be lung adenocarcinoma can cautiously be advanced to surgical resection without PTNB.

- We recommend performing a biopsy to acquire a tumor specimen for molecular profiling of lung cancer or intrathoracic metastasis.

(recommendation grade A, evidence level I)

- We recommend performing a biopsy according to the patient's desire or clinical situation.

(recommendation grade A, evidence level III)

- We recommend a multidisciplinary discussion to determine the necessity and site of the biopsy.

(recommendation grade A, evidence level III)

The 2013 ACCP guideline contained a recommendation about obtaining adequate tissue via nonsurgical biopsy for molecular analysis (15 18) (Supplementary Table 4). The same recommendation was made in the 2011 National Institute for Health and Care Excellence (NICE) guideline (25) and the 2014 Scottish Intercollegiate Guidelines Network (SIGN) guideline (19). The 2018 European Society for Medical Oncology (ESMO) guideline specified particular mutations for molecular profiling, including epidermal growth factor receptor mutations, the T790M mutation, anaplastic lymphoma kinase rearrangement, ROS1 rearrangement, BRAF V600 mutation, and programmed cell death ligand 1 expression (20). Decisions regarding the choice of procedure could be made depending upon the patient's desire and a multidisciplinary discussion (12 16).

Molecular profiling is an essential step to provide the standard of care for patients with solid metastatic tumors (26). The reimbursement of targeted drugs usually requires information on the mutational status of the malignancy, and patients sometimes are willing to undergo PTNB for a mutational analysis despite an a priori known histologic diagnosis (27). As the genetic mutational profile of a tumor can change after a targeted therapy, PTNB of the same lesion can be repeated after treatment. Repeated PTNB for molecular profiling is typically defined as a rebiopsy, whereas a repeated biopsy refers to a repeated PTNB due to diagnostic failure of the initial PTNB (28). In the literature, 78.8–90.0% of rebiopsy specimens were adequate for molecular analysis, with an acceptable range of complication rates, from 4.0–25.7% (29 30 31 32 33). For the analysis of programmed death-ligand 1 (PD-L1) expression, PTNB provided adequate specimens in 96.4% of biopsies, with a complication rate of 28.4% (34). As it is important to target viable tumor tissue in rebiopsies (33), advanced imaging studies, including contrast-enhanced CT scans, PET scans, or diffusion-weighted or dynamic contrast MRI, can be performed before PTNB to distinguish viable tumor tissue from areas of necrosis, fibrotic tissue, or post-radiation changes. When selecting the biopsy target among multiple lesions, the primary tumor and metastatic lesions are regarded as equally suitable (35). A core needle biopsy is preferred over fine-needle aspiration for molecular analysis to obtain enough tumor tissue. If a tissue sample is obtained by fine-needle aspiration, it is desirable to assure the adequacy of tumor tissue by performing an on-site evaluation of aspirated tissue (35).

- We recommend not performing a biopsy in the following circumstances, which are absolute contraindications.

- 1) Patients who do not provide informed consent

(recommendation grade A, evidence level III)

- We suggest that PTNB should be carefully considered in the following circumstances based on a multidisciplinary risk-benefit assessment.

- 1) Patients with respiratory failure or with a predicted forced expiratory volume in 1 second (FEV₁) of less than 35%
- 3) Patients with bleeding tendency or coagulopathy
- 4) Patients with pulmonary arterial or venous hypertension
- 5) Patients who underwent pneumonectomy or functionally have a single lung

(recommendation grade B, evidence level III)

The contraindications of PTNB can be categorized into absolute and relative contraindications. It is mandatory to obtain informed consent from the patient with a sufficient explanation of the benefits and potential risks of the procedure (2). PTNB is contraindicated if consent is not obtained. Vascular lesions, including pulmonary artery aneurysm or arteriovenous malformation, are absolute contraindications of PTNB. Interventionists should thoroughly evaluate preoperative CT images to avoid causing massive hemoptysis when performing PTNB due to vascular injury (36).

Relative contraindications of PTNB include respiratory failure or a predicted FEV1 of less than 35%, mechanical ventilation, bleeding tendency, coagulopathy, pulmonary arterial or venous hypertension, single lung (anatomically or functionally), and uncooperative patient. Thoracic interventionists must carefully consider whether to perform this procedure based on a multidisciplinary risk-benefit assessment (2). The minimum lung function required for PTNB is not clearly defined, but a threshold of a predicted FEV 1 of 35% is commonly used (2). PTNB in patients on mechanical ventilation requires a careful approach, as mechanical ventilation increases both the difficulty of the procedure and the risk of pneumothorax and air embolism (37). A moderate or higher risk of bleeding tendency and coagulation abnormalities should be corrected before the procedure (2).

Pulmonary artery or venous hypertension is traditionally recognized as a risk factor for bleeding after PTNB (2). However, the cutoff value of pulmonary arterial pressure as a contraindication of PTNB has rarely been specified. Right-sided heart catheterization is the reference method for diagnosing pulmonary hypertension by measuring the mean pulmonary artery pressure, but this procedure is seldom performed before PTNB in clinical practice. An enlargement of the diameter of the main pulmonary artery to 2.95 cm or larger on pre-procedural CT can be used for assessing the presence of pulmonary hypertension if the information on the mean pulmonary artery pressure is not available (38). Conflicting reports exist regarding whether enlargement of the main pulmonary artery is a risk factor for severe parenchymal hemorrhage or hemoptysis after PTNB (39 40).

Although a history of pneumonectomy has been regarded as an absolute contraindication to PTNB (41 42), Cronin et al. (43) reported that the success rate of PTNB, preferentially performed by needle aspiration, was 86% (12 of 14) in a single lung in patients with a history of pneumonectomy. Pneumothorax occurred in 25% of patients, but all cases were asymptomatic and did not require further intervention. If an experienced practitioner prepares well and performs the procedure carefully based on a multidisciplinary risk-benefit assessment, percutaneous lung aspiration may be performed in those patients.

Finally, the safety and success of PTNB relies on patient coordination (2); in particular, the patient must maintain a stable position and comply with breathing instructions during the procedure.

- We recommend checking hematocrit, prothrombin time, activated partial thromboplastin time, and platelet count before performing the biopsy.

(recommendation grade A, evidence level II)

- We recommend withholding anticoagulants before performing the biopsy.

(recommendation grade A, evidence level II)

A pre-procedural laboratory evaluation for coagulopathy is required before PTNB (2). PTNB can be accompanied by bleeding in the lung parenchyma and along the needle track during or after the procedure. Bleeding can manifest as asymptomatic pulmonary parenchymal hemorrhage, hemoptysis, hemothorax, chest wall hematoma, and pulmonary artery pseudoaneurysm. However, mortality due to bleeding after PTNB is rare (44 45 46). PTNB is designated as an interventional procedure with a moderate risk of bleeding in the 2012 Society of Interventional Radiology guideline (47) and with a high risk of bleeding in the 2019 Society of Interventional Radiology guideline (48

). The international normalized ratio needs to be maintained below 1.5 (47 48), and the minimum platelet count maintained at 70000/ μ L (47 48). Impaired coagulation status and platelet counts need to be corrected as much as possible if the above thresholds are not met. Clopidogrel may be withheld for five days before the procedure, according to the 2019 Society of Interventional Radiology guideline, while aspirin may not be required to be withheld (48). Regarding low-molecular weight-heparin, the last 1 or 2 doses need to be withheld (47 48). The 2019 guideline also emphasizes shared decision-making for planning peri-procedural management and a balanced assessment of the risks of post-procedural bleeding and thromboembolic events (48).

- We suggest performing a pre-procedural pulmonary function test in patients suspected of having severe chronic obstructive pulmonary disease.

(recommendation grade B, evidence level III)

- We recommend a multidisciplinary discussion before performing PTNB in patients suspected of having severe chronic obstructive pulmonary disease.

(recommendation grade A, evidence level III)

Patients with severe chronic obstructive pulmonary disease find it challenging to hold their breath during the PTNB procedure and are more vulnerable to respiratory failure than healthy patients if pneumothorax or hemoptysis occurs. The 2003 BTS guideline (2) recommends reviewing recent results of pulmonary function testing (spirometry) in all patients undergoing PTNB as part of the multidisciplinary risk-benefit assessment and avoiding biopsy in patients with an FEV 1 below 35%. Nevertheless, no robust minimum threshold has yet been established for FEV 1 to ensure the safety of PTNB in patients with severe chronic obstructive pulmonary disease (2). Concerning the practical point of view, it is necessary to perform a pulmonary function test before PTNB, as a post-biopsy complication can hinder an accurate measurement of baseline lung function that is essential for planning further management after a cancer diagnosis.

- We recommend obtaining chest CT images of sufficient quality for planning the biopsy, possibly with contrast enhancement.

(recommendation grade A, evidence level II)

- We suggest using an 18F-fluoro-deoxyglucose PET scan to determine the biopsy site for a pulmonary lesion suspected of having necrosis.

(recommendation grade B, evidence level III)

The pre-procedural planning of a PTNB procedure based on chest CT images is one of the most salient steps (2). A sufficient quality of chest CT images for planning the biopsy may be varyingly defined across interventionists. However, thin-section CT images without significant image noise or artifacts are generally preferred. The pre-procedural assessment includes 1) identifying alternative lesions outside the lung and safer alternative procedures than PTNB, 2) selecting the most appropriate imaging guidance modality for PTNB, and 3) planning the safest needle path for the PTNB procedure by reviewing the nodule location, characteristics, surrounding bronchovascular structures, fissure, and bullae (2).

If a pulmonary lesion is accompanied by an extrapulmonary lesion, biopsying the extrapulmonary lesion should be considered first, and a bronchoscopic approach is preferable for a central pulmonary lesion (18 19). If multiple pulmonary lesions exist, the target lesion can be chosen, primarily based on the size and location of the lesions. Larger and more superficial lesions are generally easier to be approached.

Juxtapleural lesions are the most superficial, but PTNB of juxtapleural lesions may be challenging, as respiratory motions can cause dislocation of the biopsy needle, particularly for smaller lesions in the lower lobes. The number of pleural punctures and the length of the transparenchymal passage should be minimized. It is also vital for the trajectory of the biopsy needle to avoid the penetration of fissures and bullae, resulting in pneumothorax. If the target lesion abuts major cardiopulmonary structures, it is necessary to pre-procedurally set a safety margin on the imaging guidance modality that must never be violated during the procedure. The visibility of the lesion on the guidance modality needs to be assessed (49).

Contrast-enhanced CT images allow a clearer depiction of cystic or necrotic portions within a pulmonary lesion (50) and the nature of the lesion (e.g., pulmonary vascular malformation). The interventionist can also determine whether hypertrophied systemic or pulmonary vessels are present within the lesion to avoid a potential penetration or cutting injury of the vessels during the procedure (36). PET could identify the metabolically active portion of a pulmonary lesion, likely yielding a definitive result (12). The introduction of visually or digitally co-registered PET scans improved the diagnostic accuracy of PTNB (51 52).

- We recommend that the sensitivity and specificity of the biopsy for malignancy should be higher than 85% and 90%, respectively.

(recommendation grade A, evidence level II)

- We recommend minimizing non-diagnostic results and maintaining the proportion of insufficient biopsy specimens as less than 10% of biopsies.

(recommendation grade A, evidence level II)

The accuracy of a PTNB is greatly affected by whether it was diagnostic or non-diagnostic. In general, diagnostic results correspond to malignancy or specific benign disease. Non-diagnostic results are usually categorized into three groups (53): non-specific benign results, atypical cells, and insufficient specimens. Non-specific benign results are defined as pathologic findings of a biopsy specimen suggestive of a benign pathologic nature without evidence of malignancy, but with insufficient information to render a specific diagnosis (54); this category includes acute or chronic non-specific inflammation, granulomatous inflammation, abscess, organizing pneumonia, and focal fibrosis. Atypical cells refer to a biopsy specimen containing atypical cells or a biopsy specimen that is suspicious for malignancy, but with insufficient information for a specific diagnosis. An insufficient specimen is defined as a biopsy specimen that only contains blood, necrotic tissue, normal lung parenchyma, or insufficient tissue for making any diagnosis.

According to a previous meta-analysis (23), three-fourths of PTNB procedures provide diagnostic results, while one-fourth of procedures are non-diagnostic (23). When diagnostic, the PTNB result tended to be consistent with the final diagnosis: malignancy rate when PTNB result was malignancy, 99.8%; malignancy rate when PTNBs result was specific benignity, 1.5%. However, the malignancy rates of non-diagnostic biopsy results significantly differ according to the category of the non-diagnostic biopsy result (55). On average, the malignancy rates of non-specific benign results, atypical cells, and insufficient specimens were 20.6%, 91.1%, and 59.2%, respectively (23). In line with these findings, the 2013 ACCP and 2015 BTS guidelines emphasized that non-diagnostic biopsy results do not rule out the possibility of malignancy (12 15 56).

Several guidelines have provided a summary of the diagnostic accuracy of PTNB (13 18 19 25), and a recent meta-analysis provided an up-to-date summary (23). In the meta-analysis, the pooled sensitivity and specificity of PTNB procedures reached 97% and 100%, respectively, when omitting PTNB procedures with an insufficient specimen (Supplementary Fig. 2) (23). However, when an insufficient specimen was considered a diagnostic failure, the pooled sensitivity and specificity of PTNB procedures were around 90% (23). Diagnostic failure (i.e., false-positive, false-negative,

and non-evaluable results due to insufficient specimens) could occur more frequently in certain patients and lesions (e.g., patients with emphysema, lesions smaller than 2 cm, or subsolid lesions) with certain biopsy procedures (the use of fine-needle aspiration only without a biopsy, if the introducer needle is outside the target lesion, longer procedures) depending on the final pathology (lymphoma or benign disease) or if complications occur (alveolar hemorrhage) (55).

The 2003 BTS guideline specified estimates of the accuracy of PTNB as follows: false positivity, less than 1%; the proportion of adequate biopsy samples, over 90%; and sensitivity for malignancy, 85–90% in lesions larger than 2 cm; furthermore, it recommended setting standards for PTNB through auditing (2). Thoracic interventionists should be aware of the incidence and predictors of diagnostic and non-diagnostic results in their PTNB procedures. The interventionists should try to minimize non-diagnostic results, especially those due to insufficient specimens.

- We recommend primary utilization of fluoroscopic or CT-based guidance modalities for the biopsy, including cone-beam CT and CT fluoroscopy.

(recommendation grade A, evidence level II)

- We recommend that ultrasonography can be considered as the primary guidance modality for subpleural pulmonary lesions abutting the chest wall.

(recommendation grade A, evidence level II)

- We suggest that CT-based guidance modalities or multi-planar reconstruction can be considered for pulmonary lesions 2 cm or smaller to increase the diagnostic accuracy of PTNB.

(recommendation grade B, evidence level III)

Thoracic interventionists can determine the guidance modality according to the availability of various modalities, experience and preference of the interventionists, lesion size, and location of the pulmonary lesion (2). Several guidelines have mentioned that PTNB can be performed under the guidance of fluoroscopy, CT, or ultrasonography, and did not recommend a uniform preferential guidance modality for PTNB in general (2 13 15 18 19 25). The 2003 BTS guideline (2) and the 2011 NICE guideline (25) recommended utilizing ultrasonography as a guidance modality when a pulmonary lesion abuts the chest wall. Compared with CT-guided biopsy, ultrasonography-guided biopsy provided a lower complication rate and shorter procedural time without ionizing radiation exposure, along with similar diagnostic accuracy (57 58 59). Conventional CT guidance with multi-planar reconstruction or cone-beam CT guidance may improve the diagnostic accuracy of PTNB, particularly for small pulmonary lesions (13). In a recent multicenter retrospective cohort study, the use of CT and cone-beam CT guidance reduced the diagnostic failure rate of PTNB (60), along with lowering the incidence of hemoptysis compared to fluoroscopic guidance (46). As fluoroscopy, CT, cone-beam CT, and CT fluoroscopy guidance are inevitably accompanied by ionizing radiation exposure to patients and/or interventionists, radiation exposure should be monitored and minimized during the procedure as much as possible (61 62).

- We recommend selecting either needle aspiration or cutting biopsy given the availability of cytopathologists, the risk of malignancy, lesion diameter, required amount of tissue specimens, and the interventionist's experience.

(recommendation grade A, evidence level II)

- We recommend determining the needle gauge and the number of samples based on the difficulty and risk of the biopsy procedure, the gross quality of the biopsy specimens, and the need for a subsequent examination.

(recommendation grade A, evidence level II)

Thoracic interventionists can choose the type of needle depending on their experience, available cytological support, and the location of the target lesion, along with emphasizing the importance of sufficient biopsy passes (2). In general, core needle biopsy obtains a larger amount of biopsy specimens than fine-needle aspiration. Core needle biopsy and fine-needle aspiration provide similar diagnostic accuracy for malignancy (2 18). Nevertheless, the diagnostic accuracy for benign disease tends to be lower in fine-needle aspiration than in core needle biopsy (2 18). The presence of on-site cytopathologists helps to achieve higher diagnostic accuracy with fine-needle aspiration (2). Most interventionists obtain at least two tissue samples (2). The diagnostic accuracy of PTNB increases cumulatively, but the magnitude of the incremental gain of accuracy is reduced as the number of tissue samples increases up to the third to fourth samples (63 64). Theoretically, obtaining more samples may lead to a higher rate of complications. However, such a relationship has not been evident in the literature, except for the finding that a higher number of pleural passages results in more frequent pneumothorax (46). Differences in the needle gauge may result in a different rate of non-diagnostic results (55).

- We recommend assessing the risk of pneumothorax before performing a biopsy and minimizing the risk of pneumothorax during the procedure.

(recommendation grade A, evidence level II)

- We recommend evaluating the occurrence of pneumothorax using chest radiographs or the guidance modality by an interventionist after performing the biopsy.

(recommendation grade A, evidence level II)

- We recommend determining the necessity of chest tube insertion by considering the status of the patient, amount of pneumothorax, and medical availability.

(recommendation grade A, evidence level II)

Pneumothorax, which is the most frequent complication after PTNB, may necessitate tube drainage. National multicenter surveys or large cross-sectional analyses in the United Kingdom (5444 biopsies), Japan (9783 biopsies), Korea (10568 biopsies), and United States (15865 biopsies) reported pneumothorax rates of 15.0–35.0% and rates of pneumothorax requiring tube drainage of 3.1–6.6% (17 44 45 46). Higher rates of pneumothorax were associated with older age (46 65), male sex (46 66), smoking (46 65), emphysema (46 67) (particularly emphysema along the needle path (66 68)), a deep-seated lesion (46 69), smaller lesion size (46 65 67), subpleural lesions (65 69), a higher number of pleural passages (46 66), lateral pleural puncture, traversing a fissure with the biopsy needle (68), use of large coaxial stabilizing needle (70), lack of pleural thickening (68), no previous pulmonary surgery (71), lesions in the lower lobe (66 71), a shallow pleural puncture angle (68), a wider trajectory angle (71 72), less experienced interventionists (65), and the use of core needle biopsy compared to fine-needle aspiration (73). A few preventative measures can be applied to reduce the risk of pneumothorax after PTNB. A recent meta-analysis reported that normal saline tract sealant, a rapid needle-out patient-rollover approach (74), and the use of a tract plug or blood patch reduced the likelihood of pneumothorax requiring tube drainage (75). One study reported that positioning the patient with the biopsy side down could reduce pneumothorax incidence after PTNB (76).

An upright chest radiograph should be obtained within a few hours after the biopsy to identify potential complications (2) and is sufficient to detect the majority of cases of post-biopsy pneumothorax (77). More than 90% of all pneumothoraces appeared within 3 to 4 hours of the PTNB, and most of the delayed pneumothoraces occurred within 24 hours after the procedure (78 79). Female sex, absence of emphysema, and a larger target size were associated with the

occurrence of delayed pneumothorax (78 79). Patients should be informed of the risks of delayed pneumothorax after PTNB (2). A suitably qualified radiologist should review the post-biopsy chest radiograph. The management options include observation, air aspiration, and tube drainage. The management decision will be affected by factors such as the size of the pneumothorax, the patient's condition (e.g., underlying disease such as COPD), and the patient's symptoms and signs (the degree of hypoxemia and subjective pain) (2).

- When hemoptysis occurs, we recommend monitoring vital signs and blood oxygen saturation levels, along with assessing the amount of hemoptysis.

(recommendation grade A, evidence level II)

- In cases of mild hemoptysis, we recommend conservative management with biopsy-site-down positioning.

(recommendation grade A, evidence level II)

- When massive hemoptysis occurs, we recommend supplying oxygen to maintain blood oxygen saturation, along with considering single-lumen endotracheal tube insertion.

(recommendation grade A, evidence level II)

The pooled rates of pulmonary hemorrhage after CT-guided core needle biopsy and fine-needle aspiration were found to be 18.0% and 6.4%, respectively, and the pooled rates of hemoptysis were 4.1% and 1.6%, respectively (73). Risk factors affecting the incidence or severity of hemoptysis after PTNB include a deeper-seated location (39 40 46 65 66 69 80), a small lesion (39 46 65 80), a subsolid lesion (39 40 46 66), a cavity (40), a lesion with an open bronchus sign (81), older age (39), female sex (39 46 80), dual-antiplatelet therapy (40 80), the coaxial technique (39), core needle biopsy (46 80), and a penetrating and cutting injury of bronchovascular structures (36). Conflicting reports exist about the relationship between enlargement of the main pulmonary artery diameter on CT and pulmonary hemorrhage or hemoptysis (39 40). Hemoptysis developed less frequently using CT-based guidance modalities than when fluoroscopy was used (46).

Hemoptysis is usually self-limiting. Most hemoptysis cases could be managed by maintaining the patient in the lateral decubitus position with the biopsy side down and providing appropriate reassurance (2). It is crucial to protect the airway and secure the unaffected lung from the lung where hemoptysis originates (82). Biopsy-site-down lateral positioning is effective for doing so. The patient's ability to expectorate aspirated blood is also salient for maintaining the airway (83). Massive, potentially fatal, hemoptysis may develop after PTNB. Massive hemoptysis is traditionally defined as an amount of hemoptysis of 600 mL or larger within 24 hours (84). However, measuring the amount of hemoptysis is challenging in practice, and thoracic interventionists need to determine the severity of hemoptysis by systematically considering not only the volume of hemoptysis, but also the rate of bleeding, the degree of hemodynamic instability, oxygen desaturation (36), and the patient's physiological reserves (83). It is essential to monitor vital signs and resuscitate the patient from oxygen desaturation via an oxygen supply in the biopsy-site-down position (2). If hemoptysis persists without cardiopulmonary compromise, CT angiography may be performed to identify the cause of massive hemoptysis (85), while maintaining the lateral positioning. Selective intubation into the unilateral bronchial main stem with an endotracheal tube, based on sufficient clinical expertise, can ensure that the unaffected lung is isolated from hemoptysis (2 83). Rigid bronchoscopy, transcatheter arterial embolization, or surgical management may be introduced in some centers for managing massive hemoptysis that cannot be managed conservatively (83).

- When systemic air embolism occurs, we recommend supplying oxygen at as high a concentration as possible, including hyperbaric oxygen therapy, and anticonvulsants, if needed.

(recommendation grade A, evidence level III)

- When a large amount of hemothorax occurs, we recommend conservative management, while contacting clinicians such as thoracic or general surgeons and interventional radiologists.

(recommendation grade A, evidence level III)

In reports of thousands of PTNB procedures, the incidence of air embolism was 0.02–0.18% (44 45 46). Symptoms can occur suddenly during or after the procedure and can differ according to the location of air embolism (2). A post-procedural CT scan may help make a diagnosis of air embolism in the systemic arteries, including the coronary or cerebral arteries (86). Administration of oxygen at as high a concentration as possible is the most important step to relieve hypoxia and hypoxemia and facilitate the elimination of an air embolism (86). Hyperbaric oxygen therapy is regarded as the treatment of choice for arterial gas embolism (87 88). The supine (86) or Trendelenburg position (89) is recommended in patients with arterial air embolism, although the best positioning has not been conclusively established. Whether to administer corticosteroid or aspirin treatment remains controversial (86).

The incidence of hemothorax after PTNB has been reported to range from 0.09–0.57% (45 46). If hemothorax develops after PTNB, thoracic interventionists need to manage patients conservatively and monitor the amount of hemothorax on serial chest radiographs, while correcting coagulopathy (2). If the hemothorax is large or continuously growing, CT angiography is an effective modality to evaluate the possibility of an iatrogenic injury of the intercostal or internal mammary arteries (90). Transcatheter artery embolization of the injured arteries is the first treatment option for iatrogenic intercostal or internal mammary arterial bleeding (91 92).

PTNB provides an accurate diagnosis of indeterminate pulmonary lesions. The overall complication rate is around 25% or higher, but most of the complications can be conservatively managed. The occurrence of complications can prolong a patient's hospital stay and increase medical costs. The use of fluoroscopic or CT-based guidance modalities for PTNB is accompanied by radiation exposure to patients and interventionists. The diagnostic accuracy, complication rate, and magnitude of the radiation dose can vary depending on the characteristics of the patient, lesion, procedure, and experience of the interventionist. Thoracic interventionists carefully perform PTNB based on a risk-benefit assessment and the probability of malignancy.

Most of the recommendations in the included guidelines were judged to be acceptable and applicable to domestic practice (Supplementary Table 4), except for the subsection regarding the indications of PTNB in the 2015 BTS guideline, which largely depend on the Brock model in clinical practice (13). The Brock model is not often used in the domestic setting.

The mean estimations of the patient effective dose in the literature are as follows: fluoroscopic guidance, 0.029 mSv (93); CT guidance, 0.7 to 2.7 mSv (94 95); cone-beam CT or CT fluoroscopic guidance, 7 mSv (66 95). Ultrasonographic guidance is free of radiation exposure.

These guidelines have several limitations. First, the guidelines could not fully reflect the results of the up-to-date literature, as it was based on an adaptation of pre-existing guidelines relevant to PTNB with sufficient quality. In most of the included guidelines, PTNB was covered as one of the available options to diagnose a pulmonary lesion. We introduced the results of some recent investigations and meta-analyses for each key question, but the studies were not systematically searched and might be biased. Second, we could not reflect patients' opinions on PTNB and their experiences during PTNB in the guideline, as the included guidelines rarely dealt with patients' opinions. Although PTNB is generally well-tolerated, some patients could suffer from considerable pain and discomfort (96). Third, the guidelines did not address the risk of tumor implantation along the PTNB needle track in the pleural or chest wall, which is a rare but potentially long-term complication (97 98).

We developed the first evidence-based clinical practice guideline for PTNB in Korea by adapting pre-existing guidelines. The guideline provides several recommendations for the following four main domains of key questions: indications for PTNB, pre-procedural evaluation, procedural technique of PTNB and its accuracy, and management of post-biopsy complications. We hope that these recommendations can improve the diagnostic accuracy and safety of PTNB in clinical practice and promote standardization of the procedure nationwide.

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Diagram for the inclusion of guidelines for key questions 1 to 4

Pooled sensitivity (A) and specificity (B) of percutaneous transthoracic needle biopsy in 2 by 2 (excluding biopsy cases of insufficient specimen from analysis) and 3 by 2 tables (deciding biopsy cases of insufficient specimen as diagnostic failure)

Name, affiliation and role of researchers

Detailed search strategy for key questions

Summary of quality assessments of screened guidelines

The definition of evidence level and recommendation grading followed the Methodology for Developing Evidence-Based Korean Clinical Imaging Guidelines.

CT = computed tomography, PTNB = percutaneous transthoracic needle biopsy