INTRODUCTION

With the increasing use of chest computed tomography (CT) for lung cancer screening, the frequency of detecting indeterminate peripheral lung nodules has increased, which leads to pathologic confirmation of suspicious lung lesions (1). Several procedure options including bronchoscopy and surgical resection exist, but still, a considerable proportion of patients undergo percutaneous transthoracic needle aspiration biopsy (PCNA).

Meanwhile, positron emission tomography (PET) using fluorine-18 fluorodeoxyglucose (¹⁸F-FDG) is valuable for assessment of suspicious malignant lesions (2). Due to its ability to detect increased metabolism, PET/CT may reveal malignancy in its very early stages, even before morphological changes are evident on conventional images. Furthermore, PET/CT offers visualization of the viable and biologically aggressive area within a heterogeneous tumor with multiple subregions of cancer cells, necrosis, inflammatory cells, and fibrosis (3). Accordingly, several studies have suggested that PET/CT guidance allows high diagnostic success of percutaneous biopsies for metabolically active lesions (4, 5). Some studies have reported that success rates can be improved and information from a prior PET/CT scan can be used to direct the needle tip to the most metabolically active portion of a heterogeneous mass (6-8).

Study of the Efficacy of PET/CT in Lung Aspiration Biopsy and Factors Associated with False-Negative Results

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Purpose: We compared the outcomes of percutaneous transthoracic needle aspiration biopsy (PCNA) of lung masses in cases with and without prior positron emission tomography/computed tomography (PET/CT) information, and investigated the factors associated with false-negative pathological results.  
Materials and Methods: From a total of 291 patients, 161 underwent PCNA without prior PET/CT imaging, while 130 underwent PET/CT before PCNA. Clinical characteristics, procedural variables, pathological results, and diagnostic success rates were compared between the 2 groups. Among patients with initial negative (non-specific benign) PCNA results, the radiological findings of these groups were compared to evaluate the predictors of false-negative lesions.  
Results: No significant difference was found in the clinical characteristics, procedural characteristics, and pathological results of the 2 groups, nor was the diagnostic rate significantly different between them (p = 0.818). Among patients with initial negative PCNA results, radiological characteristics were similar in both the groups. In multivariate analysis, the presence of necrosis (p = 0.005) and ground-glass opacity (GGO) (p = 0.011) were the significant characteristics that indicated an increased probability of initial false-negative results in PCNA.  
Conclusion: Routine PET/CT did not have any additional benefit in patients undergoing PCNA of lung masses. The presence of necrosis or GGO could indicate an increased probability of false-negative pathological results.

Index terms  
PET-CT  
Lung Neoplasms  
Multidetector Computed Tomography

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er, the additional clinical value of routine PET/CT in patients undergoing lung PCNA remains to be established. Thus, the purpose of our study was to determine whether the addition of PET/CT augmented the outcomes of PCNA of lung masses and to investigate factors associated with the false-negative pathologic results.

MATERIALS AND METHODS

Our Institutional Review Board approved this study (E-2015 084) and informed consent was waived for reviewing the patients' medical records.

Patient Enrollment

From March 2013 to December 2014, 307 patients who underwent PCNA were enrolled in a lung PCNA database. After enrollment, patient information was retrospectively reviewed from the electronic medical records. As a tertiary referral hospital with a comprehensive cancer center, patients were referred to the radiology department for pathologic confirmation of an abnormal lung lesion under the clinical suspicion made by an internal medicine doctor or thoracic surgeon based on clinical information, laboratory blood tests, and chest CT scans. At the time of referral, a thoracic radiologist decided whether PCNA was feasible after reviewing the contrast-enhanced chest CT scans. Sixteen patients with lesions located adjacent to critical anatomical structures such as central vessels or large bronchi, lesions with minimal solid component with prominent air bronchograms which were considered difficult to avoid by needle pass, and patients with severe respiratory compromise or non-cooperated position which precluded PCNA were excluded. Ultimately, 291 patients were included in this study. Patients underwent the lung mass evaluation process, and according to the individual situation and under the clinical decision made by the referring physician, at the time of PCNA, patients were classified into two subgroups according to the presence of PET/CT scans prior to PCNA: 1) 161 patients did not have PET/CT scans before PCNA and 2) 130 patients underwent PET/CT within 3 weeks prior to PCNA.

Procedure

Needle trajectory planning and positioning was performed in consideration of chest radiography and contrast-enhanced chest CT images. When the patient had PET/CT scans available before PCNA, the thoracic radiologist performing the procedure reviewed the PET/CT images prior to PCNA. When the mass showed heterogeneous metabolic uptake, the area with highest uptake was chosen as an adequate localization lesion for PCNA.

All procedures were performed by a single thoracic radiologist who had 5 years of PCNA experience under fluoroscopy or CT guidance. Patients were positioned in the supine or prone position, depending on the lesion location. After identification of the target lesion, the puncture area was cleaned with antisepsic solution, followed by subcutaneous injection of local anesthetic. Next, a 20-gauge Westcott biopsy needle (Argon Medical Devices, Athens, TX, USA) was inserted by freehand technique and specimens were placed in 10% neutral buffered formalin solution (BBC biochemical, Mt. Vernon, WA, USA).

Pathologic Analysis and Final Diagnosis

For all patients, the aspiration biopsy needle was placed into the target lesion and cells or lung tissues were present in the specimen. Two lung pathologists reviewed the PCNA specimens in consensus. Apart from definite benign or malignant lesions, negative pathologic results indicated "non-specific benign," which included inflammatory cells or fibrosis, suggesting the presence of benign pathological features, but not enough to make a specific diagnosis, and no evidence of malignancy. For negative (non-specific benign) pathologic results, the final diagnosis was determined by review of pathologic results of a subsequent biopsy/surgery or evaluation of follow-up images. False-negative cases were those in which malignancy was identified by pathologic confirmation from a subsequent repeated biopsy or surgical resection. True-negative cases were those in which the lesion showed complete resolution, stability at serial CT scans for at least 2 years follow-up, or proved to be benign at surgical resection (9, 10).

Radiologic Interpretation and PET

Contrast-enhanced chest CT images which were obtained less than 3 weeks prior to PCNA were reviewed by two independent chest radiologists (with 7 and 16 years of experience in chest CT interpretation, respectively) who were blinded to the
pathologic results and who did not perform any of the PCNA procedures. CT scans were obtained using the following scanners: a 16-detector scanner (Sensation 16. Siemens Healthcare, Erlangen, Germany), a 64-detector scanner (Definition AS plus, Siemens Healthcare, Forchheim, Germany; or Discovery 750, GE Healthcare, Waukesha, WI, USA), or a dual-source CT scanner (Definition, Siemens Healthcare). Images of the whole thorax were acquired using the following CT parameters: 120 kVp, 150–200 mA, section thickness = 5 mm or less; tube rotation = 0.5 s; and detector collimation = 1.25 mm or 0.625 mm.

Radiologic variables were combined atelectasis with the mass, presence of necrosis (including cavitition) within the mass, presence of consolidation (including pneumonia) abutting to the mass, the presence of ground-glass opacity (GGO) in the mass, and the presence of pleural effusion. Atelectasis was defined as increased attenuation with reduced volume adjacent to the mass associated with abnormal displacement of fissures, bronchi, or vessels (11). Low attenuated area within the mass or nodule were defined as necrosis (11). Consolidation appeared as a homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airway walls with or without air bronchograms (11). GGO was defined as an area of hazy increased opacity of the lung, with preservation of bronchial and vascular margins (11). In cases of discrepancy, final decisions were made through consensus of the radiologists.

For patients who underwent 18F-FDG PET/CT before PCNA, imaging was performed with a combined PET/CT scanner (Gemini, Philips, Milpitas, CA, USA), consisting of a dedicated germanium oxysulphide, a full-ring PET scanner, and a dual-slice helical CT scanner. Images were obtained at 60 minutes after administrating 3.7 MBq/kg 18F-FDG intravenously, from the skull base to the proximal thighs. Low-dose CT (30 mAs, 120 kVp) without any contrast material was performed and PET data were reconstructed iteratively with attenuation correction, and reoriented in axial, sagittal, and coronal slices.

**Statistical Analyses**

Comparison of the clinical characteristics, procedure related variables, and pathologic results between the two groups with and without PET/CT was performed through chi-square or Fisher’s exact test for categorical variables and the independent t-test or Mann-Whitney U test for continuous variables. To investigate any features associated with initial negative results, radiologic variables were compared between the two groups with and without PET/CT using chi-square or Fisher’s exact test.

Next, patients with initial negative results were further grouped into true-negative and false-negative subgroups. Comparison between the true-negative and false-negative lesions was performed through chi-square or Fisher’s exact test for categorical variables and the independent t-test or Mann-Whitney U test for continuous variables. After univariate analysis, multivariate logistic regression analysis was performed to reveal independent predictors of a false-negative result. Input variables were those with $p < 0.1$ at univariate analysis.

All statistical analyses were performed using SPSS for Windows software (version 18.0; SPSS Inc., Chicago, IL, USA), and $p < 0.05$ indicated statistical significance.

**RESULTS**

**Comparison between Groups with and without PET/CT**

Clinical characteristics, procedure characteristics, and pathologic results of patients who underwent PCNA between those with and without PET/CT scans are shown in Table 1. None of the variables were statistically significant between the 2 groups. Diagnostic success rates were not different [$p = 0.818; 88.5\% (115/130)$ and $87.6\% (141/161)$ for patients with and without PET/CT scans, respectively] between the 2 groups.

Among 130 patients with PET/CT scans, 4 patients had scans performed at outside hospitals, thus the maximum standardized uptake value (SUVmax) could not be measured for these patients. For 126 patients with PET/CT scans, mean SUVmax was $8.95 \pm 5.14$ (range, 1.2–24.9).

Next, for patients with initial negative PCNA results ($n = 35$), the radiological characteristics were compared between the two groups with and without PET/CT (Table 2). None of the radiological characteristics were statistically significant between the 2 groups.

**Comparison between True-Negative and False-Negative Lesions**

For patients with initial negative pathologic results, the final diagnosis was confirmed by subsequent surgery or repeated biopsy in 29 lesions, and by follow-up CT in 6 patients.
Among 35 lesions with initial negative pathologic reports, 20 lesions (57.1%) were ultimately diagnosed as malignancy, indicating false-negative results. Among 20 false-negative lesions, adenocarcinoma was the most common pathology result (11 patients; 55%), followed by squamous cell carcinoma (5 patients; 25%), malignant mesothelioma (2 patients; 10%), large cell carcinoma (1 patient; 5%), and thymic carcinoma (1 patient; 5%). Remaining 15 lesions (42.9%) were ultimately diagnosed as benign, indicating true-negative results. Among 15 true-negative lesions, 6 patients (40%) demonstrated improvement or stable CT exams during 2-year follow up, 7 patients (46.7%) were diagnosed as tuberculosis, and remaining 2 patients (13.3%) were confirmed as chronic inflammation. Table 3 shows comparison of characteristics between false-negative and true-negative lesions. Regarding the clinical and procedure characteristics, there were no significant differences in age, sex, lesion size, location, types of imaging guidance, and position between the false-negative lesions and true-negative lesions (all $p$s > 0.05). Among radiological characteristics, presence of necrosis ($p = 0.011$) was significantly higher in the false-negative group. Furthermore, the presence of PET was higher in the true-negative group and approached statistical significance ($p = 0.076$).

Table 2. Comparison of Radiological Characteristics among Patients with Initial Negative Percutaneous Transthoracic Needle Aspiration Biopsy Results

<table>
<thead>
<tr>
<th>Radiological Characteristics</th>
<th>No PET (n = 20)</th>
<th>PET (n = 15)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of atelectasis</td>
<td>2</td>
<td>2</td>
<td>0.999</td>
</tr>
<tr>
<td>Presence of necrosis</td>
<td>11</td>
<td>7</td>
<td>0.625</td>
</tr>
<tr>
<td>Presence of consolidation adjacent to lesion</td>
<td>6</td>
<td>4</td>
<td>0.999</td>
</tr>
<tr>
<td>Presence of pleural effusion</td>
<td>4</td>
<td>3</td>
<td>0.999</td>
</tr>
<tr>
<td>Presence of GGO</td>
<td>6</td>
<td>2</td>
<td>0.419</td>
</tr>
</tbody>
</table>

GGO = ground-glass opacity, PET = positron emission tomography

Table 3. Comparison of Characteristics between False-Negative and True-Negative Lesions

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>True Negative (n = 15)</th>
<th>False Negative (n = 20)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical characteristics</td>
<td>Age (years) ± SD</td>
<td>62.9 ± 13.0</td>
<td>63.0 ± 10.6</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Presence of PET</td>
<td>No PET</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Radiological characteristics</td>
<td>Presence of atelectasis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Presence of necrosis</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Presence of consolidation adjacent to lesion</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Presence of pleural effusion</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Presence of GGO</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Procedure characteristics</td>
<td>Lesion size (cm) ± SD</td>
<td>3.0 ± 1.6</td>
<td>3.9 ± 2.8</td>
</tr>
<tr>
<td></td>
<td>Upper</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Lower</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Types of imaging guidance</td>
<td>CT</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluoroscopy</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Position</td>
<td>Supine</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prone</td>
<td>8</td>
</tr>
</tbody>
</table>

*Significant p-value.

CT = computed tomography, GGO = ground-glass opacity, PET = positron emission tomography, SD = standard deviation
Prediction of False-Negative Lesions

Table 4 shows results of univariate and multivariate logistic regression analysis for predictors of false-negative lesions at PCNA. Presence of PET, presence of necrosis, and presence of GGO were included in the multivariate analysis. Results of multivariate analysis demonstrate that the presence of necrosis \( (p = 0.005) \) and presence of GGO \( (p = 0.011) \) were significant variables associated with false-negative pathologic results.

**DISCUSSION**

Our study results can be summarized to two major findings: 1) Routine PET/CT did not have additional diagnostic benefit for patients undergoing PCNA of lung masses and 2) the presence of necrosis or GGO may indicate an increased probability of false-negative pathologic results.

PET/CT has become an essential tool which reflects the metabolic characteristics of tissue and is currently widely used for initial staging, therapy monitoring, and outcome prediction of lung cancer (12-15). Several studies have shown that application of nuclear medicine imaging could improve the image-guided biopsy success rate by directly placing the needle to the hypermetabolic area of a lesion, further obviating subsequent invasive procedures and complication risks (5, 7, 16, 17). However, those studies enrolled only a small number of cases or exhibited selection bias by performing biopsy in patients with lesions which demonstrated metabolic abnormality on PET without definite CT abnormality (4, 5, 8). In the present study, the diagnostic success rates were similar between the 2 groups with and without PET/CT, thus, routine PET/CT did not have statistically significant benefit for patients undergoing PCNA of lung masses. We believe this is due to the conspicuity of lung lesions as the background lung parenchyma itself serves as an excellent tissue contrast for abnormal lesions, thus the advantage and necessity of additional metabolic information is decreased. Similarly, according to another study, the value of PET/CT was highest in skeletal lesions of which biopsy may be hampered due to low lesion visibility (7). Hence, although PET/CT exhibits excellent per-person performance for detecting malignancies and lung cancer staging, the routine use of PET/CT imaging for all patients undergoing lung biopsies warrants reconsideration.

Despite high diagnostic accuracies for malignancies with PCNA, non-specific benign results from lung biopsies still remain a key clinical problem (18, 19). In this study, two radiological factors of necrosis and GGO were significantly associated with false-negative lesions. First, regarding necrosis, sampling errors due to central necrosis of larger lung masses has also been previously reported (20, 21). Spatial heterogeneity including necrosis within a mass is related to various factors such as outgrow of tumor blood supply, hypoxia, and regional differences (22-24). In this study, although the radiologist did not obtain specimens from the necrotic areas identified on contrast-
enhanced CT images, the CT resolution may not be enough for identification of minor necrosis. In this aspect, PET/CT may be useful for identifying viable cancer tissue with higher accuracy than CT alone in patients with lung cancer (25, 26). Furthermore, Hua et al. (27) also suggested that nuclear imaging information is especially valuable in patients with large, heterogeneous masses.

Next, the presence of GGO was a significant factor for false-negative pathologic results. In the spectrum of lung adenocarcinomas, GGO frequently reflects the pathologically non-invasive component representing lepidic growth (28-30). In a previous study regarding PCNA of pulmonary GGO lesions, the diagnostic accuracy was significantly influenced by the GGO component, of which pure GGO lesions demonstrated lower accuracy than mixed GGO lesions with a solid portion (31). Other investigators have also reported underestimation of subsolid lesions by biopsy compared to surgical pathology (32, 33). Our study results showed similar aspects as aforementioned studies because GGO lesions are difficult to diagnose via aspiration due to the low cellularity of the lesions (31). According to a study by Suh et al. (34), higher SUVmax, larger lesion size, and subsolid lesions were useful predictors for malignancy in pulmonary lesions with nonspecific benign cytology results at PCNA. Our study results were similar regarding GGO lesions, but the SUVmax value and lesion size were not different between true-negative and false-negative lesions.

Notably, the presence of PET was higher in the true-negative group and approached statistical significance ($p = 0.076$). In a larger study group, we may presume that the presence of PET may be higher in the true-negative group with statistical significance compared to the false-negative group. Therefore, according to this study, although the routine use of PET/CT for all patients undergoing lung biopsies cannot be justified, PET/CT may perhaps be helpful in patients with initial negative results. This issue should be evaluated in future studies with larger study groups.

According to large database lung cancer screening studies, the American College of Radiology has recently introduced a Lung Imaging Reporting and Data System (LungRADS): a nodule discriminating standard based on screening chest CT which divides nodules according to size and content, and guides further management (35). In particular, nodules with the highest probability of malignancy are assigned to Category 4B, including large or growing solid and part-solid nodules. However, further management of Category 4B nodules is rather vague, suggesting chest CT with or without contrast, PET/CT, and/or tissue sampling. In other words, there is no established consensus at present as to whether to undergo PET/CT before tissue sampling or tissue sampling without PET/CT. Although CT provides the most important anatomic imaging, CT alone may have limitations, whereas PET provides metabolic imaging. Such two imaging modalities show different biological aspects of the same disease process, offering collaborative insights into the diagnosis of lung lesions. However, in the clinical setting, routine PET/CT may not be necessary for all patients, based on our results. For example, here is a patient with a lung mass demonstrating homogeneous enhancement without any necrosis or GGO, and is considered highly suspicious for lung cancer. Although additional PET/CT might make the possibility of lung cancer even higher, the need to obtain a lung biopsy would obviate additional diagnostic metabolic imaging for this patient in the clinical setting. Furthermore, if the mass demonstrated homogeneous uptake on PET/CT, then in this case, PET/CT would make no difference for this patient (Fig. 1). In our opinion, PET/CT may be of advantage for identifying the most hypermetabolic area of specific lung lesions which have an increased probability for false-negative pathologic results such as involving necrosis or GGO (Fig. 2). In this context, our results add to literature in assisting the selection of candidates who would benefit best from additional metabolic information prior to lung biopsy.

Our study has several limitations. First, although prospectively enrolled, patients were from a single institution, thus, the outcomes may be representative of one tertiary institution. In addition, we only investigated the impact of the presence and absence of PET/CT prior to lung PCNA. Subgroups including whether metabolic information changed the site of biopsy or had high versus low SUVmax could have been a more sophisticated study design offering more valuable information concerning the role of PET/CT prior to lung PCNA. Therefore, regarding the present study only, it may be difficult to make a conclusive statement about routine PET/CT prior to lung PNCA, but hopefully, our results will inspire further investigations. Second, our study is limited by lack of patient randomization with respect to the presence of PET/CT. Instead, the presence of PET/CT was primarily determined by the clinical evaluation flow of the refer-
Fig. 1. A 62-year-old male with a mass located at the right upper lobe posterior segment. PET/CT scan shows homogeneous uptake (SUVmax of 14.3), with no definite additional benefit before percutaneous transthoracic needle aspiration biopsy. Pathologic results revealed squamous cell carcinoma.

Fig. 2. A 61-year-old female with a heterogeneous, lobulated mass with suspicious necrosis, located at the left upper lobe. PET/CT scan demonstrates high metabolic uptake at the peripheral area of the lesion (SUVmax of 16.7). Thus, the biopsy needle tip is placed at the lesion with highest metabolic uptake. Pathologic results revealed pulmonary tuberculosis. Low-dose chest CT scan (right lower quadrant) after 6 months of anti-tuberculous treatment shows interval decrease of the lesion.
ring physician based on the nature of the lesion, clinical status of the patient including risk of lung cancer, comorbidities, insurance coverage, and economical status. Thus, potential confounding factors and selection bias based on the preference of the referring physician could have existed. However, as mentioned above, this study was performed in the clinical setting and represented everyday imaging algorithms and problems. Finally, the diagnostic accuracy of the present study is somewhat lower than those reported from previous large database studies (10, 21). However, methodology of obtaining lung tissue is different, as those studies used larger cutting needles with coaxial technique or used CT fluoroscopy. Our diagnostic rates are similar to a large database study using CT-guided fine-needle aspiration biopsy of lung lesions (6). In addition, a proportion of patients underwent PCNA using fluoroscopy. Fluoroscopy likely makes it more difficult targeting portions of lesions due to lesser ability to spatially localize as compared with CT.

In conclusion, diagnostic rates are similar regardless of the information from PET/CT scans, thus, a routine PET/CT scan prior to PCNA is not mandatory. Necrosis or GGO were factors significantly associated with false-negative pathologic results, and perhaps, metabolic information from PET/CT may be of some advantage for lesions with these characteristics.

REFERENCES


폐 흡인 조직검사 시 PET/CT의 임상적 유용성 및 위음성 결과와 관련 있는 인자
손일완1 · 이지원1,2 · 정연주1,2 · 김아롱3 · 서희봄1 · 이지원1,2*

목적: 우리는 폐종양의 경피적 침흡입생검을 시행했을 때 positron emission tomography/computed tomography (이하 PET/CT) 정보의 유무가 결과에 미치는 영향을 비교하고, 조직학적 위음성에 영향을 끼치는 인자를 조사하였다.

대상과 방법: 총 291명의 환자중에서 161명은 PET/CT 없이 경피적 침흡입생검을 시행하였고, 130명은 PET/CT를 시행 후 경피적 침흡입생검을 시행하였다. 두 군 사이에서의 임상특징, 시술변수, 병리결과 그리고 진단성공률을 비교하였다. 병리결과가 초기음성(비특이적양성)이 나온 환자에서 두 군 사이의 영상소견을 비교하고, 위음성의 예측인자를 평가하였다.

결과: PET/CT의 유무에 따른 임상특징, 시술변수, 그리고 병리결과는 차이가 없었다. 두 군 사이의 진단성공률도 의미있는 차이가 없었다 (p = 0.818). 병리결과가 초기음성인 환자에서, 두 군 사이의 영상소견도 차이가 없었다. 다변량 분석에서 과사의 존재 (p = 0.006)와 간유리음영 (p = 0.011)은 의미 있는 변수였으며, 경피적 침흡입생검시 초기위음성률을 증가시켰다.

결론: 폐종양의 경피적 침흡입생검을 시행하는 환자에서 관습적인 PET/CT는 추가적 이득이 없었다. 과사 및 간유리음영의 존재는 병리결과의 위음성률을 증가시켰다.

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