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Diagnostic Accuracy of Endoscopic Ultrasound-Guided Fine Needle Aspiration Cytology of Pancreatic Lesions

병리조직학적 진단과의 비교를 통한 췌장 내시경초음파 유도하 세침흡인 세포검사의 진단정확도 분석

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백 해 운

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Abstract

Diagnostic Accuracy of Endoscopic Ultrasound-Guided Fine Needle Aspiration Cytology of Pancreatic Lesions

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Background: Endoscopic ultrasound-guided fine needle aspiration cytology (EUS-FNAC) is currently the most commonly used procedure for obtaining cytologic specimens of pancreas. It is accurate, minimally invasive, safe and cost-effective. However, there is discrepancy between cytological and histologic diagnoses. This study was aimed at

evaluating the diagnostic accuracy of EUS-FNAC of pancreas.

Methods: A retrospective review of 191 cases of pancreatic lesion initially diagnosed by EUS-FNAC with subsequent histologic diagnosis between 2010 and 2012 in the Department of Pathology, Seoul National University Hospital, was performed. Cytologic and histologic diagnoses were categorized into five groups: negative, benign, atypical, malignant, and insufficient for diagnosis. Subsequently, 167 cases with satisfactory yield in both histologic and cytology specimens were statistically analyzed to determine correlations with diagnoses.

Results: In comparison to histologic diagnoses, cytologic diagnoses were true-positive in 103 cases (61.7%), true-negative in 28 cases (16.8%), false-positive in 9 cases (5.4%), and false-negative in 27 cases (16.1%). The diagnostic accuracy was 78.4%, sensitivity was 79.2%, and specificity was 75.7%. The positive predictive value was 92.0%, and negative predictive value was 50.9%. Diagnostic accuracy according to specific histological diagnosis was 79.1% in malignant neoplasm (76.5%, 91.7%, 62.5%, 100% in ductal adenocarcinoma, neuroendocrine neoplasm, intraductal papillary mucinous neoplasm, and the other malignant tumor, respectively), and 76.3% in benign lesion.

Conclusions: EUS-FNAC has high accuracy, sensitivity, specificity and positive predictive value. A low negative

predictive value and numerous discrepant cases were due to insufficient yield of tissue or targeting-error of the lesion by aspiration. Overcoming such limitations of EUS-FNAC will make it useful and reliable diagnostic tool for accurate evaluation of pancreatic lesions.

Keywords: Pancreas; Endoscopic ultrasound-guided fine needle aspiration cytology; EUS-FNAC; Accuracy; Diagnosis; Evaluation; Cytopathology

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INTRODUCTION

Pancreatic cancer is notorious for its poor prognosis, with a low overall 5-year survival rate of merely 8.7%. It is the fifth leading cause of cancer-related mortality in South Korea[1] because of the delayed detection of tumors, typical presentation at advanced stage, and its aggressive disease behavior. Only 20% of tumors are surgically resectable when detected. Remaining 80% of patients cannot help undergoing palliative therapy, the only treatment option for those patients. In addition, pancreatic cancer has a poor response to chemotherapy and radiation therapy, increasing the complexity of patient management. Therefore, early detection is the key in order to increase the survival rate of pancreatic cancer patients and to improve overall patient care.

Early detection, though it is crucial, is challenging since pancreatic cancer is usually asymptomatic in the initial stage and anatomically less accessible due to surrounding organs in retroperitoneum. To overcome these limitations, imaging modalities such as abdominal ultrasound, computed tomography, magnetic resonance imaging, endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography (EUS), and positron emission tomography have been used to localize the lesions.

For the detection of pancreato-biliary diseases, EUS is currently widely accepted. This technique enables precise

visualization of the lesion and the ability to proficiently determine the depth of gastrointestinal malignancies.[2] By combining advantages of EUS with fine-needle aspiration cytology (FNAC) for retrieval of specimens for pathologic diagnosis, EUS-FNAC has improved diagnostic capabilities. With EUS-FNAC, distinguishing pancreatic cancer from chronic pancreatitis, detection of tumor smaller than 2cm and staging of the cancer are superior to those with the other modalities. EUS-FNAC has become the most popular technique with which to obtain cytology specimens and diagnose patients suspected to pancreas cancer.

EUS-FNAC has been shown to be diagnostically useful, obviating unwarranted procedures and reducing costs.[3] It is also minimally invasive and comparatively safe. The conclusion from a meta-analysis stated that EUS-FNAC should be included in algorithms for the management of patients with solid pancreatic tumor due to its high accuracy as a diagnostic test.[4]

Although EUS-FNAC for diagnosis of solid pancreatic masses is recognized as ‘a nearly perfect procedure’,[5] there are still several flaws that need to be ameliorated. Problematic issues may arise due to limited skills of the endoscopy operator in terms of insufficient yield and targeting-error, misinterpretation and misdiagnosis by pathologists and absence of on-site cytopathologists for adequacy assessment.

This study was aimed to evaluate the diagnostic accuracy of EUS-FNAC of the pancreas and to further investigate the

reason for incorrect diagnosis by comparison with confirmed histological diagnosis. The discrepancy between cytological and histological specimen diagnoses was focused in this study to identify the pitfalls that pathologists may face during diagnosis. In some patients, initial diagnostic cytology specimen may be the only material that has viable tumor cells for diagnosis if the tumor is unresectable or they received neoadjuvant therapy prior to resection. This situation emphasizes the importance of the accuracy of cytopathologic diagnosis. Furthermore, on-site cytopathologic assessment for adequacy is not performed in South Korea for financial reasons,[6] making it even more challenging for pathologists in Korea to diagnose cytological specimens.

By comparison between cytology and histology diagnosis of pancreatic lesions obtained by EUS-FNAC with several clinicopathologic variables, retrospective analysis was performed to assess the diagnostic accuracy of procedure.

MATERIALS AND METHODS

A retrospective study was carried out to review 191 cases of EUS-FNAC of pancreatic lesions between January 2010 and December 2012 in Seoul National University Hospital. This study was approved by the Seoul National University Hospital Institutional Review Board (IRB Study No. H-1408-022-601).

Case selection

The data from 579 patients who underwent pancreatic FNAC over a 36-month period (January 2010 to December 2012) were obtained by computerized search of PathPACS (Humintec, Suwon, Korea), a database used at the Department of Pathology of Seoul National University Hospital. Cases with no follow-up biopsy or surgical resection were excluded from this study, leaving 207 cases. Among those cases, 191 patients underwent EUS-FNAC. Specimens from 8 patients were retrieved by intraoperative brush cytology, 4 from ultrasound-guided gun biopsy, and 4 were unclear with no specific record of the procedure. In this study, only patients who underwent EUS-FNAC were included. For statistical analysis, patients histologically diagnosed as 'atypical' or 'insufficient for diagnosis (IFD)' were further excluded since those diagnoses were not as satisfactory as confirmation of cytologic diagnosis. The remaining 167 cases were analyzed to assess the

diagnostic accuracy of EUS-FNAC.

Procedure: EUS-guided fine-needle aspiration and specimen preparation

Radial and linear endoscopic ultrasonographies were used for EUS-FNAC. Fine-needle aspiration was performed by gastroenterologists of Seoul National University Hospital. For cytopathologic analysis, aspirated specimen was smeared onto glass slides and fixed in 95% ethanol, followed by Papanicolaou staining and Diff-Quick staining. A cell block was prepared in 2 cases using a standard protocol.

Cytologic diagnosis

Diagnoses were made by several pathologists at Seoul National University Hospital. The specimen was initially rated either as adequate or inadequate. Suboptimal specimens with less than minimal pancreatic tissue needed for diagnosis were rated inadequate. Adequate samples were then categorized into four groups: negative for malignancy, benign lesion, atypical, and malignant neoplasm. Altogether there were five groups, including inadequate samples grouped as 'IFD.' Diagnosis of EUS-FNAC was then compared with subsequent corresponding histologic diagnosis.

Retrospective review of cases with discrepancy

Of the 167 included cases, 36 showed major discrepancy between cytological diagnosis and histological diagnosis.

Retrospective review of those slides was conducted by three pathologists. For non-biased review results, final histological diagnosis was blinded.

Statistical analysis

The data on patient sex, age, type of procedure, diagnosis for cytology, biopsy and resected specimen, and site of aspiration were analyzed using Microsoft Excel 2007 calculation sheets. For patients with several cytological specimens obtained from same site on same day, that with the most corresponding result with final histological diagnosis was included in the data analysis. The diagnostic accuracy, sensitivity, specificity, positive and negative predictive values, false-positive rate, false-negative rate, and false-discovery rate of EUS-FNAC results were calculated. Also, diagnostic accuracy according to specific histological diagnosis was analyzed for comparison. For the statistical analysis, cytological and histological diagnoses of 'benign lesion' were categorized as a negative result, meaning 'negative for tumor,' while 'atypical' and 'suspicious for malignancy' (the *gray-zone*) were considered and categorized as 'positive for tumor.' Although histological diagnoses of 'atypical' and 'IFD' were excluded from statistical analysis, 'atypical' and 'IFD' categories were included for cytology specimens for broader evaluation.

RESULTS

Patient characteristics

Among 191 patients who underwent EUS-FNAC, the male to female ratio was 0.95, with 93 males and 98 females. The median age of the patients was 60.25 years, ranging from 20 to 82 years.

Cytologic results consisted of 35 cases (18.3%) of 'negative for tumor,' 5 cases (2.6%) of 'benign lesion,' 37 cases (19.4%) of 'atypical,' 94 cases (49.2%) of 'malignant neoplasm,' and 20 cases (10.5%) of 'IFD' (Table 1). Specific diagnoses of cytologically 'malignant neoplasm' included 53 cases of ductal adenocarcinoma, 28 cases of 'malignant tumor, unspecified,' 10 cases of neuroendocrine neoplasm, 2 cases of mucinous neoplasm, and 1 case of squamous cell carcinoma (Table 2).

Histological results consisted of 28 cases (14.7%) of 'negative for tumor,' 9 cases (4.7%) of 'benign lesion,' 17 cases (8.9%) of 'atypical,' 130 cases (68.1%) of 'malignant neoplasm,' and 7 cases (3.6%) of 'tissue insufficient for diagnosis (TIFD)' (Table 1).

Comparison between cytological and histological diagnoses

In a comparison of cytology-histological diagnoses (Table 1), 35 cases of negative cytology diagnosis were histologically diagnosed as 'non-neoplastic lesion' in 15

cases and 'benign lesion' in 2 cases. Those cases were classified as true-negative results. On the contrary, there were 15 false-negative cases showing major discrepancy, which were initially diagnosed negative on cytology but malignant on histological specimen. Two cases with histological diagnosis of 'atypical (undetermined)' and 1 case of 'TIFD' were excluded from the statistical analysis due to unsatisfactory results of confirmation. Five cases were cytologically diagnosed as 'benign lesion' and were also diagnosed as 'benign lesion' on histological diagnosis. These cases were classified as true-negative.

There were 37 cytologically 'atypical (undetermined)' cases. Histological diagnosis of these cases was true-positive ('malignant neoplasm') in 24 cases and false-positive in 5 cases (4 'benign lesion' and one 'non-neoplastic lesion'). Eight cases that were histologically diagnosed 'TIFD' (3 cases) and 'atypical' (5 cases) were likewise excluded. As for cytological specimens diagnosed 'malignant neoplasm', 79 of 94 cases were true-positive with histological diagnosis of 'malignant neoplasm.' There were 4 false-positive results for specimens histologically diagnosed as 'non-neoplastic lesion.' In the same manner as the other categories, 9 cases of histologically 'atypical' and 2 cases of histologically 'TIFD' were excluded.

Among 20 cases of cytologically 'IFD' cases, 6 were true-negative (five histologically 'non-neoplastic lesion' and one 'benign lesion'), while 12 cases were

false-negative with a histological diagnosis of 'malignant neoplasm.' Cases with histological diagnosis of 'IFD' (1 case) and 'atypical' (1 case) were excluded. Last of all, there was a case that was cytologically diagnosed as 'suspicious for neuroendocrine tumor' but histologically diagnosed as solid pseudopapillary neoplasm, which are distinctive in diagnosis. Despite the discrepancy, this case was classified as true-positive in order to acknowledge the cytological diagnosis for recognizing a malignancy.

Statistical results

According to the data, the 167 cases remaining after applying exclusion criteria were true-positive in 103 cases (61.7%), true-negative in 28 cases (16.8%), false-positive in 9 cases (5.4%), and false-negative in 27 cases (16.1%). The diagnostic accuracy was 78.4%, sensitivity was 79.2%, and specificity was 75.7%. The positive predictive value was 92.0%, and negative predictive value was 50.9%. The false-positive rate was 24.3%, false-negative rate was 11.6%, and false discovery rate was 8.0% (Table 3). Diagnostic accuracy according to specific histological diagnosis was 79.1% in malignant neoplasm (76.5%, 91.7%, 62.5%, 100% in ductal adenocarcinoma, neuroendocrine neoplasm, intraductal papillary mucinous neoplasm, and the other malignant tumor, respectively), and 76.3% in benign lesion. (Table 4)

Analysis of discrepant cases: false-positives and false-negatives

Thirty-five cases showed discrepancy in cytological-histological correlation, and 9 cases among them were false-positive (Table 5). Cytologically diagnosed 'atypical' specimens were histologically diagnosed negative in 2 cases and lymphoplasmacytic sclerosing pancreatitis in 2 cases. Two cytologic diagnoses of 'suspected carcinoma,' one 'carcinoma,' and one 'adenocarcinoma' were also false-positive, later histologically diagnosed as 'negative for tumor.'

There were 27 cases that resulted in false-negative results (Table 5). Cytologically diagnosed 'negative for tumor' or 'IFD' were histologically diagnosed ductal adenocarcinoma in 23 cases, intraductal papillary mucinous neoplasm in 2 cases, neuroendocrine tumor in 1 case, and 'malignancy, unspecified' in 1 case.

Cytology slides of discrepant cases were reviewed to analyze reasons for such results. Cases were assigned to the following three main categories: 1) IFD (cytologic specimen with too few cells), 2) technical targeting error (aspiration of normal parenchyma or other non-lesion area), and 3) misdiagnosis by pathologists. The number of cases that fall into these categories was 12 (7.2%), 16 (9.6%), and 7 (4.2%), respectively (Table 5).

Through a group review by three pathologists, the reasons for the discrepancy in each case in category 3 were

analyzed. In 3 cases that were histologically adenocarcinoma but cytologically diagnosed negative, obvious malignant cell clusters that resembled adenocarcinoma were observed (cases Nos. 31-34) (Table 5, Fig. 1A). These cases were analyzed as misdiagnosis due to omission of tumor cells by inattentive screening. Another case diagnosed 'histologically adenocarcinoma but cytologically negative' (case No. 32) (Table 5, Fig. 1B, C) showed some malignant cell clusters that were intermixed with and camouflaged by a massive amount of benign parenchymal cells. This case was analyzed as a misdiagnosis due to misinterpretation of the pathologist.

Intraductal papillary mucinous neoplasm was diagnosed as negative in one case (case No. 35) (Table 5, Fig. 1D). Some mucin-producing epithelial cells with suspicious atypia were observed from slide review. This case was also analyzed as a misinterpretation by the pathologist.

Three cases were histologically diagnosed as 'consistent with lymphoplasmacytic sclerosing pancreatitis.' Among them, 2 cases were cytologically misdiagnosed as 'atypical,' resulting in discrepancy (cases Nos. 29 and 30) (Table 5). The remaining case was cytologically diagnosed 'negative for tumor,' which was categorized as a true-negative result in this study. In cytology specimens, inflammatory infiltrate consisted mainly of lymphocytes and plasma cells were observed.

A cytology specimen that was diagnosed as 'a few atypical cells' and histologically diagnosed schwannoma (Fig. 2) was also reviewed. This case was not included in

category 3 since it is not a serious misdiagnosis. Cytopathologic features presented mostly in tissue fragments or in fascicles, with cells fusiform and an elongated shape with poorly defined cell borders. Cytology showed low nuclear-cytoplasmic ratio with long and wavy nuclei. Nucleoli were inconspicuous, and cytoplasm was pale.

The anatomical site of aspiration in category 1 was the body in 6 cases, neck in 2 cases, uncinate process in 1 case, head in 1 case, tail in 1 case, and 'main p-duct' in 1 case. For category 2, aspirations were conducted in the body in 5 cases, neck in 4 cases, tail in 3 cases, uncinate process in 2 cases, and neck in 1 case. Category 3 cases were collected from the body in 3 cases, tail in 2 cases, neck in 1 case, uncinate process in 1 case, and distal part in 1 case (Table 5).

DISCUSSION

EUS-FNAC for pancreatic solid tumor is widely performed and has been shown to be useful.[3,5,7,8] As EUS-FNAC has gained acknowledgement as gold standard for obtaining patient specimens, the importance and demand for optimization of EUS-FNAC has increased. Follow up and review of past EUS-FNAC results were done to determine the validity of examination process. The aim of current study was to contribute to the advancement of management for pancreatic cancer patients by improving detection and diagnosis results.

To analyze accuracy, diagnosis of EUS-FNAC was compared with final diagnoses confirmed by histological examination of biopsy or surgically resected specimens. During evaluation of the diagnoses made by EUS-FNAC, agreement with the final diagnoses was emphasized.

In this study, 61.7% of cases were true-positive and 16.8% of cases were true-negative, with false-negative and false-positive cases comprising only 21.6%, which is acceptably low considering that most were due to adequacy problems with EUS-FNAC specimen. As a result, diagnostic accuracy, sensitivity, and specificity were 78.4%, 79.2%, and 75.7% respectively. The positive predictive value was 92.0%, and negative predictive value was 50.9%. The false-positive rate was 24.3%, false-negative rate was 11.6%, and false discovery rate was 8.0%. According to Yoshinaga *et al.*,[5] a

medical literature review to evaluate the role of EUS-FNAC for diagnosis of solid pancreatic masses showed 78-95% sensitivity, 75-100% specificity, 98-100% positive predictive value, 46-80% negative predictive value, and 78-95% accuracy. In comparison of such data along with the other datas from several studies,[9-12] this study showed lower but within the range values of diagnostic accuracy, sensitivity and specificity. The positive predictive value was 12% higher than the upper margin, but the negative predictive value was lower than the mean. As negative predictive value decreases when the number of false negative cases increases, the fact that majority of false negative cases in this study were due to insufficient tissue or mistargeting would be the reason for low negative predictive value result. The overall results were affirmative and supportive of continued use of EUS-FNAC for pancreatic lesion, but it is apparently lower than other institutes. This encourages us to look for an explanation and identify mechanisms for improvement. Such relatively poor result may be due to the way of manipulating raw data during patient selection and categorization of diagnoses. By adjusting the methods to be more identical to those of other studies, more satisfying results may have been gained.

After confirming that the overall results were comparatively favorable in this study, discrepancy cases were focused in order to identify the pitfalls of diagnosis and further improve the cytologic diagnosis. Slides of 35 cases which cytologic diagnosis did not concur with histological diagnosis were

reviewed and analyzed. Among those cases, 12 were due to insufficient aspiration of cells for diagnosis (category 1), and 16 were due to targeting error (category 2), containing only benign parenchyma instead of tumor. The remaining 7 discrepant cases (category 3) were due to misinterpretation and misdiagnosis by pathologists.

Categories 1 and 2 results indicate aspiration failures caused by technical variables, such as operator skills or experiences, tumor type and location. With regard to location, cases were aspirated most often from body (11 cases), followed by head (5 cases) and tail (4 cases). According to a meta-analysis[13], technical success rates are relatively low for uncinate and head lesions. An another study[14] also mentioned that approaching those locations are challenging due to poor accessibility. On the contrary, this study also noted that lesions located in body or tail were the easiest to sample and diagnostic sensitivity was not influenced by location. Therefore, higher prevalence of lesions was assumed to be the reason for body being the most aspirated location in this study, rather than due to technical difficulty.

The most common cytologic diagnosis for categories 1 and 2 was 'adenocarcinoma' (19 cases), followed by 'negative for tumor' (5 cases), neuroendocrine tumor (1 case), intraductal papillary neoplasm (1 case), and 1 case of 'malignancy, unspecified.' Considering that adenocarcinoma was the most common diagnosis overall (adequate / inadequate, discrepant / non-discrepant), tumor type may

have less impact on aspiration failure. In addition, cases of intraductal papillary mucinous neoplasm may have been underdiagnosed as 'benign lesion' in this study. Therefore, relativity of tumor type and diagnostic accuracy is still ambiguous. Also, significant influences from variability in operator skills and tumor size on EUS-FNAC results were assumed. However, the electric medical records did not document the specific operator's name and tumor size in all cases so analysis of such data was unable to be carried out.

For category 3, slides of misdiagnosed cases were reviewed to identify the factor that led to such discrepancy. Of 7 cases, four were histologically adenocarcinoma but cytologically diagnosed negative. Meticulous observation led to identification of some obviously malignant cells that resemble adenocarcinoma in 3 cases (cases Nos. 31-34) (Table 5, Fig. 1A). In these cases, misdiagnosis was most-likely due to screening failure and simple exclusion of the applicable areas on the slide. On the other hand, one histologically adenocarcinoma but cytologically diagnosed 'negative' case was actually challenging (case No. 32) (Table 5, Fig. 1B, C). As reviewers were retrospectively observing the collection of 'discrepant' cases only, interpreting this case as malignant was not difficult for it was predictable. However, tumor cells in this case were intermixed with and camouflaged by a massive amount of benign parenchymal cells, making the malignancy ambiguous. In a situation like this, a pathologist may be discouraged and hesitant to conclude a diagnosis of definite cancer.

Intraductal papillary mucinous neoplasm was misdiagnosed as negative in one case (case No. 35) (Table 5, Fig. 1D). From review of the slide, some mucin-producing epithelial cells with suspicious atypism were recognized. Assumption was made that the discrepancy in this case was due to diagnosis by a relatively inexperienced pathologist, leading to misinterpretation.

There were three cases histologically diagnosed as 'consistent with lymphoplasmacytic sclerosing pancreatitis.' Among them, 2 cases were cytologically misdiagnosed as 'atypical,' resulting in discrepancy (cases Nos. 29 and 30) (Table 5). The remaining case was cytologically diagnosed 'negative for tumor' and was categorized as a true negative result. Lymphoplasmacytic sclerosing pancreatitis, a form of chronic pancreatitis with mixed inflammatory infiltrate, clinically mimics pancreatic cancer. Preoperative detection is important because lymphoplasmacytic sclerosing pancreatitis patients usually respond to steroid therapy with reversible improvement in pancreatic morphology and function.[15] In this study, inflammatory infiltrate consisting mainly of lymphocytes and plasma cells was observed. According to Abraham *et al.*,[16] this infiltrate may also contain some macrophages and occasionally neutrophilic and eosinophilic granulocytes. Although the role of FNAC is mainly to distinguish malignant from benign cells, it is worth considering the possibility of lymphoplasmacytic sclerosing pancreatitis when investigators recognize such microscopic features because patients will benefit from earlier initiation

of therapy.

A case of schwannoma that was cytologically diagnosed as 'a few atypical cells' (Fig. 2) was also reviewed. Cytopathologic features presented mostly in tissue fragments or in fascicles, with cells fusiform and elongated with poorly defined cell borders. The cells showed a low nuclear-cytoplasmic ratio with long and wavy nuclei. Nucleoli were inconspicuous, and cytoplasm was pale. Pancreatic schwannoma is an extremely rare neoplasm, with only 47 cases reported in the English literature in last three decades.[17] Therefore, it is not routine for pathologists to suspect such schwannoma when screening. However, the possibility that cells are mesenchymal should be considered, which may suggest the diagnosis.

Navina *et al.*[18] and Kim *et al.*[6] reported that absence of an immediate on-site cytopathologist is not critical, and they found no association with on-site evaluation and specimen cellularity. However, many groups, for example, Fisher *et al.*[8], have reported that on-site evaluation was relatively accurate (77.5%) and highly specific for malignancy (100%), significantly contributing to the efficiency and accuracy of the procedures. With respect to the lower diagnostic accuracy of this study in comparison to those of other institutes, absence of on-site evaluation may be the cause since 28 of 35 discrepant cases were due to unsatisfactory specimens.

The design of this study was limited by the fact that it was a single-center retrospective review of a relatively small

number of consecutive cases over a 36-month period. Thorough adequacy assessment of pancreatic EUS-FNAC was impossible since only one representative specimen of patients with multiple aspirations was analyzed. If numerous 'IFD' cases were not excluded, there would have been a greater amount of useful data, which could have reduced the impact of incorrect results caused by technical difficulty. Also, data identifying the operator and pathologist should have been retrieved to analyze artificial error that depends on skill and experience. Further study on cases with discrepancy aimed to identify the pitfalls of diagnosis should involve more cases of misdiagnosis, increasing the power of the analysis. Awareness of such pitfalls is important to increases diagnostic confidence, resulting in improved accuracy.

In summary, the diagnostic accuracy of EUS-FNAC for obtaining pancreatic specimens suspicious of malignancy was confirmed to be high in this study. Diagnostic accuracy, sensitivity, and specificity were 78.4%, 79.2%, and 75.7% respectively. Although 35 of 191 cases showed discrepancy in cytology-histology diagnosis, most were due to insufficient aspiration or mistargeted aspiration of cells, both of which preclude proper examination. Therefore, this study concluded that EUS-FNAC is reliable and accurate. Based on these results, pathologists can be assured of their diagnosis, as EUS-FNAC provides a desirable representation of the specimen. However, particular attention to adequacy assessment and meticulous observation of samples are

critical in order to reduce the discrepancy between cytology-histological diagnoses. Though the percentage of correct diagnoses in EUS-FNAC results is relatively inferior compared to that from histological diagnosis, statistical results, such as diagnostic accuracy, were satisfactory in several studies including this study. Therefore, EUS-FNAC can be encouraged as a first-line pathologic examination for pancreatic lesion with high clinical suspicion of malignancy when patients' safety and financial benefits are the priority.

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요약(국문초록)

배경 : 내시경초음파 유도하 세침흡인세포검사(EUS-FNAC)는 현재 췌장의 세포병리 검체를 얻기 위해 이용되는 가장 흔한 술기로, 비교적 정확도가 높고 안전하며 비용 효율적이라는 장점이 있다. 그러나, 조직병리검사(생검과 절제술 검체)의 최종진단과의 진단 불일치는 여전히 발생하고 있다. 이 연구는 췌장의 EUS-FNAC 진단과 조직병리검사 결과의 비교를 통해, EUS-FNAC의 진단정확도를 분석하고 불일치에 대한 원인을 파악하여 검사 성적의 향상을 도모하고자 하였다.

대상 및 방법 : 서울대학교병원 병리과에서 2010년에서 2012년 사이에 시행된 췌장 병변에 대한 EUS-FNAC 진단 후 조직병리검사까지 시행된 191개의 증례를 대상으로 후향적 연구를 하였다. 세포검사와 조직검사의 결과는 음성, 양성종양, 비정형병변, 악성종양, 불충분 검체로 다섯 군으로 분류되었다. 이 중 충분한 양을 얻은 167개의 세포 및 조직 검체의 진단을 통계적으로 분석하여 진단 일치율 및 정확도를 비교하였다.

결과 : 췌장의 악성 혹은 양성종양을 발견하는데 있어서 최종 조직검사결과와 비교했을 때 EUS-FNAC의 진양성은 103증례(61.7%), 진음성은 28증례(16.8%), 위양성은 9증례(5.4%), 위음성은 27증례(16.1%)였다. 진단정확률은 78.4%, 민감성은 79.2%, 특이성은 75.7%, 양성 예측치는 92.0%, 음성 예측치는 50.9%였다. 조직진단별 진단정확도는 악성종양에서 79.1% (췌관 선암종 76.5%, 신경 내분비 종양 91.7%, 췌관내 유두상 점액 종양

62.5%, 그 외 악성종양 100%), 양성병변에서 76.3였다.

결론 : EUS-FNAC는 비교적 높은 정확도, 민감도, 특이도와 양성예측치를 갖는 것으로 확인되었다. 세포 및 조직검사진단의 불일치와 낮은 음성예측치는, 불충분한 조직 또는 비병변 부위가 흡인되었다는 점이 가장 큰 원인이었다. 이러한 한계를 보완하여 극복한다면 췌장 병변의 진단에 있어서 EUS-FNAC는 보다 유용하고 신뢰성이 높은 진단적 검사방법이 될 수 있다.

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주요어 : 췌장; 내시경초음파 유도하 세침흡인 세포검사;
EUS-FNAC; 진단정확도; 분석; 평가; 세포병리

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Table 1. Correlation of EUS-FNAC diagnosis and corresponding final histologic diagnosis

Cytology diagnosis	Histologic diagnosis	No. of cases	Category
Negative (35 cases, 18.3%)	Non-neoplastic lesion	15	True-negative
	Benign lesion	2	True-negative
	Atypical(undetermined)	2	Excluded
	Malignant neoplasm (n=15)		
	Ductal adenocarcinoma	13	False-negative
	Neuroendocrine tumor	1	
	IPMN	1	
Benign lesion (5 cases, 2.6%)	TIFD	1	Excluded
	Non-neoplastic lesion	0	True-negative
	Benign lesion	5	True-negative
	Atypical(undetermined)	0	Excluded
	Malignant neoplasm (n=24)	0	False-negative
Atypical (undetermined) (37 cases, 19.4%)	TIFD	0	Excluded
	Non-neoplastic lesion	4	False-positive
	Benign lesion	1	False-positive
	Atypical(undetermined)	5	Excluded
	Malignant neoplasm (n=24)		True-positive
	Ductal adenocarcinoma	18	
	Neuroendocrine tumor	2	
	IPMN	2	
	Malignant tumor, unspecified	2	
Malignant neoplasm (94 cases, 49.2%)	TIFD	3	Excluded
	Non-neoplastic lesion	4	False-positive
	Benign lesion	0	False-positive
	Atypical(undetermined)	9	Excluded
	Malignant neoplasm (n=79)		True-positive
	Ductal adenocarcinoma	57	
	Neuroendocrine tumor	10	
	Carcinoma	4	
	IPMN	3	
	Solid-pseudopapillary neoplasm	2	
	Mucinous neoplasm	1	
	Malignant mesenchymal tumor	1	
	Metastatic leiomyosarcoma	1	
Insufficient for diagnosis (20cases, 10.5%)	TIFD	2	
	Non-neoplastic lesion	5	
	Benign lesion	1	
	Atypical(undetermined)	1	
	Malignant neoplasm (n=12)		
	Ductal adenocarcinoma	10	
	IPMN	1	
	Malignant tumor, unspecified	1	
	TIFD	1	
Total		191	

TIFD, tissue insufficient for diagnosis; IPMN, intraductal papillary mucinous neoplasm.

Table 2. Specific diagnoses of cytologically 'Malignant neoplasm' group

Cytology diagnosis	Total
Ductal adenocarcinoma	53
Malignant tumor, unspecified	28
Neuroendocrine neoplasm	10
Mucinous neoplasm	2
Squamous cell carcinoma	1
Total	94

Table 3. Statistical analysis of 167 cases[a]

Category	Percentage	Equation
TP (103 cases)	61.7	N/A
TN (28 cases)	16.8	N/A
FP (9 cases)	5.4	N/A
FN (27 cases)	16.1	N/A
Diagnostic accuracy	78.4	(TP+TN)/(TP+TN+FP+FN)X100
Sensitivity	79.2	TP/(TP+FN)X100
Specificity	75.7	TN(TN+FP)X100
Positive predictive value	92.0	TP/(TP+FP)
Negative predictive value	50.9	TN/(TN+FN)
FP rate	24.3	FP/(FP+TN)
FN rate	11.6	FN/(TP+FN)

TP, true positive; TN, true negative; FP, false positive; FN, false negative; N/A, not applicable.

[a] Histologically 'atypical' (17 cases) and 'tissue insufficient for diagnosis' (7 cases) cases are excluded.

Table 4. Diagnostic accuracy according to specific histological diagnosis

Histological Diagnosis	Total number of cases	Number of true positive cases	Number of false negative cases	Diagnostic accuracy
Malignant neoplasm	129	102	27	79.1%
Ductal adenocarinoma	98	75	23	76.5%
Neuroendocrine neoplasm	12	11	1	91.7%
IPMN	8	5	3	62.5%
The other malignant tumor	11	11	0	100%
Benign lesion	38	29	9	76.3%

IPMN, intraductal papillary mucinous neoplasm.

Table 5. Discrepant cases with a false-positive or false-negative cytology diagnosis

Category[a]		Case No.	Sex	Age (yr)	Location	Cytology diagnosis	Histologic diagnosis
1	False-negative	1	F	70	Neck	IFD	Ductal adenocarcinoma
		2	F	53	Uncinate	IFD	Ductal adenocarcinoma
		3	M	69	Tail	IFD	Ductal adenocarcinoma
		4	F	65	Body	IFD	Ductal adenocarcinoma
		5	M	76	Body	IFD	Ductal adenocarcinoma
		6	M	58	Head	IFD	Ductal adenocarcinoma
		7	M	77	Body	IFD	Ductal adenocarcinoma
		8	M	76	Body	IFD	Ductal adenocarcinoma
		9	F	69	Neck	IFD	Ductal adenocarcinoma
		10	M	71	Body	IFD	IPMN
		11	F	70	Main p-duct	IFD	Malignancy, unspecified
		12	F	50	Body	IFD	Neuroendocrine tumor
2	False-positive	13	M	75	Body	Suspected carcinoma	Negative for tumor
		14	M	75	Body	Suspected carcinoma	Negative for tumor
		15	M	60	Neck	Carcinoma	Negative for tumor
		16	F	58	Body	Adenocarcinoma	Negative for tumor
		17	F	82	Head	Atypical	Negative for tumor
		18	F	38	Body	Atypical	Negative for tumor
	False-negative	19	M	57	Tail	Negative for tumor	Ductal adenocarcinoma
		20	F	61	Uncinate	Negative for tumor	Ductal adenocarcinoma
		21	F	51	Tail	Negative for tumor	Ductal adenocarcinoma
		22	F	41	Head	Negative for tumor	Ductal adenocarcinoma
		23	M	77	Body	Negative for tumor	Ductal adenocarcinoma
		24	F	67	Head	Negative for tumor	Ductal adenocarcinoma
		25	F	72	Head	Negative for tumor	Ductal adenocarcinoma
		26	M	57	Tail	Negative for tumor	Ductal adenocarcinoma
		27	F	73	Uncinate	Negative for tumor	Ductal adenocarcinoma
		28	M	64	Body	Negative for tumor	Ductal adenocarcinoma
3	False-positive	29	M	50	Body	Atypical	LSP
		30	F	60	Distal part	Atypical	LSP
	False-negative	31	M	76	Body	Negative for tumor	Ductal adenocarcinoma
		32	M	56	Head	Negative for tumor	Ductal adenocarcinoma
		33	M	61	Tail	Negative for tumor	Ductal adenocarcinoma
		34	F	58	Tail	Negative for tumor	Ductal adenocarcinoma
		35	F	70	Uncinate	Negative for tumor	IPMN

F,female; IFD, insufficient for diagnosis; IPMN, intraductal papillary mucinous neoplasm; LSP, lymphoplasmacytic sclerosing pancreatitis; M, male.

[a]Discrepancy category: 1) Insufficient for diagnosis (cytology specimen of too few cells), 2) Technical targeting error (normal parenchyma or other non-lesion area aspirated), and 3) Misdiagnosis by pathologists.

Figure 1. Cytologic specimen with false-negative discrepant results (Table 4). (A) Case No. 31 with histologic diagnosis of ductal adenocarcinoma. Obvious malignant cell clusters that resemble adenocarcinoma. (B, C) Case No. 32 with histologic diagnosis of ductal adenocarinoma. Malignant cells clusters are intermixed with and camouflaged by a massive amount of benign parenchymal cells. (D) Case No. 35 with histologic diagnosis of intraductal papillary mucinous neoplasm. Some mucin-producing epithelial cells with suspicious atypism are observed.

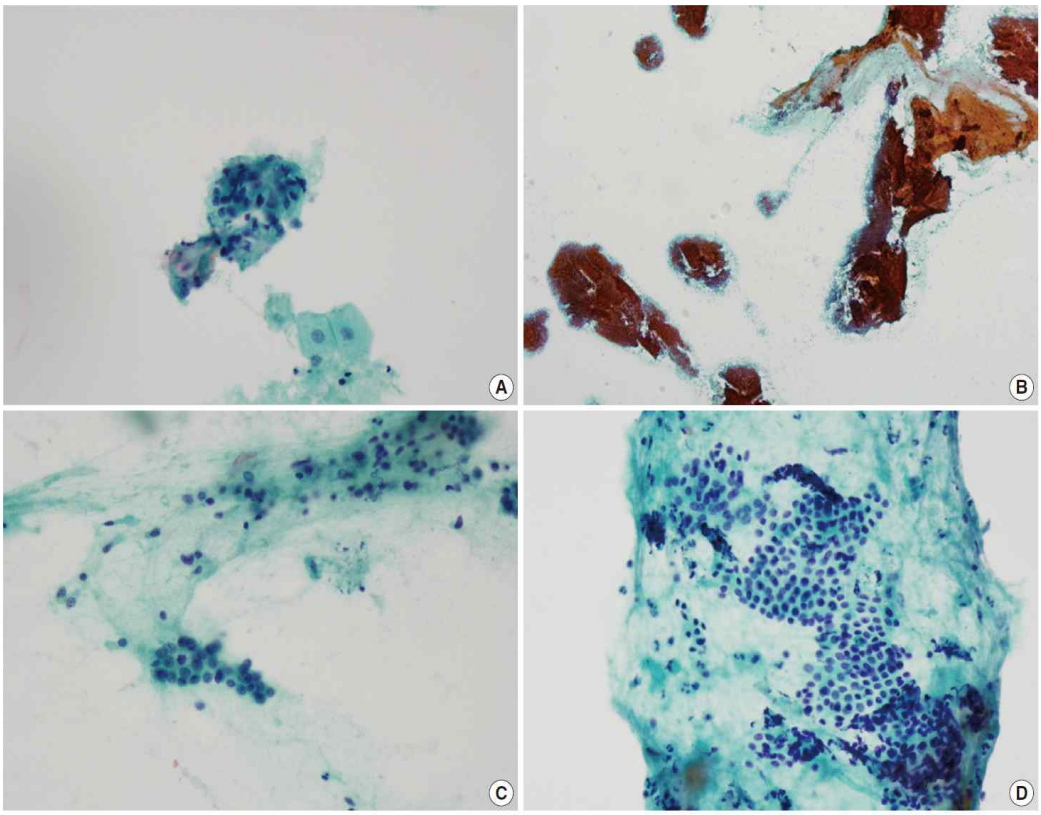

Figure 2. Cytologic specimen with corresponding histologic diagnosis of schwannoma. Cytopathologic features present mostly in tissue fragments or in fascicles, with cells fusiform and elongated with poorly defined cell borders, a low nuclear-cytoplasm ratio with long and wavy nuclei, inconspicuous nucleoli and pale cytoplasm.