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Endoscopic Ultrasonography-Guided Fine-Needle Biopsy for Patients with Resectable Pancreatic Malignancies

Ming-Sheng Chien [1], Ching-Chung Lin [1,2] and Jian-Han Lai [1,2,3,*]

[1] Division of Gastroenterology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei 104217, Taiwan; lineage2728@gmail.com (M.-S.C.); sunny.lin56@msa.hinet.net (C.-C.L.)
[2] Department of Medicine, MacKay Medical College, New Taipei City 25245, Taiwan
[3] MacKay Medicine Nursing and Management, Taipei 11260, Taiwan
* Correspondence: jiannhann@gmail.com; Tel.: +886-2-25433535

Abstract: Clinicians often use endoscopic ultrasonography to survey pancreatic tumors. When endoscopists conduct this examination and find the tumor to be unresectable, a fine-needle biopsy is subsequently performed for tissue confirmation. However, if the tumor is deemed resectable, the necessity of a pre-operative fine-needle biopsy remains debatable. Therefore, we performed a retrospective analysis of a single-center cohort of patients with pancreatic tumors who underwent an endoscopic ultrasound-guided fine-needle biopsy or aspiration (EUS-FNB or FNA) between 2020 and 2022. This study focused on patients diagnosed with resectable malignant pancreatic tumors. The exclusion criteria included individuals diagnosed with benign pancreatic lesions and those with unresectable tumors. A total of 68 patients were enrolled in this study. Histological examination revealed that pancreatic adenocarcinoma was the predominant type of tumor (n = 42, 61.8%), followed by neuroendocrine tumors (n = 22, 32.3%), and metastasis (n = 4, 5.9%). Notably, 17 patients had a history of other cancers, with 23.5% being diagnosed with a metastatic tumor rather than primary pancreatic cancer. Therefore, EUS-FNA/FNB is crucial in patients with a resectable pancreatic tumor and a history of cancer to differentiate between a primary and a metastatic tumor.

Keywords: endoscopic ultrasonography; fine-needle biopsy; malignant pancreatic tumor; resectable tumor; pancreatic surgery

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1. Introduction

Pancreatic cancer stands as a lethal malignancy, ranking among the leading contributors to cancer-related deaths [1,2]. Surgical resection is the only curative approach for resectable pancreatic cancer. Imaging examinations such as computed tomography (CT) and magnetic resonance imaging (MRI) are valuable tools in identifying malignancy and determining whether tumors are resectable or non-resectable by assessing their interaction with nearby vascular structures, such as the superior mesenteric artery and vein, portal vein, and celiac artery. However, these imaging studies are unable to differentiate between primary and metastatic tumors. The definitive determination of the tumor type and origin relies on histological examination and immunohistochemical staining.

In cases where tumors are deemed unresectable, tissue confirmation is imperative to guide subsequent systemic treatment. The decision making process regarding subsequent fine-needle aspiration or biopsy (FNA or FNB) for tissue confirmation becomes pivotal when endoscopists perform EUS in patients with pancreatic tumors. Conversely, when tumors are considered resectable, surgical resection is the primary recommendation for curative therapy. Consequently, pre-operative tissue confirmation through FNB may not be perceived as necessary for the majority of patients unless there is disagreement among surgeons regarding the pre-operative imaging study results, such as distinguishing between benign and malignant conditions. However, certain studies have documented cases in

which patients underwent surgery only owing to the final diagnosis, which unexpectedly revealed pancreatic metastasis [3]. In such instances, if a pre-operative FNB was performed, unnecessary surgeries would avoided, thereby emphasizing the significance of judicious decision making in the diagnostic process.

This study aimed to examine patients diagnosed with resectable pancreatic cancer based on pre-EUS evaluations, including CT, magnetic resonance imaging (MRI), and abdominal US. The objective of this study was to determine whether pre-operative tissue confirmation using FNA or FNB influenced the subsequent treatment plan, particularly the choice between surgical intervention and systemic treatment. Additionally, we reviewed several studies published in English to identify the distinct characteristics and features that differentiate between primary and secondary pancreatic tumors.

2. Materials and Methods

This retrospective cohort study was conducted at a medical center in Taiwan. We performed a retrospective analysis of a cohort of patients with pancreatic tumors, specifically focusing on those who underwent EUS-FNA and FNB between January 2020 and December 2022. Patients diagnosed with benign tumors or unresectable malignancy beyond stage III according to the American Joint Committee on Cancer 8th edition were excluded. The definitive diagnosis relied on both cytopathological and imaging findings, and not solely on the images. The criteria for imaging in the differential diagnosis of benign and malignant tumors were established based on previous studies [4,5]. In the EUS images, the tumor presented as a hypoechoic heterogeneous pattern, accompanied by an upstream pancreatic duct dilatation and distal pancreas atrophy, raising suspicion of malignancy. The diagnosis of background chronic pancreatitis was made using EUS based on the proposed Rosemont criteria [6].

The adequacy of the obtained tissue was determined by the presence of well-defined pancreatic ductal epithelium or stromal cells in the retroperitoneal mass. An unsuccessful FNA/B cytopathological diagnosis was defined as either a false negative or atypical result, whereas a successful FNA/B diagnosis was defined as a suspicious or positive finding of malignancy. Specimens categorized as "atypical" exhibit a spectrum of architectural and/or cellular changes that exceed the parameters of normal or reactive conditions. Nevertheless, these alterations lack adequate quantitative or qualitative criteria to categorize them as neoplastic (benign/other), suspicious, or indicative of malignancy [7]. If a patient had an unsuccessful FNA/B cytopathological diagnosis, further surgical tissue-proof or transabdominal echo-guided metastatic lesion biopsy was arranged to obtain a final histological diagnosis. Patients who were diagnosed with benign lesions underwent diagnostic imaging follow-up for at least 6 months to rule out the possibility of a missed diagnosis of malignancy.

For the analysis, we extracted the following personal and clinical data from patient records: age, sex, presentation of chronic pancreatitis, EUS findings (tumor location and size and number of FNA or FNB passes), and cytopathological results. Because CT imaging data were available for most patients, we opted to evaluate and incorporate CT findings in our study. We also recorded whether the patients had a history of other cancers before undergoing EUS.

2.1. Study Design

Patients were initially classified into two groups: those with benign and malignant tumors. If malignant tumors were suspected in the initial imaging, it was necessary to assess the possibility of a tumor resection based on evidence of large vessel invasion and regional lymph node metastasis [8]. The characteristics of patients who had resectable malignant pancreatic tumors were recorded, such as age, sex, and history of cancer. Details of EUS and FNB procedures were documented, including the FNB pass number and the success rate of cytopathological diagnoses. Tumor characteristics, including location and final histological diagnosis, were also recorded. We further analyzed patients with a history

of cancer and those without, with a particular focus on comparing the rates of primary and metastatic tumors between these two subgroups of patients. Furthermore, this retrospective chart review received approval from the Institutional Review Board of Mackay Memorial Hospital, Taiwan. The Ethics Committee waived the requirement for informed consent, and the medical records of each patient were anonymized and de-identified before access.

2.2. EUS-FNB

All EUS-FNA/FNB procedures were performed with the patients in the left lateral decubitus position, under conscious sedation using midazolam and fentanyl. Additional sedatives were administered by endoscopists to achieve moderate conscious sedation. All EUS-FNA/B procedures were performed by three endoscopists who had completed the FNA learning curve [9]. The procedures were performed using a GF-UCT260 curvilinear echoendoscope (Olympus Optical Co., Ltd., Tokyo, Japan). A 22-gauge FNA needle (EZ Shot 3 Plus, Olympus, Tokyo, Japan) or a 22-gauge FNB needle (TopGain®, Medi-Globe, Achenmühle, Germany; Acquire TM, Boston Scientific, Natick, MA, USA) was employed.

A fanning method was used for FNA/B, involving aspiration from at least four different areas within the target lesion using a stylet slow-pull or low negative suction technique. Subsequently, the endoscopists preserved the acquired tissues in ethanol and formalin to prepare cytological smears and pathological samples, respectively. Rapid onsite cytological evaluation was not available in our hospital setting, and the decision regarding the requisite number of FNA/FNB passes for each case was individually made by the endoscopists, considering the condition of the patient and the volume of tissue obtained (macroscopic onsite quality evaluation) [10].

2.3. Statistical Analysis

Continuous variables were presented as the mean ± standard deviation, and categorical variables were expressed as frequencies and percentages. The baseline clinical characteristics of the two comparison groups were assessed using independent samples *t*-test, Chi-square test, and crosstabs statistics, depending on the data type. Student's *t*-test for continuous variables was applied for the comparison between two groups, and Chi-square or Fisher's exact test (when cell had an expected frequency less than 5) for categorical variables was applied for measures of association. Statistical analyses were performed using SPSS software (version 27.0; SPSS, Chicago, IL, USA), with a significance level set at a two-sided *p*-value of 0.05.

To estimate the required sample size for our study, G*Power 3.1 software was utilized, employing Fisher's exact test to compare two independent proportions. The underlying assumptions included a Type I error (α) set at 0.05 and a desired statistical power of 0.80. The proportions of interest, denoted as p1 and p2, were assumed to be 0.65 and 0.95, respectively, with a ratio of the sample sizes between the two groups (N2:N1) maintained at 3:1. Based on these parameters, the calculated adequate sample size necessary to detect a statistically significant difference between the two proportions with the specified power and Type I error rate was determined to be 64 participants.

3. Results

A total of 180 patients with pathologically confirmed pancreatic tumors were retrospectively reviewed. Among them, 112 patients were excluded from the analysis because they were diagnosed with either benign (n = 6) or unresectable (n = 106) tumors. A flow diagram of the participant selection is presented in Figure 1. The clinical characteristics of the patients are shown in Table 1. Patients diagnosed with resectable malignant pancreatic tumors and undergoing EUS-FNB comprised 27 men and 41 women, with a mean age of 64.53 ± 13.5 years. Seventeen patients had a history of cancer, accounting for 25% of all cases. FNB tissue confirmation achieved a success rate of 88.4%, with an average of 3.01 passes. The most common sites of tumor occurrence were the uncinate process and head (n = 47, 69.1%), followed by the body and tail (n = 21, 30.8%). The most frequent

histological types of pancreatic malignancies were pancreatic adenocarcinoma (n = 42, 61.8%), neuroendocrine tumors (n = 22, 32.3%), and metastases (n = 4, 5.9%).

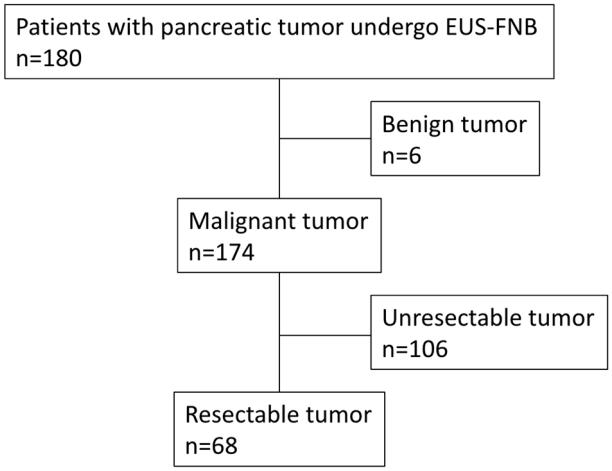

Figure 1. Flowchart of patients considered for inclusion in the study.

Table 1. Patients with resectable malignant pancreatic tumors who underwent EUS-FNB (n = 68).

Age (year)	64.53 ± 13.5
Male	27 (39.7%)
History of cancer (n, %)	17 (25%)
EUS-suspected malignancy	68
Pass number (n)	3.01
Successful FNB tissue proof (n, %)	61 (88.4%)
Location of tumor	
-Uncinate process and head	47 (69.1%)
-Body and tail	21 (30.8%)
Kinds of tumor (PDAC/NET/Metastasis) (n, %)	
-PDAC	42 (61.8%)
-NET	22 (32.3%)
-Metastasis	4 (5.9%)

EUS, endoscopic ultrasound; FNB, fine-needle biopsy; PDAC, pancreatic ductal adenocarcinoma; NET, neuroendocrine tumor.

The patients were divided into two groups: those with a history of cancer (n = 17) and those without (n = 51), as shown in Table 2. Of the patients with a history of cancer, three had lung cancer, seven had breast cancer, one had esophageal cancer, and six had other types of cancer, such as hepatocellular carcinoma, endometrial carcinoma, pheochromocytoma, and carcinoid tumors of the mediastinum. The diagnosis of pancreatic metastatic tumors was confirmed by tissue proof via EUS-FNB/A and pathohistology, which included IHC staining. The patient with solitary fibrous lung tumors was the oldest, at 68 years old, while the patient with lung adenocarcinoma was the youngest, at 58 years old. These cases presented without typical features, consistent with their respective primary origins and, in general, posed diagnostic challenges. There was no significant difference in the mean age (p = 0.27) or sex (p = 0.66) between the two groups. The mean size of primary pancreatic tumors was 2.25 ± 0.86 cm, compared with secondary cases, with a mean size of 3.2 ± 2.60 cm (p = 0.07). In our study, the incidence of metastatic pancreatic tumors tended to be higher in patients with a history of malignancy (23.5%) than in those with no cancer

history ($p < 0.001$). Notably, all patients without a history of cancer were diagnosed with primary pancreatic cancer (either adenocarcinoma or neuroendocrine tumors).

Table 2. Individuals with and without a history of cancer.

	History of Cancer (*n* = 17)	**No History of Cancer (*n* = 51)**	***p*-Value**
Male (*n*, %)	6 (35.3%)	21 (41.2%)	0.668
Age (year)	61.41 ± 14.7	65.57 ± 13.24	0.275
Underlying cancer (*n*)			
Lung	3 (17.6%)	0	NA
Breast cancer	7 (41.2%)	0	NA
Esophagus	1 (5.9%)	0	NA
Others	6 (35.3%)	0	NA
Pancreas tumor (*n*, %)			0.003
Primary	13 (76.5%)	51 (100%)	
Metastasis	4 (23.5%)	0 (0%)	

Additionally, eight (11.8%) EZ Shot 3 Plus needles were utilized for FNA, while forty-nine (72.1%) AcquireTM needles and eleven (16.2%) TopGain needles were employed for FNB. The cytopathological success rate was comparable across the various needle types used ($p = 0.607$).

Two cases of metastasis are presented to illustrate the challenges in diagnosing primary and secondary pancreatic tumors. In the first case, the patient had undergone right lung lobectomy for lung cancer 10 months previously. A new pancreatic tumor was discovered during regular follow-up CT (Figure 2). It appeared to be resectable and presented as a hypoechoic heterogeneous lesion on EUS imaging. Distinguishing adenocarcinoma from metastasis based on imaging alone remains challenging. An FNB confirmed a metastatic diagnosis originating from previous lung cancer. Consequently, unnecessary pancreatectomies were avoided. In another case, a patient with a 2.5-year history of lung cancer was informed of a new finding of a pancreatic head tumor. EUS revealed a hypoechoic tumor causing pancreatic duct dilatation, resembling the presentation of a primary adenocarcinoma (Figure 3). FNB confirmed that the tumor was a metastatic adenocarcinoma of lung origin. Consequently, the patient underwent chemotherapy instead of a pancreatectomy. Without FNB, these patients may have received incorrect diagnoses and undergone unnecessary surgeries, underscoring the critical role of a pre-operative FNB in accurate diagnosis and treatment planning.

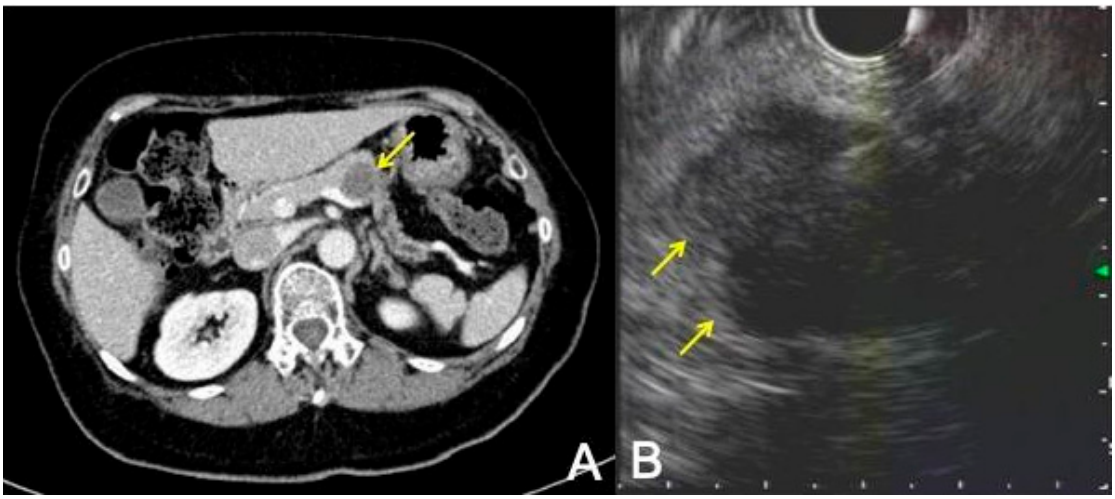

Figure 2. (**A**) The computed tomography scan revealing a well-defined resectable tumor in the pancreatic body, accompanied by pancreatic duct dilatation (arrow). (**B**) During the EUS examination, the tumor exhibits a hypoechoic and heterogeneous appearance. Subsequently, an FNB was performed, confirming it to be a metastatic tumor originating from the previous lung adenocarcinoma (arrow).

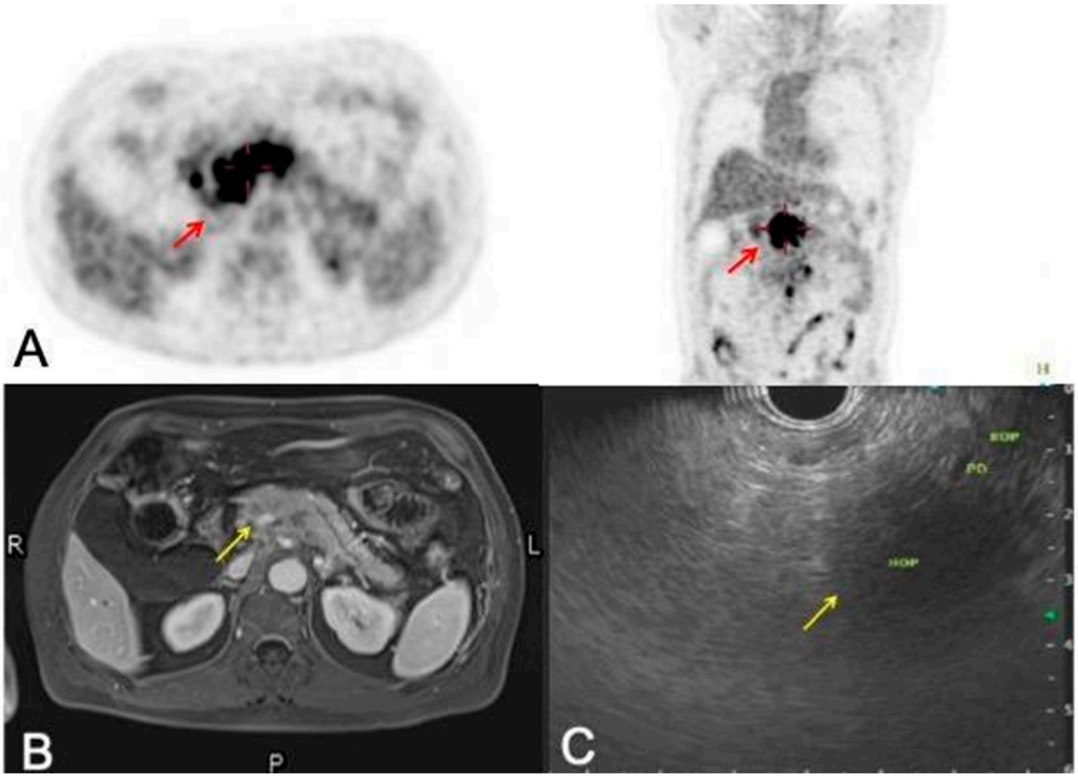

Figure 3. (**A**) The positron emission tomography scan revealing a malignant tumor located at the pancreatic head (arrow). (**B**) Magnetic resonance imaging discloses an ill-defined mass in the pancreatic head region, leading to pancreatic duct dilatation (arrow). (**C**) In the EUS examination, a hypoechoic tumor was identified, leading to pancreatic duct dilatation. A subsequent FNB confirmed it to be a pancreatic lesion metastasized from lung adenocarcinoma (arrow).

4. Discussion

Pancreatic lesions, primarily pancreatic ductal adenocarcinomas, constitute over 90% of pancreatic neoplasms, and despite surgical interventions, the prognosis remains challenging [1,11,12]. The incidence of pancreatic metastasis from cancers of other origins is notably low, ranging from 3% to 12% [13]. Although rare, it poses a significant challenge

for clinics in terms of diagnosis, and even surgeons have expressed concerns, as they are reluctant to perform unnecessary pancreatectomies and risk unexpected diagnoses.

Initially, secondary pancreatic tumors are often asymptomatic. In typical cases, an asymptomatic patient may exhibit evidence of prior surgical interventions, such as nephrectomy, lobectomy, or colon resection, during CT or abdominal US examinations. As the disease progresses, symptoms such as epigastric pain, jaundice, and weight loss may manifest, mirroring those observed in primary pancreatic tumors. CT and MRI are instrumental in providing a general assessment of the disease and evaluating the surrounding lymphadenopathy, distal metastasis, and potential resection [14]. EUS plays a crucial role in offering a final diagnosis through tissue proofing and aids in the selection of the most effective treatment for the patient [15].

Analysis of autopsies and surgical cases identified prevalent nonhematologic neoplasms that exhibited pancreatic metastasis, including renal cell carcinoma, melanoma, pulmonary small-cell carcinoma, breast carcinoma, and sporadic cases of prostate carcinoma, colon adenocarcinoma, pulmonary squamous cell carcinoma, and gastrointestinal stromal tumors [16–18]. Notably, pancreatic metastases predominantly target the pancreatic head, followed by the pancreatic body and tail [17]. Contrary to a previous study that focused on renal cell carcinoma (RCC), our analysis suggested that lung cancer is more commonly linked to secondary pancreatic tumors (50%). However, considering the limited number of patients and the inclusion of only resectable tumors in this study, it is important to acknowledge the potential for bias.

The presentation timeframe of pancreatic metastasis varies, with instances documented to manifest long after the initial diagnosis and treatment of the primary tumor averaging more than 8 years, with a maximum duration of 17 years [19]. On average, in our study, the onset of a second pancreatic cancer occurred approximately 42 months after the initial cancer diagnosis, with the longest duration extending up to 120 months. The most common locations of secondary pancreatic tumors were the pancreatic head and body. These findings are consistent with those of previous studies [17].

In CT and MRI, some secondary pancreatic tumors may present with characteristics of the original malignancy. RCC is the most common cancer to metastasize to the pancreas [19]. It typically shows either intense homogeneous enhancement in small lesions or rim enhancement in large lesions. In contrast, the outer regions of colorectal metastases showed no difference from the normal pancreatic tissue, whereas the inner area showed hypo-enhancement due to central necrosis [20]. Additionally, a distinctive lesion may be present in the pancreas that lacks the classic double duct sign typically observed in primary pancreatic cancers. This is because, quite often (approximately one-third of the time), tumors are initially thought to be primary pancreatic tumors upon imaging studies [12]. Hence, if a patient has a history of cancer and is newly diagnosed with a pancreatic mass, the possibility of metastasis should be fully evaluated. It can either initiate the most effective treatment or decrease mortality and morbidity resulting from unnecessary surgery.

In EUS, the morphology of metastatic pancreatic tumors varies. They are typically located at the head of the pancreas with regular borders, although they are occasionally irregular. Hypoechogenic tumors are predominant; however, hyperechoic metastases from bladder cancer and anechoic metastases from melanoma have also been observed. Mixed characteristics of metastatic pancreatic tumors are common, such as renal cell carcinoma, in which echogenicity can vary. Similarly, the consistency of metastatic pancreatic tumors may vary from solid to cystic or heterogeneous [20,21]. In our study, the four metastatic pancreatic tumors exhibited a hypoechoic heterogeneous pattern on EUS images, similar to the primary tumors. Consequently, relying solely on imaging for an accurate diagnosis in these cases is challenging. Emphasizing the importance of a thorough history taking, particularly regarding cancer, before performing EUS is crucial. It is highly likely that the history of cancer was the sole piece of information hinting the possibility of metastasis to the endoscopist.

A contrast-enhanced ultrasound (CE-EUS) was not employed in this study because at our hospital, patients must pay for it out of pocket, and not every patient agreed to its use. Although CE-EUS has been recognized as useful for diagnosing primary pancreatic tumors, its efficacy in detecting metastasis remains a subject of debate. A recent study suggested its potential usefulness in the diagnosis of pancreatic metastases [22]. RCC metastasis typically exhibits a hyperenhanced pattern, which distinguishes it from primary adenocarcinoma, which typically displays a hypoenhanced pattern. However, it can still be challenging to differentiate it from a neuroendocrine tumor, which also presents with a hyperenhanced pattern. In contrast, metastases from other origins, such as the stomach, colon, and ovaries, exhibit a hypoenhanced pattern [23]. Therefore, the use of contrast to distinguish between primary and metastatic pancreatic tumors has no value. Tissue acquisition remains the gold standard for diagnosis.

In accordance with the current guidelines, including the ESMO and NCCN, if a patient presents with a suspected malignant pancreatic tumor, lacks a history of cancer, and imaging studies suggest a resectable tumor. Non-diagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high [24,25]. However, when a patient has a history of cancer, it becomes crucial to consider the possibility of metastatic pancreatic cancer originating from various organs. While rare, pancreatic metastases pose a considerable clinical challenge due to their potential to influence treatment decisions and affect patient outcomes. In such cases, a biopsy is necessary to differentiate between a primary and metastatic lesion before initiating treatment. EUS with an FNA/FNB is preferred for this purpose due to its superior diagnostic yield, safety profile, and potential to mitigate the risk of peritoneal seeding compared to the CT-guided approach [26–28].

In addition to tumor morphology, cytological and immunohistochemical staining (IHC) were performed to confirm the final diagnosis. In this comprehensive single-center study, EUS-guided tissue sampling proved to be valuable and had a significant clinical impact [21]. EUS-FNA was developed to acquire tissues using negative pressure for cytological analyses. Cytological samples acquired using EUS-FNA exhibit a relatively high diagnostic accuracy. Nonetheless, reliance solely on cytological evaluation is insufficient to diagnose metastatic pancreatic cancer. Recently, the introduction of FNB needles has been aimed at enhancing the quality of tissue sampling, and they are generally considered more effective in obtaining tissue cores, compared with traditional FNA needles [7,29]. Tissue cores obtained through an FNB allow for the preservation of architectural features and facilitate the implementation of an IHC, which is a critical component in the diagnosis of secondary pancreatic tumors. Moreover, an FNB is a safe procedure for obtaining tissue samples even from older patients who often have comorbidities and are undergoing anticoagulation therapy [30]. Therefore, an FNB is the primary choice for pancreatic tumor tissue sampling. A surgical biopsy is considered an alternative method if an FNB is unsuccessful.

Notably, in this study, all the patients with no history of cancer had primary pancreatic malignancies. Therefore, in daily practice, when endoscopists encounter a pancreatic tumor during an EUS that appears malignant (Figure 4), they should initially differentiate between resectable and unresectable tumors. If the tumor is deemed an unresectable malignancy, a subsequent FNB should be performed for tissue sampling. Conversely, if the tumor is resectable, a subsequent FNB should only be performed in patients with a history of cancer. An FNB may not provide additional information or influence the subsequent surgical plan in patients without a history of cancer. Therefore, an FNB should be avoided in these patients and surgical resection should be performed without pre-operative tissue confirmation. This approach ensures a more efficient and tailored diagnostic process based on individual patient profiles.

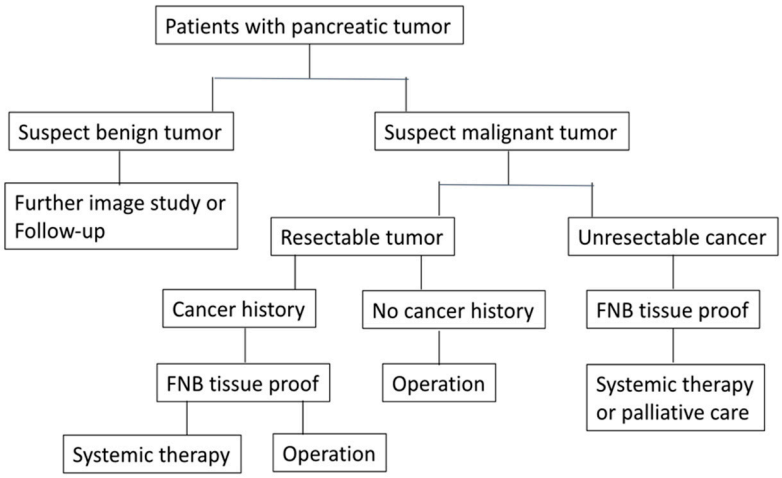

Figure 4. The decision making process of EUS management in pancreatic tumors.

Pancreatic surgery is a possible curative management strategy not only for primary pancreatic tumors, but also metastatic tumors. However, the incidence of major complications is more than 40%. These complications may arise from inherent risks associated with pancreatectomy or preexisting comorbidities. Due to the associated risks of morbidity and mortality in pancreatic surgery, it is advisable to perform pancreatic resection when clinically necessary. Notably, when dealing with a pancreatic mass, it is crucial to consider its potential as a metastatic lesion, among other diagnostic possibilities. Hence, the clinical background and pathological confirmation are necessary prior to tumor resection. They can not only detect the involvement of major vessels, such as the celiac artery, splenic artery, splenic vein, and superior mesenteric artery, but can also provide tissue confirmation for a definitive diagnosis [31,32].

The advantage of a surgical resection in terms of the overall survival has not yet been demonstrated, and the introduction of tyrosine kinase inhibitors (TKIs) has changed the outcomes of patients with unresectable metastatic disease. The median overall survival from a pancreatic metastatic RCC diagnosis was more than 7 years for both resected and unresected patients. Specifically, in patients who underwent pancreatic surgery for pancreatic metastasis–RCCs, the median overall survival was 103 months, with 43% still alive and 42% of the resected patients without disease recurrence. For patients with an unresected pancreatic metastatic RCC, the median overall survival was 86 months, with 75% still alive at the time of analysis. However, the difference in the overall survival between resected and unresected patients was not significant ($p = 0.201$) [33]. Based on the results of this study, the efficacy of surgery for pancreatic metastases remains a topic of debate and surgery should not be the primary option, with systemic treatment being the preferred choice. Therefore, an accurate diagnosis through EUS tissue sampling is crucial.

In this study, we aimed to assist endoscopists in making decisions during EUS examinations, including whether to perform an FNB when a resectable pancreatic malignancy is encountered. As a result, our focus was solely on patients who underwent EUS with an FNB, and we did not include those who did not undergo a pre-operative FNB. Therefore, separate and more extensive studies are needed to evaluate resectable tumors across the entire patient population. Other limitations of this study are its retrospective study design and relatively small number of patients.

5. Conclusions

Imaging tests such as CT and EUS assess malignancy and tumor resectability based on vascular involvement but cannot distinguish between primary and metastatic tumors. EUS with an FNA/B is crucial as it provides a definitive histological diagnosis for patients, especially those with a prior history of cancer, helping differentiate between metastatic and primary pancreatic tumors. This strategy not only aids in avoiding unnecessary surgeries,

but also facilitates the prompt initiation of appropriate treatments, thereby optimizing patient outcomes through a timely intervention.

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