Review Article

Resectable pancreatic solid lesions: Time to move from surgical diagnosis?

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ABSTRACT

Benign or malignant conditions can present as pancreatic solid lesions (PSLs), and a thorough diagnostic workup is necessary to differentiate them. The need to acquire a tissue sample to reach a definitive diagnosis should be stratified by the findings at multidetector computed tomography (MDCT) with a pancreatic protocol. Tissue biopsy is currently indicated in patients fit for chemotherapy in whom a metastatic tumor or a locally advanced unresectable lesion are discovered. For these patients, EUS-guided tissue acquisition, with fine-needle aspiration (FNA) or biopsy represents the gold standard to provide a definitive cyto- and/or histopathologic diagnosis, with a high rate of accuracy. For resectable PSLs with a nonhypoenhancing MDCT pattern, which is not disease specific, a tissue diagnosis to distinguish benign from malignant etiologies appears mandatory. On the other hand, for hypo-enhancing PSLs, the debate of whether to obtain a preoperative definitive diagnosis still favors direct surgery. However, availability of novel EUS-guided fine-needle biopsy needles, which can ameliorate the negative predictive value of EUS-FNA and allow performance of DNA and RNA whole-genome extraction and RNA sequencing, coupled with the increasing evidence that preoperative neoadjuvant chemotherapy can be of value for these patients may change completely the diagnostic and therapeutic approach to resectable PSLs. These recent breakthroughs suggest the need for a new multidisciplinary consensus meeting to integrate them into the decision-making process assessing the need for preoperative tissue diagnosis in resectable PSLs.

Key words: EUS, EUS-guided tissue acquisition, pancreatic solid lesion, resectable pancreatic mass

INTRODUCTION

Pancreatic solid lesions (PSLs) comprise a wide array of benign and malignant diseases, each necessitating a different therapeutic approach. The clinical presentation along with a thorough diagnostic workup using state-of-the-art imaging techniques helps to differentiate

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between neoplastic and inflammatory or autoimmune diseases. The presence of symptoms is more frequently associated with a malignant etiology, compared to incidental PSLs discovered in asymptomatic individuals. The presence of jaundice, back pain, and weight loss are associated in about 80% of cases to pancreatic ductal adenocarcinoma (PDAC).[1] In case of incidental PSLs, the most commonly encountered diagnoses are pancreatic neuroendocrine tumors (PanNETs) (23%–42%), followed closely by PDAC (31%–34%), solid pseudopapillary tumors (3%–15%), and focal chronic pancreatitis (0%–11%).[2] The decision to perform biopsy should be determined once proper diagnostic workup has been completed. Imaging may not only help in the differential diagnosis but provides additional information on the extent of the disease in terms of both the presence of distant metastases and relationship between PSLs and adjacent structures (*e.g.*, major loco-regional vessels, bile duct, or duodenum), which are vital for further management decisions. In this last regard, a reasoning process is crucial to assess the need for tissue diagnosis in PSLs.

WHEN TO PERFORM TISSUE ACQUISITION

Although tissue biopsy is currently indicated in the case of metastatic pancreatic tumors and borderline/locally advanced lesions, some concern is still present in the literature for resectable tumors. More specifically, in patients with liver metastases fit for chemotherapy, percutaneous biopsy represents the first diagnostic option, unless in cases of isolated lesions that are difficult or impossible to be reached percutaneously (such as in the caudate liver lobe). In such difficult situations, EUS-guided tissue acquisition (EUS-TA) with EUS-FNA or fine-needle biopsy (EUS-FNB) of both primary and secondary sites should be performed in the same session. In patients with metastatic PanNETs, in whom Ki-67 index can be different between primary and metastatic sites, dual sampling can affect treatment decisions.[3] Similarly, in the near future, tissue from both the primary tumor and liver metastases in PDAC could also become a valuable driver for proper therapeutic decisions.[4]

In patients with locally advanced or borderline resectable PDAC scheduled to undergo neoadjuvant chemotherapy (NAC), tissue confirmation is mandatory, and EUS-TA is the gold standard for the acquisition of cytologic and/or histologic specimens needed for a definitive diagnosis. A retrospective study by Volmar *et al.*[5] on 1050 cases of PSLs, reported that the biopsy performed under EUS-guided approach (n = 843) was more accurate than the percutaneous one under computed tomography (CT; n = 67) or ultrasound (US; n = 140). In particular, EUS was significantly more accurate than US/CT in diagnosing lesions <3 cm (P = 0.015).[5] A subsequent prospective randomized study,[6] comparing 41 EUS-FNA and 43 CT/US-FNA patients, reported a sensitivity to detect malignancy of 62% for the CT/US approach and of 84% for the EUS-guided biopsy, with a trend over a superior accuracy of EUS-FNA *versus* CT/US-FNA (P = 0.074). From a practical point of view, local expertise and availability of EUS or interventional radiology guide the choice between one or the other sampling method.[7] The percutaneous approach may be more indicated in patients with risk for sedation-related complications or with surgically altered upper GI anatomy. On the other hand, EUS has the advantage of providing additional staging information, such as presence of inter-aortal-caval and/or peri-aortal lymph nodes that are nonloco-regional stations metastases, discovery of previously undetected small liver metastases and/or small pockets of ascites, the latter highly indicative for peritoneal involvement.

The approach to resectable masses is not so straightforward and the need for tissue confirmation of malignancy before performing surgery remains controversial. Balance between benefits *versus* risks of EUS-TA for each individual patient should be carefully evaluated. Two recent papers have addressed this topic.[8,9] Hartwig *et al.*[8] performed a systematic review of the literature from January 1966 to July 2008. They screened 794 abstracts, from which they excluded 682. Among the remaining 112, evaluation of the full articles excluded additional 59 papers for a total of 53 articles eligible for revision. Data extraction revealed a negative predictive value (NPV) for percutaneous FNA of only 58% (range 23%–100%). NPV of EUS-FNA was found to be better (72%; range 16%–92%), but still too low for a negative result to reliably exclude malignancy. Importantly, the sensitivity of EUS-FNA to exclude malignancy is even poorer in patients with chronic pancreatitis, completely questioning the utility of preoperative tissue diagnosis in this clinical setting.[10] Additional fears of the authors in performing preoperative tissue diagnosis were: (i) Post-sampling acute pancreatitis, which can delay surgery and in some cases, make an originally resectable

tumor unresectable;[11] (ii) The risk of seeding. Overall, EUS-FNA of PSLs is safe with very low adverse events rates.[12] Regarding seeding, Micames *et al.* evaluated the risk of peritoneal seeding comparatively between patients undergoing percutaneous (n = 43) or EUS-guided FNA (n = 46) followed by NAC.[13] Only one patient in the EUS-FNA group as opposed to seven who had undergone percutaneous FNA (2.2% *vs.* 16.3%; $P < 0.025$) developed peritoneal carcinomatosis,[13] which was not detected in any patient with potentially resectable tumors in the EUS-FNA group. Moreover, in the case of a transduodenal approach, since the needle tract is resected during pancreaticoduodenectomy (PD), EUS sampling eliminates seeding concerns. However, based on all the above-mentioned data, the authors recommended not to perform preoperative biopsy in patients with resectable PSLs.[8]

In a second consensus statement paper by the International Study Group of Pancreatic Surgery, the authors focused their attention on patients who had undergone PD for head and/or uncinate process PSLs.[9] The literature review was performed from January 2008 to February 2013. All relevant literature and a summary of the extracted data were then reviewed by a subgroup of participants, who prepared a first draft that was subsequently discussed and finally approved. The incidence of benign disease on surgical specimens after PD for a presumed malignancy ranged between 5% and 13%,[9] without a decrease over time. In these cases, the most frequent diagnosis on surgical specimens was chronic pancreatitis, which was probably of autoimmune etiology in a significant number of cases. The authors utilized the same preoperative NPV values for both percutaneous and EUS-FNA previously reported by Hartwig *et al.*, thus reaching the same conclusions, that biopsy proof of malignancy before surgery is not required, unless autoimmune pancreatitis is suspected (strong recommendation) or when NAC before surgery is planned (strong recommendation).[9] In addition, lack of any effect of EUS-TA on overall and cancer-specific survival in resectable cases described in another study added an additional argument against preoperative diagnosis.[14]

IS IT TIME TO CHANGE OUR EUS-TISSUE ACQUISITION PRACTICE?

In 2019, in view of the numerous changes that have occurred in this field, the conclusions of the two expert opinion papers need some considerations. First, most studies evaluating the diagnostic performance of EUS-FNA included in the analysis of the two above-mentioned papers were outdated, mostly performed without the use of rapid on-site cytopathology evaluation (rapid on-site evaluation [ROSE]), and with a relatively small sample size (total number of patients 4155, median 81; range 41–611). A subsequent very rigorous meta-analysis that included 41 studies (total patients 4776), in which extensive efforts were made to calculate the real number of true-positive, false-positive, true-negative, and false-negative results, found that EUS-FNA for the evaluation of patients with PSLs had a very low negative likelihood ratio (0.17; 95% confidence interval [CI], 0.13–0.21).[15] This means that a negative EUS-FNA could reliably rule out malignancy. Consequently, in the decision when to make a preoperative tissue diagnosis, this result must be balanced with the 5%–13% incidence of benign disease on surgical specimens after PD for a presumed malignancy,[9] and the related morbidity and mortality of PD (around 30% and 5%, respectively in most centers).[16]

Rapid on-site cytopathology evaluation to assess specimen adequacy can achieve higher EUS-TA accuracy rates, even though this assumption is still questioned.[17-20] In the largest randomized controlled trial published so far, among all various technical aspects of EUS-FNA that may have an impact on EUS-FNA performance, only ROSE availability really affected the procedure outcome.[21] Three hundred and fifty-two PSLs patients were randomized according to needle size (25G *vs.* 22G) and use or no use of negative pressure suction. In the presence of ROSE, all four subcategories had similar, high diagnostic accuracy (mean diagnostic accuracy 96.6%).[21] Overall, there were five false-positive and 11 false-negative results determining a NPV of 83.3 (95% CI, 72.1–91.4) and a negative likelihood ratio of 0.041.[21]

Second, the rate of false-positive and false-negative results can theoretically be reduced by the availability of core biopsy samples, which give the opportunity to evaluate tissue architecture and the relationship of cells with stroma. In this regard, over the past 4 years, new needles specifically designed to perform EUS-FNB have been introduced and represent a breakthrough innovation, which can completely change the paradigm of EUS-TA. The essence of

this innovation is contained in two studies. The first one is a randomized cross-over study comparing the performance of a standard 22G FNA needle with the 22G Franseen FNB needle (Acquire™, Boston Scientific Inc., Marlborough, MA, USA), which were both utilized in randomized order to obtain a sample for cell-block in 46 consecutive patients with PSLs.[22] The overall performance was significantly higher for the FNB needle than for the standard 22G regarding variables that could be evaluated on obtained tissue specimens, such as median area of: (i) total tissue (6.1 mm^2 *vs.* 0.28 mm^2, $P < 0.0001$), (ii) tumoral tissue (0.68 mm^2 *vs.* 0.099 mm^2, $P < 0.0001$), (ii) desmoplastic stroma (3.9 mm^2 *vs.* 0, $P < 0.0001$), and in terms of retained tissue architecture (93.5% *vs.* 19.6%, $P < 0.0001$) and cell block diagnostic yield (97.8% *vs.* 82.6%, $P = 0.03$). The authors were also able to prove by using specialized imaging software for the quantification of individual tissue components, the true histologic tissue procurement with the 22G FNB needle.[22] The same authors demonstrated that another FNB needle, the 22G SharkCore™ needle (Medtronic Plc, Fridley, Minnesota, USA) had completely comparable performance to the Acquire™ needle in 50 patients with PSLs.[23] The two needles showed an extremely high comparable diagnostic accuracy performance for both cell-block (96% *vs.* 92%) and ROSE (94% *vs.* 98%). These results made the authors conclude that these new-generation FNB needles may even obviate the need for ROSE.[23]

In the second relevant study,[24] among 1662 pancreaticobiliary solid lesions that underwent EUS-FNA (1028) or EUS-FNB (634), diagnostic adequacy evaluated on cell block was significantly higher in the EUS-FNB than in the EUS-FNA arm (92.7 *vs.* 69.9%, $P < 0.001$). In addition, among 2127 patients with pancreaticobiliary solid lesions who underwent EUS-FNA (1449) or EUS-FNB (678) with ROSE, diagnostic adequacy did not differ (98.6% *vs.* 99.1%, $P = 0.28$) between the two arms. This means that ROSE can be equally done using an FNB needle, which can be then utilized to acquire additional samples for histological evaluation. A sample for ROSE evaluation using an FNB needle can be obtained by using the touch imprint cytology technique, in which a solid component ("worm-like" core tissue sample) of the acquired material is separated from blood, transferred on a clean slide, and then gently pushed and rubbed down with another slide before evaluation under microscope.[24]

STRATIFICATION OF THE NEED FOR SAMPLING OF RESECTABLE PANCREATIC SOLID LESIONS BASED ON IMAGING STUDIES RESULTS

Third, a very important aspect is that not all resectable PSLs are PDACs and diverse entities need to be managed differently, fact that was not really taken into consideration in the two expert opinion papers discussed above. We strongly believe that stratification of patients with resectable PSLs should be performed first based on lesion behavior at multi-detector CT (MDCT) with pancreatic protocol, which represents the gold standard to investigate PSLs [see algorithm in Figure 1]. In particular, the vascular PSLs patterns evaluated by MDCT can guide toward the most probable diagnosis and on whether to perform EUS-TA. By comparing the contrast enhancement of PSLs with that of the surrounding normal pancreatic parenchyma, three different patterns can be observed: hypoenhancing, isoenhancing, and hyperenhancing.

The hypoenhancing pattern is the most commonly observed in PDACs, in which it has a sensitivity of 92%–96% and diagnostic accuracy of 82%–95%, respectively.[25-27] The non-hypoenhancing pattern (*i.e.*, isoenhancing and hyperenhancing) is associated in 95% of cases with a wide range of PSLs other than PDAC,[25] each with a different prognosis and aggressiveness.[28,29] Nonhypoenhancing PSLs are most commonly associated with PanNETs,[30] pancreatic metastases,[31] acinar cell carcinoma,[32] pseudosolid serous cystadenoma,[33] accessory intrapancreatic spleen,[34] solid pseudopapillary neoplasm,[30] mass-forming pancreatitis,[35] and other rare tumors.[30,36] However, the positive predictive value of the hyperenhancing pattern to predict a PanNET is only about 56%,[26] thus resulting in inappropriate pancreatic surgery for benign lesions suggestive of PanNETs, as reported by several studies.[33,37] Moreover, neither iso- nor hyperenhancing behaviors have been associated with lesion aggressiveness.[38] Accordingly, in all these iso- or hyper-enhancing lesions, EUS-TA seems appropriate to reach a definitive diagnosis and to determine the risk category for some lesions, as for example in PanNETs in which likewise dimension (smaller or bigger than 2 cm), Ki-67 expression affects treatment decision.

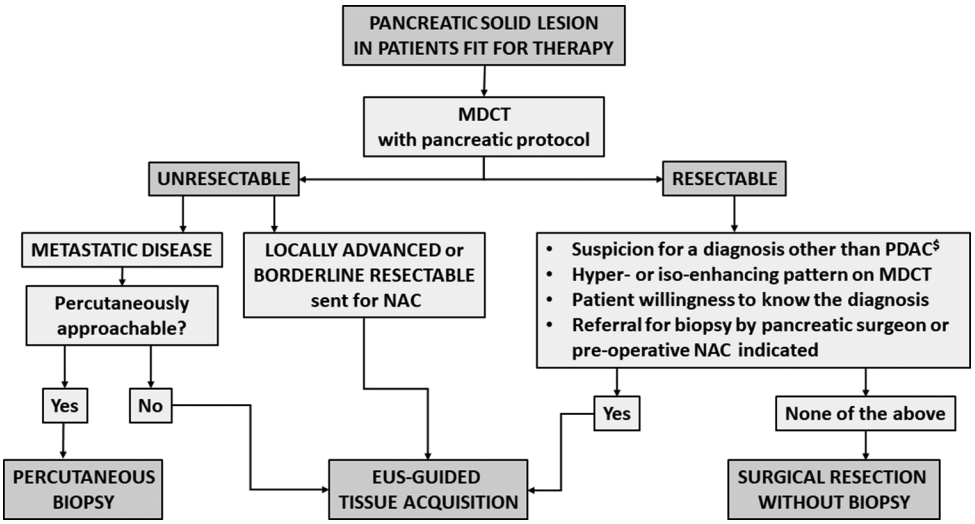

Figure 1. Algorithm for diagnostic and therapeutic stratification of patients with pancreatic solid lesions. $Other diagnostic entities such as autoimmune pancreatitis or pancreatic lymphoma. MDCT: Multidetector computed tomography; NAC: Neoadjuvant chemotherapy; PDAC: Pancreatic ductal adenocarcinoma

MDCT may also indicate the most suspicious diagnosis through morphological characterization of the lesions. Irregularity of shape or margins has been linked to aggressiveness in a large retrospective series of surgical patients diagnosed with PanNETs.[39] Capsulated, non-aggressive tumors have smooth, well-defined borders, while the more aggressive ones have usually irregular/not-defined margins that can be expression of tumor pseudopodia and infiltrative growth.

BREAKTHROUGH INNOVATIONS

The third important novel aspect is the development of major innovations occurring in the last couple of years, which may become a real breakthrough in the approach to resectable PSLs. In inoperable cases, recent data seem to favor NAC, with the rationale to select those patients in whom a positive response to NAC makes them the best candidates for surgery while sparing major operations for those who do not respond or progress during NAC.[40-42] If this becomes standard of care, tissue diagnosis will become indispensable before NAC administration in all resectable cases. Moreover, recent whole-genome sequencing of PDAC has revealed four subtypes (aberrantly differentiated endocrine exocrine [ADEX], progenitor, squamous, and immunogenic),[43] which can have different behaviors in terms of both prognosis and response to therapy. Up to recently, molecular characterization that may be predictive and/or provide prognostication and therapeutic stratification has been performed on surgical specimens only, because it requires substantial neoplastic tissue. A very recent work from the University of Glasgow has demonstrated that all types of new generation FNB needles can acquire enough material to perform DNA and RNA whole-genome extraction and RNA sequencing, with the opportunity to investigate molecular subtypes in PDAC, ushering pancreatic cancer therapy into the era of personalized medicine.[44]

CONCLUSIONS

At present, the debate on the need of preoperative tissue diagnosis in patients with resectable PSLs remains open. Distinction between hypoenhancing *versus* nonhypoenhancing (iso-and hyperenhancing) lesions using MDCT is imperative to drive the diagnostic and therapeutic algorithm. EUS-TA should be performed in almost all iso-and hyperenhancing PSLs, because these patterns are both not disease-specific and can be observed in PSLs of different prognosis and aggressiveness, each requiring a specific management. For hypoenhancing lesions, a balance between risks of tissue biopsy and the chance of discovering a benign disease in the surgical specimen should be weighted. This decision process can be changed by the newly available EUS-FNB needles that can (i) increase NPV by decreasing false positive and false negative rates; (ii) assess PDAC subtypes that may be predictive and/or provide prognostication and therapeutic stratification; and (iii) provide tissue diagnosis necessary for pre-operative NAC. In patients with resectable PSLs, is it time to move from the surgical biopsy? To answer this important question an updated consensus agreement

workshop involving not only surgeons but also oncologists and endoscopists is highly needed.

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Conflicts of interest
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