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Through-the-needle forceps biopsy for pancreatic cystic lesions: multiple meta-analyses but limited prospective data

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With the mounting quality and utilization of cross-sectional imaging, pancreatic cystic lesions (PCLs) increasingly are being identified, particularly in asymptomatic and elderly patients. However, accurate classification among the various PCLs remains a persistent clinical challenge with the current standard-of-care diagnostic tools, consisting of endoscopic ultrasound (EUS), fine-needle aspiration (FNA), cyst fluid analysis (CEA), and cytology. While the primary challenge is in accurate differentiation of mucinous from non-mucinous PCLs, precise identification of mucinous PCLs with advanced neoplasia (high-grade dysplasia and/or adenocarcinoma) is also difficult. There have thus been several guidelines for management of pancreas cysts, but these still result in modest diagnostic accuracy. In fact, EUS-FNA has a sensitivity of at most 63 % for malignant PCLs with inadequate specimens in up to two-thirds of cases. Given these findings, up to 30 % of PCLs are incorrectly diagnosed as mucinous cysts, resulting in a large number of unnecessary surgical resections with postoperative morbidity approaching 40 % [1]. Improved accuracy in classifying PCLs, therefore, would reduce unwarranted pancreatic surgeries and associated complications, and save costs on unwarranted follow-up. Because of this, enormous effort has been put into development and evaluation of novel diagnostic modalities for PCLs, including cyst fluid molecular analysis, confocal laser endomicroscopy (CLE), and through-the-(EUS) needle microforceps.

This issue of Endoscopy International Open features a study from Guzman-Calderon et al. [2], who performed a systematic review of eight studies with 423 patients to evaluate the safety, efficacy, and accuracy of through-the-needle biopsy (TTNB) for PCLs. Use of microforceps biopsy resulted in a 95.6 % (95 % confidence interval [CI] 93.2–97.3 %; I^2 [measure of heterogeneity] = 82.1 %) pooled technical success rate with adequate specimens obtained in 82.2 % (95 % CI 78.5–85.8 %) of attempts. The TTNB forceps identified the specific pancreas cyst type in 74.6 % (95 % CI 70.2–78.7 %; I^2 = 87.3 %) of cases, the majority (approximately one-third) of which were mucinous cystic neoplasms (MCNs), followed by intraductal papillary mucosal neoplasms (IPMNs) and serous cystadenomas. The overall rate (pooled) of adverse events (AEs) was 10.1 % (95 % CI 7.3–13.6; I^2 = 80.13 %) of cases with the most common being intracystic bleeding that was self-limited without the need for medical intervention. Acute pancreatitis occurred in 10 patients (2.7 % of 375) experiencing a procedural-related complication.

The TTNB microforceps is 0.8 mm in diameter, facilitating easy passage through a 19-gauge EUS-FNA needle and has a jaw-opening width of 4.3 mm. Under EUS guidance, the PCL is initially punctured with the FNA needle and following removal of the stylet, the microforceps is advanced to sample the epithelium lining the wall of the cyst. The majority of studies addressing the application of this device for PCLs have primarily been retrospective. Their initial findings have been promising in regards to the feasibility, safety, and diagnostic yield of TTNB, but given limited study sizes, it has been challenging to assess the clinical impact. Further, significant rates of AEs have been noted, which is a cause for concern. A more recent multicenter prospective study in 114 consecutive patients demonstrated technical success in 97 % of patients with adequate samples obtained in 83 % of cases compared to 38 % for cytology alone. The AE rate was 12 %, primarily consisting of intracystic bleeding; six patients (5.3 %) developed post-procedure acute pancreatitis [3].

▶ **Table 1** Meta-analyses on through-the-needle microforceps biopsy in PCLs (publications in 2020).

	Studies, patients (n)	Technical success[1]	Specimen adequacy[2]	Diagnostic yield[3] or accuracy[4]	Adverse events
Guzman-Calderon et al [2]	8,423	95.6 % (93.2–97.3 %) I^2 = 82.1 %	82.2 % (78.5–85.8 %) I^2 = NA	74.6 %[1] (70.2–78.7 %) I^2 = 87.3 %	10.1 % (7.3–13.6) I^2 = 80.1 %
Tacelli et al [4]	9,454	98.5 % (97.3–99.6 %) I^2 = 88.6 %	86.7 % (80.1–93.4 %) I^2 = 84.3 %	69.5 %[2] (59.2–79.7 %) I^2 = 84.7 %	8.6 % (4.0–13.1) I^2 = 77.2 %
Facciorusso et al [5]	11,490		85.3 % (78.2–92.5 %) I^2 = 41.5 %)	78.8 %[1] (73.4–84.2 %) I = 28.4 %	6.1 % (pooled estimate = NA)

PCLs, pancreatic cystic lesions; I^2, measure of heterogeneity; NA, not available.
[1] Technical success: Successful puncture of pancreatic cyst and obtaining at least one microbiopsy
[2] Sample adequacy: The ability to achieve tissue samples adequate for diagnosis
[3] Diagnostic yield: The proportion of cysts with a definitive diagnosis out of the total number of EUS-TTNB procedures performed (true positive/total number of patients)
[4] Diagnostic accuracy: Definitive diagnosis of the exact kind of pancreatic cyst (true positive + true negative/ total number of patients)

Given the paucity of large, randomized trials evaluating TTNB in PCLs, multiple systematic reviews and meta-analyses have sought to further evaluate the utility of this device. This year alone, and including the study featured in this issue, a total of three meta-analyses will be published (▶ **Table 1**). A recent systematic review with meta-analysis evaluated nine studies on TTNB in PCLs, noting technical success was achieved in 98.5 % (95 % CI 97.3–99.6 %. I^2, 88.6 %) [4]. Although specimen adequacy was achieved in 86.7 % (95 % CI 80.1–93.4 %), there was significant degree of heterogeneity (I^2 = 84.3 %; P < 0.001). The pooled diagnostic yield was 69.5 % (95 %CI 59.2–79.7 %) with significant heterogeneity (I^2 = 84.7 %; P < 0.001). The diagnostic yield was higher (83.4 %) in studies with more than three TTNB passes with low heterogeneity. The pooled rate of AEs was 8.6 %, with the most common being intracystic bleeding. Mild acute pancreatitis occurred in 24.5 % of the patients experiencing a complication [4].

A more recent meta-analysis noted similar findings with pooled data from 11 studies (▶ **Table 1**) [5]. Technical success was not reported, but 85.3 % (95 % CI 78.2–92.5 %; I^2 = 41.5 %) of specimens were adequate for diagnosis. A mean of 3.1 (95 % CI 2.98–3.25; I^2 = 16.46 %) passes were required to achieve this histologic adequacy. Pooled diagnostic accuracy from eight of the studies with this endpoint was 78.8 % (95 % CI 73.4–84.2 %) I^2 = 28.4 %. When they further removed all studies without reference surgical histopathology, accuracy increased to 88.3 %. They similarly found an AE rate of 8.98 %, with self-limited bleeding being the most common complication in patients [5].

Other newer diagnostic modalities in evaluation of PCLs include cyst fluid molecular analysis and EUS-guided needle-based confocal laser endomicroscopy (EUS-nCLE). Molecular cyst fluid analysis uses various established mutations to detect (sensitivity approaching 100 %) mucinous pancreas cysts as well as PCLs with advanced neoplasia [6]. EUS-nCLE allows for real-time microscopic imaging of pancreas cyst epithelium, and two large prospective studies (a total of > 100 patients with surgical pathology) have demonstrated a significant improvement in diagnostic accuracy for mucinous PCLs compared to the current standard of care [6, 7]. A more recent retrospective study with fewer confirmatory surgical resections found the combination of EUS-FNA with TTNB and nCLE resulted in a higher diagnostic yield (93.2 %) than any singular modality, although this was not statistically significant [8].

While we can hypothesize that use of EUS with TTNB can improve accuracy in differentiating mucinous from non-mucinous PCLs relative to the current standard of care (cross-sectional imaging, EUS morphology, and FNA of cyst fluid including CEA and cytology), there are specific limitations for this innovative diagnostic modality. Small numbers of studies with surgical histopathology as a reference standard prevent the true comparative analysis of TTNB and current standard of care. Recent meta-analyses report a not-insignificant rate of AEs compared with standard EUS-FNA. Next, the majority of available studies employ diagnostic yield as the main endpoint or use this interchangeably with diagnostic accuracy. Diagnostic yield describes the likelihood of a positive finding and is not the same as diagnostic accuracy. Diagnostic yield is typically the initial step, but does not provide specifications for sensitivity or specificity, hence, reporting the diagnostic accuracy is a better estimate of a management strategy. While the aforementioned analyses and previous studies have found that TTNB of PCLs results in a higher diagnostic yield compared with FNA alone, lack of randomized and prospective multicenter studies impedes the ability to truly compare these two modalities. It is of concern that given the limited number of studies, of which most are retrospective, numerous meta-analyses and systemic reviews have been performed on this novel modality.

A major issue arising from current studies evaluating microforceps biopsy is that many retrospective studies with EUS-TTNB appear to repeat data from multiple centers, which results in inaccurate data secondary to double counting. This unfortunate issue arises from centers providing data to multiple studies; thus, it is difficult to ascertain the accuracy of systemic reviews and meta-analyses unless the data are disclosed and potential redundancy is accounted for. The current study aims to ensure that included data were not redundant.

Incidentally found PCLs result in a cohort of patients with a high risk of operative complications but a relatively low risk of

malignant potential. Therefore, accurate differentiation of mucinous from non-mucinous pancreas cysts is paramount for patient benefit. Novel modalities such as cyst fluid molecular analysis, EUS-nCLE, and TTNB may serve as adjuncts to the current standard-of-care evaluation with improved diagnostic accuracy. However, more well-designed, multicenter, prospective trials with surgical histopathology references are necessary to further establish the true benefit of TTNB over EUS-FNA.

Similarly, in regard to nCLE and DNA sequencing of PCL fluid, multicenter studies with cost-effectiveness analyses and determination of minimally required genes, respectively, are warranted. Eventually, these novel diagnostic modalities may serve to increase the precision in avoiding unwarranted surgical resections of benign PCLs and promote the resection only of those cysts with impending malignant transformation.

Competing interests

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