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Tissue Acquisition and Handling in Gastrointestinal Endoscopy

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ABSTRACT

Multiple endoscopic pinch biopsy forceps modifications are available, including serrations and fenestrations on the cup and spike to impale the biopsied tissue. Besides the standard biopsy forceps, smaller caliber and large-cup (jumbo) biopsy forceps are available. Special miniature forceps for passage through a cholangioscope and even a 19G fine needle aspiration (FNA) device is commercially available. Besides advancements in brushing cytology from the biliary tract, newer cytology acquisition devices are being developed for a wide-field sampling of Barrett's epithelium (BE) for screening and surveillance. Endoscopic ultrasound (EUS) fine needle aspiration and biopsy (FNA and FNB) devices are also discussed with practical advice on processing the acquired cytology, cell-block, cyst fluid, and microcores in the endoscopy suite before submission.

KEYWORDS: Biopsy forceps; Spy Bite forceps; Moray forceps; Endoscopic-ultrasound; Fine-needle aspiration; Fine-needle biopsy; Brush cytology.

Most endoscopic procedures involve tissue acquisition with diagnostic and monitoring intent. Endoscopic mucosal (submucosal) biopsies are routinely procured for varied gastrointestinal diseases. Other settings where tissue acquisition is commonly required are biliopancreatic pathologies, usually strictures with or without a visible mass. These situations usually require intra-ductal brushings and microforceps biopsies (**Table 1**). Endoscopic ultrasound (EUS) has enabled extra-luminal tissue sampling from adjacent structures. EUS-guided tissue acquisition for mural and peri-luminal pathologies requires familiarity with the sampling needle devices.

This review will discuss the nuances of endoscopic tissue acquisition and handling, including forceps biopsies, cytology brushings, and EUS-guided tissue acquisitions.

Endoscopic Biopsy Forceps

Biopsy forceps are used to acquire pinch mucosal biopsy specimens, which sometimes includepart of the submucosa. Standard biopsy forceps can generally obtain a full-thickness mucosal specimen except for the greater curve of the gastric body, where the folds usually are thicker.

Endoscopic biopsy forceps consist of a flexible, metal-coil outer sheath that houses one or two steel cables connecting the plastic handle of the forceps to opposed metal biopsy cups. Dual pull wires allow for consistent

opening and closing of cups with a stronger bite force. Some biopsy forceps sheaths are coated with a synthetic polymer like endoglide, to reduce friction while passing through the endoscope accessory channel.

Multiple modifications of the biopsy cup have been done with the aim of acquiring a larger or better-oriented biopsy specimen. The biopsy cup may be round, oval, or elongated, fenestrated or non-fenestrated, and with smooth or serrated jaws. The holes in fenestrated biopsy cups allow mucus to flow out and the specimen to bulge, potentially allowing a larger biopsy specimen to be retained. However, no consistent improvement in specimen quality has been found with any of these modifications.[1]

Table 1: Biopsy guidelines for some commonly encountered benign gastrointestinal conditions.

Suspected condition	Tissue acquisition	Comments
Barrett's mucosa	4-quadrantic biopsy every 2-cm along the length of metaplastic columnar epithelium (Seattle protocol)	• Reduce sampling length to every 1cm longitudinally if dysplasia known or suspected. • If moderate to severe esophagitis (Los Angeles B-D) present, repeat endoscopy should be performed after 8 to 12 weeks of high-dose PPI.(91)
Eosinophilic esophagitis	At least 6 biopsies from 2 different locations.	Target areas of endoscopic abnormalities, especially white exudates and longitudinal furrows.
Biopsy urease testing	2 samples recommended (One each from the antrum and corpus). The two biopsy pieces may be combined in the same test. (92)	• Stop PPI at least 2 weeks before testing for H pylori infection and antibiotics at least 4 weeks beforehand to avoid false negative results.(93, 94) • Areas of obvious intestinal metaplasia or ulceration should be avoided. (95)
Gastritis classification	5 sites biopsied as per updated Sydney classification system: One piece each from the lesser and greater curvature of the antrum, both within 2 to 3 cm of the pylorus; the lesser curvature of the corpus about 4 cm proximal to the incisura; middle portion of the greater curvature of the corpus, approximately 8 cm from the cardia; and the incisura angularis. (96)	
Celiac disease	4 to 6 biopsy specimens are collected from the duodenum, including 1 or 2 biopsies from the duodenal bulb.	• Include at least 1-2 biopsies from the duodenal bulb in a separate container. • Approximately 10% of cases will have mucosal changes confined to the duodenal bulb. • A single biopsy collected per pass has been recommended to improve orientation. (8)
Inflammatory bowel disease (IBD)	Biopsies should be obtained from both normal and affected mucosa, consisting of 2 biopsy specimens from at least 5 separate sites including the ileum and rectum. (97)	Specimens from different locations should be submitted separately.
Ileoanal pouch anastomosis(98)	Neo-terminal ileum 20cm proximal to pouch, and>6 samples from pouch body, and 3-4 bites from the rectal cuff.	Avoid suture lines in the pouch.
Indeterminate biliary strictures	Minimal of 3 cholangioscopy directed biopsies.	

Some biopsy forceps have a needle spike between the opposing biopsy cups (**Figure 1**). These forceps allow the acquisition of two biopsy pieces per pass, lesion impalement, and collection of deeper biopsies compared to non-needle biopsy forceps.[2] Without the spike, attempts at multiple tissue sampling with single-bite forceps may result in the loss of specimens and crush artifacts.

Most pinch biopsy forceps fit through a 2.8 mm biopsy channel with a closed cup diameter of 2.2-2.3 mm. Infants and young children often have biopsy specimens taken with smaller forceps that fit through a 2.2 mm biopsy channel. These smaller forceps are indicated for children weighing less than 10 kg. The large-cup ('jumbo') forceps require a larger biopsy channel of 3.6 mm or more. These larger capacity forceps biopsies yield two to three times the surface area than standard forceps but are not generally much deeper.[3,4]

Figure 1:A double-bite forceps with a needle spike between opposing biopsy cups. This forceps allows the acquisition of two biopsy pieces per forceps passes. The first biopsy specimen is secured on the needle spike during the collection of the second specimen.

Tips For Obtaining Better Forceps Biopsies

1. Rotating the endoscope to display the target lesion close to the 6 O clock position on the screen makes obtaining biopsies easier.
2. Increasing tension or stretch of the biopsy site by pushing the biopsy forceps reduces the quality of the specimen obtained. Partial lumen deflation usually helps capture better specimens by bunching up the mucosa. Folds or valvulae may also be selectively targeted for biopsy specimens.
3. Slow pulling back the closed forceps to tent the mucosa may provoke a crush artifact. The closed forceps should be snapped back quickly.
4. The 'turn-in technique' may be used when biopsies must be taken at an oblique angle, as in the esophagus. The opened forceps is first drawn back flush with the endoscope tip. The endoscope tip is then deviated towards the area to be biopsied with the open forceps; the forceps may be advanced a bit and some suction may be used to improve tissue capture. There is usually a visual red-out at the moment of obtaining the biopsy with the turn-in technique.
5. The biopsy specimen should be removed from the forceps cup using a blunt probe to push the specimen out from the base of the opened cups. Pushing the specimen out from the top side of the forceps cup, or picking at it, may lead to squashing of the specimen.
6. Shaking biopsy specimens off the forceps into a fixative bottle should be avoided. Extracting the captured specimen by shaking the forceps may traumatize the tissue and cause epithelial denudation, especially in gastric body specimens. Detached epithelium in gastrointestinal mucosal biopsies is a common feature encountered by pathologists.
7. Shaking off biopsy specimens with surface exudate into the fixative may peel off the exudate that often contains the evidence for the infecting organisms, especially Candida and Herpes simplex. These organisms reside in the surface exudate or epithelial slough.

Biopsy Orientation, Fixation, And Embedding

Biopsies that include the muscularis mucosa can contract, making the mucosal surface convex. This can impact the interpretation of small bowel biopsies where poor orientation will lead to crypts cut tangentially during sectioning (**Figure 2a**). This may falsely increase the villous-to-crypt ratio, leading to an underestimation of histological abnormalities. Inaccurate orientation can also result in crushing or partial fusion of adjacent villi, wrongly suggesting partial villous atrophy or

causing difficulties in intra-epithelial lymphocyte (IEL) count.[5] A well-oriented small bowel biopsy specimen is defined by four consecutive, parallel, crypt-villous units that are visualized along their entire lengths (**Figure 2b**). In contrast, round cross-sectional crypts indicate a non oriented biopsy. In practice, duodenal biopsies are not oriented in most endoscopy suites or pathology departments before processing and embedding biopsy specimens in paraffin tissue blocks. It has been reported that over 30% of the duodenal biopsy specimens may be poorly oriented.[6]

In the colon, oriented sections permit assessment of crypt branching (architectural distortion), allowing diagnosis of chronicity. Correctly oriented colonic biopsy specimens also allow assessment of lesser grades of dysplasia by crypt architectural disorganization instead of only cytologic change in cross-cut sections.

Orienting biopsy specimens in the endoscopy unit before fixation helps to improve the quality of submitted specimens.[5] The biopsy specimens are placed with the mucosal surface upwards on a small filter paper. Handling the biopsies under a stereomicroscope or magnification lens may help to orient the biopsy specimen. Serum exudate will stick the biopsy to the filter paper in 20-30 sec, after which the filter paper-mounted specimen can be transferred to a formalin container.[7] Smaller biopsies that may not include the muscularis mucosae can be impossible to orientate.

Latorre et al. demonstrated improved orientation of biopsy specimens with a single biopsy per forceps passes, compared with a double biopsy per pass using spiked biopsy forceps. They showed that duodenal biopsies obtained with the double-biopsy technique were often damaged and poorly oriented.[8]

In the pathology lab, using 0.1% eosin stain before the fragments are plucked up from the filter papers and embedded would help identify the darkly stained mucosal surface during grossing. Small endoscopic biopsies should ideally be embedded singly since this allows reorientation, if necessary, which is impracticable if a block contains multiple specimens in different planes. Most pathology technicians cannot line up more than 4-5 biopsy specimens in a tissue block during embedding and sectioning, to represent them in optimal orientation for interpretation.

Specialized Miniature Biopsy Forceps

There have been many modifications to the biopsy forceps, some of which have been detailed above. This section will discuss two specialized versions of the biopsy forceps for use through a cholangioscope (SpyBite™ forceps) and a

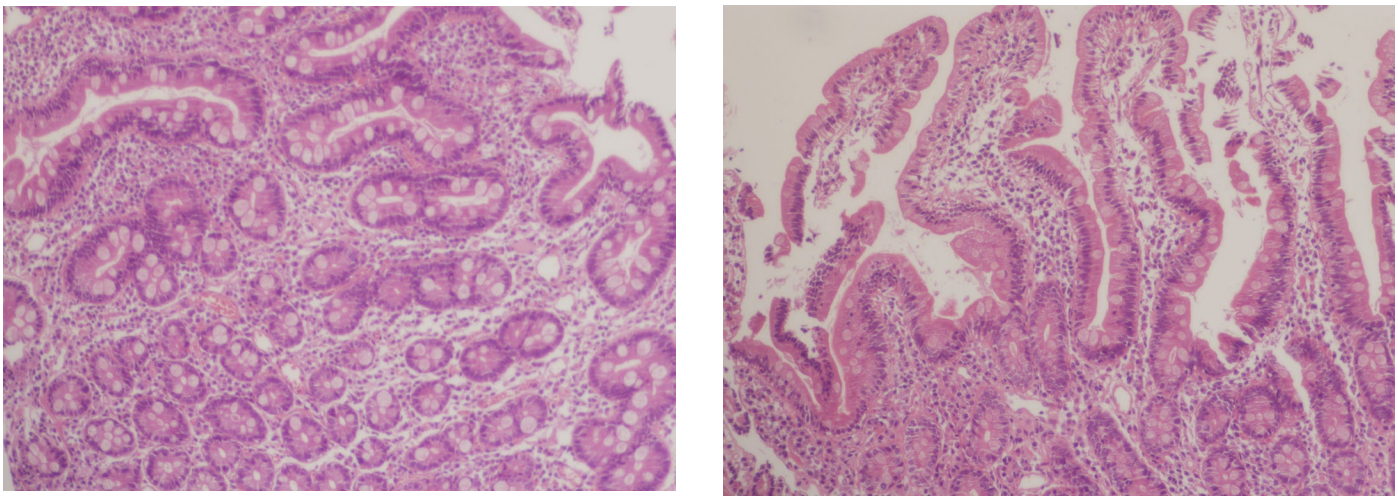

Figure 2: (a) A poorly oriented duodenal biopsy specimen. Sections show transversally sections crypts, and the relationship with its corresponding villi are lost. Cross sections of villi and crypts are seen and villous length cannot be determined (H&E, 20x magnification). (b) A well oriented duodenal biopsy specimen. Sections show well organised villi (finger like projections) lined by absorptive and goblet cells along with well oriented crypts (H&E, 20x magnification).

19G EUS-FNA needle (Moray TM microforceps).

Cholangioscopic SpyBite™ and SpyBite Max™ forceps

Indeterminate biliary strictures are those in which cross-sectional imaging (computed tomography or magnetic resonance imaging) and endoscopic retrograde cholangiopancreatography (ERCP) with cytologic brushing or biopsy are non-diagnostic.[9] Although most of these biliary strictures have a malignant etiology, up to one-fourth of these suspected malignant biliary strictures ultimately turn out benign.[10] Cholangioscopic visual impression has higher sensitivity than directed biopsies for malignant etiology of a biliary stricture; however, the specificity of visual impression is lower than cholangioscopic guided biopsies.[11-13] Hence it may not be appropriate to conclude the diagnosis based on visual impression alone and directed intraductal biopsies should be taken whenever feasible.[10]

A new generation of biopsy forceps has recently become available (SpyBite Max™, Boston Scientific) for use through the 1.2 mm working channel of the digital SpyScope cholangioscope (Boston Scientific). One to 2 miniature biopsies are obtained per pass of the forceps (**Figure 3**).

In a recent systematic review of 15 studies by Badshah et al., cholangioscopy-targeted biopsies were highly specific (99.1%) but had suboptimal sensitivity (71.9%).[14] To maximize diagnostic accuracy for indeterminate strictures to approximately 90%, a minimum of 3 biopsies are recommended.[15,16] The addition of rapid on-site evaluation (ROSE) using touch imprint cytology is not superior to 3 standard biopsies without ROSE in a recent randomized controlled trial (RCT).[16] It remains to be seen if the new-generation biopsy forceps (SpyBite Max) can improve the diagnostic accuracy of cholangioscopy-targeted biopsies.

There is limited evidence from a retrospective study that balloon dilatation before intraductal biopsies of malignant bile duct stenosis may increase the diagnostic yield.[17] However, the role of routine stricture dilatation before acquiring intraductal biliary biopsies is unsettled.

Several intraductal biopsy sampling technique modifications have been used to improve diagnostic accuracy. These include triple sampling (bile cytology and brush cytology and intraductal biopsies), fluorescent in-situ hybridization (FISH), ROSE of touch imprint cytology, and genetic mutational analysis with next-generation sequencing (NGS). Discussion of these ancillary techniques is beyond the scope of this review.

Figure 3: SpyBite TM (right) and SpyBite Max TM (left) biopsy forceps. The SpyBite Max forceps is 286 cm long, 1 mm in diameter, jaw opening of 4.1 mm, and has serrated teeth and elongated fenestration holes in the biopsy cups to acquire larger tissue specimens.

Moray™ Micro-biopsy Forceps

Moray™ through the needle (micro) biopsy (TTNB) forceps These microforceps have been used to obtain histologic samples from pancreatic cyst walls and subepithelial wall tissue (**Figure 4**). An extraction pick is included to facilitate specimen removal from the microforceps. In addition to the cyst wall biopsy, FNA cytology of the cyst wall or any solid component can also be performed with the 19G needle.

Studies have shown that TTNB with the Moray™ microforceps can yield adequate tissue for histology in 80-90% and may be superior to cyst fluid analysis for providing specific cyst diagnosis.[18-22] In particular, demonstration of ovarian-type stroma in the subepithelial cyst wall tissue can conclusively differentiate a mucinous cystic neoplasm (MCN) from an intraductal papillary

mucinous neoplasm (IPMN). Moray™ microforceps can also provide tissue for histology and ancillary studies to confirm the diagnosis of serous cystadenoma, cystic pancreatic neuroendocrine tumors, and acinar cell cystadenoma.[22-24]

Brush Cytology

Various cytology brushes are available for tissue sampling in the luminal gastrointestinal tractand the pancreatic and biliary ducts. Design modifications include brushes of variable sizes and stiffness, wire-guided or non-wire-guided, single or multi-lumen, and with or without a flexible guide tip. Outer sheaths for brushes used in ERCP are 6Fr to 8Fr.[25,26] Brush cytology remains an established diagnostic technique for biliary strictures, but its diagnostic yield remains low, with sensitivity ranging between 40-56% and a specificity between 90-97% for detecting cholangiocarcinoma.[27-30] In a systematic review and meta-analysis, the pooled sensitivity of brush cytology for cholangiocarcinoma was 45% (95% confidence interval [CI], 40-50%).[31] The accuracy of brush cytology is negatively influenced by flat-type bile duct cancer, non-bile duct cancer, short length (<30 mm) of the stricture, and underlying inflammatory cholangiopathies like primary sclerosing cholangitis (PSC).[32] The effect of prior balloon dilatation of the stricture on the yield of biliary brushings is inconclusive.[33-35]

Newer Cytology Acquisition Devices

Newer cytology acquisition devices are being developed for a wide-field sampling of Barrett's epithelium (BE) for screening and surveillance.

Wide-area transepithelial sampling (WATS) method uses a stiff wire brush to sample the BE segment combined with 3-dimensional computer-assisted analysis to identify concerning tissue for cytopathological review.[36] Studies have reported a 48% increase in dysplasia detection with WATS compared to biopsies alone.[36]

The Cytosponge is a polyurethane sponge compressed into a gelatinous capsule attached to a thread. On reaching the stomach, the capsule dissolves, releasing the sponge to expand to roughly the diameter of the esophagus. The mesh is then withdrawn by slowly retracting the thread, sampling up to one-million

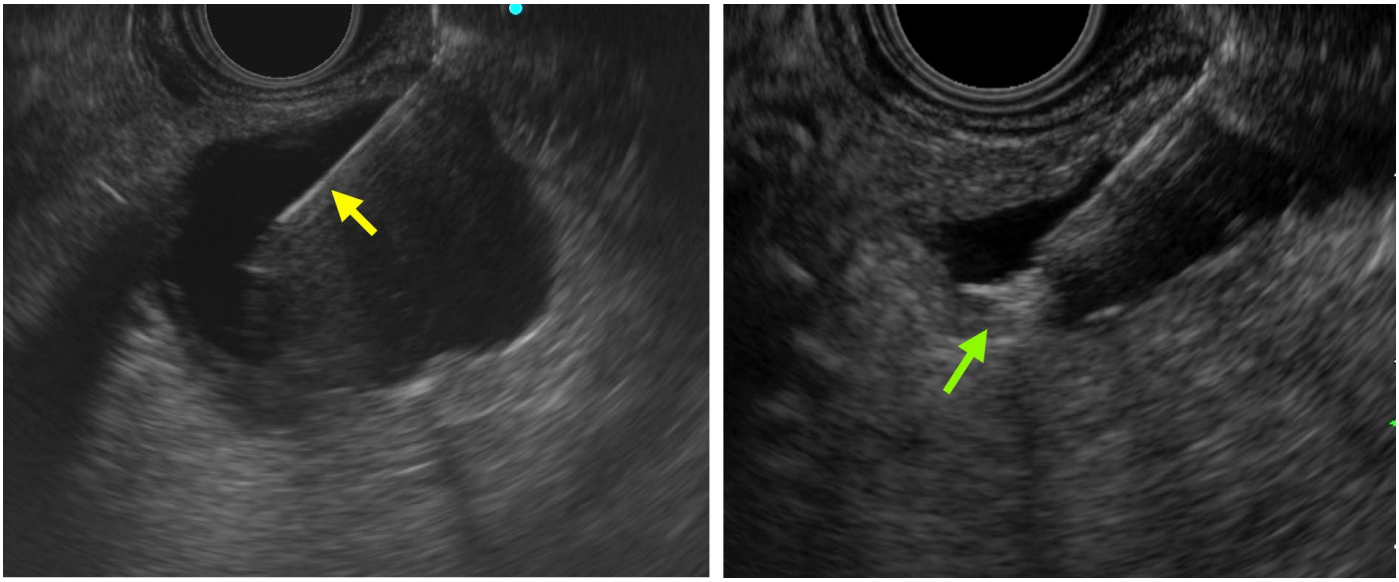

Figure 4: Use of a Moray TM micro-biopsy forceps for tissue sampling of a pancreatic cyst wall. A 19G FNA needle is first used to puncture the cyst (left figure); some cyst fluid is first aspirated for analysis, with resultant partially collapse of the cyst. Moray TM micro-biopsy forceps with a 0.8mm sheath diameter and 230cm length is then passed through the 19G FNA needle into a pancreatic cyst (right figure). The forceps is opened inside the cyst to obtain two to three bites from the cyst wall, septations, nodules, or adjacent solid components with each pass.The open jaw width of these forceps is 4.3 mm.

cells from the surface of the gastric cardia, esophagus, and oropharynx.[37] The sampled cells are transported in an ethanol-based preservative and processed into a standard paraffin block. Sections are stained with hematoxylin and eosin and immunohistochemistry for trefoil factor 3 (TFF3), which is a specific biomarker for intestinal metaplasia (IM).[38] The Cytosponge is safe, easy to swallow, and has good sensitivity and specificity, especially for circumferential Barrett's mucosa >3 cm long.[39] The Cytosponge is being studied in concert with multidimensional biomarker panels with attempts to discriminate between dysplastic and non-dysplastic BE.[40]

Other evolving esophageal cytology sampling devices include the EsoCheck™ and EsophaCap™. The EsoCheck™ is a balloon sampling device that is swallowed in a pill-sized capsule, inflated in the stomach, and then gently withdrawn to collect epithelial cells.[41] The EsophaCap™ is similar in concept to the Cytosponge but has a smaller diameter of 2.5 cm and a finer sponge material.[42] These novel sampling devices are combined with DNA methylation markers and targeted panels and may be minimally invasive alternatives to standard endoscopic sampling protocols for BE.

Endoscopic-Ultrasound Fine Needle Aspiration (EUS-FNA) Needles for Cytology and Cell-Block Acquisition

All EUS-FNA needles have the same basic design and are single-use devices. The hollow FNA needles are made entirely of metal to permit effective longitudinal force delivery, unlike injector needles which usually have a metal tip affixed to a long hollow plastic cylinder. The FNA needles have a rounded or beveled stylet pre-loaded inside. These needles can be extended up to 8 - 8.5 cm from the distal end of the sheath. There are markings at 1 cm intervals on the handle and a 'needle stopper' or 'safety screw' on the handle to limit needle advancement beyond the intended depth. Approximately 1cm of distal FNA needle is modified (by laser etching, mechanical dimpling, or sandblasting) to enhance its echogenicity and visibility in the ultrasound field.

Different FNA needles are available from different manufacturers (**Figure 5**). The latest and most widely used EUS-FNA needles include EZ Shot 2™ (Olympus), Expect and Expect Slimline™ needles (Boston), EchoTip Ultra™ (Cook), and SonoTip Pro Control™ (Mediglobe). Each of these needle types are available in three sizes: 19G, 22G, and 25G. There has been no comprehensive head-to-head comparison of the latest FNA needles regarding ease of use, ergonomics, and efficiency of tissue acquisition. The choice between FNA needles remains an individual preference.

Smaller vs. Larger FNA needles for Cytology

Two meta-analyses have shown the superiority of the 25G over the 22G FNA needles for solid pancreatic lesions. This is likely due to ease of passage of the thinner 25G needle in angulated scope positions into often firm pancreatic cancer tissue.[43,44] The diagnostic yields of 22G and 25G needles are similar for non-pancreatic lesions and lymph nodes.[45,46] In addition, 25G needles may provide superior cytological smears with less blood contamination compared with the larger 22G needles. There is no incremental diagnostic yield of cytology with the 19G needle compared with 22G or 25G needles.[47,48]

Stylet and Suction for EUS-FNA

The rationale of using a stylet inside the FNA needle is to unclog the needle of any plugging gastrointestinal tract contaminants after needle advancement the target lesion. However, no advantage of using a stylet regarding specimen quality and diagnostic yield has been demonstrated.[49-53] FNA needles may be used with or without stylet as per operator preference.

Similarly, the use of suction should be individualized. Using suction leads to increased cellularity at the expense of more hemodilution.[54-56] European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend using suction for EUS-FNA of solid masses/cystic lesions and not using suction for EUS-FNA of lymph nodes.[57] In practice, depending on the gross appearance of the first aspirate, suction may or may not be used in the subsequent passes.

Pre-submission Aspirate Preparation in the Endoscopy Suite

Poor handling of the FNA aspirates negates the utility of the entire procedure. Using an air-filled syringe to expel the tissue from the FNA needle often leads to an uncontrolled spray of the aspirate and should be avoided. We prefer slowly reintroducing the stylet to expel the aspirated material from the needle in a controlled droplet-by-droplet manner on the slide. With a proper oval-shaped smear, the larger tissue fragments are seen in the center and single cells are dispersed at the periphery.

Based on the differentials considered, aspirates from cystic pancreatic lesions are sent for estimation of glucose, amylase, and carcinoembryonic antigen (CEA) levels, cyst fluid viscosity, molecular-genetic analysis, and for cytology. Details of cyst fluid analysis are beyond the scope of this review.

Wet-fixation or Air-drying of FNA Cytology Smears

Alcohol-fixation, air-drying, or both methods can be used to fix the prepared slides and should be discussed

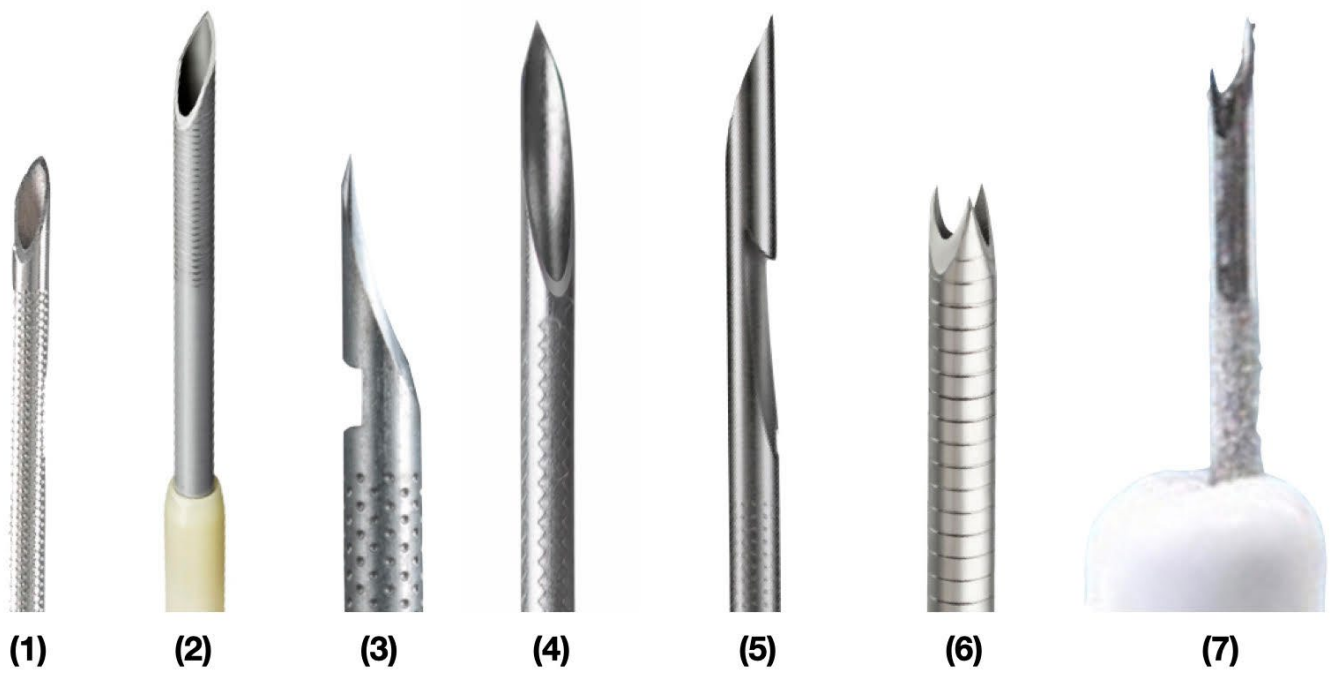

Figure 5: EUS-FNA and FNB needle line-up.
(1) EchoTip Ultra™ (Cook Medical) made of stainless steel with a lancet tip.
(2) Expect needles™ (Boston Scientific) made of Cobalt-Chromium alloy, with a lancet tip. A 'Flex' version of the19G Expect needles made of Nitinol is also available for easier deployment in flexed scope position.
(3) EzShot3 needle™ (Olympus Medical) made of nitinol alloy, with a Menghini tip, and a side-port. Needle versions without side-port are also available.
(4) SonoTip Pro Control™ (Mediglobe) made of stainless steel, with lancet tip with a shallow 150 bevel for easy puncture and enhanced tissue acquisition.
(5) ProCore FNB needles™ (Cook Medical) made of stainless steel, with a lancet tip and reverse side-bevel. A newer 20G ProCore with forward bevel and Menghini tip is also available.
(6) Franseen FNB needle™ (Boston Scientific) made of Cobalt-Chromium alloy, with a crown-tip with 3 symmetric cutting edges at 1200.
(7) Fork-tip FNB needles™ (Medtronic), also called 'shark-core' needles, have 6 distal cutting surfaces, with a longer sharp 'access tip,' and opposing 'catch bevel.'

with the pathology department. The smears must still be wet when immersed in a 95% ethanol fixative jar. These alcohol-fixed slides are stained with Papanicolaou (Pap) or Hematoxylin & Eosin stains. Pap smear highlights the nuclear details, chromatin quality, and 3-dimensional cellular clusters. Air-dried slides are stained with Romanowsky-type stains (Diff-Quick, May-Gruenwald-Giemsa, or Hemacolor).[58] Romanowsky stains highlight the intra-cytoplasmic material and extra-cellular substances. Air drying of slides also allows rapid on-site evaluation (ROSE). Hence, alcohol-fixed and air-dried smears provide complementary information.

Rapid On-Site Evaluation (ROSE)

The presence of an on-site cytopathologist leads to a 10-15% increase in the diagnostic yield.[59,60] There is an approximate 20% rate of non-diagnostic aspirates without ROSE.[61] In our experience, on-site reporting with EUS-FNA is more complex than with percutaneous FNA because of frequently encountered esophageal, duodenal, and gastric contaminants. ROSE also helps to limit the number of passes and directs additional sample collection for ancillary tests such as microbiological cultures or flow cytometry.

In the absence of ROSE, we advise making 4-5 passes in solid pancreatic lesions and 2-3 passes in lymph nodes, liver, and adrenal lesions.[62]

When and How to Make Cell Blocks?

Cytology alone may be insufficient with the following differentials: non-ductal carcinoma pancreatic tumors (like acinar cell carcinoma, solid-pseudopapillary tumor, metastasis), autoimmune pancreatitis, lymphoma, mesenchymal tumors like gastrointestinal stromal tumor (GIST), leiomyoma, or schwannoma, neuroendocrine tumors (NETs), non-small cell lung cancer (NSCLC), and some cystic pancreatic tumors. Cell blocks recapitulate morphology seen on tissue sections but are usually fragmented, minute, and seldom sufficient for diagnosis. The leading utility of cell blocks is as a repertoire of tissue for immunohistochemistry (IHC) panels and molecular analysis. Cell blocks should be considered a replacement for cytological smears.

Usually, two committed passes for cell-block preparation are made. The material is expelled in a cell-preservative solution like Roswell Park Memorial Institute Medium (RPMI-1640). We can also collect material in isotonic saline. However, the lifespan of cells in saline is only about 1 hour, so samples in saline must be transported to the laboratory immediately.

Traditionally, cells are harvested by centrifuging the collection tube. Because of the specimens' comparatively minute amount and fragmented nature, either an agarose gel or fibrin clot is used to hold the specimen together as a 'tissue fragment' before embedding in paraffin.

EUS-guided Fine Needle Biopsies (FNB)

Core biopsies should be obtained when tissue architectural details are required to establish a specific diagnosis. These situations include certain well-differentiated tumors, tumors with extensive desmoplasia, and tumors like GIST when adequate cellular specimens are difficult to obtain. Lymphomas, mainly low-grade varieties, also need histological (architectural) evaluation for a conclusive diagnosis. Unlike malignancies, many benign pathologies like autoimmune pancreatitis (AIP) are less cellular and need tissue architectural details for a diagnosis. Like cell blocks, core biopsies allow extensive IHC panels and molecular analysis.

EUS-guided liver biopsy (EUS-LB) is also being increasingly used, in-lieu of percutaneous liver biopsy. EUS-guided approach may have the advantage of a relatively painless procedure done with sedation. In addition, obesity does not hamper the procedure, and bi-lobar sampling can be done when indicated. The standard contraindications to percutaneous liver biopsy like coagulopathy and large ascites, also apply to EUS-LB. The reported specimen adequacy (biopsy length and width, and complete portal tract number) rates of EUS-LB in comparison to percutaneous liver biopsy is still controversial. Current data suggest that specimen adequacy of EUS-LB may be maximized with the use of 19G Franseen needle with wet heparin suction. As further data is accrued these recommendations may be modified.

Recently, core biopsies have been increasingly obtained when an on-site evaluation is unavailable,

driven by the wide availability of dedicated core-biopsy needles. The accuracy of dual sampling (cytology and core biopsies) is superior to either technique alone.

EUS-guided fine needle biopsies (EUS-FNB) can be obtained with either large-bore standard bevel aspiration needlesor specially modified needles with complex distal cutting edges (**Figure 5**). The latter category includes needles with side bevels, Franseen (Crown-tip) needles, and fork-tip (shark-core) FNB needles. All these dedicated FNB needles have different modifications of the distal part to enhance tissue cutting and capture. The EUS-Trucut needle is no longer commercially available.

To acquire tissue cores, the direction of FNB needle movements should be carefully changed within the mass, and repeated 'jabbing' at one area should be avoided. The needle should be moved back and forth at each location within the mass only two to three times. It is usually unnecessary to carry out more than three passes for tissue cores in a single lesion.[63]

The designs and performance of these FNB needles are discussed below.

Standard Bevel Needles for FNAB

Standard bevel 19G, and even 22G FNA needles can be used to procure core tissues for histology.[64] Studies have demonstrated yields of tissue cores or cell blocks ranging from 75-80% when using standard bevel 22G FNA needles and 59-100% when using standard bevel 19G FNA needles.[65, 66]

19G needles are stiff and difficult to deploy in the duodenum. A commercially available flexible nitinol 19G needle (Expect™ 19G Flex needle, Boston Scientific) was developed for use under challenging positions. Ease of trans-duodenal deployment and high rates of adequate core tissue acquisition with this flexible 19G needle has been found by some[64,67] but not by other authors.[68]

Side-Bevel FNB Needles

Needles with reverse bevel are commercially available in three sizes: 19G, 22G, and 25G (EchoTip ProCore™ needles, Cook Medical). A new 20G ProCore needle (ECHO-HD-3-20C™, Cook Medical) with an automatic recoiling stylet, forward bevel, and coil spring sheath for increased flexibility is now available. The side bevel on these needles hooks and cut the tissue like a cheese grater and traps it in the needle during its motion. In addition, the side hole is also postulated to function as a vent for the air column, facilitating the filling of the needle with tissue cores. Because of the side bevel size, these needles are unsuited for small (<10 mm) lesions or vascular lesions.

19G side-bevel needles are stiff, and difficulties may be encountered with their trans-duodenal passage. The yield with 25G side-bevel needles is sub-optimal, gathering tissue core samples in only about 40% of the cases.[69,70] Most studies have utilized the 22G side-bevel needles and reported around 80% (70% to 90.2%) core biopsy acquisition rates in various pancreatic and non-pancreatic lesions.[71,72] However, side-bevel needles have not been found superior to standard hollow bore needles in pancreatic mass lesions.[73-76] The only advantage with the 22G side-bevel needles is a requirement for fewer passes.

Franseen Tip FNB Needle

The Franseen FNB needle(Acquire™, Boston Scientific) has a crown-tip with three sharp cutting edges 120 degrees apart and three symmetric cutting surfaces instead of the usual single bevel. The Franseen needle geometry incorporates a larger inclination angle and a smaller included angle.[77] A high inclination angle translates into more force to penetrate tissue, while a smaller included angle translates into maximal sharpness at cutting.

A high yield of 22G and 25G Franseen FNB needles has been reported in published studies.[78-80] Multiple studies have reported a better yield of histologic specimens with 22G Franseen FNB needles compared with 22G and 19G standard bevel needles.[81-85]

Fork-Tip FNB needle

The fork-tip needle (SharkCore™, Medtronic) has a needle tip designed with six distal cutting surfaces. It has a longer sharp 'access tip', and an opposing 'catch bevel' to improve tissue capture as the needle movement shears it off.

A high yield of histological diagnosis is reported in multiple lesion types with the 22G and 25G fork-tip FNB needles.[86] Comparative studies have found significantly better yield of histological specimens with fork-tip FNB needles (19G, 22G, and 25G) than standard bevel needles of similar sizes and also side-bevel needles.[87-89]

Pre-submission Handling of EUS Core Biopsy Specimens in the Endoscopy Suite

There are two related ways to handle the specimens obtained from core biopsy needles:

1. Expel the entire material in 10% formalin and process it as tissue cores.
2. Expel the material on a glass slide or petri-dish, and micro-dissect out the tissue cores with a small tweezer or a needle.

The expelled material from cutting needles is seen as elongated red or red and whitish pieces. The whitish fragments are tissue pieces, and the red cylinders are coagulated blood. However, the red coagulum may also contain tumor tissue. Often the blood clots far exceed the tissue cores in quantity. However, once paraffin-embedded, the tissue micro-cores can usually be identified. These distinctive features of the EUS-acquired tissue cores must be conveyed to the pathologist for proper sample processing.

Although gross visual inspection may suggest that the specimen is adequate for histology, false-positive misinterpretation occurs in about 13.5%–33% of cases. (90) Collecting tissue fragments for histology still allows further cytopathological evaluation of the remaining specimen.

Ancillary Tests

Commonly used ancillary tests in EUS-guided aspirates include polymerase chain reaction (PCR) and culture for tuberculosis, flow cytometry (FC), and mutational analysis by reverse transcriptase polymerase chain reaction (PCR) with or without direct sequencing methods, like Sanger sequencing or next-generation sequencing (NGS). The discussion of these techniques is beyond the scope of this review.

Conclusion

Collecting appropriate gastrointestinal luminal and extra-luminal samples during endoscopic procedures not only requires a thorough knowledge of the endoscopic tools, but also close understanding of the pathologic and laboratory processing of the collected samples. A close liaison with the concerned laboratory personnel is essential for obtaining optimal results of endoscopic tissue acquisition.

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