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General Principles of Biopsy Diagnosis of GI Disorders

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Tissue sampling of the gastrointestinal tract at the time of endoscopy is the cornerstone of many gastrointestinal diagnoses. The development of a flexible endoscope and the subsequent ability to directly acquire tissue under optical guidance has been one of the most important advancements in the field of gastroenterology throughout its history. Although tissue sampling can be performed through nonendoscopic devices, the ability to directly correlate precise locations and target biopsies to specific areas of disease is critical to our ability to diagnose and further understand gastrointestinal pathology. Many of the advancements in our understanding of the basic pathology and molecular biology of gastrointestinal disease can be directly attributed to our ability to acquire tissue for histological, molecular, and genetic analyses. An excellent example is our deep understanding of the molecular pathology of colorectal cancer development from normal colonic epithelium to adenoma to colorectal cancer, a discovery made possible because of colonoscopic access to precursor lesions such as adenomatous polyps and early cancers.

In this chapter, we will review general principles of tissue acquisition at the time of endoscopy including the following topics:

- Endoscopic equipment for obtaining tissue including endoscopic accessory channels, biopsy forceps, snare devices, needle aspiration and cytology brush.
- General principles of optimal sampling technique.
- Methods of tissue preparation in the endoscopy laboratory to optimize diagnostic accuracy.
- The role of endoscopic ultrasound (EUS)-guided fine-needle aspiration cytology.

Endoscopic Equipment for Tissue Sampling

Modern endoscopic equipment can be divided in two general categories: the endoscope that allows access to the gastrointestinal tract and accessory devices that are typically passed through the working channel of the endoscope to directly acquire tissue, including biopsy forceps, snares, fine-needle aspiration devices, and cytology brushes. Recent developments in tissue sampling include devices that are capable of wide-field, often definitive, endoscopic resection of early neoplasia and invasive carcinoma.

A modern endoscope is a remarkably robust and versatile instrument including a light source, optical lenses with a video capture device, image processing, and display equipment, and importantly for the purposes of tissue acquisition, an accessory channel ranging from 1 to 6 mm (typically 3–4 mm), which allows passage of devices for mechanical collection of tissue (Figures 1.1 and 1.2).

There is a general trade-off between the diameter of the instrument and the ease and comfort with which it can be passed through the natural orifices of the body such as the mouth and anus. In general the larger the outer diameter, the larger the accessory channel is to accommodate larger instruments for tissue acquisition. A fundamental limitation of most flexible endoscopes, as opposed to surgical instruments, is that all accessories pass through a single access point of the endoscope. As compared to surgical instruments with multiple access points, the endoscopic devices do not typically allow triangulation to acquire a large bulk tissue or resect entire organs. For this reason, most tissue is sampled through pinch forceps, needle

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Figure 1.1 Endoscope with control handle and tip. The tip contains a light source, imaging window, and accessory channel through which various tissue acquisition devices can be passed.

Figure 1.2 Endoscopic processor, which converts the light captured from the endoscope tip into a visible image for display. *Source:* Olympus America, Inc. With permission.

aspiration, or wire loop snare devices. More recently, electrosurgical needles and other cutting tools have been developed, which have allowed wide-field resection of tissues of virtually any diameter (Figure 1.3).

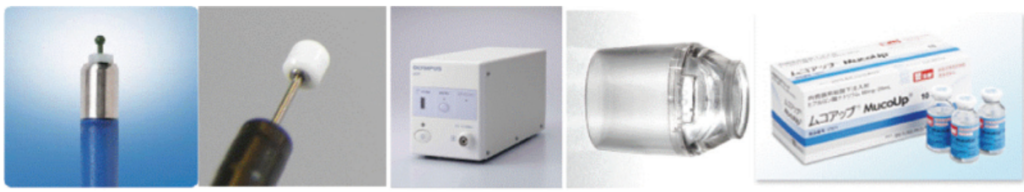
Pinch Biopsy Forceps

The flexible pinch biopsy forceps have been one of the most versatile of all instruments for tissue acquisition. These typically involve a flexible steel cable and lever device with two sharp-edged cups, which can be opened and closed to acquire tissue (Figure 1.4).

Standard endoscopic sampling typically acquires tissue from the mucosa and occasionally a submucosal depth of the intestinal wall; however, large-capacity forceps as well as multiple sampling including "bite on bite" allow sampling of the deeper layers. Pinch biopsy forceps come in multiple sizes from very small instruments such as a pediatric forceps, which can be passed through very small working channels. Recent development of very tiny forceps makes it possible to pass them through special endoscopes into the bile or pancreas duct and to pinch biopsy outside of the traditional gastrointestinal lumen (Figure 1.5).

Studies comparing jumbo forceps to standard forceps have generally not shown significant advantages of larger capacity forceps. A limitation of most forceps is the inability to sample tissue in the submucosa routinely. This is highlighted in studies looking for Barrett's esophagus after the surface epithelium has been ablated. Biopsy forceps can remove tissue with mechanical closure alone or with electrocautery ("hot biopsy") although the use of hot biopsy has diminished significantly due to increased risks of complication and tissue damage in the biopsy specimen.

(a) (b) (c) (d) (e)



Jet B knife
Zeon medical

IT knife nano
Olympus medical

CO2 insufflator
Olympus Medical

ST hood short type
Fujifilm medical

MucoUp
Johnson and Johnson

Figure 1.3 (a) Tools for performing endoscopic resection including endoscopic submucosal dissection (ESD). *Source:* Zeon Medical. (b) Standard and insulated tip electrocautery knives for incision and dissection. *Source:* © 2017 Korean Society of Gastrointestinal Endoscopy. (c) CO_2 insufflator for luminal distension, which is preferred to air given rapid reabsorption. *Source:* Olympus. (d) Distal attachment hood to facilitate maintaining view within the submucosal space. *Source:* Fujifilm medical. (e) Injection fluid (hyaluronic acid; Mucoup [Johnson and Johnson]) for submucosal lifting. *Source:* Gut and Liver.

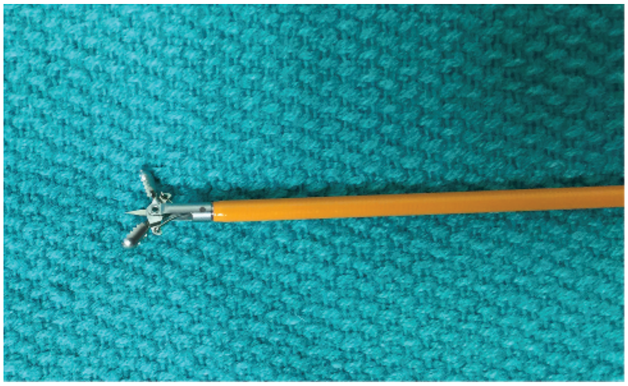


Figure 1.4 Endoscopic biopsy forceps in the open position. The needle-like pin in the center holds the tissue in place so one to two samples can be obtained per pass.

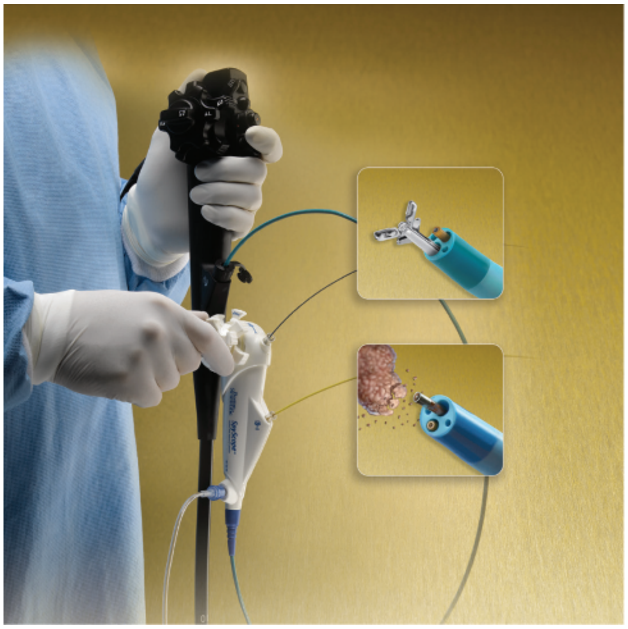


Figure 1.5 Micro biopsy forceps <1 mm in diameter, which can be passed through specialized endoscopes into the bile duct, pancreas duct, or via 19-gauge needles for extraluminal tissue sampling. *Source:* Boston Scientific Corporation with permission.

Endoscopic Snare Devices

Endoscopic snare devices have also been widely used for resection of polypoid as well as flat lesions throughout the gastrointestinal tract. They have been remarkably versatile and effective over the past four decades. Endoscopic snares typically involve a metallic wire, which may braided or monofilament (Figure 1.6).

A wire loop is generally constrained within a small caliber plastic catheter. At the distal end of the catheter, the wire loop can be opened to various sizes to grasp and resect polyps of different sizes. Typical sizes include loops 5–30 mm in diameter. There are numerous different shapes including

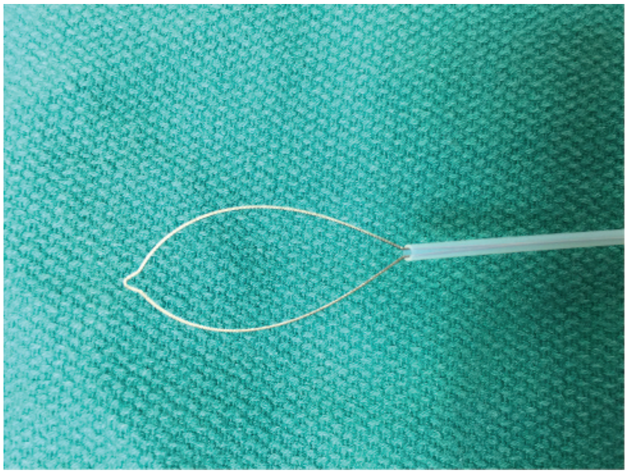


Figure 1.6 Endoscopic snare for polypectomy. The wire loop is extended in the open position outside the plastic sheath. When closed, the wire loop is strangulated and resects the polyp tissue.

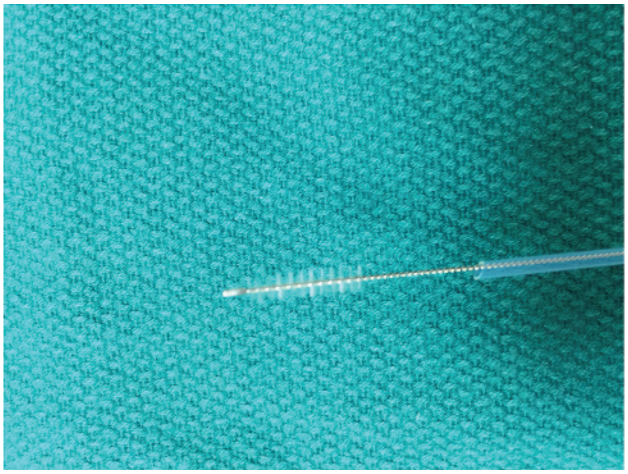


Figure 1.7 Endoscopic cytology brush. Note the abrasive brush extended beyond the protective plastic sheath.

oval, hexagonal, and asymmetric "duck bill." Snares also come in various degrees of stiffness, which allow resection of lesions of many shapes and sizes. Tissue can be resected with mechanical closure alone (so-called "cold snare") or with mechanical plus electrosurgical cutting ("hot snare"). Recent studies suggest that cold snare is associated with lower risk of bleeding and bowel wall injury.

Endoscopic Brush Cytology

Abrasive brush cytology has been used in many different fields of tissue sampling. Typical endoscopic brush is constrained within a plastic catheter similar to endoscopic snares (Figure 1.7).

After passing through the accessory channel of the endoscope, the abrasive brush is exposed and rubbed against the area of tissue sampling. This is most commonly applied to obtain specimens for microbiology, particularly fungal specimens. These have also been widely applied in the biliary tract for sampling of suspicious biliary strictures. More recent advances include a highly abrasive wide-area tissue sampling system that has been recently studied and Barrett's esophagus as an alternative to pinch forceps, as well as nonendoscopic abrasive sponge sampling, which has the potential to offer inexpensive population-based screening for esophageal neoplasia (Figure 1.8).

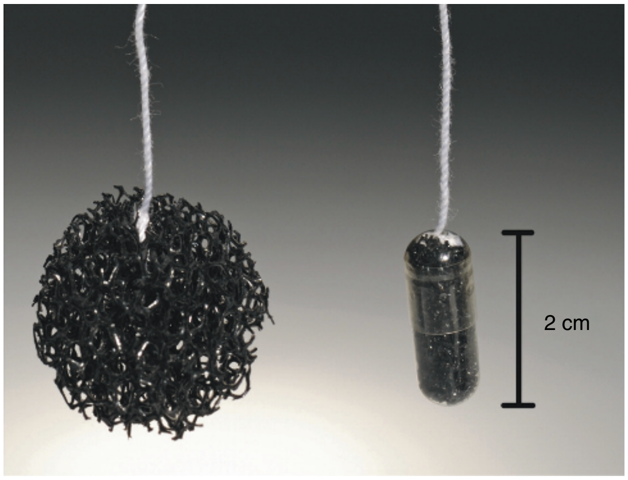


Figure 1.8 Nonendoscopic abrasive cytology brush. *Source:* From Kadri, S.R., Lao-Sirieix, P., O'Donovan, M. et al. (2010). Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. *BMJ* 341: c4372. doi: https://doi.org/10.1136/bmj.c4372. Open access article.

Endoscopic Fine-Needle Aspiration (FNA) Devices

The most common application of FNA devices in endoscopy is endoscopic ultrasound-guided tissue sampling (EUS-FNA). The development of endoscopic ultrasound in the 1970s and 1980s significantly expanded the reach of endoscopic tissue sampling into the pancreas and other extraluminal organs such as lymph nodes and now virtually any organ within reach of the proximal or distal GI tract lumen (Figure 1.9).

Other needle aspiration devices include biliary sampling needles often used in conjunction with forceps and brush sampling, or so-called "triple sampling." EUS-FNA devices come in various sizes from 19- to 25-gauge. These devices are typically attached to a handle, which allows the endoscopist to puncture and make to-and-fro movements within the target lesion and also apply negative pressure. With various methods, both cytologic and histologic material can be obtained through these needle devices. Recent efforts to develop Tru-Cut devices have been met with variable success.

Tissue Processing in the Endoscopy Laboratory

An excellent recent review on the topic of tissue acquisition has been published by the American Society for gastrointestinal endoscopy. For most routine tissue sampling the biopsy material is placed in formalin and subsequently embedded in paraffin for histological analysis. Other specific preparations include sampling for microbiological evaluation, molecular or genetic testing, and electromicroscopy. These

(a) (b)

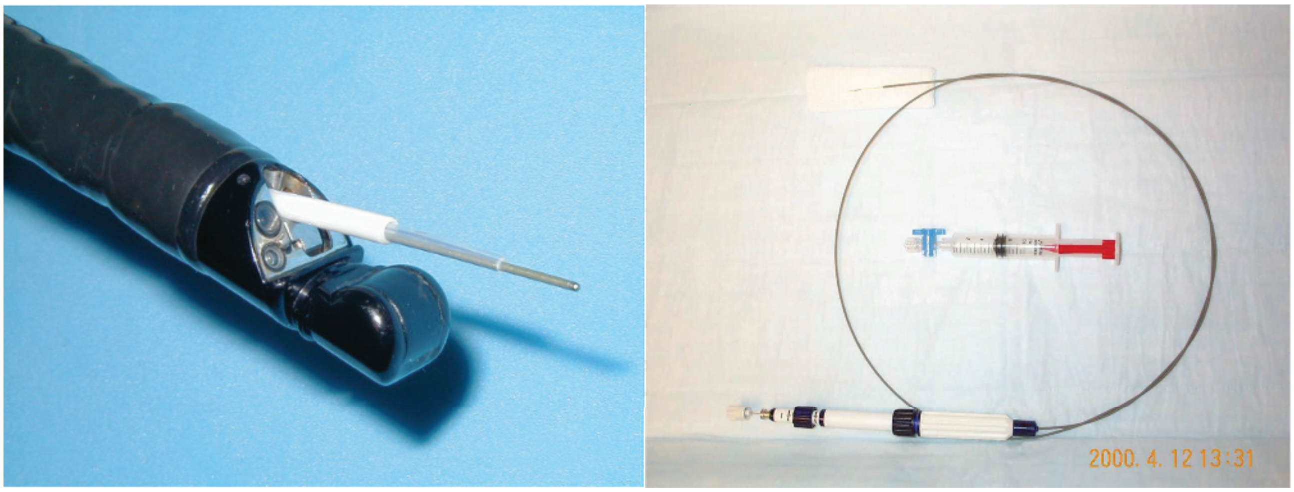


Figure 1.9 (a) and (b) Endoscopic ultrasound endoscope and guided fine-needle aspiration (EUS-FNA) device.

special samples should be handled according to local institutional guidelines. In general, samples that are obtained for culture should be obtained prior to placing forceps into formalin as formalin residue can destroy or inactivate live microbial tissue.

Non-oriented Samples

Most pinch biopsy samples are placed directly in formalin without orientation. This is also true for small polyps where the likelihood of invasive cancer is very low. The sample is placed directly into a small formalin jar. The needle or forceps should be rinsed if it comes in direct contact with formalin as subsequent contact with living tissue can cause chemical injury.

Oriented Samples

Increasingly, endoscopic resection is being used for definitive oncologic removal of precancerous and invasive lesions. In these cases it is advantageous to orient the specimen so that precise staging as well as margin assessment can be performed. A typical situation is in endoscopic resection of early neoplasia in the esophagus such as Barrett's esophagus. In this case a sample is frequently obtained through endoscopic mucosal resection. Large pieces of tissue, typically 1–2 cm in diameter, can be obtained to a depth of the submucosa. In this case the sample should be removed from the patient in a way that does not damage or distort the tissue. This is typically performed by suctioning the tissue into a distal attachment cap/hood and then removing the endoscope. Alternative retrieval devices include a modified snare with a protective net. These tissues should then be immediately oriented at the bedside typically by placing them on a paraffin or similar firm block. The tissue should be flattened typically with the mucosal side up and the edges carefully pinned so that the tissue remains flat (Figure 1.10).

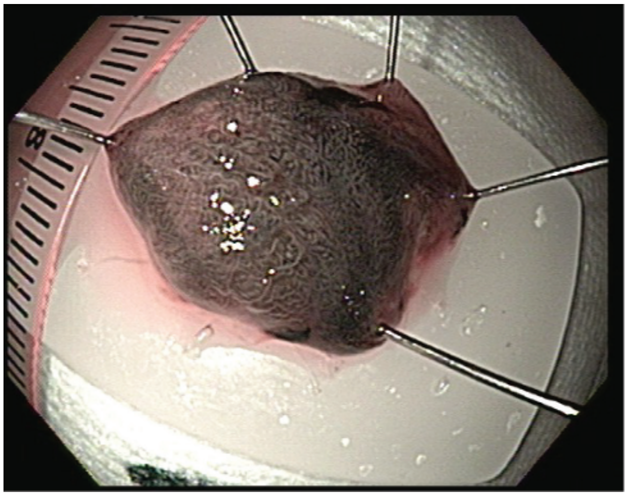


Figure 1.10 Pinned and oriented resection tissue from Barrett's esophagus-associated neoplasia. Note the mucosal side facing up and the lateral margins pinned to prevent curling of the edges.

Cytology Samples

Cytology samples obtained from either brush or fine-needle aspiration can be processed in a variety of ways. Most commonly these are prepared as thin smear on glass slides, which can be evaluated either immediately as an air-dried sample stained with a modified Romanowsky stain, or as an alcohol-fixed slide evaluated with Papanicolaou staining. It is often helpful to place additional excess material in a cytological preservative or formalin. Special handling is required for samples where lymphoproliferative disease is considered. Typically these include cytological preservatives such as Roswell Park Memorial Institute (RPMI) medium that allow subsequent flow cytometry. As a practical matter, placement in such a preservative should be considered even when likelihood is low since cells preserved in such solution can always be examined with routine cytological methods; however, cells that are placed in formalin or alcohol cannot be evaluated for flow cytometry. The use of rapid on-site evaluation (ROSE) cytology has been shown in many studies to increase diagnostic yield and reduce the need for repeated procedures.

Culture Samples

Samples obtained for culture should be placed in a sterile specimen container. Sterile saline maybe needed to prevent drying of the specimen. Attention should be paid to minimize contamination although it is recognized that the endoscope and the organs throughout which it is passed are not sterile and is not possible to obtain a purely sterile access into the gastrointestinal lumen. Contamination with oropharyngeal organisms or colonic organisms is not uncommon.

Specific Organ Sampling Methods

Esophagus

Diagnostic Sampling

Indications for diagnostic sampling of the esophagus include Barrett's esophagus and other suspected neoplastic disorders, inflammatory disorder such as eosinophilic esophagitis, gastroesophageal reflux disease, and infectious esophagitis.

The most common indication in Western countries for tissue sampling from the esophagus is likely Barrett's esophagus. There are established guidelines for sampling of the esophagus. These have traditionally been based on the notion that early neoplasia is not visible endoscopically and thus random sampling of the mucosa should be performed to ensure adequate detection of early neoplasia. The most widely used standard is the so-called Seattle protocol. The American Society for Gastrointestinal Endoscopy (ASGE) guideline for tissue sampling calls for surveillance of non-dysplastic Barrett's esophagus in four quadrants every 2 cm with a large-capacity forceps for the entire Barrett's mucosa. Patients with established low-grade dysplasia sampling should be more intensive with four-quadrant biopsies every 1–2 cm. For patients who choose to undergo surveillance for high-grade dysplasia, sampling every 1 cm should be performed; however, more recent evidence suggests that patients with established low-grade and high-grade dysplasia should likely undergo therapy to eradicate the Barrett's esophagus. Advances in endoscopic imaging, such as high-definition narrow-band imaging, confocal laser endomicroscopy, and chromoendoscopy, have significantly increased the yield of biopsy and allow much more targeted sampling although these have not yet replaced the need for random biopsy. These advances are likely to reduce the need for random biopsies and focus more on targeted sampling.

For eosinophilic esophagitis the ASGE recommends two to four biopsies from the proximal esophagus and two to four biopsies from the distal esophagus. Biopsy should also be obtained from the gastric antrum and duodenum when diffuse eosinophilic gastroenteritis is suspected.

For suspected infectious esophagitis, multiple biopsies from the margin and base of a visualized ulcer should be obtained and the sample should be sent for standard histology as well as immunohistochemical and possibly viral cultures and PCR. For candidal esophagitis, multiple biopsies of the affected area as well as cytology brushings may be complementary to biopsy.

Therapeutic Sampling

Increasingly, endoscopic resection methods are being applied to early neoplasia the esophagus, particularly Barrett's esophagus and early squamous cell carcinoma. These are largely confined to tumors suspected to be T1 or nodular high-grade dysplasia. Endoscopic mucosal resection (EMR) methods generally involve an EMR device such as a modified band ligator followed by snare resection of the pseudopolyp (Figure 1.11–1.13).

Other methods include endoscopic submucosal dissection (ESD) in which the lateral margins of the suspected area are incised with electrocautery knife followed by dissection along the submucosal plane to obtain an en bloc specimen. EMR devices can typically obtain samples 1–2 cm in diameter into

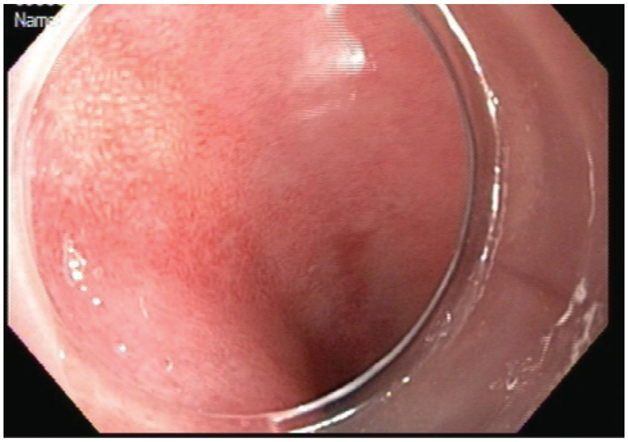


Figure 1.11 Barrett's esophagus with flat neoplasia (9 o'clock) for targeted endoscopic resection.

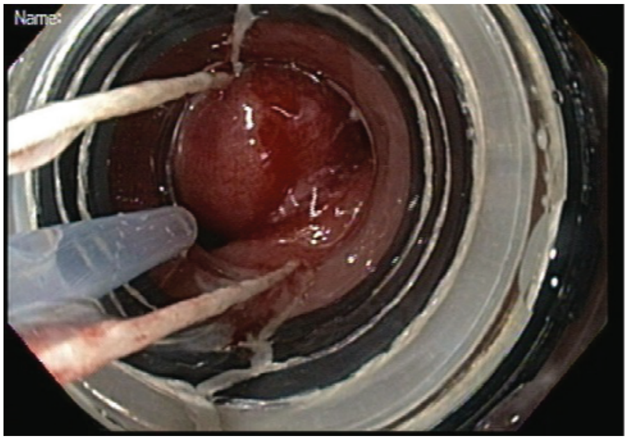


Figure 1.12 Multiband mucosectomy device. The black rubber bands are mounted on the outside of a plastic cap. The tissue is suctioned into the cap and a band deployed to create a pseudopolyp, which is then removed by snare.

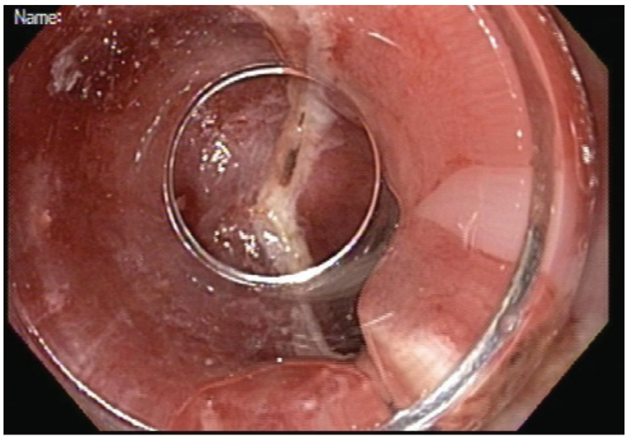


Figure 1.13 Area of resection at 6–12 o'clock includes the entire region of suspected neoplasia at 9 o'clock. The remaining tissue at the 9 o'clock area represents intact deep submucosa and muscularis propria.

the depth of the mid-submucosa. Endoscopic submucosal dissection can obtain samples of any lateral diameter and generally to the base of the submucosa.

One major advantage of these techniques is the ability to perform wide-field or en bloc resection and orient the sample. Samples should be retrieved without causing trauma to the tissue, preferably by removal through the endoscopic cap or through a snare-net as opposed to suctioning via the accessory channel, which can traumatize or fragment the tissue. Once retrieved the tissue should be handled as with other endoscopic resection specimens by orienting the specimen and pinning it on a fixed material such as a paraffin block. En bloc specimens can be oriented in terms of the oral and anal side of the lesion and assessed for lateral and deep margins. For resections that are performed piecemeal such as with multiband mucosectomy, the lateral margins cannot be accurately assessed and so complete resection relies on the endoscopic inspection intraluminally. The specimens should still be oriented and assessed for the deep margin.

Stomach

Diagnostic Sampling

Major indications for diagnostic sampling of the stomach include assessment for *Helicobacter pylori* infection, diagnosis of gastritis, metaplastic atrophic change, gastric polyps, and suspected neoplasia, particularly in the setting of gastric ulceration or early gastric cancer.

***H. pylori* Sampling** Biopsy is one of several recommended methods for *H. pylori* sampling that also includes urease breath testing and stool testing for *H. pylori* antigen. When using endoscopic tissue sampling, there are two general methods including non-histological testing of the tissue for the presence of urease using the traditional Campylobacter-like organism test (CLO-test). In this case, the tissue should be placed in the standard agar well and visually inspected for a pH change following the instructions for use in this product. Histological sampling can also be performed with one of two methods. One method is to take three biopsies including one from the angularis corpus antrum junction, one from the greater curvature of the corpus, and one from the greater curvature of the antrum. Alternatively, the updated Sydney protocol may be followed, which includes five biopsies including one from the antrum lesser curve, antrum greater curve, gastric corpus lesser curve, and greater curve, and one from the angularis of the stomach.

Environmental Metaplastic Atrophic Gastritis (EMAG) Current guidelines recommend 7–12 biopsies including 4-quadrant biopsies including an antrum, 2 from the angularis, 4 from the corpus, and 2 from the cardia.

Gastric Polyps Gastric polyps are very frequently encountered, particularly in patients who are on chronic proton pump inhibitor therapy. Current ASGE guidelines for management of gastric polyps suggest that polyp should be sampled by biopsy. Fundic gland polyps larger than 1 cm should be removed by polypectomy. Hyperplastic polyps larger than 5 mm should be removed by polypectomy, and all adenomatous polyps should be removed by polypectomy. In patients who have numerous polyps, particularly where endoscopic inspection is highly consistent with fundic gland polyps, the largest of the polyps should be removed by polypectomy and representative sampling performed of smaller polyps.

Ulcer Disease Because of the potential for neoplasia in the setting of ulcers, numerous biopsies should be obtained from the base as well as the margins of the ulcer to exclude malignancy. Cytology may also be helpful. Sampling for concurrent *H. pylori* infection should be performed as suggested above.

Therapeutic Sampling

Endoscopic resection in early gastric cancer is now widely performed throughout the world. The endoscopic resection methods include endoscopic mucosal resection typically with a cap-assisted device as in the esophagus, or injection of a submucosal agent such as saline followed by snare resection of the lifted tissue. Lesions larger than 1–2 cm should generally be removed en bloc by endoscopic submucosal dissection when early gastric cancer is suspected. Tissue should be handled in the same manner as discussed above in esophagus.

Small Intestine

Major indications for tissue sampling of the small intestine include celiac disease as well as resection of early neoplasia.

Diagnostic Sampling

Currently established protocols for sampling for celiac disease recommend four to six biopsies from the duodenum including the duodenal bulb and distal duodenum.

All other suspicious areas should be sampled using routine biopsy technique. Sampling of the papilla should be performed with caution as biopsy in this area can cause pancreatitis. When a suspected neoplastic lesion is seen in the region of the papilla, it is preferred to take a biopsy that does not immediately injure the orifice of the bile duct or the pancreas duct.

Therapeutic Sampling

Adenomatous polyps of the duodenum are handled in a similar manner to adenomatous lesions anywhere in the gastrointestinal tract. Endoscopic mucosa resection can be performed with injection followed by snare. There appears to be higher risks of bleeding and perforation associated with endoscopic resection of duodenal lesions. This is particularly true were using cap-assisted devices where the thin wall of the duodenum is suctioned into the cap leading to inadvertent full-thickness resection.

Special attention is required for resection of lesions involving the ampulla of Vater. In these cases, typically the lesion is resected followed by placement of a stent in the pancreatic and bile duct orifice to prevent stricturing of these and acute pancreatitis.

Another special situation is polypoid lesions in the distal small intestine, which can now be accessed with deep enteroscopy methods. Polyps are generally removed in the same manner as polypoid lesions elsewhere in the gastrointestinal tract by snare polypectomy. Special circumstances include numerous polyps such as those developed in patients with Peutz–Jeghers syndrome. These can be particularly large and numerous. It may not be possible to resect and retrieve all tissues. Because of the laborious process of deep enteroscopy, it is often not feasible to extract the endoscope with each large polypoid tissue. Thus diagnostic sampling can be performed by biopsy of the lesion or fragmentation of the lesion with a snare followed by complete therapeutic excision of the lesion.

Colon

Major indications for diagnostic sampling of the colon include detection of both overt and microscopic colitis and surveillance for dysplasia in inflammatory bowel disease.

Perhaps the most commonly performed tissue sampling in the field of gastroenterology involves removal of colorectal polyps and tissue sampling of more advanced colorectal neoplasia.

Diagnostic Sampling

In patients with chronic diarrhea and suspected microscopic colitis, random biopsies should be taken throughout the colon including at least two biopsies from the right, transverse, descending, and sigmoid colon. For limited sampling the flexible sigmoidoscopy is also a reasonable approach. In this case at least two biopsies should be obtained from the sigmoid and descending colon as well as transverse colon if this can be reached with the sigmoidoscope.

In the setting of inflammatory bowel disease, biopsy sampling should be performed to establish the diagnosis and to assess the extent. For the initial diagnosis, the American Society for gastrointestinal endoscopy recommends two biopsies from each of five sites including the ileum and rectum.

Surveillance of inflammatory bowel disease is a special circumstance and is evolving. Traditionally, random biopsies were obtained throughout the colon. Current guidelines recommend biopsy of each colonic segment with four-quadrant biopsies every 10 cm from the cecum to the rectum for a minimum total of 33 biopsy samples. In cases where the entire colon is not affected, four samples should be obtained every 10 cm of the affected areas. More recently, it has been shown that using dye spray such as indigo carmine or methylene blue can identify areas of dysplasia with high accuracy and thus guide directed sampling without the need for random biopsy. Biopsies should however also be assessed from each colonic segment to assess for inflammation.

Therapeutic Sampling

Endoscopic resection methods of flat and lateral spreading colorectal polyps has expanded rapidly over last 10 years. Most noninvasive neoplastic lesions of the colon can now be removed through advanced endoscopic methods such as EMR or ESD avoiding the need for surgery. Lesions less than 2 cm can typically be removed en bloc with endoscopic mucosal resection involving injection of a fluid cushion under the lesion followed by snare resection. Where there is suspected early (mucosal or superficial submucosal) invasive carcinoma, en bloc resection should be performed using either EMR or ESD depending on the size of the lesion. The tissue processing should be the same as for other neoplastic lesions with orientation of the specimen and pinning of the specimen to assess the lateral and deep margins (Figure 1.14).

The final histological analysis allows for detailed staging, as well as matching the corresponding histological and endoscopic findings; note the lavender line overlays indicating sites of advanced neoplasia. The close collaboration between pathologists and endoscopists further improves the accuracy of each procedure (Figure 1.15).

Summary

The role of pathology in gastrointestinal endoscopy remains critical. Gastroenterologists should have a thorough knowledge of optimal methods of tissue removal and initial processing to allow optimal diagnosis and therapeutic results. Advances in endoscopic resection have allowed complete resection of many early cancers but require closer cooperation between the endoscopist and pathologist to ensure the tissue is properly handled and staged. With EUS-FNA, the direct interaction of pathologist with rapid on-site cytological evaluation has led to higher accuracy, and reduced the need for repeat procedures. Finally, advances in imaging will continue to improve the targeting of tissue sampling and reduce the need for low-yield random sampling methods.

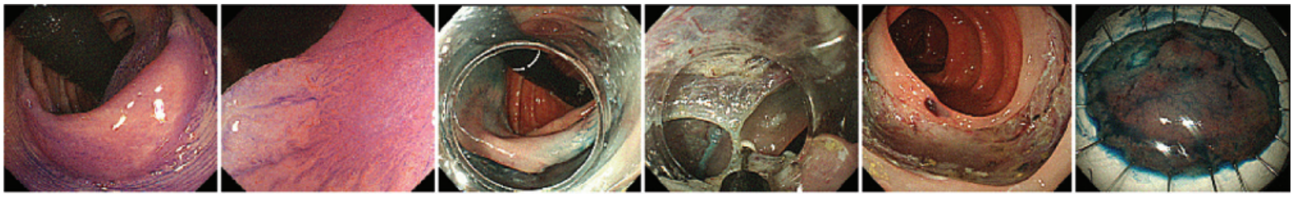


Figure 1.14 Endoscopic submucosal dissection (ESD) procedure. A flat neoplastic lesion is seen in panel 1–2 after staining with cresyl violet. The margins are incised (panel 3) with the endoscope retroflexed (black tube). The submucosal plane is dissected with a needle knife (panel 4). The final resection site (panel 5) and corresponding resection specimen prepared for pathology processing (panel 6).

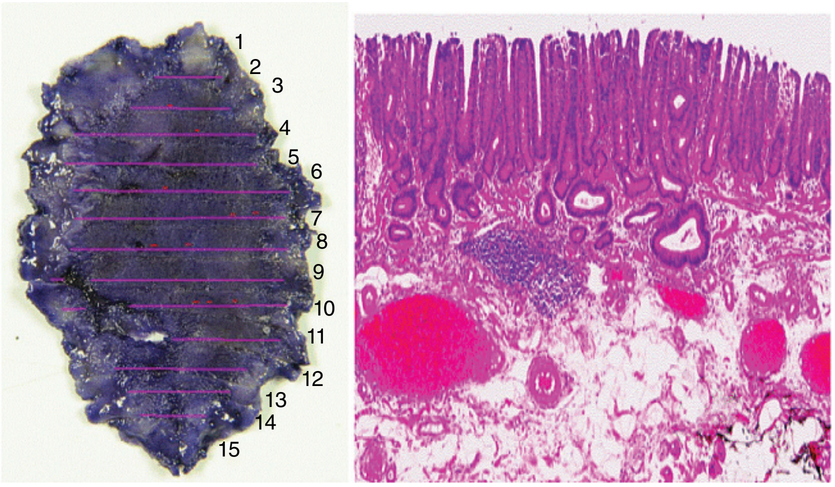
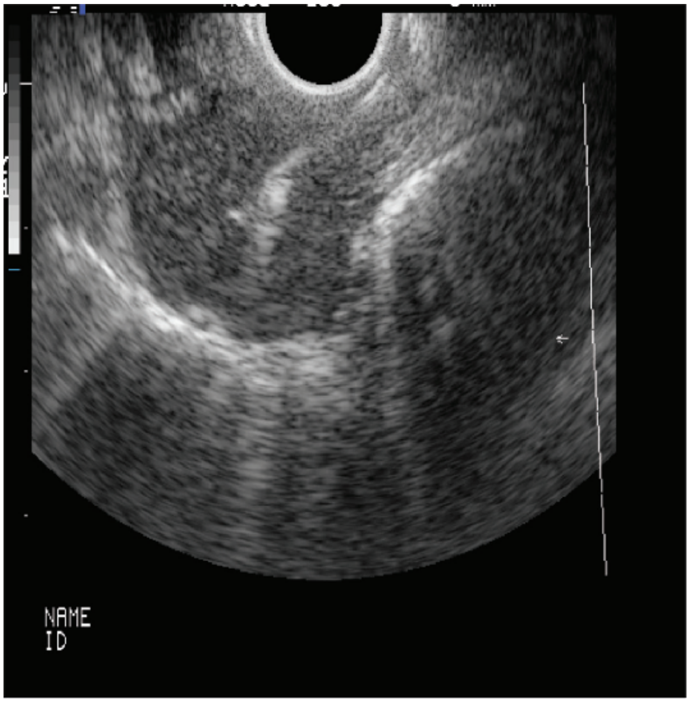


Figure 1.15 Endoscopically resected en bloc well-differentiated adenocarcinoma 28 × 17 mm with superficial submucosal invasion and no lymphovascular invasion and negative horizontal and vertical margins. This sample meets criteria for endoscopic curative resection.

Figure 1.16 Large mediastinal lymph node sampled with EUS-FNA. The needle is seen entering from the upper right of the screen into the tumor in the center of the image.



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