Gastrointestinal Specimens: General Comments

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1.1 Anatomy

The type of histopathology resection specimen received is dictated by the nature of any previous operations and the current disease process, its distribution, and degree of local spread within the organ and to adjacent structures. Resection surgery must provide adequate clearance of longitudinal and deep circumferential radial margins. It must also take into account the lymphovascular supply to achieve satisfactory anastomoses and the regional lymph node drainage for an adequate radical cancer operation. Site location within any given organ may influence the nature of the pathological abnormality and surgical procedure undertaken, e.g., anterior resection for high rectal cancer versus abdominoperineal resection for low rectal cancer, or mid-esophagus (squamous carcinoma) versus distal esophagus (adenocarcinoma). Multifocal distribution may be seen in both inflammatory (Crohn's disease) and neoplastic (malignant lymphoma) disorders. Inflammatory disease can be mucosa confined (ulcerative colitis), transmural (Crohn's disease), or mixed (ischemic colitis). Tumor growth may be predominantly polypoid and intraluminal, with only a minor mural component and variable presentation depending on the organ involved, e.g., symptomatic dysphagia due to esophageal polypoid carcinoma or asymptomatic iron-deficiency anemia with a cecal carcinoma. Often cancer ulcerates and deeply invades the wall, stenosing and obstructing the proximal bowel with early access to mesenteric nodes, lymphovascular channels, and peritoneum, and potential perforation. Alternatively the tumor may be characterized by an intact mucosa and incipient thickening of the wall with a tendency for longitudinal spread and skip lesions (diffuse gastric carcinoma – linitis plastica). Thus, normal anatomy is variably distorted by differing disease processes, and this must be considered in handling the specimen to obtain appropriate management and prognostic data, e.g., depth of local tumor spread, peritoneal and regional lymph node involvement, and excision margin clearance. Allowance must also be made for variation in normal anatomy between and within individuals. For example, harvest of lymph nodes from the mesorectum is scanty compared to the sigmoid mesocolon, and in some patients

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few mesorectal nodes will be found. This is also made more difficult by preoperative radiotherapy, emphasizing the importance of taking into account the previous treatment history and request form information. The surgical histopathology specimen also acts as an audit tool for surgical practice and expertise, e.g., rates of anterior resection versus abdominoperineal resection or completeness of mesorectal excision in rectal cancers. Similarly it allows close correlation with preoperative clinical and radiological (e.g., MRI) assessment, and is a gauge of thoroughness of pathological examination. Thus, preoperative and operative techniques alter the specimen anatomy, resulting in differing management and prognostic implications for an equivalent degree of tumor spread in similar specimens from different patients.

1.2 Clinical Presentation and Investigations

Site-specific symptomatology and investigations are alluded to in the relevant chapters, but some general features can be noted. Clinical presentation can be nonspecific, such as weight loss or anemia, or focused on either the upper (nausea, vomiting, hematemesis) or lower (abdominal pain, bleeding per rectum, change in bowel habit) gastrointestinal tract. An iron-deficiency anemia as measured by the hemoglobin level, red blood cell indices, and serum iron/ferritin levels often means occult blood loss from ingestion of NSAIDs or from the surface of an ulcer or polypoid lesion. Serum albumin levels are decreased due to reduced food intake, protein-losing enteropathy, or liver disease. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are increased in neoplasia, vasculitis, and acute flare-up of chronic inflammatory bowel disease. Peripheral white blood cell counts and body temperature are often elevated in acute infection or neoplasia, e.g., leukemia. Features of malabsorption can be due to either small intestinal or pancreatic disease. Liver function (LFTs) and coagulation tests are altered in hepatic and biliary disease.

Various general radiological investigations are also helpful in diagnosing gastrointestinal disorders:

- CXR (chest X-ray) – to detect metastatic deposits in the lung fields or any enlargement of the lung hilum, heart, or aorta that might compress the esophagus; also to show air under the diaphragm following perforated duodenal ulcer
- AXR (straight erect abdominal X-ray) – to demonstrate calcification in pancreatitis or bowel loops distended by fluid levels due to intestinal obstruction
- ELUS (endoluminal ultrasound) and MRI (magnetic resonance imaging) scans – to gauge the depth of spread of a tumor through the gastrointestinal wall into adjacent structures, assess locoregional lymph node enlargement, and soft tissue margin status
- CT (computerized coaxial tomography) scan chest/abdomen/pelvis – to gauge the extent of local and metastatic tumor spread
- PET (positron emission tomography) scan – to help detect metabolically active distant metastases in tumor staging and to distinguish local tumor recurrence from post-radiotherapy fibrosis
- USS (ultrasound scan) abdomen/pelvis – to detect gallstones; biliary tract dilatation; cysts in the liver, pancreas, appendix, or retrorectal space; and mixed solid/cystic abdominopelvic tumors
- Radioisotope scan – to detect metastatic disease in gastrointestinal endocrine tumor (octreotide scan).

Serological markers of use in diagnosing and also detecting recurrence of gastrointestinal cancer are CA19-9 (pancreatic carcinoma), alpha-fetoprotein (AFP – hepatocellular carcinoma), and carcinoembryonic antigen (CEA – metastatic colorectal carcinoma), although sensitivities and specificities are limited.

Diagnostic laparoscopy allows inspection and biopsy of the peritoneal cavity in various disorders, e.g., tuberculous peritonitis, or, more usually, staging of tumor spread from a gastric carcinoma – a finding that would contraindicate primary surgical resection of the stomach.

The mainstay of investigation is gastrointestinal endoscopy and biopsy.

1.3 Biopsy Specimens

1.3.1 Flexible Endoscopy

Gastrointestinal mucosal biopsy specimens are obtained by flexible endoscopy due to its ease of operation and relative lack of complications. Flexible endoscopes are complex pieces of equipment consisting of a flexible shaft with a maneuverable tip and a control head which the operator holds. The control head is connected to a fiber-optic light source. Other channels such as air, water, suction, etc. pass through the light source. A channel for the passage of therapeutic or diagnostic instruments is located in the control head. The picture from the tip is transmitted to a television screen. Modern endoscopes also incorporate sophisticated magnification capacity to allow close inspection of the topography of mucosal surfaces and lesions.

Upper endoscopy involves informed consent, fasting for 6 h, intravenous sedation, and passage of the endoscope via a mouth guard with direct inspection of the esophagus, stomach, and duodenum, which can be biopsied in relevant areas. Measurements are printed on the shaft of the endoscope so that the operator knows the position of the tip relative to the incisor teeth. Lower endoscopy requires adequate bowel preparation to remove fecal debris and careful insufflation of air via the endoscope to dilate the bowel and allow navigation of the various contours. Due to the fragility of the tissues in some conditions, e.g., toxic megacolon or ischemic colitis endoscopy may be contraindicated to avoid perforation.

1.3.2 Specimen Collection

A copy of the digital endoscopy report is a great aid to the reporting pathologist, and can easily be modified to function as the histopathology request form, maximizing the clinical information provided and removing the issue of illegibility.

In diagnostic endoscopy, tissue biopsies will usually be taken sometimes supplemented by cytology specimens, and there are various accessories designed for this function.

- Forceps: These consist of a pair of sharpened cups attached by a metal cable to a control handle. The forceps are passed down the channel within the endoscope. The cups are opened and closed by an assistant pulling and pushing the plastic handle. The site for biopsy is approached perpendicularly and firm pressure applied while the cups are closed. In the esophagus the approach is tangential and so forceps with a central spike can be used to prevent them from "sliding" off the tissue to be biopsied. At least six tissue samples should be taken from a lesion. Biopsies of ulcers should include samples from the four quadrants and the base, although basal specimens may only yield necrotic slough. If malignancy is suspected, it is prudent to take several specimens from the same place as this allows the outer necrotic layer to be penetrated. With polypoid lesions the crown and base of the polyp as well as the adjacent flat mucosa should be adequately sampled. In some conditions such as Barrett's metaplasia or chronic ulcerative colitis, segments of mucosa are sequentially sampled and mapped by multiple serial biopsies to detect precancerous epithelial dysplasia. Site distribution of lesions is also helpful in differential diagnosis, e.g., ulcerative colitis versus Crohn's disease. The biopsy forceps are withdrawn through the endoscope each time and the tissue sample removed from them by an assistant. A final larger biopsy can be taken if the tissue sample is held in the cups of the forceps while the endoscope is removed.

  The tissue sample is then either put directly into fixative, or after placement onto an orientation millipore (cellulose) filter or polycarbonate strip, preferably mucosal surface upward to avoid flattening the glandular or villous architecture.
- Cytology brushings: Small-spiralled brushes on a metal cable can be used for surface cytology of a lesion. The brush is retracted into a covering plastic sleeve, which protects the

specimen during withdrawal. It is then either promptly made into direct smears or cut off and placed in a suitable transport medium for laboratory processing.

- Fine-needle aspiration cytology (FNAC): FNAC can sample submucosal, mural, and extrinsic lesions not accessible to mucosal biopsy. The syringe needle contents are gently expelled into suitable transport medium, promptly transported to the laboratory, and cytocentrifuged onto glass slides for staining and interpretation.

Mucosal biopsies are generally 2–4 mm diameter and 1 mm deep, but this varies with patient anatomy, the success of the endoscopy procedure, and the nature and configuration of the lesion. Biopsy site and technique also influence specimen size. For example, pinch biopsies obtained via the colonoscope are smaller than rectosigmoidoscopy samples using grasp or jumbo forceps or a strip technique where glucose solution or saline is injected submucosally. A wider diameter biopsy channel can accommodate jumbo forceps or a suction capsule, the latter being of use where mucosal orientation (reflux esophagitis) or deeper tissues (submucosa for the assessment of Hirschsprung's disease) are required.

Mucosal polyps vary in size and appearance. For example, in the colorectum, metaplastic polyps are often 1–2 mm diameter, while adenomas can be similar but are not infrequently larger (1–2 cm), with a distinct head and stalk or even sessile. Small polyps may be removed in toto by usual biopsy forceps, or monopolar hot biopsy forceps, which results in variable diathermy distortion of the mucosal detail. Stalked adenomas are suitable for total excision by an electrosurgical snare. This is facilitated by elevation of the mucosa after submucosal injection of adrenaline, glucose, or saline – a technique that is also used for local endoscopic mucosal resection (EMR) of sessile lesions.

Needle biopsy cores of liver and pancreas are obtained endoscopically, percutaneously, or at operation transabdominally by a variety of needles of differing lengths and caliber. They can be spring-loaded or manually operated with the cutting edge of the needle delivering a core of tissue into its lumen. The needle is then retracted and withdrawn with careful removal of its contents and placement into formalin fixative. The procedure may be done blind, under X-ray control, or at operation direct vision, depending on the individual case. A 16G needle provides a much more substantial specimen than an 18G needle and is especially recommended for "medical" liver biopsies, i.e., evaluation of diffuse liver disease processes. The larger needle is, however, associated with a slightly greater risk of bleeding. Regardless of needle size, the patient should have an adequate coagulation status confirmed beforehand and, during the procedure, vascular structures avoided to minimize any risk of bleeding. Endoscopic, percutaneous, or transabdominal FNAC can traverse abdominal viscera with no detrimental effect to sample abdominal and retroperitoneal masses not accessible to usual endoscopic procedures.

1.3.3 Specimen Handling

Fragments, *non-orientated*:

- Usually multiple fragments, free floating in fixative, non-orientated.
- Count.
- Place in cassette between foam insert pads or loosely wrap in moist filter paper.
- Insert levels label.
- Align in the block at the embedding stage as this facilitates microscopic assessment and fragments are not missed.
- Separate specimens: use separate cassettes and site identification labels appropriate to the request form information. Alternatively multiwall cassettes may be submitted by the endoscopist.
- Cut through multiple levels.

Fragments, *orientated*:

- This allows better assessment of mucosal architecture and site distribution of lesions, e.g., colonic strip biopsy in chronic inflammatory bowel disease.
- Filter paper: count the fragments and note any that have detached. Process intact between foam insert pads or covered by moist filter paper to preserve orientation for embedding and cutting through multiple levels.
- Polycarbonate strip (Fig. 1.1): the endoscopist allows a 2–4 min period of air drying prior to

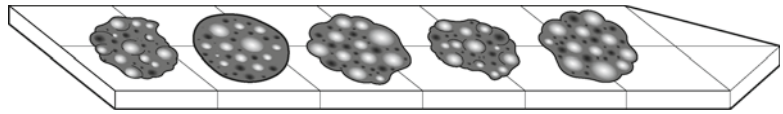

Fig. 1.1 Colonoscopic biopsies mounted on a polycarbonate or Millipore strip (Reproduced, with permission, from Allen and Cameron (2004))

formalin fixation, ensuring adherence of the mucosal fragments to the strip, which is designated according to a pre-agreed protocol, e.g., the cut pointed end is distal or anorectal. Strict alignment of the fragments on the strip by the clinician is essential as it is embedded intact and on its edge for cutting to allow representation of all the fragments at the same level in the block. Count the fragments and cut through multiple levels.

Polyps (Fig. 1.2):

- Non-orientated fragments: these are handled as indicated above.
- Snare specimens:
  ≤0.5 cm diameter – bisect vertically down through the stalk/base and embed both cut surfaces face down. Cut through multiple levels.
  >0.5 cm diameter – obtain a central, vertical mid-slice (3 mm thick) down through and to include an intact stalk/base. Embed face down in the block and the lateral trimmings in a separate block. Cut both through multiple levels. If there is a long stalk, precluding submission of a central mid-slice in one block, an initial transverse section of its resection margin may be taken.
- Local mucosal resection: endoscopic or transabdominal; this is used for stalked polyps (see above) or sessile lesions. Ideally the latter should be submitted by the surgeon to the laboratory already carefully pinned out onto a corkboard or piece of card. Remove after fixation and paint the deep and lateral mucosal resection margins. Obtain multiple vertical transverse serial slices (3 mm thick) to include the lesion and underlying base. Where the lesion edge is to within 3 mm of the mucosal margin sample at right angles to it from a 10 mm slice. Embed the slices face down in the block and cut through multiple levels.

Wedge biopsy:

- Usually derived from the edge of a perforated ulcer detected at surgical laparotomy for an acute abdomen. Its base is oversewn and a biopsy taken if the edges show any unusual features, e.g., rolled margins.
- With the mucosal surface upward, bisect or cut into multiple vertical serial slices. Embed the slices face down and cut through multiple levels.

Needle core biopsy:

- Up to 2 cm long and 1–2 mm diameter, core size is influenced by the patient's anatomy, the nature of the lesion being biopsied, the needle that is used, the route of acquisition (e.g., percutaneous or transjugular), and operator expertise. Some scirrhous carcinomas can be difficult to sample, whereas other disease processes lead to fragmentation of the core, e.g., cirrhosis of the liver. Skinny needle cores can be particularly fine, requiring careful handling and even painting or immersion in dye (e.g., alcian blue) prior to embedding so that the tissue can be seen when the block is faced at cutting.
- Count and measure the maximum core length (mm).
- Place intact in cassette between foam insert pads or loosely wrap in moist filter paper.
- Cut through multiple levels.

Fresh tissue:

- The vast majority of specimens are submitted in formalin fixative, but some cases require fresh tissue for frozen sections, e.g., acetylcholinesterase staining in Hirschsprung's disease, or an inflammatory versus malignant lesion at diagnostic laparotomy.

1.4 Resection Specimens

1.4.1 Fixation

- Ideally specimens are submitted fresh to the laboratory to facilitate sampling for research or biobanking and accurate measurement, as

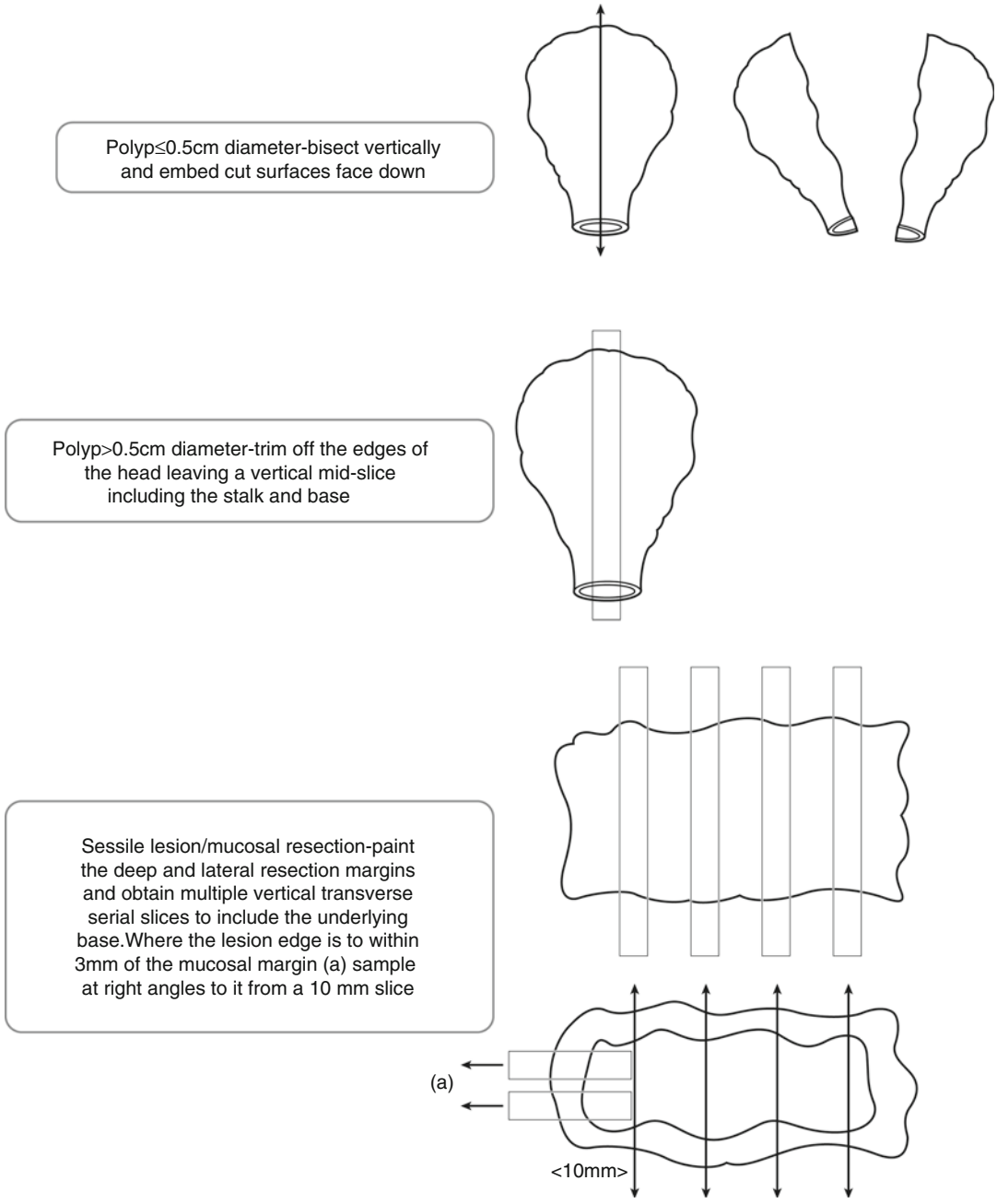

Fig. 1.2 Gastrointestinal mucosal polyps and local mucosal resections (Reproduced, with permission, from Allen and Cameron (2004))

fixation results in considerable shrinkage (15–30% on average) and discrepancy between clinical and pathological dimensions, e.g., longitudinal margins of tumor clearance. Fresh submission also permits cleaning out of the specimen and either partial or total opening for pinning out and fixation. This avoids specimen distortion and ultimately allows dissection appropriate to the specimen and tumor type, e.g., the assessment of circumfer-

ential resection margins. Adequate fixation of a cleaned, opened specimen requires 36–48 h immersion in formalin. Where it is normal practice to submit resection specimens to the laboratory already in fixative, the theater staff should be instructed on how to partially open and clean out the specimen but to avoid transecting the tumor segment, thereby compromising margin assessment.

1.4.2 Margins

Longitudinal, circumferential, and anatomical margins are considered.

- Longitudinal margins: circumferential, transverse sections are taken in non-neoplastic disorders such as ischemia or chronic inflammatory bowel disease to assess involvement. In cancer resections, separate anastomotic rings are often submitted and these constitute the longitudinal margins rather than those of the main specimen. In the absence of an anastomotic ring, the longitudinal margin should be circumferentially sampled although if the tumor is close (≤0.5–1 cm) to it a longitudinal block may be more practicable. The significance of longitudinal margin clearance varies, e.g., a macrosopic tumor clearance of 2–3 cm in an anterior resection for rectal cancer is considered satisfactory, whereas it is not for diffuse gastric or esophageal cancers where multifocal epithelial and discontinuous submucosal or mural skip lesions can occur. Longitudinal margins should be blocked first prior to dissection of the tumor to avoid knife carry-in of tumor fragments.
- Circumferential radial margin (CRM): this gives an assessment of the extent of lateral or radial spread of a tumor and its adequacy of excision, features that are strongly related to subsequent local recurrence and morbidity. Prior to dissection, the CRM should be painted and both macroscopic and microscopic measurements of tumor clearance are then made. In the mesorectum, direct tumor spread or tumor within a lymph node or lymphatic to within ≤1 mm of the CRM is considered involved. CRM involvement may indicate the need for postoperative radiotherapy. The amount and completeness of excision of circumferential tissues depend on the anatomical site and expertise of the surgeon. For example, adventitial tissues in an esophagectomy specimen may be scanty, whereas the posterior and lateral mesorectum is usually 2–3 cm deep. The success of total mesorectal excision (TME) relates to surgical training and the available time resources to carry out an adequate procedure, but TME grading by the pathologist is an important part of auditing surgical practice. The significance of tumor at the mesocolic edge or that of the gastric lesser omentum is less established but should be reported by the pathologist.
- Anatomical margins: The serosa or peritoneum is a visceral margin and breech of it allows tumor to access the abdominal and pelvic cavities with potential for transcelomic spread, e.g., diffuse gastric cancer with bilateral ovarian metastases (Krukenberg tumors). Thus, gastrointestinal cancers may present clinically with deposits at another abdominopelvic site and this should be borne in mind on assessment of tumor macroscopic and microscopic appearances. Tumor at and ulcerating the serosa represents pT4 disease and is a decision factor in selection for postoperative chemotherapy. It should be distinguished from the more common finding of carcinoma in a subserosal inflammatory fibrous reaction but not at its free surface (pT3).

1.4.3 Dissection

1.4.3.1 Cancer Resections

For optimal demonstration of the deepest point of tumor spread, its relationship to the CRM and correlation with ELUS/CT cross-sectional imaging multiple, serial, 3–4 mm thick slices of the cancer in the transverse axis are recommended. The slices can then be laid out in sequence and a digital photographic record taken. Generally four or five blocks of the tumor and wall are selected

to adequately define the pT stage. Some pathologists leave the tumor segment unopened during fixation and transverse slicing to keep the CRM intact – others open it carefully avoiding suspect areas of the CRM to ensure adequate tumor fixation and ascertain tumor measurements. Either approach is justifiable as long as it is done with care and consistency. Sometimes the local anatomy or proximity of the tumor to a longitudinal margin necessitates dissection in the longitudinal plane. Such a block can be useful in a poorly differentiated carcinoma when the adjacent mucosa may show a point of origin or clue as to its histological type. Mucosal blocks away from the tumor may also demonstrate its histogenesis, e.g., metaplasia/dysplasia/cancer sequence in the stomach, or, multifocality. Multiple colonic cancers are blocked and reported individually. A clear block index within the pathology report facilitates case review, e.g., for multidisciplinary team meeting discussion, and tumor block selection for future immunohistochemical or molecular assays.

All regional lymph nodes should be sampled as size alone is not a reliable indicator of metastatic involvement and pN staging relates to total and involved numbers of nodes. Small nodes seen histologically in the tumor blocks are also counted and may only measure ≥1 mm diameter but are recognizable by their subcapsular sinus. A limit node is identified adjacent to a mesenteric pedicle suture tie – some specimens, e.g., transverse colon, may have more than one. Dukes staging for colorectal cancer varies according to whether the limit node is involved (C2) or not (C1). Techniques such as xylene clearance have been advocated to increase nodal yields, but, in general, there is no substitute for experienced, careful dissection. The TNM (tumor-node-metastasis) system recommends what is considered an appropriate regional lymphadenectomy for each type of cancer resection. Regular departmental audit of median lymph node counts for relevant pathology specimen types ensures standards are met and maintained. Preoperative radio-/chemotherapy can lead to marked tumor degeneration and fibrotic reaction compromising nodal yields and identification of residual primary tumor or nodal deposits. Most general laboratories submit small nodes (<5 mm) intact, trimmed, or bisected, and a mid-slice of larger ones. It is important that the same node is not counted twice. Alternatively nodes are serially sliced at 2–3 mm intervals and submitted in their entirety in individual cassettes.

1.4.3.2 Non-neoplastic Resections

An important descriptive feature in differential diagnosis is disease distribution, e.g., diffuse, segmental, mucosal, or transmural. Overt lesions may show only end-stage, nonspecific florid ulceration and reactive changes – the disease distribution and changes in the intervening mucosa give important diagnostic clues. For example, ulcerative colitis is mucosal and diffuse; Crohn's disease is segmental and transmural, with intervening aphthous ulcers and serosal fat wrapping; chronic ischemic stricture is preferentially located at the splenic flexure; and clostridium difficle infection shows mucosal pseudomembranes. Non-neoplastic colonic specimens therefore require sequential labeled blocks of abnormal and normal (e.g., every 10 cm) areas, with a clear block index in the report to aid case review. As the mucosa is arranged in transverse folds, long axis blocks are taken. Longitudinal limits are transverse sectioned to look for disease involvement and although mesenteric nodes are usually reactive only, they may show helpful diagnostic pointers such as granulomas in Crohn's disease. In ischemic conditions, mesenteric vessels are also sampled for signs of vasculitis or embolic thrombi. Some vascular anomalies, e.g., angiodysplasia of the colon, may require close liaison with the surgical and radiological teams necessitating preoperative injection of radio-opaque contrast medium. In some cases, e.g., gastric resections, it is not possible to tell macroscopically if the ulcer, adjacent mucosa, or regional nodes are benign or malignant or to gauge the extent of mural spread – dissection and block selection must be sufficiently comprehensive to allow for this.

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