Guidance on the effective use of upper gastrointestinal histopathology

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ABSTRACT

Given the ever-increasing demand for upper gastrointestinal endoscopy, for diagnosis and surveillance, there is a need to consider when it is appropriate, and when it is not appropriate, to take an endoscopic biopsy for histological evaluation. In this article, we consider this in relation to each of the anatomical compartments encountered during oesophagogastroduodenoscopy, and in relation to the common clinical scenarios and endoscopic abnormalities encountered. There are clear indications to biopsy suspicious ulceration or mass lesions and for investigation of some inflammatory conditions, such as eosinophilic oesophagitis and coeliac disease. Increasing guidance is available on optimal biopsy sites and biopsy numbers to maximise yield from histology. Outside these areas, the endoscopist should consider whether biopsy of normal or abnormal appearing mucosa is likely to contribute to patient management, to ensure effective use of limited healthcare resources.

INTRODUCTION

Upper gastrointestinal endoscopy is usually performed to investigate symptoms such as weight loss, haematemesis and/or melaena, dyspepsia, heartburn, dysphagia or abdominal pain, or in the workup of patients with anaemia. It may also be performed in asymptomatic patients as surveillance for neoplasia, for example, in Barrett's oesophagus (columnar-lined oesophagus (CLO)) or to corroborate a diagnosis histologically, for example of coeliac disease. This article will concentrate on the role of the diagnostic pinch biopsy.

Polyps, ulcers or areas of mucosal irregularity should always be biopsied if there is any suspicion of a neoplastic process. In the setting of ulceration, intact mucosa at the ulcer edge should generally be targeted. Biopsies taken only from the centre of an ulcer, benign or

malignant, are likely to yield non-diagnostic ulcer slough or granulation tissue. An exception to this is if cytomegalovirus infection is suspected, in which case diagnostic viral inclusions may be best detected by examination of material from the ulcer bed. In contrast, the histological diagnosis of herpes simplex virus infection, most commonly encountered endoscopically in the oesophagus, requires evaluation of intact mucosa to demonstrate the characteristic viral inclusions.

Mesenchymal masses, such as gastrointestinal stromal tumour and leiomyoma, are usually submucosal or intramural, and will not be sampled by endoscopic biopsy, unless ulcerating the mucosal surface. If a submucosal (or deeper) lesion is suspected, this should be indicated clearly on the histology request form, so the pathologist is alerted to examine mesenchymal tissue at the deeper aspects of the biopsy material.

The most appropriate biopsy site therefore depends on the clinical scenario and the endoscopic appearances. Some diseases may be patchy, endoscopically and histologically, and some may show no endoscopic abnormality. The oesophagus, stomach and duodenum will be discussed individually with respect to indications for endoscopic biopsy.

OESOPHAGUS

Heterotopic columnar mucosa

Heterotopic columnar mucosa (HCM, 'inlet patch') is often seen high in the cervical oesophagus, more frequently on withdrawal than insertion of the endoscope. This is a congenital abnormality. It is present in 0.2–5% of cases when looked for.^{1–3} Less than 30 cases of adenocarcinoma arising in HCM have been reported worldwide.^{4–5} In view of

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the rarity of malignant transformation, biopsy or surveillance of simple HCM with no nodules or other worrying features is not indicated.

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) is extremely common and reflux oesophagitis is evident in 20% of individuals in Western populations undergoing oesophagogastroduodenoscopy for reflux symptoms. There is poor correlation between endoscopic and histological assessment of severity. Endoscopic biopsy is not indicated unless there is clinical suspicion of another underlying cause of ulceration, such as infection, especially in the immunosuppressed setting, neoplasia or drugs (so-called 'pill oesophagitis'), or if there is clinical suspicion of CLO.⁶

Gastro-oesophageal junction

Routine biopsies from an oedematous or inflamed oesophagogastric junction are not indicated, if there is no endoscopic suspicion of CLO. This is a common endoscopic scenario which frequently generates biopsies unnecessarily. If pathology demonstrates intestinal metaplasia in this context, most likely arising in the cardia or so-called 'ultrashort segment Barrett's oesophagus', the significance of this finding is unknown and consequently the impact on clinical management unclear. Therefore, oesophagogastric junction biopsies should be avoided unless there is endoscopic evidence of CLO or another significant endoscopic abnormality.^{7 8}

Barrett's oesophagus

The most common indication for oesophageal biopsy is in the diagnosis and follow-up of patients with CLO. As some aspects of CLO surveillance remain contentious, a decision on surveillance should be made after patient discussion in a 'shared decision making' process, with subsequent documentation of the agreed surveillance protocol and adherence to this. Recent British Society of Gastroenterology (BSG) guidelines on CLO include a comprehensive discussion of initial and surveillance biopsy protocols.⁹ The key recommendations are summarised here.

Barrett's oesophagus is defined as endoscopically visible and histologically confirmed replacement of the normal distal oesophageal squamous mucosa by metaplastic columnar epithelium, with the proximal limit of the longitudinal gastric folds on minimal air insufflation deemed the preferred landmark to delineate the gastro-oesophageal junction.^{10 11} The Prague criteria are recommended for documenting extent of CLO.¹² The appropriateness and frequency of endoscopic surveillance should take into consideration patient choice and risk factors for neoplastic progression, including the presence of intestinal metaplasia and the length of the Barrett's segment. Quadrantic biopsies at 2 cm intervals, in addition to sampling

(and labelling separately) any visible lesions, are recommended (the so-called Seattle protocol).¹³ Adherence to such a protocol enhances detection of early lesions while failure to do so results in a lower rate of detection of dysplasia.^{14 15} Advanced imaging modalities, such as chromoendoscopy or 'virtual chromoendoscopy', are not yet recommended as an aid to targeting areas of potential dysplasia.⁹

Patients with short segments of CLO (<3 cm) and without intestinal metaplasia, are likely to have a low risk of progression to cancer.^{16–19} For such patients, a repeat endoscopy with quadrantic biopsies is recommended. If repeat endoscopy confirms the absence of intestinal metaplasia, consideration should be given to discharge from surveillance as the risks for endoscopy likely outweigh the benefits. This new recommendation would significantly reduce demand for endoscopic surveillance if adopted.

Brush cytology has been employed for surveillance of CLO.²⁰ It has the ability to sample a greater mucosal area than endoscopic biopsy but has a low sensitivity for the detection of low grade dysplasia. Ancillary studies such as fluorescent in situ hybridisation have been employed to help increase sensitivity, but brush cytology remains largely a research tool in CLO.^{21 22}

In the setting of CLO, a diagnosis of dysplasia (all grades) or indefinite for dysplasia should be confirmed by a second gastrointestinal pathologist and the reason for use of the indefinite category indicated within the report to guide management. For example, if the indefinite categorisation is due to glandular atypia associated with heavy inflammation, repeat endoscopy in 6 months after maximal acid suppression therapy may be appropriate. If the pathology report indicates that it is due to poor orientation of one or more fragments making assessment of maturation impossible, earlier repeat endoscopy may be preferable.

Endoscopic therapy is preferred over oesophagectomy for high grade dysplasia and early cancer, with treatment options discussed at a suitable specialist multidisciplinary team meeting. In-depth discussion of these issues is beyond the remit of this article. It is important however that any patient with a confirmed diagnosis of dysplasia of any grade has a careful follow-up endoscopy with thorough sampling of the entire Barrett's segment and attention paid to any areas of mucosal irregularity, with additional sampling from such areas and appropriate specimen labelling to allow histological distinction between dysplasia localised to a potentially endoscopically resectable lesion and a more diffuse neoplastic process requiring a different management approach.

Eosinophilic oesophagitis

This clinicopathological entity was first described in 1978 but interest in the condition has only developed

significantly in the last decade.^{23–24} A Swedish study of 1000 asymptomatic individuals has indicated that the incidence of eosinophilic oesophagitis may be as high as 1% of the population, which would potentially represent a significant health burden for a relapsing disease without a cure.²⁵ A diagnosis of eosinophilic oesophagitis requires correlation between clinical symptoms, endoscopic appearances and histology. Adults typically describe dysphagia or food bolus impaction, the latter reportedly associated with eosinophilic oesophagitis in more than 50% of individuals, including those presenting acutely.^{26–27}

A range of characteristic endoscopic abnormalities have been described in eosinophilic oesophagitis, including linear furrowing, rings (so-called ‘feline oesophagus’), strictures, mucosal friability, ‘crêpe paper’ mucosa and white exudates (figure 1).^{28–30} Although none are pathognomonic, these appearances should alert the endoscopist to the diagnostic possibility. More importantly, endoscopy may show no abnormality, as reported in large series of adult and paediatric patients.^{31–32}

Mucosal biopsies are therefore always indicated when a diagnosis of eosinophilic oesophagitis is considered clinically, even in the presence of a normal

endoscopy. This is particularly important in all patients presenting with dysphagia.^{33–34} The histological appearances are characterised by marked basal layer hyperplasia and mucosal eosinophilia, often with superficial accentuation of the infiltrating eosinophils and sometimes eosinophilic microabscesses and degranulation (figure 1). The microscopic features may be patchy and discontinuous and wide ranges of eosinophil numbers per high-power field have been reported.³⁵ There is no standardised biopsy protocol for mucosal sampling in suspected eosinophilic oesophagitis and most reports do not specify the high-power field area used.³⁶ One study of adult patients reported a sensitivity of 100% when five mucosal samples were taken, using a cut-off of 15 eosinophils per high-power field.³⁵ A further study demonstrated 97% and 100% sensitivity when three and six biopsies were taken, respectively.³⁷ It is important to note that oesophageal eosinophils are commonly encountered in other conditions, including GORD, Crohn’s disease, drug-associated oesophagitis and eosinophilic gastroenteritis. Typical cases of eosinophilic oesophagitis have eosinophil numbers vastly in excess of 15 per high-power field, as well as other characteristic histological features, notably basal layer hyperplasia, so a diagnostic cut-off for eosinophil count is not considered a major issue in routine practice, especially as the diagnosis always requires clinicopathological correlation. As GORD changes are typically confined to, or most pronounced, within distal oesophageal mucosa, it is diagnostically helpful to compare the appearances from proximal and distal oesophagus. We therefore recommend that at least three biopsies should be taken from proximal and distal oesophagus and the two sites identified separately to the pathologist.

STOMACH

Ulcer or malignancy

Any suspicious mass, ulcer or mucosal irregularity should be extensively sampled to evaluate for neoplasia (figure 2). The diffuse (signet ring or poorly cohesive) type of gastric adenocarcinoma may present without any mucosal abnormality and cause great diagnostic difficulty. Poor gastric distension on insufflation, in addition to systemic features of malignancy, may be the only diagnostic clues. This finding alone should trigger a careful search for minor mucosal changes and multiple biopsies. Poor gastric preparation for endoscopy may also hinder detection of a subtle mucosal abnormality.

Underestimation of the significance of a lesion is a recognised risk of forceps biopsy, in comparison with the more substantial specimen provided by endoscopic resection.^{38–39} Another issue is the possibility of multiple deep forceps biopsies creating submucosal fibrosis, potentially creating a false non-lifting signing if subsequently endoscopic mucosal resection is being

Figure 1 Endoscopy (upper) of eosinophilic oesophagitis showing oesophageal ridging and furrows. Corresponding histology (lower) shows basal layer hyperplasia and infiltrates of eosinophils throughout all layers of the squamous mucosa (inset, high power).

Figure 2 Endoscopy (upper) of a gastric ulcer in the upper body. Histology (lower) shows inflamed and ulcerated gastric mucosa, with a discohesive population of malignant cells lying within ulcer slough (inset, high power), indicating diffuse type adenocarcinoma manifesting as a malignant ulcer.

considered.³⁸ This problem has also been reported in the colon.⁴⁰ Despite these potential problems, on balance, when a gastric ulcer or suspected malignancy is noted, it is recommended that at least eight biopsies should be taken to minimise the risk of a false negative diagnosis on the basis of undersampling.⁴¹ Gastric ulcers require endoscopic follow-up with repeat biopsy until healing is confirmed, to avoid missing malignancy, a well recognised problem with upper gastrointestinal endoscopy, mainly related to missed gastric cancer.^{42–43}

Gastric polyps

The management of gastric polyps has been the subject of recent BSG guidelines.⁴⁴ These recommend sampling of all gastric polyps detected at endoscopy with additional sampling of intervening non-polypoid mucosa except those clinically suspected to be fundic gland polyps (figure 3), which are by far the most common gastric polyps encountered currently, other types being collectively rare by comparison. If the endoscopist is confident that all polyps evident are typical fundic gland polyps, biopsy confirmation is not necessary. It is recommended that gastric polyps >1 cm in diameter, those <1 cm with biopsy proven dysplasia and those causing symptoms, should be removed completely. However, whether to monitor and biopsy or completely remove hyperplastic polyps is contentious, balancing the risks of developing

Figure 3 Endoscopy (upper) of multiple fundic gland polyps involving the gastric body. Histology (lower) shows characteristic cystic dilatation of specialised fundic glands.

neoplasia versus those of the polypectomy procedure, and practice varies widely. In the setting of multiple, small (<1 cm) hyperplastic polyps, it is reasonable to biopsy and offer surveillance endoscopy, although American Society for Gastrointestinal Endoscopy guidelines suggest multiple non-adenomatous polyps do not require surveillance if adequate sampling is done at initial endoscopy.⁴⁵ If histology of a polyp reveals an adenoma, complete endoscopic removal should be confirmed given the significant risk of progression to cancer, and the adjacent and surrounding mucosa extensively sampled to look for background chronic atrophic gastritis, intestinal metaplasia and ‘flat’ dysplasia. Further surveillance in a year is indicated.

Guidelines on the management of neuroendocrine tumours (NETs), including those of the stomach, have also been published recently and endorsed by the BSG.⁴⁶ Briefly, gastric NETs now have a well established classification based on pathogenesis. Types I and II are associated with hypergastrinaemia, secondary to chronic atrophic gastritis in type I and primary in type II. Type III gastric NETs are sporadic and have normal serum gastrin levels. Types I and II essentially behave in a benign fashion and can be managed

conservatively.^{47 48} Type III gastric NETs are aggressive tumours which require surgical resection.^{49 50} Given differing management strategies, accurate classification of type is important. Background mucosal biopsies taken at initial endoscopy or follow-up and submitted separately to any polyps will be helpful to look for features of chronic atrophic gastritis, helping classify as above alongside serum gastrin levels.

Gastritis

The relevance of endoscopic gastritis and whether random biopsies of the normal stomach are justified are both controversial topics. Endoscopic appearances of gastritis do not correlate with symptoms.⁵¹ One study found equivalent rates of endoscopic gastritis and atrophic gastritis in healthy volunteers and patients with dyspepsia.⁵² Many publications recommend gastric biopsy to characterise gastritis and exclude precancerous conditions which cannot be distinguished endoscopically, with at least four biopsies covering proximal and distal stomach on greater and lesser curvatures.^{53 54} The justification is that a finding of extensive atrophy or intestinal metaplasia is a risk factor for gastric adenocarcinoma and could merit surveillance. However those authors acknowledge that the cost-effectiveness of this approach has not been demonstrated. By contrast, The Royal College of Pathologists document, 'Histopathology and cytopathology of limited or no clinical value', suggests that there is no support for biopsy of the normal stomach and that biopsy for histological categorisation of gastritis is unlikely to change management.⁸ That document emphasises the importance of agreeing a local policy. Our view is that in the absence of high-risk factors such as family history, it is not necessary to biopsy for histological assessment a stomach endoscopically showing no abnormality or only gastritis, as we can find no evidence that such biopsies influence management.

Helicobacter pylori

Helicobacter pylori status should be checked by urease test in the presence of visible gastroduodenal inflammation (and treated if present). A urease test is significantly cheaper than histological assessment and provides a result before the patient leaves the endoscopy unit. Non-invasive tests such as the urea breath test and faecal antigen sampling avoid the need for endoscopy solely to assess *H pylori* status. Resistant infection may require endoscopy and biopsy sent to microbiology for culture and sensitivities. For these reasons, gastric biopsy taken only to look for *H pylori* histologically is not recommended.

DUODENUM

By far the most common indication for duodenal biopsy is the investigation of possible coeliac disease. This diagnosis is typically considered in patients

undergoing investigation for weight loss, anaemia or diarrhoea. Investigation for coeliac disease may also be appropriate in high-risk groups, including patients with diabetes mellitus or a variety of other autoimmune diseases or in relatives of patients with coeliac disease. Often this is for histological confirmation of the diagnosis after positive coeliac serology. Serological investigations for coeliac disease, notably antiendomysial and antitissue transglutaminase antibodies, have high sensitivity and specificity for the diagnosis, but these are not 100%.⁵⁵ Sensitivity in particular is reduced with lesser degrees of villous atrophy and therefore negative serology does not exclude the diagnosis of coeliac disease.^{56 57} In the paediatric context, it has recently been recommended that duodenal biopsies are not needed to confirm coeliac disease if the following criteria are met: (1) patient is symptomatic (2) IgA-TG2 level exceeds 10× upper limit of normal, (3) antiendomysial antibodies are positive on a separately taken blood sample, and (4) HLA-DQ2 or HLA-DQ8 status is confirmed.⁵⁸

In the investigation of possible coeliac disease, two key questions are: how many duodenal biopsies to take and from where. Previous guidelines recommended taking biopsies "from D2 or beyond", as biopsies from the duodenal bulb (D1) may cause difficulty in interpretation for pathologists, resulting either from inflammatory changes associated with peptic duodenitis or from poorly formed villi mimicking villous atrophy. This can typically be seen overlying Brunner's glands, which are often prominent in the duodenal bulb. These issues are less problematic in more distal duodenal biopsies. However, it is well recognised that, although coeliac disease usually manifests as diffuse mucosal injury, it may be patchy in distribution (figure 4). Several studies have suggested

Figure 4 Duodenal biopsies labelled as 'D2' from a patient with newly diagnosed coeliac disease (positive anti-EMA and anti-TTG antibodies) demonstrating patchy mucosal change; villous atrophy, lamina propria inflammation and intraepithelial lymphocytosis was confined to a single fragment (left, lower).

Table 1 Summary of recommendations for taking biopsy during upper gastrointestinal endoscopy

	What to biopsy?	What not to biopsy?
Oesophagus	Any mucosal lesions suspicious of neoplasia Barrett's oesophagus (as per an agreed protocol) Normal or abnormal mucosa if clinical suspicion of eosinophilic oesophagitis	Uncomplicated reflux oesophagitis Inflamed oesophagogastric junction Heterotopic columnar mucosa (inlet patch)
Stomach	Any mucosal lesions suspicious of neoplasia Polyps unless endoscopically typical of fundic cyst polyp Background mucosa between biopsied polyps	Normal mucosa (without clinical suspicion of neoplasia) Typical fundic cyst polyps Uncomplicated gastritis (to define aetiology or look for <i>Helicobacter pylori</i>)
Duodenum	Any mucosal lesions suspicious of neoplasia Polyps Normal or abnormal mucosa if clinical suspicion of coeliac disease	Minor abnormalities of the duodenal cap

that the duodenal bulb may be the most reliable biopsy site for detection of patchy coeliac disease, being most consistently involved.^{59 60} Another recent study has furthermore suggested targeting the 9-o'clock or 12-o'clock position within the duodenal bulb on the basis of increased diagnostic yield, but this is difficult to explain on a biological basis.⁶¹ This finding in a small study sample may simply further reflect patchiness of disease.

Accepting there is some evidence for taking duodenal bulb biopsies for evaluation of possible coeliac disease, we don't consider this evidence is as yet sufficient to recommend this routinely. The recommendation therefore remains of taking four good-sized biopsies from D2 or beyond. If there is a high clinical suspicion of coeliac disease, such as abnormal coeliac serology, and initial D2 biopsies demonstrate normal histology, repeat endoscopy and biopsies to include the duodenal bulb should be considered. Importantly, if bulb biopsies are taken, they should be labelled as such and submitted in a different specimen container from more distal biopsies, to allow interpretation of the histology in context of the biopsy site. Orientation of the fragments at endoscopy is not necessary as this can be done at the embedding stage of pathology processing, if the fragments are large enough to reveal their mucosal aspect, and even random processing of multiple fragments usually yields sufficient orientation in at least some fragments for adequate evaluation of villous architecture.

Aside from investigation of possible coeliac disease, duodenal biopsies are usually taken to diagnose duodenal or periampullary polyps or other mass lesions, or to look for infections such as giardiasis, particularly but not exclusively in the setting of immunosuppression. Minor insignificant abnormalities of the duodenal cap are often observed, and these do not require biopsy if there is no suspicion of neoplasia.

CONCLUSIONS

Our recommendations on what to biopsy and what not to biopsy during upper gastrointestinal endoscopy are summarised in table 1. In brief, there are clear indications for endoscopic biopsy in evaluating mass lesions and investigating some inflammatory

conditions, such as eosinophilic oesophagitis and coeliac disease, with increasing guidance available on optimal sites and biopsy numbers to maximise yield from histology. Outside these indications, it is important to consider whether biopsy of normal appearing or inflamed mucosa is likely to contribute to patient management in upper gastrointestinal disease.

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Competing interests None.

Ethics approval This report includes only anonymised patient images for illustrative educational purposes, hence ethical approval was not required.

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