British Society of Gastroenterology, Association of Upper Gastrointestinal Surgery of Great Britain and Ireland and Royal College of Pathologists Delphi consensus guidance on biopsy sampling during upper gastrointestinal endoscopy in adult patients

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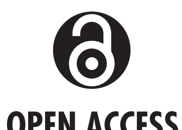

British Society of Gastroenterology, Association of Upper Gastrointestinal Surgery of Great Britain and Ireland and Royal College of Pathologists Delphi consensus guidance on biopsy sampling during upper gastrointestinal endoscopy in adult patients

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ABSTRACT

These guidance statements represent a practical approach to tissue sampling in the upper gastrointestinal tract during endoscopy in adult patients, outlining instances when biopsies should and should not be taken. Analysis of data from the UK National Endoscopy Database has shown wide variations in biopsy practice among endoscopists. Endoscopy providers with high rates of post-endoscopy upper gastrointestinal cancer take more inappropriate and less appropriate biopsies during endoscopy.

This guidance document was commissioned by the British Society of Gastroenterology (BSG) as part of its Upper Gastrointestinal Endoscopy Quality Improvement programme and developed in line with the BSG guidance methodology. A systematic literature review was performed to review the evidence base. However, due to the low quality of evidence in this area, application of GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was not possible and therefore Good Practice Statements, along with Expert Opinions, were used for recommendations.

In total, 32 statements or recommendations were initially created and voted on by members of the Guidance Development Group on a five-point scale (strongly agree to strongly disagree). Statements achieving over 80% agreement were adopted. Following voting, one statement did not achieve consensus and was removed, and one statement was amended. All statements achieved over 80% agreement following a second round of voting.

In formulating this guidance document, we hope that it will standardise biopsy practice for upper gastrointestinal endoscopy. Outlining when not to undertake tissue sampling will in turn reduce pressure on histopathology services, reduce costs in the National Health Service, and improve sustainability in endoscopy and pathology.

EXECUTIVE SUMMARY OF KEY RECOMMENDATIONS

When to biopsy

Statement 1. We recommend obtaining at least eight biopsies for diagnostic purposes in suspected advanced upper gastrointestinal cancer that is not suitable for endoscopic resection.

Statement 2. We recommend obtaining only one to two targeted biopsies from

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gastric and oesophageal neoplasia which could be endoscopically resectable.

Statement 3. We recommend that when linitis plastica is suspected, at least 10 bite-on-bite biopsies are taken from areas of mucosal abnormalities or poor distensibility of the stomach.

Statement 4. We recommend obtaining at least six biopsies if a new stricture is found in the oesophagus, stomach or duodenum.

Statement 5. We recommend obtaining six biopsies if feasible from oesophageal and gastric ulcers (mucosal breaks larger than 5 mm) including both the edge and base.

Statement 6. We recommend that when an oesophageal or gastric ulcer is not biopsied (eg, due to the risk of bleeding), an early repeat endoscopy is performed within 2 weeks.

Statement 7. We recommend obtaining targeted biopsies from reflux oesophagitis which is Los Angeles grade C or D or atypical in appearance, focusing on areas of mucosal abnormality.

Statement 8. We recommend that for Barrett's oesophagus (columnar mucosa ≥1 cm above the proximal margin of the gastric folds) without known dysplasia, targeted biopsies should be taken from visible abnormalities, followed by four quadrant biopsies every 2 cm within the Barrett's segment.

Statement 9. We recommend that all suspected gastric adenomas and hyperplastic polyps should be biopsied. The background mucosa should also be assessed and, if appropriate, biopsied to diagnose gastric atrophy or intestinal metaplasia through Sydney protocol biopsies.

Statement 10. We recommend obtaining five biopsies in total if gastric atrophy or intestinal metaplasia is suspected endoscopically as per the Sydney protocol, with two biopsies from the antrum, two from the corpus and one from the incisura.

Statement 11. We recommend that if a duodenal adenoma needs histological confirmation (eg, prior to resection), only one or two targeted biopsies are taken so as not to compromise subsequent endoscopic resection.

Statement 12. We recommend that where there is a suspicion of eosinophilic oesophagitis, at least six biopsies should be taken from at least two levels, targeting areas of mucosal abnormalities, and placed in two separate containers or separate compartments in a labelled cassette.

Statement 13. We recommend that in cases of suspected viral oesophagitis, at least six biopsies are taken from the ulcer edge and base if possible, depending on the size of the ulcer.

Statement 14. We recommend all patients with iron deficiency anaemia or weight loss undergoing upper gastrointestinal endoscopy should have tissue transglutaminase (tTG) testing and the results should be available prior to endoscopy. Patients with IgA tTG titres of≥10 times the upper limit of normal do not need duodenal biopsies for the confirmation of coeliac disease. If biopsies are needed due to, eg tTG antibody levels not meeting these diagnostic criteria, then two biopsies should be taken from the duodenal bulb and four from the second part of the duodenum and placed in two separate containers or separate compartments in a labelled cassette.

Statement 15. We recommend biopsy for microbial testing (eg, for Helicobacter culture and sensitivity) before any contact of the biopsy forceps with fixation fluid for other biopsies for histology.

Statement 16. We recommend that all detected lesions have photodocumentation prior to biopsy.

Statement 17. We recommend that all endoscopists follow-up histology results for their continuing professional development, particularly when there is endoscopic uncertainty over the diagnosis.

When not to biopsy

Statement 18. We do not recommend biopsies for common uncomplicated endoscopic conditions such as oesophagitis (Los Angeles grade A/B), 'gastritis' and 'duodenitis' (gastric or duodenal erythema).

Statement 19. We do not recommend biopsies of columnar-lined oesophagus<1 cm above the proximal margin of the gastric folds, in the absence of a visible mucosal abnormality within this area.

Statement 20. We do not recommend biopsies to confirm oesophageal candidiasis. Biopsies are only required for mycological analysis in treatment-resistant cases.

Statement 21. We do not recommend routine biopsy of fundic gland polyps unless located in the antrum, over 1 cm, ulcerated or atypical in appearance.

Statement 22. We do not recommend biopsy and histological analysis solely for testing of *Helicobacter pylori* status.

Statement 23. We do not recommend biopsies of gastric mucosa solely for iron deficiency anaemia.

Statement 24 We do not recommend biopsy of subepithelial lesions found during endoscopy.

Statement 25. We do not recommend biopsies of duodenal ulcers in the absence of features suggestive of malignancy.

Statement 26. We do not recommend biopsies that would not change the patient's management. This would usually include biopsies for premalignant conditions such as Barrett's oesophagus or gastric atrophy or intestinal metaplasia in frail or comorbid patients.

ENDOSCOPY UNIT RECOMMENDATIONS

Statement 27. We recommend that each endoscopy unit has a local standard operating procedure in place concerning the responsibility for histology results, particularly those that arise from straight-to-test endoscopy or endoscopy requests from outside the specialties of gastroenterology or upper gastrointestinal surgery.

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Statement 28. We recommend that in the absence of a local standard operating procedure for handling of histology results, the default responsibility should be with the endoscopist performing the biopsy.

Statement 29. We recommend that electronic histology result alert systems are available from histopathology to inform the upper gastrointestinal cancer multidisciplinary team directly of any histology with cancer or dysplasia.

Histology handling recommendations

Statement 30. We recommend that a biopsy of any focal abnormality that is potentially dysplastic or malignant is placed in a separate container or a separate compartment of a labelled cassette.

Statement 31. We suggest that Seattle protocol biopsies from different levels of Barrett's oesophagus are placed in different compartments of a labelled cassette to reduce environmental impact.

Miscellaneous recommendations

Statement 32. The biopsy guidance in this document is applicable to the smaller volume biopsy forceps used with a transnasal endoscope.

INTRODUCTION

Over 1 100 000 endoscopies occur annually in the UK, with 45% of diagnostic endoscopies involving a biopsy.[1 2] To date, there is no UK national guidance on tissue sampling during upper gastrointestinal endoscopy. Analysis of biopsy practice from the National Endoscopy Database has shown inconsistent biopsy practice for lesions that could represent cancer, such as gastric ulcers, with many endoscopists failing to obtain the recommended six biopsies to exclude malignancy.[2] Furthermore, preliminary results from the Post Endoscopy Upper Gastrointestinal Cancer (PEUGIC) Root Causes Analysis Project have shown that 29% of inadequate endoscopies identified during the root causes analysis had poor biopsy or lesion management, which contributed to the PEUGIC. Additionally, when cancer-associated lesions (eg, gastric ulcers or oesophageal strictures) were reviewed as part of the root cause analysis process, only 18% had the recommended six biopsies taken to effectively rule out cancer.[3] Endoscopy providers with the highest PEUGIC rate also had the poorest compliance with biopsy recommendations for cancer-associated lesions and were additionally found to take higher numbers of biopsies of low value.[4] There are currently a large number of biopsies of low value taken, amounting to 236 755 biopsies when the endoscopic diagnosis is either uncomplicated gastric or duodenal inflammatory conditions (erosive or non-erosive gastritis or duodenitis).[2]

It is vitally important that biopsy practice is improved across the UK, as there has been a 4.5% year-on-year increase in the quantity of histopathology requests, putting an already stretched histopathology service under greater pressure.[5] Additionally, there are significant economic and environmental costs associated with low value biopsies. Processing each biopsy pot generates 0.29 kg of CO_2, and at current calculations, 78 000 kg of additional CO_2 is produced each year from low-value biopsies in the UK and this amounts to £8 500 000 of additional cost to the National Health Service.[2 6–8]

This document, therefore, is aimed at all endoscopists performing upper gastrointestinal endoscopy in an effort to standardise biopsy practice during endoscopy to ensure sufficient biopsies are taken when needed, low value biopsies are avoided and to improve sustainability in endoscopy and pathology. This is the first national guidance on biopsy sampling during upper gastrointestinal endoscopy published for the UK.

METHODS

The British Society of Gastroenterology (BSG) and Royal College of Pathologists (RCPath) commissioned this guidance document as part of the BSG Upper Gastrointestinal (UGI) Endoscopy Quality Improvement Programme (EQIP). This consensus guidance document was developed in accordance with the BSG guidance methodology and was reported using the ACCORD (Accurate Consensus Reporting Document) checklist (online supplemental table 1.[9 10] This study involved a consensus development process and therefore prospective registration was not required.

Guidance development group

The BSG UGI EQIP held a workshop to develop interventions aimed at improving the quality of endoscopy in the UK in December 2023. The meeting included 28 delegates from England, Scotland, Northern Ireland and Wales; English regional endoscopy leads; training academy leads; and representatives of the BSG and the Joint Advisory Group (JAG) on gastrointestinal endoscopy. During the course of that meeting, a key area identified for improvement was biopsy practice and the need for a guidance document. Members from the EQIP workshop were invited to join the guidance development group (GDG), and additional stakeholders from pathology and upper gastrointestinal surgery were also invited to join the GDG, by the guidance chair. The GDG comprised gastroenterologists with representatives from the BSG and JAG, a representative from the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) and representatives from the RCPath. Due to the technical nature of the guidance, no patient representatives were involved in guidance development. All members completed conflict of interest forms and no conflicts of significance were reported.

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CONSENSUS METHODOLOGY

A modified Delphi process was followed as the consensus methodology for this document. The initial scope of the guidance document was outlined during the face-to-face BSG EQIP meeting held in December 2023 and agreed with all members of the GDG, prior to literature search and statement writing.

EVIDENCE AND LITERATURE SEARCH

Literature searches were performed to generate the evidence base for the guidance by two of the authors and a librarian. We searched for studies assessing the sensitivity and specificity of biopsy sampling for the diagnosis of lesions in the upper gastrointestinal tract in adult patients of at least 16 years of age. Additionally, we searched for studies demonstrating the value of biopsy of minor pathology encountered during endoscopy to assess whether such biopsies were of clinical value or not. We sought relevant published articles and abstracts by searching MEDLINE and EMBASE from inception using the OVID interface (the search strategy is outlined in online supplemental material) and manual searches of reference lists of biopsy guidelines from other endoscopy associations.[11] Language was restricted to articles in English. Searches were up to 16 September 2024.

ASSESSMENT OF EVIDENCE AND FORMULATION OF RECOMMENDATIONS

The development of this guidance followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE). However, following a review of the evidence base, the vast majority of studies on biopsy practice were assessed to be of low or very low quality using the GRADE methodology. Therefore, Good Practice Statements (GPS) were developed according to the following principles: (1) clear and actionable; (2) without guidance, clinicians fail to take appropriate action; (3) the net benefit is high with limited harm; (4) collecting and summarising the evidence is a poor use of the GDG's time and resources; and (5) there is a large amount of indirect evidence that supports the recommendations.[12–14]

Expert opinion statements were created for recommendations the GDG believed were important based on the members' clinical experience, but lacked an evidence base to use a GRADE process and did not meet the GPS criteria.[15]

STATEMENT DEVELOPMENT AND CONSENSUS VOTING

Preliminary statements were developed with supporting text by the first author and lead author using evidence synthesised from the literature search. The statements were then shared with all members of the GDG online, with adaptation of the statements and addition of new statements following feedback from the GDG. Once finalised, statements including supporting text were uploaded onto an online voting platform. GDG members were invited to vote on the statements using a five-point scale ranging from strongly agree to strongly disagree (second round). Statements achieving over 80% agreement (either strongly agree or agree) achieved consensus and were adopted. Statements that failed to achieve consensus were modified or removed, and revised statements underwent further voting rounds (third round) until consensus was reached. Additionally, voters were able to provide written feedback on statements to inform revisions. Responses were collected anonymously by a member of the BSG administrative team for quantitative and qualitative analysis of responses. The guidance document was reviewed by the BSG endoscopy section, who advised an additional statement on subepithelial lesions (voted on in a further round), AUGIS, the RCPath Cellular Pathology Specialty Advisory Committee and BSG Clinical Services and Standards Committee.

DISSEMINATION AND IMPLEMENTATION OF THE GUIDANCE

This guidance document serves as a practical tool to aid endoscopists performing tissue sampling during diagnostic endoscopy in adults. Dissemination will be via a peer-reviewed journal and through presentations at national conferences, as well as incorporation into relevant endoscopy training courses.

We anticipate that the guidance will need review and updating in 5 years.

RESULTS

Following three rounds of voting, consensus was achieved on 32 statements. Figure 1 outlines the guidance development process and Figure 2 summarises the recommendations in this guidance document. One statement relating to coeliac disease was removed and merged with another statement to form a comprehensive statement on coeliac disease.

RECOMMEND BIOPSY

Statement 1. We recommend obtaining at least eight biopsies for diagnostic purposes in suspected advanced upper gastrointestinal cancer that is not suitable for endoscopic resection. *Good Practice Statement. Level of agreement: 93%*

Any cancer that is likely to not be amenable to endoscopic resection should have a standardised assessment involving a description of the site, size, Paris classification (0–III) and photodocumentation, including images with virtual chromoendoscopy prior to biopsy. The most suspicious area of the tumour should be targeted for biopsies (depressed, demarcated, loss of or irregular pits, loss of or irregular vessel patterns). Previous studies examined the number of biopsies required to provide a high sensitivity for cancer detection

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Face to face meeting (round one)
- Scope of the guidance outlined

Literature search
- Literature search performed and evidence base for biopsy practice assessed

Second round
- GDG voted 32 statements (September 2024)
- Consensus achieved on 31/32 statements

Third round
- 1 statement removed and 1 modified (October 2024)
- New statement voted on and achieved consensus

External review
- 31 statements finalised: 17 related to when to biopsy; 8 when not to biopsy; 3 endoscopy unit recommendations; 3 on biopsy handling and 1 miscellaneous recommendation

Fourth round
- 1 new statement created following external review (January 2025)
- New statement voted on and achieved consensus

Guidance finalised
- 32 statements finalised: 17 related to when to biopsy; 9 when not to biopsy; 3 endoscopy unit recommendations; 3 on biopsy handling and 1 miscellaneous recommendation

GDG Guidance development group

Figure 1 Guidance development process.

and suggested at least six biopsies are required, but this is no longer sufficient.[16–18] To allow the molecular testing required to inform oncological treatment decisions, such as human epidermal growth factor receptor 2 status, at least eight biopsies are required.[19] Biopsies from other sites should not be taken with the biopsy forceps used to biopsy a malignant lesion, due to the theoretical risk of disseminating cancer. Biopsy channel contamination by cancer cells and tumour shedding cancer cells is also possible; so all other therapies, instrumentation and biopsies should be avoided. Although there is limited evidence in the upper gastrointestinal tract, a study on seeding risk during colonoscopy has suggested a risk of 0.3–0.6% and demonstrated the plausibility of seeding cancer by repeated use of biopsy forceps.[20]

Statement 2. We recommend obtaining only one to two targeted biopsies from gastric and oesophageal neoplasia which could be endoscopically resectable. *Good Practice Statement. Level of agreement: 85%*

Suspected dysplasia or early cancers that are potentially endoscopically resectable should have a standardised assessment involving a description of the site, size, Paris classification (0–I or 0–II) and photodocumentation, including images with virtual chromoendoscopy. In order to reduce the risk of submucosal fibrosis, which may impair endoscopic resection, we recommend a maximum of two biopsies from such lesions, targeting areas of highest suspicion.[11 21]

Statement 3. We recommend that when linitis plastica is suspected, at least 10 bite-on-bite biopsies are taken from areas of mucosal abnormalities or poor distensibility of the stomach. *Good Practice Statement. Level of agreement: 85%.*

Linitis plastica is notoriously difficult to diagnose, and a biopsy approach similar to that for advanced cancers is likely to result in false negative biopsies. This is because linitis plastica infiltrates the submucosal layer, and as a result, superficial mucosal biopsies may not detect the cancer. To reduce this risk, 10 bite-on-bite biopsies (each biopsy is directly on top of the previous one, also termed 'tunnelled biopsy') are recommended from five sites of mucosal abnormality to allow sampling of the submucosal layer during the index endoscopy and prevent a delay in diagnosis. Due to the diffuse nature of the disease and in some cases absence of mucosal abnormalities, biopsies should also focus on areas of poor distensibility of the gastric lumen.[22 23] Endoscopic ultrasound-guided biopsy is the preferred approach to diagnosing linitis plastica and should always be considered if the tunnelled biopsy method does not confirm cancer.[24–27] Additionally, endoscopic mucosal resection or endoscopic submucosal dissection assisted biopsy has been shown to be a useful alternative approach

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Consensus guidance on biopsy sampling during upper gastrointestinal endoscopy in adults

BSG BRITISH SOCIETY OF GASTROENTEROLOGY
The Royal College of Pathologists — Pathology: the science behind the cure
AUGIS — ASSOCIATION OF UPPER GASTROINTESTINAL SURGERY OF GREAT BRITAIN AND IRELAND

General Recommendations

- We do not recommend biopsies that would not change the patient's management.
- All detected lesions have photodocumentation prior to biopsy.
- All endoscopists follow-up histology results when uncertainty over the diagnosis.

	Biopsy recommended and number	Biopsy NOT recommended
Suspected Upper GI cancer	Advanced upper gastrointestinal cancer ≥ 8 Endoscopically resectable neoplasia ≤2 Linitis plastica ≥10 bite on bite	
Upper GI ulcer	Oesophageal and gastric ulcers ≥6 - including both edge and base If an ulcer not biopsied repeat endoscopy within 2 weeks.	Duodenal ulcers in absence of features suggestive malignancy
Upper GI stricture	New stricture ≥6 - Sample proximal, stenosis and distal margins	
Oesophagitis	Reflux LA grade C or D — Targeted biopsy - sample mucosal abnormality (if present) Eosinophilic oesophagitis ≥6 - sample two levels Viral oesophagitis ≥6	Reflux oesophagitis (LA grade A/B) Oesophageal candidiasis: Biopsies only required for mycological analysis in treatment resistance
Barrett's oesophagus	Targeted biopsies from visible abnormalities + four quadrant biopsies every 2 cm Biopsies from different levels should be placed in different compartments of labelled cassette.	Columnar-lined oesophagus <1 cm above proximal margin gastric folds in absence of visible mucosal abnormality.
Gastric polyps & premalignant stomach	Adenomas and hyperplastic polyps — Targeted biopsy + assess for Gastric atrophy or intestinal metaplasia 2 corpus + 2 antrum + 1 incisura	Fundic gland polyps: unless antral, greater than 1 cm, ulcerated, or atypical appearance Subepithelial lesions
Gastritis & Helicobacter pylori	Biopsy for microbial testing if indicated - Sample before biopsy forceps contact histology fixation fluid.	"Gastritis" or "duodenitis" or testing H. pylori status. Gastric biopsy in iron deficiency anaemia without mucosal abnormality
Coeliac disease	1. *Refractory iron deficiency anaemia* with no other cause, irrespective tTG level 2. *Weight loss + symptom suggestive of malabsorption* with no other cause, irrespective tTG level 3. *Positive tTG but less than x10 ULN* ≥2 Duodenal Bulb + ≥4 D2	Patients with IgA tTG ≥10×ULN Patients with weight loss or anaemia should have tTG testing prior to endoscopy to avoid biopsies if possible
Duodenal adenoma	Duodenal adenoma suspected ≤2 - Only if optical diagnosis not possible	

Figure 2 Summary illustration of the guidance recommendations. GI, gastrointestinal; LA, Los Angeles; ULN, upper limit of normal.

in rare patients where both tunnelled biopsy and endoscopic ultrasound are unsuccessful.[28 29]

Statement 4. We recommend obtaining at least six biopsies if a new stricture is found in the oesophagus, stomach or duodenum. *Good Practice Statement. Level of agreement: 100%.*

If a stricture is found on endoscopy, it requires an adequate assessment to exclude cancer so that

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appropriate therapy can be considered. Biopsies should be taken from the proximal margin, inside the stenosis, and the distal margin if possible, to maximise sensitivity for detecting cancer. If the stricture is not passable with a normal endoscope and the distal margin is not accessible, the stricture should be assessed and the distal area sampled with an ultra-slim endoscope if possible.[30] Additionally, when strictures are benign in appearance (simple strictures that are uniform in shape without mucosal abnormality), biopsies for eosinophilic oesophagitis should be considered (see Statement 12), in particular when they are refractory to dilation.

Statement 5. We recommend obtaining six biopsies if feasible from oesophageal and gastric ulcers (mucosal breaks larger than 5 mm) including both the edge and base. *Good Practice Statement. Level of agreement: 93%*

If an ulcer is found on endoscopy, it requires an adequate assessment to exclude cancer so that an appropriate management plan can be created. Only ulcers in the oesophagus and stomach usually need to be biopsied, as the risk of duodenal ulcers harbouring cancer is extremely low.[31] Irregular areas, if present in the ulcer edge, should have targeted biopsies. Additionally, biopsies of the ulcer base are recommended if the base is irregular or partially healed, as this has been shown to increase the pick-up rate of cancer.[32 33] It is also important to note that the malignant potential of an ulcer is greater the more proximal it is in the stomach. This recommendation is dependent on the size of the ulcer; however, cancers are usually associated with larger solitary ulcers.[34] If an ulcer appears malignant, then at least eight biopsies are required. Oesophageal ulceration in the context of severe oesophagitis should be managed as outlined in Statement 7.

Statement 6. We recommend that when an ulcer is not biopsied (eg, due to the risk of bleeding), an early repeat endoscopy is performed within 2 weeks. *Good Practice Statement. Level of agreement: 93%.*

If it is not possible to biopsy oesophageal or gastric ulcers due to the risk of bleeding or the need for therapy, we recommend an early repeat endoscopy within 2 weeks to prevent delays in cancer diagnosis if the ulcer is malignant. Analysis of biopsy practice using the National Endoscopy Database shows that biopsy of oesophageal or gastric ulcers is less likely to occur during inpatient endoscopy OR 0.66 (95% CI 0.55 to 0.79) or therapeutic endoscopy OR 0.37 (95% CI 0.36 to 0.39).[2] In such circumstances where cancer has not been excluded, an up to 12-week delay in repeat endoscopy is not appropriate. If, at follow-up, an ulcer scar is present, we recommend that it should be biopsied, as raised scars are often difficult to distinguish from early gastric cancer.[32] If the ulcer is still present and confirmed to be benign on biopsy, recommendations on ulcer follow-up within 12 weeks to ensure healing should be followed.[35] These recommendations should be considered depending on the frailty and comorbidity of the patient.

Statement 7. We recommend obtaining targeted biopsies from reflux oesophagitis which is Los Angeles grade C or D or atypical in appearance, focusing on areas of mucosal abnormality. *Good Practice Statement. Level of agreement: 93%*

If severe reflux oesophagitis (Los Angeles grade C or D) is diagnosed, we recommend biopsies to rule out complications of gastro-oesophageal reflux disease including malignancy, which is present in approximately 2% of severe oesophagitis.[35–38] Particular attention should be focused above the gastro-oesophageal junction at the 12–3 o'clock positions, as this is the area where Barrett's neoplasia is most frequently encountered.[39] Additionally, areas of nodularity or contact bleeding should be biopsied, as these are associated with dysplasia and cancer.[39] There is no evidence on the appropriate number of biopsies for severe reflux oesophagitis and furthermore the number of biopsies possible will be dependent on the size of the area effected. In the absence of mucosal abnormality, we recommend biopsies should be taken of mucosal breaks just above the gastro-oesophageal junction. Patients should undergo repeat endoscopy in 6 weeks if clinically appropriate in line with the BSG quality standards in upper gastrointestinal endoscopy, as on repeat endoscopy in 13% a new pathology, most commonly Barrett's oesophagus or oesophageal stricture, is found.[35 38]

Statement 8. We recommend that for Barrett's oesophagus (columnar mucosa $\geq$1 cm above the proximal margin of the gastric folds) without known dysplasia, targeted biopsies should be taken from visible abnormalities, followed by four quadrant biopsies every 2 cm within the Barrett's segment. *Good Practice Statement. Level of agreement: 100%.*

Please refer to the BSG guidelines on the diagnosis and management of Barrett's oesophagus for supportive evidence for this recommendation.[40] We recommend targeted biopsies should be taken from distal lesions first and then proximal lesions, followed by Seattle protocol biopsies working distally to proximally.

Available: https://www.bsg.org.uk/clinical-resource/bsg-guidelines-barretts-oesophagus

Or via QR code

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It is important to note that the whole of the Barrett's segment should be examined on white light and image enhancement prior to biopsy so as to improve the accuracy of targeted biopsies and increase pickup of dysplasia.[41] Additionally, we advocate the use of the 'turn-and-suction' method for obtaining larger and more accurate biopsy samples. This biopsy technique involves positioning the open forceps against the endoscope tip, torquing the scope to engage the target mucosa, applying suction to draw tissue into the forceps and then closing the forceps to obtain the sample.[42] If it is not possible to perform all biopsies at the endoscopy that diagnoses Barrett's oesophagus, an early repeat procedure should be performed (within 6 months, provided there is no visible lesion in the Barrett's segment or dysplasia on biopsy).[40]

Statement 9. We recommend that all suspected gastric adenomas and hyperplastic polyps should be biopsied. The background mucosa should also be assessed and, if appropriate, biopsied to diagnose gastric atrophy or intestinal metaplasia through Sydney protocol biopsies. *Good Practice Statement. Level of agreement: 85%.*

Please refer to the BSG guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma for supportive evidence for this recommendation.[43]

Available: https://www.bsg.org.uk/clinical-resource/diagnosis-and-management-of-gastric-adenocarcinoma

Or via QR code

If it is not possible to perform all biopsies at the index endoscopy, an early repeat procedure should be considered (within 6 months, provided there is no visible lesion or dysplasia on initial biopsy).[43]

Statement 10. We recommend obtaining five biopsies in total if gastric atrophy or intestinal metaplasia is suspected endoscopically as per the Sydney protocol, with two biopsies from the antrum, two from the corpus and one from the incisura. *Good Practice Statement. Level of agreement: 93%.*

Please refer to the BSG guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma for supportive evidence for this recommendation.[43] We recommend that biopsies should target areas of atrophy or intestinal metaplasia and that two biopsies from the antrum and one from the incisura are placed in one container or compartment in a labelled cassette, with the remaining two body biopsies placed in a separate container or compartment.[43] Image enhancement tools, for example, narrow band imaging, can help target areas of atrophy or intestinal metaplasia for biopsy.

Statement 11. We recommend that if a duodenal adenoma needs histological confirmation (prior to resection), then only one or two targeted biopsies are taken so as not to compromise subsequent endoscopic resection. *Good Practice Statement. Level of agreement: 85%.*

All duodenal adenomas should be considered, if appropriate for the patient, for endoscopic resection due to the risk of malignant transformation. So as not to cause submucosal fibrosis and impair endoscopic resection, we recommend a maximum of two biopsies from suspected adenomas if histological confirmation or exclusion of cancer is required. The biopsies should target nodular areas rather than flat areas. It is important to note, however, that the sensitivity of biopsies for confirming duodenal adenomas is low at 37.5% (95% CI 18.8% to 59.4%).[44,45] If there is a high confidence optical diagnosis of a duodenal adenoma, then patients can be referred directly for endoscopic mucosal resection with appropriate images without biopsy. Endoscopists should be familiar with the normal location and appearance of the ampulla. If there is uncertainty over whether the lesion is an ampullary adenoma or a prominent ampulla, we advise adequate photodocumentation, use of image enhancement and discussion with an endoscopist that performs duodenal adenoma resection initially, as biopsy of the ampulla is associated with a small risk of pancreatitis.[46]

Statement 12. We recommend that, where there is a suspicion of eosinophilic oesophagitis, at least six biopsies should be taken from at least two levels, targeting areas of mucosal abnormalities, and placed in two separate containers or separate compartments in a labelled cassette. *Good Practice Statement. Level of agreement: 93%.*

Please refer to the BSG and the British Society of Paediatric Gastroenterology, Hepatology and Nutrition guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults for supportive evidence for this recommendation.[47]

Available: https://www.bsg.org.uk/clinical-resource/consensus-guidelines-on-eosinophilic-oesophagitis

Or via QR code

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Statement 13. We recommend that in cases of suspected viral oesophagitis, at least six biopsies are taken from the ulcer edge and base if possible, depending on the size of the ulcer. *Good Practice Statement. Level of agreement: 93%.*

Viral oesophageal ulcers are most commonly caused by Herpes simplex virus (HSV1 or 2) or Cytomegalovirus (CMV) in immunocompromised or elderly patients. Ulcers may have associated vesicles, or 'volcano-shaped' mucosal structures. Biopsies from the edge and base allow for differentiation between HSV, which is found at the ulcer edge, and CMV, which is usually found in the base of ulcers.[48 49] The request to histology must clearly state that a viral infection is suspected, so that additional immunohistochemical testing can be done.

Statement 14. We recommend all patients with iron deficiency anaemia or weight loss undergoing upper gastrointestinal endoscopy should have tissue transglutaminase (tTG) testing and the results should be available prior to endoscopy. Patients with IgA tTG titres of≥10 times the upper limit of normal do not need duodenal biopsies for the confirmation of coeliac disease. If biopsies are needed due to, eg tTG antibody levels being elevated but not meeting these diagnostic criteria, then two biopsies should be taken from the duodenal bulb and four from the second part of the duodenum and placed in the different containers or separate compartments of a labelled cassette. *Good Practice Statement. Level of agreement: 93%.*

IgA tTG titres of≥10× the upper limit of normal (ULN) are highly indicative of a diagnosis of coeliac disease. In those patients who meet this criteria, we do not recommend biopsy for confirmation of coeliac disease, as the positive predictive value of a high titre is 98%.[50] In those with iron deficiency anaemia, the prevalence of seronegative coeliac disease is extremely low (less than 0.005%).[51] Endoscopy providers should be aware that there is significant variability in the results of tTG assays commercially available and used across the National Health Service.[52 53]

If the endoscopist has a high clinical suspicion of coeliac disease or the tTG is elevated but<10×ULN, then biopsies should be taken from the duodenal bulb so as not to miss ultra-short coeliac disease, as well as the second part of the duodenum.[54 55] The use of water immersion, narrow band imaging and magnification can help identify villous atrophy in patients with possible coeliac disease.[56 57] There is evidence of better biopsy orientation with performing single bite biopsies in the diagnosis of coeliac disease, so where possible, single bite biopsies are recommended.[58]

Analysis of data from the National Endoscopy Database has shown that 499 278 biopsies from 27.4% of patients undergoing diagnostic upper gastrointestinal endoscopy were taken from the duodenum with likely low clinical value and high environmental impact.[2] Endoscopy services should ensure coeliac serology is tested prior to endoscopy in all patients who are referred for endoscopy for weight loss or iron deficiency anaemia, given the high negative predictive value, cost saving and environmental benefit. tTG serology costs £16.81 versus endoscopy and biopsy which costs £780 to diagnose coeliac disease.[59]

Biopsies for coeliac disease should also be considered in the following scenarios:

1. Clinical suspicion of coeliac disease but tTG antibody not checked prior to endoscopy, to avoid patient repeating the endoscopy if the tTG is later found to be positive but<10×ULN
2. Treatment refractory iron deficiency anaemia when no other cause is found, irrespective of tTG level.[51]
3. Weight loss+additional symptoms suggestive of malabsorption, irrespective of tTG level[60–63]

Statement 15. We recommend biopsy for microbial testing (eg, for Helicobacter culture and sensitivity) before any contact of the biopsy forceps with fixation fluid for other biopsies for histology. *Good Practice Statement. Level of agreement: 93%*

Where a biopsy for culture and sensitivity is required in the case of treatment-resistant *H. pylori* infection or tuberculosis culture and sensitivity, such samples should be placed in a universal container containing sterile water so that culture and sensitivity testing are possible. Contact with fixation fluid causes the destruction of bacteria, which will prevent accurate culture and sensitivity testing.[64 65]

Statement 16. We recommend that all detected lesions have photodocumentation prior to biopsy. *Expert Opinion. Level of agreement: 100%*

In order to allow for appropriate management of histology results, which may be acted on by clinicians other than the endoscopist, adequate photodocumentation of lesions biopsied is recommended with white light and, if possible, with electronic image enhancement. The endoscopist should ensure adequate mucosal cleansing prior to photodocumentation so that the lesion can be appropriately characterised. If photodocumentation is not available, a thorough lesion description should be documented in the report using recognised nomenclature, and the report should state that image capture was not available.

Statement 17. We recommend that all endoscopists follow-up histology results for their continuing

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professional development, particularly when there is endoscopic uncertainty over the diagnosis. *Expert Opinion. Level of agreement: 100%*

Follow-up of histology results is a critical component of reflective practice and continuous professional development for endoscopists. This practice fosters improved lesion recognition, informs future biopsy decisions and contributes to the refinement of endoscopic judgement. While not mandated in all settings, embedding histology follow-up into routine practice aligns with the principles of lifelong learning and clinical governance.

DO NOT RECOMMEND BIOPSY

Statement 18. We do not recommend biopsies for common uncomplicated endoscopic conditions such as oesophagitis (Los Angeles grade A/B), 'gastritis' and 'duodenitis' (gastric or duodenal erythema). *Good Practice Statement. Level of agreement: 100%*

The pick-up rate for any significant pathology following a biopsy for simple inflammatory conditions is extremely low and causes a significant environmental impact and burden on pathology services. For oesophagitis that is Los Angeles grade A or B, a biopsy is not required for the confirmation of gastro-oesophageal reflux disease, and the prevalence of Barrett's oesophagus in this group is low.[66] In the stomach, biopsies for simple endoscopic gastritis or 'red stomach' are unlikely to provide any clinically useful information.[67 68] Instead, we recommend endoscopists are trained to recognise the endoscopic features of gastric atrophy and intestinal metaplasia and to take biopsies under these circumstances, when there will be clinical benefit for the patient (see Statement 10). The preliminary findings from the PROSPERO study reported that endoscopists failed to recognise 75% of cases of chronic atrophic gastritis or gastric intestinal metaplasia and there is clearly opportunity for improvement among endoscopists. [69] The biggest area for potential improvement in reducing biopsies taken is for endoscopic duodenitis, as again, there is little clinically useful information to be gained from biopsies of redness of the duodenum.[67]

Statement 19. We do not recommend biopsies of columnar-lined oesophagus<1 cm above the proximal margin of the gastric folds in the absence of a visible mucosal abnormality within this area. *Good Practice Statement. Level of agreement: 93%.*

If the columnar epithelium is<1 cm above the proximal margin of the gastric folds, biopsies are not required in the absence of a focal mucosal abnormality that may represent dysplasia or early cancer. Such areas of columnar epithelium are not an uncommon finding during endoscopy and do not require biopsy or follow-up, as the risk of dysplasia or malignancy in this group is similar to the background population.

Statement 20. We do not recommend biopsies to confirm oesophageal candidiasis. Biopsies are only required for mycological analysis in treatment-resistant cases. *Good Practice Statement. Level of agreement: 85%*

Oesophageal candidiasis can be diagnosed optically by the presence of white or yellowish plaques on the oesophageal mucosa with exudates that are easily removable with washing. The presence of such lesions has a high positive predictive value for confirmation of oesophageal candidiasis, and with variable sensitivity from biopsy and histological assessment, biopsy to confirm this diagnosis is not recommended.[70 71] In those patients who have not responded to treatment, mycological biopsies may be required to confirm sensitivity to anti-fungal treatment. Samples sent for sensitivity analysis should be sent in sterile water in a universal container, free from contact with histology fixation fluid.

Statement 21. We do not recommend biopsy of fundic gland polyps unless located in the antrum, over 1 cm, ulcerated or atypical in appearance. *Good Practice Statement. Level of agreement: 93%.*

The diagnosis of fundic gland polyps can usually be made endoscopically, and the need for a biopsy is rare. Fundic gland polyps are the most commonly encountered polyp and are associated with chronic proton pump inhibitor usage. Excluding patients with a polyposis syndrome, the prevalence of dysplasia and malignancy is very low. Characteristically, fundic gland polyps are less than 1 cm and located in the body of the stomach. They are pale with a glossy, translucent appearance. If, however, the polyp is found in the antrum, this is an atypical location for a fundic gland polyp and possibly more suggestive of an adenoma, and such lesions should be biopsied.[43] Additional atypical features include size over 1 cm, irregular surface, depressions and redness or erosions.[72]

Statement 22. We do not recommend biopsy and histological analysis solely for testing of *H. pylori* status. *Good Practice Statement. Level of agreement: 100%*

This mode of testing carries the highest carbon footprint and cost and is not justifiable when the sensitivity and specificity of alternative tests are high, such as rapid urease testing, stool antigen testing or urea breath testing.[6] In order to improve the sensitivity and specificity of rapid urease testing, a biopsy should be taken from the antrum and the corpus.[73 74] Endoscopists should be aware of the significant false negative rates of rapid urease and histology testing (and stool antigen or urea breath testing) when patients are taking proton pump inhibitors and such investigations are not reliable, if the patient has not stopped these medications for at least 2 weeks.[75]

Statement 23. We do not recommend biopsies of gastric mucosa solely for iron deficiency anaemia. *Good Practice Statement. Level of agreement: 100%*

This pick-up of any significant pathology from a biopsy of normal appearing gastric mucosa is very low.

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Iron deficiency anaemia can be associated with chronic atrophic gastritis because of the loss of acid production, which leads to decreased iron absorption. Endoscopists should make an optical diagnosis of chronic atrophic gastritis or gastric intestinal metaplasia and only then perform Sydney protocol biopsies.[76] In unexplained iron deficiency anaemia, *H. pylori* testing should be offered in line with international consensus guidelines, but this can be undertaken through rapid urease testing in the absence of proton pump inhibitors or later non-invasively through, for example, stool antigen testing.[77]

Statement 24. We do not recommend biopsy of subepithelial lesions found during endoscopy. *Good Practice Statement. Level of agreement: 100%.*

Subepithelial lesions are found in approximately 1 out of every 300 upper gastrointestinal endoscopies, with the majority being found in the stomach.[78–80] They are characterised by a protrusion of a mass into the gastrointestinal lumen with overlying normal mucosa. Subepithelial lesions comprise a heterogenous group of lesions from those with no malignant potential, such as lipomas, varices and ectopic pancreas, and those with malignant potential such as gastrointestinal stromal tumours.[81] There is no evidence that such lesions can be correctly characterised by standard white light or image enhanced endoscopy alone.[82] Studies examining tunnelled biopsies have shown that the diagnostic yield is lower compared with endoscopic ultrasound and fine needle biopsy.[83] Furthermore, use of tunnelled biopsy for the diagnosis of gastrointestinal stromal tumours is associated with unacceptably high levels of bleeding requiring haemostatic therapy in one in three cases[83,84] and may have serious consequences for the patient if a varix is biopsied. If a subepithelial lesion is found at endoscopy, the first investigation should be cross-sectional imaging, followed by endoscopic ultrasound if needed and appropriate to the patient.

Statement 25. We do not recommend biopsies of duodenal ulcers in the absence of features suggestive of malignancy. *Good Practice Statement. Level of agreement: 100%*

The incidence of duodenal cancer is extremely low, with the majority of duodenal ulcers being peptic in origin. In a case series of 16 000 patients with duodenal ulcers, the risk of malignancy was 0.05%.[31] If a duodenal ulcer with no atypical features such as irregular areas has been diagnosed, this should be followed by testing for *H. pylori* infection and treatment with proton pump inhibitors. Biopsies are not required for typical peptic ulcers in the duodenum.[31,85]

Statement 26. We do not recommend biopsies that would not change the patient's management. This would usually include biopsies for premalignant conditions such as Barrett's oesophagus or gastric atrophy or intestinal metaplasia in frail or comorbid patients. *Good Practise Statement. Level of agreement: 100%.*

This decision should be made on a case-by-case basis with discussion with the patient and next of kin, ideally prior to endoscopy. No age cut-off is recommended, and a holistic assessment of the patient should be made, taking into account functional status, comorbidity, patient wishes and anticipated life expectancy. Although quantification of life expectancy is difficult, the Charlson Comorbidity Index is likely to be the most suitable for estimation of life expectancy in patients undergoing endoscopic procedures and the benefit of surveillance in patients with a life expectancy of less than 10 years is minimal.[86] A more user-friendly tool which highlights patients actively deteriorating is the SPICT-4ALL tool (Supportive and Palliative Care Indicators Tool) which outlines indicators for deteriorating health and additional comorbidities, which together identify patients likely to benefit from supportive and palliative care.[87]

ENDOSCOPY UNIT RECOMMENDATIONS

Statement 27. We recommend that each endoscopy unit has a local standard operating procedure in place concerning the responsibility for histology results, particularly those that arise from straight-to-test endoscopy or endoscopy requests from outside the specialties of gastroenterology or upper gastrointestinal surgery. *Good Practice Statement. Level of agreement: 100%.*

Statement 28. We recommend that in the absence of a local standard operating procedure for handling of histology results, the default responsibility should be with the endoscopist performing the biopsy. *Expert Opinion. Level of agreement: 85%.*

Statement 29. We recommend that electronic histology result alert systems are available from histopathology to inform the upper gastrointestinal cancer multidisciplinary team directly of any histology with cancer or dysplasia. *Good Practice Statement. Level of agreement: 85%.*

The national PEUGIC root cause analysis project has shown instances where histology has not been acted on in a timely manner.[3,88] Particular areas where there are issues more commonly are those endoscopies that are requested as straight-to-test procedures or from outside the specialties of gastroenterology or upper gastrointestinal surgery, or when endoscopies are undertaken by locum or agency staff. In order to mitigate this, a standard operating procedure is required to ensure that histology results from such investigations are acted on. If there is no standard operating procedure in place for management of histology results from straight to test procedures or external referrals, we recommend that the default responsibility should be with the endoscopist, as they will have the best knowledge of the lesion that led to the biopsy. We also recommend an electronic alerting system direct to the upper gastrointestinal cancer multi-disciplinary team for cancer or dysplasia to decrease the possibility of

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patients not having their histology acted on in a timely manner.[88]

HANDLING OF HISTOLOGY

Statement 30. We recommend that a biopsy of any focal abnormality that is potentially dysplastic or malignant is placed in a separate container or a separate compartment of a labelled cassette. *Expert Opinion. Level of agreement: 100%*

This practice ensures precise anatomical correlation, reduces the risk of sample contamination or misidentification and facilitates targeted diagnostic reporting. It also supports multidisciplinary decision-making by allowing pathologists to distinguish between background mucosa and potentially neoplastic lesions.

Statement 31. We suggest that Seattle protocol biopsies from different levels of Barrett's oesophagus are placed in different compartments of a labelled cassette to reduce environmental impact. *Expert Opinion. Level of agreement: 85%*

Traditionally, biopsies from each level are placed in separate containers to preserve anatomical orientation. However, this practice contributes to increased plastic waste. To mitigate environmental impact without compromising diagnostic accuracy, we suggest placing biopsies from different levels into separate compartments of a multicompartment cassette. We recommend all biopsies which would previously be placed into one container be placed into one compartment of the cassette. Then the cassette labelled externally allows for which compartment corresponds to which site.

MISCELLANEOUS

Statement 32. The biopsy guidance in this document is applicable to the smaller volume biopsy forceps used with a transnasal endoscope. *Good Practice Statement. Level of agreement: 93%*

There have been no studies to date showing a decrease in diagnostic yield from biopsies taken using transnasal endoscopes, and as a result, the above guidance also applies to those performing endoscopy by the trans-nasal route.[89]

FUTURE RESEARCH

During the guidance development process, it was recognised that upskilling of endoscopists in the identification and characterisation of lesions encountered during upper gastrointestinal endoscopy is required to improve biopsy practice. Additional research in the following areas may also result in significant changes to biopsy practice:

- The value of single versus double bite biopsies in for example, dysplasia detection in Barrett's oesophagus.
- The use of wide-field tissue sampling (eg, capsule sponge) for the diagnosis and surveillance of Barrett's oesophagus and assessment of eosinophilic oesophagitis.
- The impact of artificial intelligence on lesion detection and characterisation and resultant biopsy practice.
- Further research is required to understand the impact of advancing endoscopic technology with improved definition, magnification and image enhancement on biopsy practice.
- Further research is needed to understand if biopsy practice can be used as a key performance indicator for endoscopy.

The impact of this guidance can be monitored by review of data extracted from the National Endoscopy Database and analysis of adherence to the biopsy guidance in this document along with post-endoscopy upper gastrointestinal cancer rates.

STRENGTHS AND LIMITATIONS

These statements are in line with recommendations by other endoscopy organisations,[11] however, there is a lack of high quality evidence in this field, leading to the use of GPS and expert opinions. In order to mitigate subjectivity, this document was derived from a robust multidisciplinary consensus process involving peer review by all stakeholders in endoscopy.

CONCLUSIONS

We have developed evidence-based, consensus-driven statements on biopsy practice during upper gastrointestinal endoscopy in adults. These 32 pragmatic statements guide endoscopists on when to perform a biopsy and when not to, with the aim to standardise biopsy practice across the UK, along with improving quality and sustainability in endoscopy.

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