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Guidelines:Barrett's

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Published: 2014

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Cancer Council Australia Barrett's Oesophagus and Early Oesophageal Adenocarcinoma Working Party. [Australian clinical practice guidelines for the diagnosis and management of Barrett's esophagus and early esophageal adenocarcinoma](#) J Gastroenterol Hepatol. 2015 May;30(5):804-20. doi: 10.1111/jgh.12913.

Further resources for health professionals
[Decision tree for the management of Barrett's Oesophagus](#)

For further supporting documentation please email guidelines@cancer.org.au

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After successful endoscopic treatment for BO neoplasia, how frequently should patients undergo endoscopy?

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After successful endoscopic treatment for BO neoplasia, how frequently should patients undergo endoscopy?

Introduction

There has been a paradigm shift in the management of high grade dysplasia (HGD) and oesophageal intramucosal adenocarcinoma (IMCa) within Barrett's Oesophagus. Previously this condition was managed with oesophagectomy, however endoscopic therapy with endoscopic mucosal resection (EMR), radiofrequency ablation (RFA) or both, is now more commonly used.^{[1][2][3][4]} Endoscopic management of intramucosal malignant lesions requires EMR. This also provides the benefit of a histological specimen for accurate staging of the malignant lesion. Resected lesions that demonstrate submucosal involvement carry an unacceptable risk of lymphatic spread which indicates surgical intervention.^[5] Several studies have demonstrated that clearance of intramucosal adenocarcinoma can be achieved by endoscopic mucosal resection alone or in combination with radiofrequency ablation to ablate residual Barrett's.^[6] Radiofrequency ablation alone is not considered a satisfactory modality for treatment of intramucosal adenocarcinoma. Integral to successful endoscopic management of Barrett's HGD and IMCa is a commitment to long term endoscopic surveillance. Presently the surveillance intervals used vary by institution and are not evidence based.

A systematic review of the literature was performed to find consensus guidelines for endoscopic surveillance post successful endoscopic treatment of Barrett's HGD and IMCa. This found that there is a paucity of literature in this area. A review of the available literature provides some consensus based (i.e. practice points) rather than evidence based recommendations.

Confirmation of successful endoscopic treatment for BO neoplasia

A reasonable consensus recommendation for confirming successful eradication of Barrett's HGD/IMCa would be three monthly endoscopic assessment with oesophageal biopsies as per the Seattle protocol. Some would advocate a more stringent protocol with 1cm/ four quadrant biopsies and/or targeted biopsies. Many would advocate the benefits of combining white light endoscopy and NBI, as well as spending additional time for a more thorough examination.^[7] Further endoscopic treatment of any residual pathology would be performed on the basis of the endoscopic and histological findings. Three monthly endoscopic assessment and biopsies would be performed until endoscopic and histological clearance is achieved.^[8]

Suggested endoscopic surveillance recommendations after clearance of BO neoplasia

A reasonable consensus recommendation, after clearance is achieved, would be surveillance gastroscopy with Seattle protocol every six months for one year, then annually thereafter. Again some may advocate 1cm/four quadrant biopsies and/or targeted biopsies. Endoscopic resection of any nodularity in the squamous epithelium should be considered to clarify possible recurrent or metachronous IMCa from subsquamous glands.^[8]

Higher risk patients may require closer surveillance gastroscopy after clearance of Barrett's Oesophagus neoplasia is achieved (i.e. initially 3 monthly for a year). These would include patients with prior synchronous IMCa lesions, those who required multiple endoscopic resections to clear a single IMCa lesion, those with prior histologically deeper intramucosal adenocarcinoma (i.e. T1Am3) and those with prior background Barrett's with multi-focal high grade dysplasia.^[8]

There is presently no consensus about the potential benefits of other mucosal imaging modalities (e.g. confocal laser endomicroscopy). Ideally any further endoscopic management and ongoing surveillance should be discussed in a multi-disciplinary collaborative setting within an experienced tertiary setting.^{[8][9]}

Evidence summary and recommendations

Practice point?

Consider three monthly surveillance gastroscopy with Seattle protocol during the endoscopic treatment phase to confirm clearance of intramucosal adenocarcinoma (IMCa) and residual Barrett's. Once clearance has been achieved, consider 6 monthly endoscopic surveillance for one year, then annually. Higher risk patients (as outlined above) may require closer surveillance gastroscopy after clearance of Barrett's Oesophagus neoplasia is achieved (i.e. initially 3 monthly for a year). Endoscopic resection of any nodularity in the squamous epithelium should be considered to clarify possible recurrent or metachronous IMCa from subsquamous glands.

Issues requiring more clinical research study

- What are the evidence based recommendations for an endoscopic surveillance protocol post endoscopic management of Barrett's HGD and IMCa to confirm clearance?
- What are the evidence based recommendations for an optimal biopsy protocol for endoscopic surveillance post endoscopic management of Barrett's HGD and IMCa?
- What are the evidence based recommendations for an endoscopic surveillance protocol post endoscopic management of Barrett's HGD and IMCa after confirmation of clearance?
- What are the potential benefits of using other mucosal imaging modalities (ie confocal laser endomicroscopy) for surveillance post Barrett's endotherapy?

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Are there any medical or surgical interventions that cause regression of BO?

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Are there any medical or surgical interventions that cause regression of BO?

Introduction

Regression of Barrett's Oesophagus is defined by a reduction in the length or area of metaplastic columnar epithelium. The significance of partial or complete regression in Barrett's Oesophagus is unclear. There are insufficient data to indicate that regression of the Barrett's segment leads to a reduced incidence of adenocarcinoma. Available evidence is limited by a lack of randomised trials, variations in the definition of Barrett's regression and differences in the method and duration of intervention. The degree of Barrett's regression appears to be largest amongst case series of patients undergoing anti-reflux surgery although a randomised trial comparing surgical and medical therapy found the differences to be insignificant.

Medical therapies

Combined analysis of randomised trials has not demonstrated a regression of Barrett's Oesophagus with medical therapy.^[1] Several studies including a case series of 188 patients treated with a proton-pump inhibitor over a mean follow-up of 5.1 years have reported an increase in the development of squamous islands within the Barrett's segment although the significance of this finding is uncertain.^[2]

Surgical therapies

Although medical therapies reduce oesophageal acid exposure, gastro-oesophageal reflux of bile and other noxious agents may continue to occur. Anti-reflux surgery has therefore been proposed as a more effective treatment than medical therapy. Studies are largely in the form of case series and different surgical approaches have been described, reporting the incidence of regression at between 0-73%. Only one trial has compared surgery (Nissen fundoplication) with medical therapy in a randomised fashion.^[3] The surgically treated group had a small but statistically significant reduction in the median length of the Barrett's segment at a median follow-up of five years (5cm versus 4cm) and the medical group had a significant increase in the median length (4cm versus 5cm) although no difference in the rate of progression to high grade dysplasia or adenocarcinoma was found between the two groups.

Evidence summary and recommendations

Evidence summary	Level	References
There are no medical therapies that result in clinically significant regression of Barrett's Oesophagus.	I	[1]
Anti-reflux surgery may induce regression of Barrett's Oesophagus although this is not associated with a decreased risk of high-grade dysplasia or adenocarcinoma.	II	[3]

Evidence-based recommendation?	Grade
There is insufficient evidence to recommend the use of acid suppressive therapy for the	B

Evidence-based recommendation?	Grade
regression of Barrett's Oesophagus.	

Evidence-based recommendation?	Grade
Insufficient evidence exists to routinely recommend anti-reflux surgery for the regression of Barrett's Oesophagus.	C

Practice point?
Acid suppressive therapy and anti-reflux surgery can be used to control symptoms and heal reflux oesophagitis in patients with Barrett's Oesophagus. There is insufficient evidence to recommend high dose (twice daily) acid suppressive therapy when symptom control or mucosal healing is achieved with standard dosing.

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Are there any treatments that prevent progression of BO to cancer?

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Are there any treatments that prevent progression of BO to cancer?

Introduction

Barrett’s Oesophagus arises in individuals with moderate to severe gastro-oesophageal reflux. Treatment of reflux has been recommended to prevent progression to cancer, as have various endoscopic ablation therapies, and the use of COX inhibition. Whilst there is an extensive literature that addresses this issue, only a few randomised trials have evaluated ablation treatments, and no high level evidence is available which addresses the role of anti-reflux treatment or chemoprevention.

Treatment of reflux

Proponents of medical and surgical therapies for the treatment of gastro-oesophageal reflux have at various times recommended the use of proton pump inhibitor medication or antireflux surgery to prevent cancer developing in Barrett’s Oesophagus. Unfortunately there is no high level evidence or randomised trials which support this contention. Whilst clinicians who treat individuals with gastro-oesophageal reflux would like to believe that their treatments make a difference to cancer prevention, evidence supporting this is lacking, and for now decisions to use medication or surgery to treat reflux in individuals with Barrett’s Oesophagus should be based on the need to manage reflux symptoms, rather than cancer risk.^[1]

Ablation of Barrett's Oesophagus

Various endoscopic techniques have been investigated for eradicating Barrett's Oesophagus epithelium with or without dysplasia (see also [What is the appropriate management of low grade dysplasia in patients with BO?](#), [What is the best endoscopic treatment for high grade dysplasia in patients with BO?](#), [What is the best endoscopic management of early oesophageal adenocarcinoma?](#)). Focal ablation techniques (argon plasma coagulation (APC), multipolar electrocoagulation, laser heater probe, and endoscopic mucosal resection (EMR)) and field ablation techniques (photodynamic therapy (PDT) and radiofrequency ablation (RFA)) have been all been described. What is clear from the literature pertinent to this area is that in patients undergoing treatment of gastro-oesophageal reflux by either medical or surgical therapy, the destruction of Barrett's Oesophagus epithelium, irrespective of the method used, is followed in most individuals by regeneration with a squamous mucosa. However, ablation is often followed by areas of persistent Barrett's Oesophagus mucosa in the form of Barrett's islands. Further, recurrence of the Barrett's Oesophagus mucosa occurs in some individuals, and ablation also fails in some individuals. The rationale behind ablation is that it is hoped that the post-ablation squamous mucosa (neosquamous mucosa) has a reduced cancer risk, or even that the risk of cancer is eliminated. The evidence supporting this is limited. The potential for malignancy to arise in islands of retained columnar mucosa or in buried areas of columnar mucosa lying underneath neosquamous mucosa is uncertain, as is the potential for cancer to arise from within the neosquamous mucosa. There has been a case report of cancer arising in neosquamous mucosa,^[2] and there have been reports of HGD and oesophageal adenocarcinoma developing following an endoscopically assessed 100% complete eradication response to ablation.^{[3][4]}

Much of the evidence addressing outcomes following ablation therapy is limited to low quality studies - e.g. uncontrolled case series. However, four randomised controlled trials have compared ablation using PDT, APC or RFA to ongoing endoscopic surveillance.^{[5][6][7]}

Photodynamic therapy

PDT entails administering a photosensitising drug which sensitises the Barrett's Oesophagus mucosa to specific wavelengths of light. Light of the appropriate wavelength is then delivered via an endoscope to activate the photosensitiser, and this "burns" the Barrett's Oesophagus mucosa. Circumferential ablation over a 3-7cm segment length can be achieved. PDT is associated with morbidity including chest pain and odynophagia, photosensitivity, and up to one third of treated patients develop an oesophageal stricture.^[8] In countries with strong sunlight such as Australia, this treatment is not practical, and hence it is not available.

In 2005 Overholt et al reported a randomised trial of PDT ablation versus surveillance in patients with Barrett's Oesophagus and high grade dysplasia (HGD).^[9] The trial recruited 208 patients and randomised them 2:1 to PDT versus surveillance. All patients used omeprazole 20mg twice daily for reflux control. The results showed less progression to cancer at five years following PDT (15.2% versus 28.6%), with the risk of cancer halved. Follow-up in the study was incomplete, and one third of the PDT group also developed an oesophageal stricture which required dilatation. However, this trial did show that the risk of malignancy in Barrett's Oesophagus with HGD can be reduced by endoscopic ablation, although the risk was not eliminated.

Argon Plasma Coagulation (APC)

Argon Plasma Coagulation (APC) ablation is widely available and relatively inexpensive. It uses monopolar electrocautery, via an argon gas stream to carry electrical charge to the closest mucosal surface. This achieves ablation without direct contact. Recently, APC has fallen out of favour as an ablation technique, and it is being replaced by RFA in many parts of the world.

The only randomised trial evaluating APC versus surveillance was conducted in Adelaide. One hundred and twenty six (126) patients with non-dysplastic Barrett's Oesophagus or low grade dysplasia (LGD) were enrolled into two randomised controlled trials of APC ablation versus endoscopy surveillance.^{[5][6][10]} One trial enrolled patients in whom reflux was controlled by proton pump inhibitor therapy,^[5] and in the other patients had undergone effective anti-reflux surgery to control reflux.^[10] In both studies 95-100% macroscopic (endoscopic) ablation was achieved after two to six treatment sessions. In patients who underwent ablation after fundoplication, a stable neosquamous epithelium was confirmed five or more years after ablation. However, only one patient progressed to high grade dysplasia (HGD) across the follow-up period, and this study failed to demonstrate any role for APC ablation in preventing cancer progression in patients with non-dysplastic Barrett's Oesophagus.^[6]

Radiofrequency ablation

RFA employs a bipolar array to create an electrical field, which is mounted on either a circumferential balloon-based catheter or an endoscope-mounted device. Ablation is achieved relatively uniformly to a depth of 0.5 to 1 mm. Reported results are generally good, but follow-up in most studies remains short.

Shaheen et al reported a multicentre randomised trial of RFA ablation versus surveillance in 127 patients with dysplastic Barrett's Oesophagus.^{[4][11]} Approximately half had HGD, and the remainder has low grade dysplasia (LGD) at enrolment. When assessed 12 months after commencing treatment, complete regression was achieved in 77% following RFA versus 0% in controls, and complete remission of HGD was achieved in 80% of the treated group.^[11] RFA ablation was associated with a decreased rate of progression to cancer in the first 12 months, although the number of cancers was small; 1/84 versus 4/43, $p=0.04$. Three year follow-up was reported two years later. 25% of patients who initially had dysplasia and had complete eradication of intestinal metaplasia developed recurrent Barrett's Oesophagus.^[4] They also reported progression to HGD or Cancer in 4.2% of the ablation group (1.37% per patient per year), and hence concluded that the RFA treated population remains at a significant risk, requiring ongoing endoscopy surveillance.

Phoa et al recently reported a randomised trial of RFA versus endoscopic surveillance in patients with Barrett's Oesophagus and low grade dysplasia.^[7] In this study 68 patients underwent RFA ablation versus 68 controls. At 3 years follow-up, progression to high grade dysplasia or cancer was reduced from 18/68 (26.5%) in the control group to 1/68 (1.5%) in the RFA ablation group, offset by a higher complication rate (19.1%) in the RFA group. However, the effect on progression to cancer was less - 6/68 (8.8%) in the control group versus 1/68 (1.5%) following RFA ablation, and cancer progression was not completely prevented following RFA. Of note, the definition of low grade dysplasia in this trial was stringent, and excluded a significant proportion of patients who would currently be diagnosed with low grade dysplasia in Australia. The definition of low grade dysplasia used

probably better matches the definition used for high grade dysplasia elsewhere, and for this reason the trial results better reflect RFA treatment for high grade dysplasia in the Shaheen trial,^{[11][4]} and lend support to ablation for high grade dysplasia, but not low grade dysplasia as currently defined and diagnosed in Australian practice. As with the Shaheen trial, the RFA treated group still remains at risk of cancer progression and require ongoing endoscopy surveillance. Currently Medicare funding for RFA in Australia is only available for patients diagnosed with high grade dysplasia.

Chemoprevention

Researchers have speculated that COX or COX-2 inhibition might prevent the progression of Barrett's Oesophagus to cancer, but high quality evidence to support the use of aspirin or COX-2 inhibitors to prevent cancer development remains lacking. Heath et al^[12] reported a randomised controlled trial which enrolled 222 patients with Barrett's Oesophagus to 48 weeks treatment with 200mg per day Celocoxib versus placebo. One hundred patients had dysplastic Barrett's Oesophagus (either LGD or HGD). No differences were seen for the treated versus control group for the outcomes of dysplasia development, regression of dysplasia, surface area of Barrett's Oesophagus, or biomarker expression. From these data the authors concluded that the COX-2 inhibitor Celocoxib was ineffective as a preventer of cancer progression in Barrett's Oesophagus.

In a short term outcome study which included 114 patients, Falk et al^[13] evaluated the impact of the proton pump inhibitor esomeprazole with or without aspirin and showed reduced tissue concentrations of prostaglandin E2 in Barrett's Oesophagus mucosa. From this they concluded that high dose aspirin and esomeprazole as a cancer prevention strategy should be evaluated further. However, whilst showing some interesting laboratory results, the study did not actually address the issue of cancer prevention in a clinically relevant context.

A recent health economic modeling study from Hur et al,^[14] claimed that daily aspirin is likely to be cost effective as a chemoprevention agent for preventing cancer progression in Barrett's Oesophagus. However, the major assumption underlying this study and its conclusions was that aspirin will reduce cancer progression by 50%, but if this cannot be achieved then the model's outcomes might be very different.

Emerging evidence

A large randomised controlled trial is being conducted to evaluate the efficacy of aspirin as a cancer preventer in individuals with Barrett's Oesophagus which has not progressed to HGD,^[15] and this study appears powered to give a definitive answer about whether or not aspirin should be recommended for prevention of cancer. This is a four arm trial which is using a 2x2 design, randomising patients to 20mg versus 80 mg per day esomeprazole, and 300mg aspirin versus no aspirin. The study has enrolled 2513 individuals, but follow-up will not complete until 2019. Hence, at present, there remains no high quality evidence to support the use of COX inhibitors as preventers of oesophageal adenocarcinoma in individuals with Barrett's Oesophagus, and a positive outcome from the large randomised trial is needed before an aspirin based prevention strategy should be recommended to individuals with Barrett's Oesophagus in the wider community.

Summary

There is currently only limited evidence supporting strategies which aim to prevent the development of oesophageal adenocarcinoma in Barrett's Oesophagus. The choice of antireflux therapy - proton pump inhibitors versus antireflux surgery - has not been shown to influence progression to cancer, although few would argue against aiming for reflux symptom control in individuals with Barrett's Oesophagus. Interest has been shown in using COX inhibitors, but unless the outcome of the large aspirin chemoprevention trial, when available in 2019, shows benefit, there will be no high level evidence to support the wider use of aspirin in patients with Barrett's Oesophagus. Ablation therapies have shown benefit in randomised trials, but only in individuals who have already developed dysplasia. In these individuals, the risk of cancer progression appears to be reduced by approximately 50% by both PDT and RFA ablation techniques, but cancer risk is not eliminated. The only randomised trial^[6] to evaluate ablation (APC) in non-dysplastic Barrett's Oesophagus, failed to show benefit for ablation in this group, and for this reason ablation should remain limited to individuals with HGD, who are at imminent and high risk of developing oesophageal adenocarcinoma.

Evidence summary and recommendations

Evidence summary	Level	References
Ablation of Barrett's Oesophagus with radiofrequency ablation or photodynamic therapy in individuals who have already developed high grade dysplasia, reduces, the risk of progression to oesophageal cancer by approximately 50%, although cancer progression is not eliminated.	II	[4], [8], [9], [11], [7]

Evidence-based recommendation?	Grade
Ablation of Barrett's Oesophagus should remain limited to individuals with high grade dysplasia in Barrett's Oesophagus who are at imminent risk of developing oesophageal adenocarcinoma.	B

Practice point?
The treatment of gastro-oesophageal reflux with either proton pump inhibitors or antireflux surgery has not been shown to influence progression to oesophageal adenocarcinoma.

Practice point?

There is currently no good evidence supporting the use of COX inhibitors for prevention of oesophageal adenocarcinoma.

Issues requiring more clinical research study

- Long term outcome studies for cohorts of patients undergoing endoscopic ablation of Barrett's Oesophagus are required.
- Long term outcome studies for randomised trials evaluating endoscopic ablation of Barrett's Oesophagus are required.

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Are there biomarkers for the diagnosis (presence) of BO?

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Are there biomarkers for the diagnosis (presence) of BO?

Introduction

Numerous biomarkers have been proposed for the diagnosis of BO, including tissue biomarkers to supplement standard histopathology, serum biomarkers as a non-invasive alternative to endoscopy and biopsy, or use of technology such as magnifying endoscopy to aid in the identification of BO for accurate targeting of biopsies. However, none have been implemented as standard clinical practice.

Accepting the limited observational evidence that early detection and surveillance leads to improved survival,^[1] ^[2] to be of clinical value a new biomarker would need to demonstrate improved accuracy compared to current practice, or similar accuracy with other benefits, such as being less invasive. A biomarker would be clinically valuable if it had improved sensitivity (higher true positive rate) compared to standard histopathology examination with acceptable specificity (acceptable false positive rate) and cost. If the new biomarker is more sensitive but less specific than histopathology, its acceptability would need to be assessed by considering the trade-off between the clinical benefits of detecting additional true positive cases that may benefit from surveillance versus the harms of additional false positive results that may lead to unnecessary surveillance procedures.

In the updated 2008 practice guidelines for the diagnosis, surveillance and therapy of Barrett's Oesophagus, Wang et al.^[3] proposes the ideal biomarker panel for the diagnosis of BO to be "non-invasive (ie - non-endoscopic) and sensitive - 85% or better". We have implemented this benchmark in order to evaluate the size of effect. For example, to assign a grade '3' ('the confidence interval does not include any clinically important effects'), the 95% confidence interval for test sensitivity falls below and does not include the 85% benchmark.

Biomarkers for the diagnosis of Barrett's Oesophagus

Twenty studies reporting on the clinical performance of biomarkers proposed for the diagnosis of BO were eligible for inclusion in the systematic review. These included:

- i) seven diagnostic case control studies^{[4][5][6][7][8][9][10]} and one systematic review^[11] reporting on the accuracy of cytokeratin staining pattern to distinguish between BO and gastric intestinal metaplasia. The Nurgalieva review^[11] included sixteen studies published from 1983-2005, which included six of the seven studies analysed here as well as nine studies that were ineligible for the present review because they were published prior to the publication of the Ormsby study.^[4]
- ii) two studies (one perspective diagnostic case control study and one prospective cohort study) reporting on the accuracy of Trefoil Factor 3 (TFF3) collected using a cytosponge to detect BO;^{[12][13]}
- iii) six retrospective diagnostic case control studies reporting on the accuracy of different immunohistochemical biomarkers to detect goblet cells and distinguish BO from gastric intestinal metaplasia (Mucin expression^{[14][15]}; Hepatocyte expression^{[16][17]}; Human defensin 5^[18]; and CDX2 and Villin^[19]);
- iv) two studies (one prospective diagnostic case control study and one diagnostic cohort study) reporting on the accuracy of using magnifying endoscopy to detect BO^{[20][21]};
- v) one prospective case control study investigating a potential tissue protein biomarker AG2^[22] and
- vi) one prospective case control study investigating a potential serum biomarker G-17.^[23]

Appendix - Body of evidence assessment

Evidence summary and recommendations

Evidence summary	Level	References
Seven studies provided low quality evidence for evaluation of cytokeratin staining for distinguishing BO from gastric intestinal metaplasia. Estimates of diagnostic accuracy were inconsistent across studies.	III-2, III-3	[4], [5], [6], [7], [9], [8], [10]

Evidence-based recommendation?	Grade
Insufficient evidence exists to recommend cytokeratin staining to aid in the diagnosis of Barrett's Oesophagus.	D

Evidence summary	Level	References
Four studies provided low quality evidence for evaluation of immunohistochemistry biomarkers for distinguishing Barrett's Oesophagus from cardiac intestinal metaplasia. It was not possible to estimate the clinical accuracy of the biomarkers in	III-3, IV	[16], [18], [17], [19]

Evidence summary	Level	References
the proposed test population due to the methodological limitations in the selection of cases, controls and reporting of the reference standard.		

Evidence-based recommendation?	Grade
Insufficient evidence exists to recommend the implementation of immunohistochemistry biomarkers to aid in the diagnosis of Barrett's Oesophagus.	D

Evidence summary	Level	References
Two studies provided low quality evidence for evaluation of mucin (MUC) immunostaining of non-goblet epithelium for the diagnosis of Barrett's Oesophagus. Test accuracy estimates were inconsistent between these studies but established proof of concept of the test as a potential strategy to overcome problems of sampling error when used in addition to the current method for diagnosis of Barrett's Oesophagus.	III-3	[15], [14]

Evidence-based recommendation?	Grade
Insufficient evidence exists to recommend mucin (MUC) expression immunostaining in formalin-fixed, paraffin-embedded tissue to aid in the diagnosis of Barrett's Oesophagus.	D

Evidence summary	Level	References
Two studies provided a satisfactory evidence base for evaluation of a non-endoscopic capsule sponge device coupled with immunohistochemistry for Trefoil factor 3 (TFF3) for BO screening with estimates of test accuracy approaching that of the current clinical standard. As a non-endoscopic test, the potential clinical impact is substantial. Implementation is dependent on further high quality evidence from representative populations.	III-2, III-3	[12], [13]

Evidence-based recommendation?	Grade
Insufficient high quality evidence exists to recommend the non-endoscopic capsule sponge	C

Evidence-based recommendation?	Grade
device coupled with immunohistochemistry for trefoil factor 3 (TFF3) to replace the current clinical standard for the diagnosis of Barrett's Oesophagus.	

Evidence summary	Level	References
One study provided low quality evidence for evaluation of serum G17 as a biomarker for the diagnosis of Barrett Oesophagus. Reported poor specificity indicates an unacceptably large number of non-BO cases are incorrectly identified as Barrett's Oesophagus by this test.	III-3	[23]

Evidence-based recommendation?	Grade
Insufficient evidence exists to recommend the implementation of serum G17 for the diagnosis of Barret's Oesophagus.	D

Evidence summary	Level	References
One study provided low quality evidence for evaluation of AG2 expression in fresh tissue as a protein biomarker for the diagnosis of Barrett's Oesophagus. Reported sensitivity was poor and well below that of the current clinical standard.	III-3	[22]

Evidence-based recommendation?	Grade
Insufficient evidence exists to recommend evaluation of AG2 expression as a protein biomarker in fresh tissue to aid in the diagnosis of Barrett's Oesophagus.	D

Evidence summary	Level	References
Two studies provided a satisfactory level of evidence for evaluation of the use of magnifying endoscopy to aid in the identification of Barrett's Oesophagus. Evidence was inconsistent between these studies but established proof of concept of the test to overcome problems of sampling error when used in addition to the current method for diagnosis of BO. Neither study gave a valid comparison with current	II, III-3	[20] , [21]

Evidence summary	Level	References
clinical standards for the diagnosis of BO in an appropriate target population.		

Evidence-based recommendation?	Grade
Insufficient evidence exists to recommend magnifying endoscopy to aid in the diagnosis of Barrett's Oesophagus.	D

Practice point?
Thorough endoscopic sampling (Seattle protocol) coupled with H&E staining of sections and interpretation by trained, expert pathologists is advised for the diagnosis of Barrett's Oesophagus. More clinical research is required before biomarkers for Barrett's Oesophagus can be implemented as standard clinical practice.

Issues requiring further clinical research study

- Proof of concept of mucin (MUC) immunostaining of non-goblet epithelium for the diagnosis of BO has been established by Glickman et al.^[14] and McIntire et al.^[15] Application of a more rigorous study design (such as a prospective cohort study) to this question is required to attain further high quality evidence to establish test accuracy. A valid comparison to the subset of patients missed by sampling error (false negative) using the current clinical standard is required.
- Further high quality evidence (prospective cohort study or randomised clinical trial) to confirm the accuracy of a non-endoscopic capsule sponge device coupled with immunohistochemistry for Trefoil factor 3 (TFF3) for the diagnosis of BO is required for the test to be considered for implementation as clinical practice. Economic implications of implementation of the test have not yet been investigated.
- Proof of concept of the use of magnifying endoscopy overcome problems of sampling error and aid in the identification of BO has been established by Endo et al.^[20] and Norimura et al.^[21] Application of a more rigorous study design to this question is required to attain further high quality evidence to establish test accuracy. A valid comparison to the current clinical standard for the diagnosis of BO in an appropriate target population is required.

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Are there groups of patients with BO that can be discharged from surveillance?

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Are there groups of patients with BO that can be discharged from surveillance?

Introduction

The aim of surveillance in non-dysplastic Barrett's Oesophagus (BO) is to detect evidence of the progression to cancer to provide intervention that is curative. If there is a subgroup of cases which progress to cancer at a low or negligible rate, then these cases may be effectively discharged from surveillance as no benefit for the surveillance would exist. Similarly, if a subgroup of cases is unlikely to benefit from intervention, then these cases may also be discharged from surveillance. The majority of studies that investigate factors in the progression to oesophageal adenocarcinoma (OAC) concentrate on risk factors that increase the progression rate, rather than protective factors that may reduce or normalise this rate (see also [What are the risk factors for progression from non-dysplastic BO to high grade dysplasia and adenocarcinoma?](#)). In addition, there are no randomised studies and no long term data reporting outcomes of surveillance of patients in low risk groups, or groups where surveillance was ceased. However, on extrapolation from available data, a number of recommendations may still be made based on observations from these studies.

What are the endoscopic and/or histological factors of non-dysplastic BO patients that may lead to discharge from surveillance?

Shorter segments of BO and the absence of dysplasia have been shown to have lower rates of progression to cancer than longer BO length and the presence of dysplasia. Short segment BO, defined as biopsy proven BO of less than 3cm length from the gastro-oesophageal junction (GOJ), has been observed to have a lower incidence of progression to OAC of 0.19% per year (compared with 0.33% per year overall).^{[1][2]} Histological evidence of intestinal metaplasia in cases with normal appearing GOJ has been reported (termed “cardiac intestinal metaplasia”). This has been observed in a number of studies to have a low or negligible rate of progression to dysplasia and/or cancer.^{[3][4][5]}

A further subgroup of patients may have a columnar lined oesophagus (CLO) with histological evidence of gastric differentiation, but without evidence of intestinal differentiation i.e. do not have identified goblet cells at histology. These are defined as “gastric metaplasia”. At this stage, it is still unclear whether patients with evidence of gastric metaplasia are a further subgroup of patients with a defined risk of OAC, and international guidelines differ in their advice. The British Society of Gastroenterology (BSG) guidelines include these within the spectrum of BO based on studies which show that there is malignant potential with similar observed rates.^[6] Furthermore, subsequent sampling in these patients has been shown to result in observed intestinal metaplasia, as reported in a prospective study by Gatenby et al.^[7] Hence, continued surveillance is recommended in BSG guidelines for these patients, particularly if the observed segment is ≥ 1 cm. However, the American Gastroenterology Association (AGA) guidelines exclude these cases as it is felt that these do not represent true intestinal differentiation,^[8] and recent studies support a low malignant potential if this is observed.^[9] At this stage, patients with CLO may be recommended surveillance using similar protocols if the length of CLO is greater than 3cm. If the length is less than 3cm, then patients may be discharged from surveillance if certain criteria are met (see section below, [What is the suggested surveillance protocol that may lead to discharge from surveillance?](#)).

What are the patient factors of non-dysplastic BO patients that may lead to discharge from surveillance?

At this stage, there is a lack of strong evidence about factors that may reduce the incidence of progression from BO to OAC. There are number of factors which have been independently associated with lower progression rates to OAC, including female gender,^{[9][10]} never smokers,^[11] and normal body mass index.^[12] These factors alone are not sufficient to recommend complete discharge from surveillance, but lifestyle changes may be recommended to reduce risk of progression. There are number of studies which show a benefit for chemopreventative medications such as anti-inflammatories,^[13] acid suppressive medications,^[14] and statins,^[15] which are hypothesised to reduce factors which may drive malignancy. A randomised study is currently being conducted studying the role of anti-inflammatories and proton pump inhibitors in the progression to OAC.^[16] However, further study is required to determine if the reported risk reduction of these medications will be significant enough to recommend discharge for surveillance.

What is the suggested surveillance protocol that may lead to discharge from surveillance?

To summarise the current international guidelines regarding patients with non-dysplastic BO, the AGA does not recommend surveillance for patients with CLO without intestinal metaplasia regardless of length. The BSG recommends no surveillance if the observed CLO (without intestinal metaplasia) is less than 1cm, and those 1cm or greater may continue surveillance using the same protocol as intestinal metaplasia. As there is no high level evidence to support either position, clinicians should be guided by their index of suspicion regarding the appropriate surveillance for these patients. These international guidelines (i.e. BSG and AGA) imply that if intestinal metaplasia or dysplasia is observed, then surveillance should continue indefinitely (see also [How frequently should patients with BO undergo endoscopy?](#), [What is the appropriate management of low grade dysplasia in patients with BO?](#) and [What are the goals of treatment of high grade dysplasia in patients with BO?](#)).

There are currently no guidelines that outline management if there is observed “regression” of BO length or the observation of gastric metaplasia in the setting of a previous diagnosis of intestinal metaplasia. Due to (a) inter-observer variation during endoscopy, (b) possible sampling error and (c) no observed reduction in the rate of progression to OAC, normal endoscopic surveillance should continue if “regression” of BO is suspected (see also [Are there any medical or surgical interventions that cause regression of BO?](#)).

In addition, there are no guidelines as to what age and after how many years that surveillance may cease. It may be considered that if other co-morbidities significantly reduce the expected life expectancy, or if there is likely to be significant morbidity associated with procedural intervention for dysplasia/OAC, then these patients may be discharged from surveillance.

Evidence summary and recommendations

Evidence summary	Level	References
Short segment BO (<3cm) has a lower rate of progression to oesophageal adenocarcinoma, but not low enough to recommend discharge from surveillance.	III-2	[1], [2]
Cardiac intestinal metaplasia (intestinal metaplasia without endoscopic evidence of Barrett's Oesophagus) has a low or negligible rate of progression to dysplasia /oesophageal adenocarcinoma.	IV	[3], [4], [5]
Patients with evidence of columnar lined oesophagus (i.e. gastric metaplasia without intestinal metaplasia) may be considered to have surveillance, particularly if subsequent intestinal metaplasia is identified.	III-2	[6], [7]
There is lack of strong evidence for factors that may reduce incidence enough to consider discharge from surveillance, although studies are in progress which may yield risk reducing modifiers.	II, III-2, III-3	[11], [12], [13], [15]

Evidence-based recommendation?	Grade
For patients with < 1cm of columnar lined oesophagus that do not have evidence of intestinal metaplasia or dysplasia on Seattle protocol biopsy of the segment, endoscopic surveillance is not recommended	C

Evidence-based recommendation?	Grade
Patients with one or more modifiable risk factors for progression from Barrett's Oesophagus to oesophageal adenocarcinoma (such as smoking or obesity) should be encouraged to make lifestyle changes.	D

Practice point?
Patients with evidence of “regression” of Barrett's Oesophagus i.e. reduced Barrett's Oesophagus length or absence of intestinal metaplasia, can still continue surveillance.

Practice point?
Patients with significant co-morbidities, or those whom are unable to tolerate procedural intervention for dysplasia/oesophageal adenocarcinoma may be considered to be discharged from surveillance.

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Are there groups of patients with non-dysplastic BO that require more frequent surveillance?

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Are there groups of patients with non-dysplastic BO that require more frequent surveillance?

Introduction

The aim of surveillance is to detect evidence of the progression of Barrett's Oesophagus (BO) to dysplasia and early cancer at a stage where an effective intervention will reduce morbidity and mortality. Overall, the surveillance protocol for patients with BO is based on observational studies on the conversion rate to oesophageal adenocarcinoma (OAC).^[1] (See also "[How frequently should patients with BO undergo endoscopy?](#)"). A group of patients which may be targeted for more frequent surveillance may be defined as one which has evidence of a higher rate of progression to OAC. A number of studies have investigated risk factors for progression to OAC (see also [What are the risk factors for progression from BO to neoplasia?](#)), but these studies have been limited by features such as selection bias, low progression rates to OAC, high numbers of loss to follow up, retrospective reporting and the incomplete study of risk factors. However, a number of recommendations may still be made based on the available evidence. Note that these recommendations do not include patients with evidence of dysplasia, which is covered in a separate section (see also [What is the appropriate management of low grade dysplasia in patients with BO?](#)).

What are the endoscopic and/or histological factors of non-dysplastic BO patients that may require more frequent surveillance?

Longer BO length has been consistently observed to have a higher rate of progression. Three meta-analysis have distinguished a higher incidence of progression to OAC in patients diagnosed with long (>3cm) versus short (<3cm) segment non-dysplastic BO ^{[1][2][3]}. A recent study confirmed these findings, reporting an increased risk of progression in patients with long BO length (hazard ratio 7, 95% CI 1.71 – 28.64).^[4] In addition, three multi-centre studies consistently show on multi-variant analysis the increased relative risk of length (per centimetre) in the order of 1.1 – 1.21.^{[5][6][7]}

Other observed features at endoscopy which may also be associated with a higher incidence of progression to OAC include the observation of ulcers, nodules and oesophageal strictures, with relative risk of 3.0 to 7.6 in these case series.^{[6][8]} These features may be a marker of prevalent (i.e. pre-existing) dysplasia and/or OAC, thus confirming the need to biopsy all abnormal areas at endoscopy (see also [What is the optimal tissue sampling at endoscopy for diagnosis of BO?](#)).

Clear evidence for a sub-group of patients with a higher rate of progression to OAC is those with histological evidence of dysplasia.^{[9][10][11]} The recommended management and surveillance for these patients is found in section [What is the appropriate management of low grade dysplasia in patients with BO?](#) and [What are the goals of treatment of high grade dysplasia in patients with BO?](#).

What are the patient factors of non-dysplastic BO patients that may require more frequent surveillance?

A number of patient factors which have been independently associated with increased risk of progression include age ^{[12][9][11]}, male gender ^{[11][13]} and smoking. ^{[14][12]} Interestingly, those who have been on surveillance for BO for greater than 10 years have a higher cumulative incidence of OAC (9.2%, 95% CI 2.2 – 17.0). ^[5] Although the increased relative risk of each may be statistically significant, the rate of progression has yet to be determined and hence no recommendations have been suggested for a surveillance strategy. In addition, the combination of risk factors has not been studied and a risk algorithm for progression is yet to be developed and validated. However, it is likely that the combination of age, male gender and smoking may have the additive effect on progression to OAC. ^{[15][16]}

There are a number of other factors that have been suggested to be associated with the development of BO but yet to be fully studied as also contributing to an increased risk of progression to OAC. These include a strong family history of BO and/or OAC ^[17], racial/regional factors ^{[18][19]}, dietary factors ^[20] and patients with poorly controlled gastro-oesophageal reflux disease. ^[4] However, it has observed that those who have regular use of proton-pump inhibitors have a significantly reduced relative risk of developing OAC (RR 0.29, 95% CI 0.12 – 0.79), ^[21] suggesting that the control of acid reflux has an important role in preventing the onset of OAC.

What is the suggested surveillance protocol and management for a high risk group?

The suggested surveillance protocol should account for patient factors such as co-morbidities and patient preference. A multi-disciplinary meeting can aid the decision making processes for individual patients. Recommendations for patients may also take in to account current international guidelines. (See also [How frequently should patients with BO undergo endoscopy?](#)).

Patients with BO ≥ 3 cm have a higher incidence of progression to OAC than those < 3 cm, and it is recommended that they continue surveillance indefinitely. British guidelines, ^[22] recommend surveillance endoscopy intervals of 2 to 3 yearly (as opposed to 3 to 5 yearly for those < 3 cm), whereas American guidelines do not make this distinction. ^[23] Those with BO for greater than 10 years may also have closer surveillance endoscopy intervals, although the time interval has not been outlined in other guidelines.

There is currently no evidence for an intensive surveillance protocol for one or more other risk factors e.g. male, older age, smoking, uncontrolled GORD. Modifications such smoking cessation, weight loss in obese patients and acid suppression therapy may be encouraged but there is currently no data on their outcomes.

Evidence summary and recommendations

Evidence summary	Level	References
Patients with a longer length of BO (particularly ≥ 3 cm) are a higher risk group for progression to OAC.	III-2	[1], [2], [7], [4], [3], [6], [5]

Evidence summary	Level	References
Patients with risk profiles such as, older age, male and smokers may also be at higher risk of progression to OAC.	II, III-2	[9], [11], [12], [13], [14]

Evidence-based recommendation?	Grade
Patients with Barrett's Oesophagus length equal to or greater than 3cm may have intensive surveillance, possibly every two to three years following the Seattle protocol.	C

Evidence-based recommendation?	Grade
Patients with one or more modifiable risk factors for progression to oesophageal adenocarcinoma (such as smoking) should be encouraged to make lifestyle changes.	D

Practice point?
Patients with Barrett's Oesophagus length equal to or greater than 3cm may have more frequent surveillance than those less than 3cm.

Issues requiring more clinical research study

- Are there other risks factors that may modify progression rates that are not yet studied? Eg family history, medications
- Is there an algorithm that may be used to quantify the risk of progression to BO?
- Does modification of known risk factors improve patient outcomes?
- Are there other means to risk stratify patients requiring intensive surveillance, eg the use of biomarkers?

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For which populations is screening for BO cost-effective?

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For which populations is screening for BO cost-effective?

Eight studies were included in this review, which were published between 2000 and 2012. A non-systematic review of the literature which included five of these eight papers was also considered in developing these recommendations. ^[1] Four studies used Markov modelling, ^{[2][3][4][5]} three decision analysis ^{[6][7][8]} and one microsimulation ^[9] to model the outcomes and associated costs in various hypothetical cohorts. All studies were based on US data with the exception of a single UK study. ^[9]

All studies compared endoscopic screening versus no screening. In addition, one study also compared ultra-thin endoscopy versus no screening; ^[2] one study compared capsule endoscopy versus no screening; ^[5] and one study compared a non-endoscopic cytosponge as the screening test versus no screening. ^[9] Seven of the eight studies screened populations with a history of gastro-oesophageal reflux disease (GORD), which was defined to varying degrees of precision. Only one study screened an asymptomatic population of 50-year old men and women who were attending for screening colonoscopy. ^[8] One study included 50-year old men and women with GORD ^[2] and another study 60-year old men and women with GORD. ^[6] The other five studies screened 50-year old men with GORD, of which three specified that only white men were included. ^{[4][5][7]}

Assumptions about the prevalence of Barrett's Oesophagus and dysplasia varied considerably across studies: prevalence estimates for Barrett's Oesophagus ranged from 1-10% but were not necessarily consistent across studies for the same hypothetical population. As discussed elsewhere in this guideline, assumptions about other key model estimates such as transition rates and treatment protocols were not consistent across studies or based on robust data. Similarly there was some variation in assumptions about the utilities of different states and none accounted for the potential psychological harms of screening or disutility of chronic GORD. Only three studies included endoscopic therapies for Barrett's Oesophagus. ^{[9][8][3]} Importantly estimates of effectiveness are not based on data from randomised controlled trials.

The table below summarises the key findings from the included studies, reporting only the estimates of the incremental cost-effectiveness ratio for the base-case assumptions. All studies report sensitivity analyses for a range of different assumptions for the key model parameters. The prevalence of Barrett's Oesophagus in the screened population is clearly a major driver of cost-effectiveness.

Author	Population screened	Prevalence of BO	Incremental cost-effectiveness ratio
Inadomi 2003 [7]	50-yr white men with GORD	10%	\$10,444 per QALY
Rubenstein 2006 ^[4]	50-yr white men with GORD	10%	\$13,721 per QALY
Rubenstein 2007 ^[5]	50-yr white men with GORD	10%	\$11,254 per QALY
Gerson 2004 [3]	50-yr men with GORD	10%	\$12,140 per QALY
Benaglia 2012 [9]	50-yr men with GORD	8%	\$22,167 per QALY for endoscopy \$15,724 per QALY for cytosponge
Nietert 2003 [2]	50-yr men and women with GORD	3%	\$86,883 per QALY for standard endoscopy \$55,764 per QALY for ultra-thin endoscopy
Soni 2000 ^[6]	60-yr men and women with GORD	10%	\$24,718 per QALY
Gupta 2011 ^[8]	50-yr men and women attending for screening colonoscopy	1%	\$95,559 per QALY

QALY = (Quality Adjusted Life Years)

Conclusion

Despite the limitations of the studies discussed already, there is consistent evidence that the most cost-effective strategy is one-off screening of 50-year old men with GORD. This could potentially be refined further to only white men, recognising that this is based on hypothetical populations from the US. The generalisability of this to the Australian population is uncertain. Both the cytosponge and ultra-thin endoscopy may be more cost-effective compared to standard endoscopic screening. Screening men and women with GORD at aged 60 would be an alternative screening model which would still be considered cost-effective on current standards, albeit less so than screening only symptomatic men at 50 years. General population screening, even if conducted coincident with colonoscopy screening, is not cost-effective and would also not be consistent with current Australian recommendations for general population screening for colorectal cancer.

Evidence summary and recommendations

Practice point?

There is no evidence to support general population screening for Barrett's Oesophagus.

Practice point?

In the absence of Randomised Controlled Trial evidence of effectiveness, screening for Barrett's Oesophagus would be most cost-effective if limited to 50-year old men with gastro-oesophageal reflux disease.

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How effective is endoscopic management compared with surgical management for high grade dysplasia in patients with BO?

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How effective is endoscopic management compared with surgical management for high grade dysplasia in patients with BO?

Introduction

The diagnosis of high grade dysplasia (HGD) in a patient with Barrett's Oesophagus increases the risk of either harbouring or developing oesophageal adenocarcinoma. Treatment options for HGD can range from surgical resection through to endoscopic treatments. Data from surgical resections performed in patients with HGD have noted the presence of adenocarcinoma varies, with reported rates between 7%^[1] and 36%.^{[2][3]} A systematic review reported the presence of T1b / submucosal adenocarcinoma in 12.7% cases.^[4] The majority of this data is from a period prior to the routine use of EMR around 2005 which enables improved staging and detection of both T1a and T1b lesions. Surgical resection is effective in removing the dysplastic area but is associated with potentially significant perioperative morbidity and mortality as well as an impact on quality of life. Recent developments in endoscopic techniques have led to improved methods for resecting and ablating the dysplastic epithelium. The understanding of lymph node risk associated with lesions as they progress from HGD to T1b lesions allows us to use this information to tailor treatment options for our patients.^{[4][5]}

Surgery

Oesophagectomy is major surgery with associated perioperative morbidity and mortality. There is data to support that oesophageal surgery should be performed in specialised units and in these centres the perioperative mortality is reduced to 2-4% or less.^{[6][7]} Perioperative morbidity remains an issue after oesophageal surgery, with major morbidity reported in 25-40% of patients.^{[8][7]} The benefit of surgical resection is the ability to remove all dysplastic epithelium and any undiagnosed adenocarcinoma and the locoregional nodal basins. This allows for a long term disease free survival greater than 90% without the need for ongoing surveillance.^[8]

Endoscopic therapies

Endoscopic therapies (photodynamic therapy, argon plasma coagulation, radiofrequency ablation, endoscopic mucosal resection) for HGD have evolved significantly recently. They can be broadly divided into resection or ablation techniques. Endoscopic mucosal resection can be used as both a diagnostic and therapeutic tool and has the benefit of providing a histopathological specimen. It can be combined with ablative techniques such as radiofrequency ablation to treat larger areas of mucosa. A systematic review of endoscopic treatments has found that they are generally safe with only one death reported in the pooled data of 2831 cases.^[9] The morbidity associated with endoscopic treatments is less than that associated with surgery. The short term efficacy in eradication of HGD varies from 66-100% and long term data is lacking.^[9]

Surgery versus endoscopic therapies

There are no randomised controlled trials comparing surgery with endoscopic treatments for HGD. A Cochrane review updated in 2012 excluded 13 non-randomised retrospective studies comparing outcomes between surgery and endoscopic treatments.^[8] A meta-analysis of seven non-randomised studies comparing endoscopic and surgical management has also been performed.^[10] These studies demonstrate similar overall survival and cancer related mortality between the two groups with the endoscopic group having a higher neoplasia recurrence rate, however, 78-100% patients were able to undergo repeat endoscopic treatment successfully.

There was no statistical difference in procedure related mortality and the endoscopic group have less procedure related morbidity.^[10] The studies utilised in these reviews come from world leading centres with excellent results, but all highlight, that to achieve these results multiple endoscopic sessions are needed. Intensive endoscopic follow protocols are also paramount to detect and manage any local recurrences^{[11][12][13]} (see also [After successful endoscopic treatment for BO neoplasia, how frequently should patients undergo endoscopy?](#)).

Evidence summary and recommendations

Evidence summary	Level	References
In specialist centres, endoscopic treatment of patients with high grade dysplasia provides similar outcomes to surgery with regard to overall survival and cancer related mortality.	III-2	[8], [9], [10], [11], [12], [13]
In specialist centres, patients with high grade dysplasia undergoing endoscopic treatments compared to surgery have less morbidity, but a higher incidence of local recurrence.	III-2	[8], [9], [10], [11], [12], [13]

Evidence-based recommendation?	Grade
It is recommended that patients with high grade dysplasia in Barrett's Oesophagus be managed in centres with high volume experience of the condition. The treatment and follow-up should occur in those specialist centres.	C

Practice point?
<p>Patients with high grade dysplasia in Barrett's Oesophagus can be discussed at a multidisciplinary team meeting at a specialist centre.</p> <p>Endoscopic treatment will be the first line treatment option for the majority of patients with high grade dysplasia in Barrett's Oesophagus. There will be a group of patients for whom endoscopic treatment is not appropriate or successful and will be best treated with surgery in a specialist centre.</p>

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How frequently should patients with BO undergo endoscopy?

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How frequently should patients with BO undergo endoscopy?

Introduction

Endoscopic surveillance in patients with Barrett's Oesophagus (BO) is the current standard of practice.^[1]

^[2] The aim of surveillance is to effectively detect Barrett's dysplasia and early cancer that can be

 **Uncertainty regarding risk of low grade dysplasia progression**

curatively treated with the least invasive modality, thereby improving survival and reducing death from oesophageal adenocarcinoma. The decision to commence an endoscopic surveillance programme is based on multiple factors including age, co-morbidities and the patient's wishes and ability to adhere to the recommended surveillance schedule.

The management of patients diagnosed with Barrett's oesophagus with low grade dysplasia (LGD) is currently uncertain, as there is considerable debate about the risks of progression to high grade dysplasia (HGD) or cancer in this group. Population-based studies which have followed Barrett's oesophagus patients diagnosed with LGD in the community have reported rates of progression to cancer of ~0.5% p.a. ([Hvid-Jensen et al 2011](#)). In contrast, studies undertaken in academic centres in which diagnoses of LGD are made only after review by expert gastrointestinal pathologists report rates of progression as high as 13% p.a. ([Curvers et al 2010](#)). Importantly, in those studies, about 85% of patients diagnosed originally with LGD were down-staged to non-dysplastic Barrett's oesophagus upon expert review. In the group of down-staged patients, the rate of progression was ~0.5% p.a - about the same as the rate observed in the community-based studies. These apparently conflicting data have implications for [how LGD is diagnosed](#), [how patients are managed](#) and [frequency of surveillance](#).

What is the evidence that endoscopic surveillance is effective?

Although endoscopic surveillance is the current standard of practice, there is no direct evidence based on randomised controlled trials for its effectiveness. There is indirect evidence based on earlier stage and improved survival in those patients with oesophageal adenocarcinoma detected in a surveillance program, although these retrospective studies are subject to potential lead and length time bias.^{[3][4]} A recent case-control study has shown that endoscopic surveillance of Barrett's Oesophagus patients was not associated with a substantially decreased risk of death from oesophageal adenocarcinoma, although a small to moderate benefit could not be excluded.^[5]

What is the evidence for frequency of endoscopic surveillance?

There are no prospective studies comparing the effectiveness of differing frequencies of endoscopic surveillance. A prospective UK cohort study found no relationship between the frequency of detection of dysplasia and frequency of endoscopic surveillance in patients with non dysplastic Barrett's Oesophagus.^[6] In those with low grade dysplasia, more frequent (< three monthly) endoscopic surveillance was associated with

an increased detection of high-grade dysplasia and adenocarcinoma. However those patients, who underwent endoscopy more frequently than third monthly, were also more likely to have oesophageal strictures and ulcers, both of which are associated with advanced lesions. 40% of adenocarcinomas diagnosed in the overall cohort were diagnosed at endoscopies done for symptoms rather than at the time of a scheduled surveillance procedure. This study was limited by no standardisation of endoscopic and biopsy protocol with low adherence to Seattle biopsy protocol and wide variation in endoscopic surveillance in low grade dysplasia.

What is the evidence for basing endoscopic frequency on previous endoscopic and histological findings?

Current international guidelines use the presence or absence of dysplasia on previous protocol biopsies to determine the frequency of endoscopic surveillance.^{[1][2]} There has been no prospective study comparing the effectiveness of differing frequencies of endoscopic surveillance based on these factors. Indirect evidence comes from studies that have shown a previous history of any grade of dysplasia,^[7] low grade dysplasia^{[8][9]} and high grade dysplasia, aneuploidy and increased 4N (tetraploidy)^[10] are associated with an increased risk of progression to high grade dysplasia and adenocarcinoma. The British Society of Gastroenterology guidelines also use the presence or absence of intestinal metaplasia and segment length to determine the frequency of endoscopic surveillance. Again this is based on indirect evidence of a higher risk of progression to adenocarcinoma in those with intestinal metaplasia compared to those without^[9] and in those with longer Barrett's segment length.^{[11][12]}

What non-patient factors influence current endoscopic surveillance practice?

A number of studies in countries outside Australia have surveyed practitioners regarding their endoscopic surveillance practice. 50-60% of practitioners reported adhering to endoscopic frequency and biopsy guidelines.^{[13][14][15]} Factors that influenced adherence to guidelines included younger practitioner age,^[13] practice in an academic centre,^[13] belief in the efficacy of Barrett's surveillance^{[16][17]} and medico-legal considerations.^{[16][18]}

A US cross-sectional study found that 65% of patients with non-dysplastic Barrett's Oesophagus had endoscopic over-surveillance.^[19] Patient related factors, including numeracy skills and patient perception of cancer risk were not associated with over-surveillance, suggesting that non-patient factors may influence the frequency of endoscopic surveillance.

An Australian study found that dissemination of guidelines to endoscopists had little effect on adherence to endoscopic frequency and biopsy guidelines. However, introduction of a Barrett's Oesophagus surveillance officer led to a marked sustained improvement in adherence to endoscopic frequency (17% to 92%) and biopsy protocols (45% to 83%).^[20]

Economic analyses

In an attempt to overcome the lack of high quality clinical evidence, mathematical modelling studies have examined the cost-effectiveness of varying endoscopic surveillance strategies, including different endoscopic frequencies.^{[21][22][23]} These studies have significant limitations including predating the use of endoscopic treatment for high grade dysplasia and early adenocarcinoma, inconsistent methods and delivery of surveillance and variable data regarding the incidence of progression of BO to high-grade dysplasia and carcinoma. A large systematic review with economic modelling concluded that there was insufficient evidence available to assess the clinical effectiveness of endoscopic surveillance of Barrett's Oesophagus^[24] (see also [Is surveillance cost-effective for follow-up of patients with BO?](#)).

Transient low grade dysplasia results in a substantial increase in endoscopic workload (28-61% of endoscopies) and costs (\$509,549 over 10 years in a cohort of 95 patients) in a Barrett's surveillance programs.^[25] The authors recommended returning to a non-dysplastic surveillance program after two endoscopies that showed no dysplasia.

Current recommendations of other international guidelines

Currently, both the British Society of Gastroenterology (BSG) and American Gastroenterological Association (AGA) have published guidelines for endoscopic surveillance of BO.^{[1][2]} The guidelines differ in the criteria for the diagnosis of BO with both requiring a columnar lined oesophagus (CLO) but the AGA also requiring intestinal metaplasia to be present in biopsies from the CLO. This Australian guideline uses the AGA criteria for a diagnosis of BO (see also [What is the endoscopic definition of BO and how is it described?](#) and [What is the histological definition of BO?](#)). Both guidelines use the grade of dysplasia found at endoscopy to determine the timing of the subsequent surveillance endoscopy. These recommendations are based on the evidence of an increased risk of oesophageal adenocarcinoma with increasing degrees of dysplasia. In those with no dysplasia, the BSG guidelines also take into account the absence of intestinal metaplasia and short-segment (<3cm) length, both of which appear to be associated with a decreased risk of malignant progression (see also [Are there groups of patients with BO that can be discharged from surveillance?](#)). Both guidelines recommend biopsies of any visible lesion or mucosal irregularity and quadrantic biopsies. The BSG guidelines recommend quadrantic biopsies every 2 cm in all surveillance endoscopies. The AGA guidelines recommend Seattle protocol biopsies with quadrantic biopsies every 2 cm unless there is suspected or known dysplasia where every 1 cm is recommended. These biopsy protocols have been shown to increase the detection of advanced (high grade and early adenocarcinoma) lesions.^{[26][27]} However, there is low adherence to the protocols^[6] resulting in lower detection rates of dysplasia.^[28]

Recommendations for frequency of endoscopic BO surveillance

The recommendations of this Australian guideline for frequency of surveillance of BO are shown in Tables 1-4. For a diagnosis of BO, the guidelines require both a CLO and the presence of intestinal metaplasia in biopsies from the CLO. Recommendations for CLO without intestinal metaplasia are discussed below. After careful and meticulous examination of the Barrett's segment for any lesion or visible abnormality, Seattle protocol biopsies

from the CLO are recommended at the time of endoscopic surveillance. In this protocol biopsies are taken of any mucosal irregularity (labelled separately) and quadrantic biopsies every 2cm unless known or suspected dysplasia then quadrantic biopsies every 1cm. The presence of dysplasia (indefinite, low and high grade) should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist (see also [What is the histological definition and grading of dysplasia in patients with BO?](#) and [What is the appropriate management of low grade dysplasia in patients with BO?](#)).

The management of patients diagnosed with BO with low grade dysplasia is currently uncertain, as there is considerable debate about the risks of progression to high grade dysplasia or cancer in this group. This has implications for how low grade dysplasia is diagnosed and how patients with low grade dysplasia are managed (see also [What is the histological definition and grading of dysplasia in patients with BO?](#) and [What is the appropriate management of low grade dysplasia in patients with BO?](#)).

Decisions regarding the frequency of endoscopy and management of patients with BO also need to take into consideration clinical judgement and individual patient circumstances including:

- a) The presence of concurrent erosive oesophagitis within the BO segment (see also [What is the optimal tissue sampling at endoscopy for diagnosis of BO?](#)).
- b) The presence of a lesion or visible abnormality within the BO segment at endoscopy (see also [What are the endoscopic features of neoplasia \(dysplasia and early cancer\) within a BO segment?](#) and [What is the best endoscopic management of early oesophageal adenocarcinoma?](#)).

Table 1-4: Recommended frequency of endoscopic surveillance of patients with Barrett’s Oesophagus

BO SURVEILLANCE PROTOCOL	
NO DYSPLASIA ON ENDOSCOPIC ASSESSMENT AND SEATTLE PROTOCOL BIOPSY*	
Short (<3cm) segment	Long (≥ 3cm) segment
Repeat endoscopy in 3-5 years.	Repeat endoscopy in 2-3 years.
*Note: If there has been previous low grade dysplasia, see low grade dysplasia protocol.	

BO SURVEILLANCE PROTOCOL
INDEFINITE FOR DYSPLASIA ON BIOPSY
The changes of indefinite for dysplasia on biopsy should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist. If indefinite for dysplasia is confirmed, then the following endoscopic surveillance is recommended:
Repeat endoscopy in 6 months with Seattle protocol biopsies for suspected dysplasia (biopsy of any mucosal irregularity and quadrantic biopsies every 1cm) on maximal acid suppression.
If repeat shows no dysplasia then follow as per non-dysplastic protocol.
If repeat shows low grade or high grade dysplasia or adenocarcinoma then follow as per protocols for these respective conditions.

BO SURVEILLANCE PROTOCOL

INDEFINITE FOR DYSPLASIA ON BIOPSY

If repeat again shows confirmed indefinite for dysplasia, then repeat endoscopy in 6 months with Seattle protocol biopsies for suspected dysplasia (biopsy of any mucosal irregularity and quadrantic biopsies every 1cm).

BO SURVEILLANCE PROTOCOL

LOW GRADE DYSPLASIA ON BIOPSY

The changes of low grade dysplasia on biopsy should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist. If low grade dysplasia is confirmed, then the following endoscopic surveillance is recommended:

Repeat endoscopy every 6 months with Seattle protocol biopsies for dysplasia (biopsy of any mucosal irregularity and quadrantic biopsies every 1cm). If two consecutive 6 monthly endoscopies with Seattle dysplasia biopsy protocol show no dysplasia, then consider reverting to a less frequent follow up schedule.

BO SURVEILLANCE PROTOCOL

HIGH GRADE DYSPLASIA OR ADENOCARCINOMA ON BIOPSY

Referral to a referral centre that has integrated expertise in endoscopy, imaging, surgery and histopathology.

Endoscopic surveillance in patients with CLO without intestinal metaplasia

In some patients, despite Seattle protocol biopsies from a CLO, there will be no intestinal metaplasia or dysplasia within the biopsies from the CLO. In these patients, if there is evidence of a long (≥ 3 cm) segment of CLO, it is recommended that they continue endoscopic surveillance as per the protocol for long segment BO (i.e. every 2-3 years). If there is 1- <3 cm of CLO without intestinal metaplasia or dysplasia, a repeat endoscopy in 3-5 years is suggested with consideration of discharge from endoscopic surveillance if the repeat endoscopy with Seattle protocol biopsies again shows no intestinal metaplasia or dysplasia within the CLO. In patients with CLO less than 1cm without intestinal metaplasia or dysplasia on biopsies from the CLO, no endoscopic surveillance is suggested. If dysplasia is found in any biopsies from a CLO without intestinal metaplasia, then recommendations are as per the protocols for BO with dysplasia.

Evidence summary and recommendations

Practice point?

In the absence of any randomised trial evidence, the frequency of surveillance endoscopy in Barrett's Oesophagus can be guided by currently available practice guidelines.

Practice point?

It is advisable to undertake endoscopic surveillance in suitable patients with Barrett's Oesophagus. The frequency of surveillance is based on the presence or absence of dysplasia on previous Seattle protocol biopsies and length of Barrett's Oesophagus.

Practice point?

A diagnosis of dysplasia (indefinite, low and high grade) should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist.

Practice point?

It is recommended that oesophageal biopsies at the time of endoscopic surveillance of Barrett's Oesophagus be taken according to the Seattle protocol.

Issues requiring more clinical research study

- Is endoscopic surveillance in Barrett's Oesophagus effective?
- What factors are associated with an increased risk of progression in Barrett's Oesophagus?
- Does integration of these risk factors into endoscopic surveillance protocols improve their effectiveness?

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Is surveillance cost-effective for follow-up of patients with BO?

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Is surveillance cost-effective for follow-up of patients with BO?

Background

Australia’s health system faces increasing pressure to contain healthcare costs, while still maintaining high quality and optimal care. Cost-effectiveness analysis is a process that systematically compares the relative healthcare costs and benefits of alternative strategies to inform policy-makers of the strategies with the best value.^[1] There are a number of economic considerations in deciding whether the surveillance of Barrett’s Oesophagus is worthwhile. These include:

- A surveillance program involves repeated invasive endoscopies that are also costly when low-risk individuals will be examined frequently, although it is the only method to detect early stage oesophageal cancer and avoid death from advanced disease;

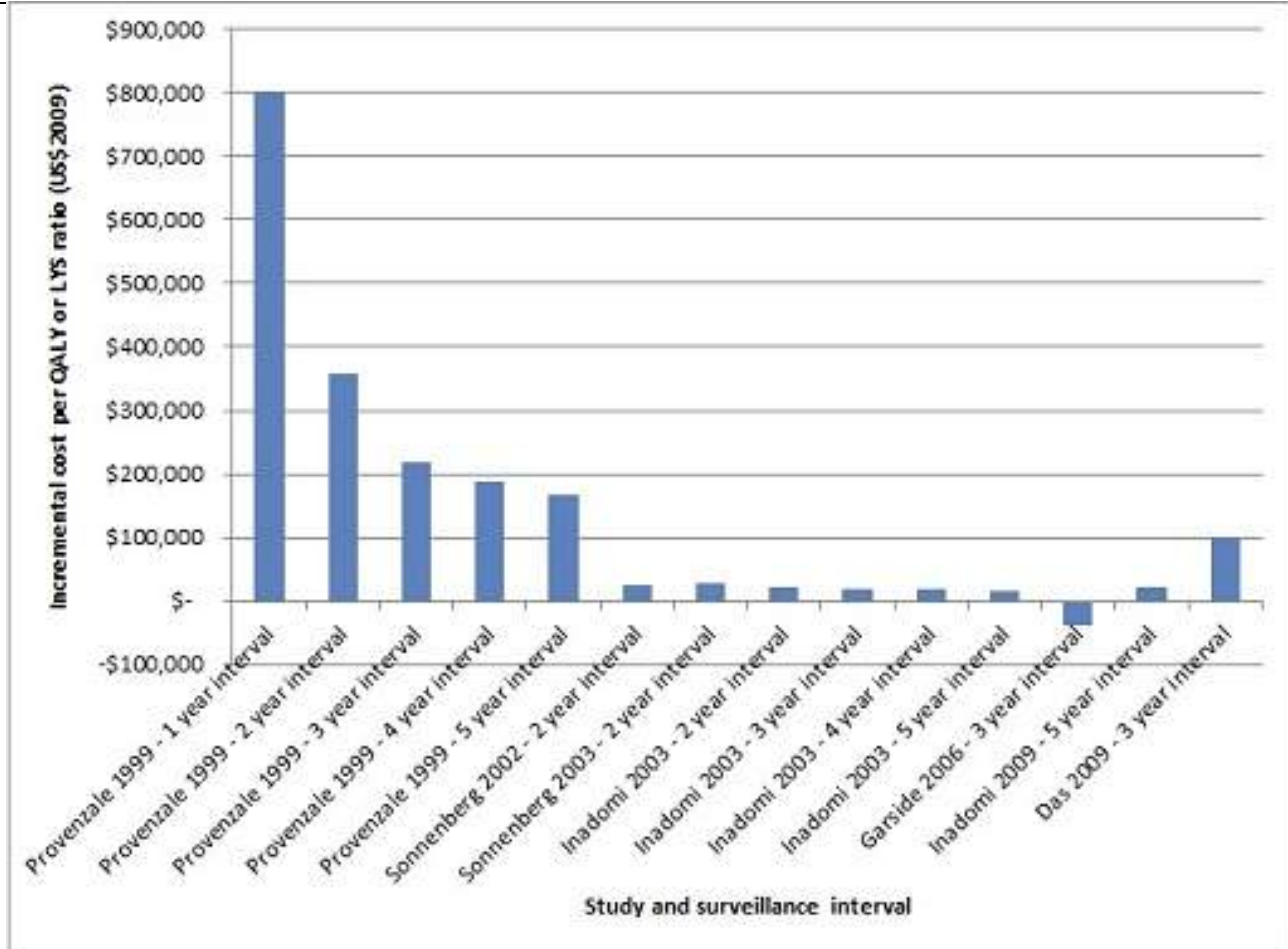
- Efficacy of surveillance should be established first before assessment of cost-effectiveness but no large-scale trial has been undertaken and it is unlikely one will be given that recruitment is usually slow, the yield of cancer cases is low and very high numbers of participants are required;
- To undertake a high-quality cost-effectiveness study, robust data on the natural history of disease progression, the effectiveness of surveillance, and evidence of health resources used are required. However, data on all of these has been scarce, until more recently,^{[2][3]}
- Treatment costs for oesophageal cancer are changing with newer less-invasive endoscopic technologies; and
- The cost-effectiveness of treatments for oesophageal cancer and high-grade dysplasia and the associated impact on the economic benefit of surveillance programs is unknown.

Whether surveillance of Barrett's Oesophagus is cost-effective or not depends on if the incremental costs of surveillance (versus no surveillance) and the incremental health gains (versus no surveillance) are acceptable. Economic studies addressing this question have used mathematical modelling to synthesize the 'best available' evidence required for cost-effectiveness analysis and importantly address the uncertainty inherent in the model estimates.^[4]

Review of the evidence

One systematic review summarizes the evidence for cost-effectiveness of endoscopic surveillance of non-dysplastic Barrett's Oesophagus.^[5] The review included seven studies that met the inclusion criteria^{[6][7][8][9][10][11][12]} which were; 1) it had to be a comparison of surveillance for individuals with Barrett's Oesophagus versus no surveillance, and 2) it had to include the key outcome of either quality-adjusted life year (QALY) or life-years saved (LYS) and 3) included both costs and health benefits in the analysis. Figure 1 illustrates the key results for the studies included in the review for the incremental cost per QALY/LYS ratios of endoscopic surveillance versus no surveillance strategy. Two studies by Sonnenberg et al. reported incremental cost per LYS.^{[11][12]}

Figure 1. Key findings of cost-effectiveness of surveillance versus no surveillance (incremental cost per QALY/LYS gained ratios)



Source: Data from Hirst et al. (2011)^[5]

All studies were US-based with the exception of one UK study^[7] and published from 1999-2009. All studies used decision-analytic Markov models to track hypothetical patient cohorts able to move between health states and reflect observed disease progression. The models were lifetime duration over 25-30 years or until death. The findings were inconsistent about the value of surveillance, ranging from being cost-effective to highly cost-ineffective.^{[6][8][9][10]} In addition, the studies in the review used data that is largely outdated now. New evidence is available on quality of life, proportion of patients progressing among dysplasia grades, improved mortality rates for oesophagectomy and estimates on the natural history of Barrett's Oesophagus.^[3] Clinical practice has also improved with greater use of less invasive endoscopic techniques that promise to reduce treatment costs.

Key Limitations of the evidence in Hirst N et al. (2009) include:

- No randomised controlled trial for surveillance of Barrett's Oesophagus
- Author assumptions made for key model estimates not based on robust data;^[5]
- Studies have only partially addressed key aspects of uncertainty in the analyses;

- Applicability to Australia is limited due to differences in practice patterns, health care prices and organisation of the health system.
- Heterogeneity in surveillance program delivery
- Endoscopic screening/surveillance methods were not always consistent^{[13][14]}
- Heterogeneity in definition of Barrett's Oesophagus, i.e., confirmed intestinal metaplasia or other.

One study in the UK by Roberts KJ et al.^[15] that was published after the review period by Hirst claimed annual surveillance was cost-effective at £4,493 per life year gained. This study had 'prevalent cases of cancer' as the comparator and it is unclear if this is a suitable comparison. In addition, the analyses did not apply discounting or sensitivity analyses which are standard practice in health economic studies.

Current directions – surveillance of high-risk individuals

Patients who are most likely to benefit from surveillance programs are those at high-risk of developing malignancy. At the same time a targeted surveillance program will minimise unnecessary use of hospital resources. Three cost-effectiveness studies were identified that specifically addressed high-risk individuals; two involved biomarker testing^{[16][17]} and one involved individuals with long-segment Barrett's oesophagus.^[18]

Rubenstein's approach was to determine how sensitive and specific a biomarker test would need to be, and how cheap, to be a cost-effective surveillance program.^[16] In Gordon et al, the cost-effectiveness of surveillance in Australia was favourable under the hypothetical scenario of biomarker testing and where patients testing negative for biomarkers did not receive surveillance in the following five years and received two-yearly surveillance thereafter.^[17] However, the model assumed that no cancers progress to advanced stage disease under such modified surveillance protocols, that is, all early cancers were successfully eradicated and there is only limited evidence available to support this.^[17] Most recently, Kastelein et al concluded that surveillance was cost-effective in the Dutch healthcare system among individuals with long-segment Barrett's oesophagus (median 4cm) at intervals of 5 years for patients with non-dysplasia and 3 years for low-grade dysplasia.^[18] These studies highlight the importance of the frequency of endoscopy surveillance which, if scheduled less frequently, can improve the cost-effectiveness of surveillance. However, currently surveillance intervals are consensus rather than evidence-based (see also [How frequently should patients with BO undergo endoscopy?](#)^[18])

Presently, the appropriateness of biomarker testing, its efficacy within a surveillance program, its feasibility and its acceptance are yet to be determined. Further clinical and economic research involving patients with positive biomarkers and additional high-risk factors (e.g., male, the presence of oesophagitis, length of Barrett's Oesophagus, and length of time with Barrett's Oesophagus^[19]) is required to assess outcomes from a more targeted high-risk surveillance population.

Conclusion

Economic evaluations are designed to assist with efficiently allocating scarce health care resources, that is, to minimise costs for given health outputs. Therefore, the cost-effectiveness of appropriate management strategies for patients with Barrett's oesophagus should be considered. Based on the evidence of the malignant potential of Barrett's Oesophagus in the general population versus those reported in surveillance program audits, surveillance of all patients with non-dysplastic Barrett's oesophagus may not be cost-effective. Further work to identify high-risk individuals, those with long-segment Barrett's or positive biomarkers, appear promising to improve the economic efficiency of endoscopy-based surveillance of Barrett's oesophagus.

Implications for practice

- Cost-effectiveness of endoscopic surveillance of patients with Barrett's Oesophagus is limited in the absence of a randomised clinical trial to confirm the efficacy of surveillance
- Mathematical modelling studies estimate that endoscopic surveillance of patients with non-dysplastic Barrett's Oesophagus is likely not be cost-effective and remains controversial
- Identifying patients at high-risk of progression to adenocarcinoma substantially improves cost-effectiveness
- Using Clinical Practice Guidelines and consensus statements to guide practice around surveillance protocols will increase the cross-comparison of research audits and could be used to feed into cost-effectiveness analyses.

Issues requiring more clinical research study

- New technologies used in the treatment pathways for patients identified for surveillance of Barrett's oesophagus need to be assessed for their cost-effectiveness
- Identification of high-risk individuals via positive biomarkers, long-segment Barrett's oesophagus or other known risk-factors shows promise in improving the cost-effectiveness of endoscopic surveillance and clinical research evidence to confirm this is required.

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Is there a role for ablative therapy to treat BO?

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Is there a role for ablative therapy to treat BO?

Introduction

There is considerable interest in the possibility of ablating the Barrett's mucosa in an effort to reduce the risk of progression to malignancy and perhaps obviate the need for ongoing endoscopic surveillance. There have been a number of endoscopic therapies that have been studied to ablate Barrett's mucosa. These have mostly been tested in patients with non-dysplastic mucosa (see also [Are there any treatments that prevention progression of BO to cancer?](#)).

Photodynamic therapy

Photodynamic therapy involves the administration of a photosensitiser drug and then subsequent exposure of the target tissue (Barrett's mucosa) with a laser light. There are two photosensitisers that have been mainly studied and these are aminolevulinic acid (given orally) and Photofrin (given intravenously). The studies have all been published in North America and Europe due to the potentially severe skin sensitivity that arises after administration of the photosensitiser. In the case of aminolevulinic acid this can last days and for Photofrin possibly months. During this time the subject must remain in a darkened environment. This issue restricts the use of this technology to cooler climate countries. Studies comparing the photosensitisers and various doses and times of administration favour aminolevulinic acid over Photofrin as being more effective.^[1] Most published studies however are small and methods vary widely making comparisons difficult.^[2] One study includes a large number of patients from 30 centres in four countries.^[2] This study may be prone to institutional variations and inconsistent application of the study protocol. Photodynamic therapy is able to reliably ablate Barrett's mucosa and in up to 77% of patients there is complete ablation.^{[3][4]} Comparisons have been made between photodynamic therapy and argon plasma coagulation but a clear difference has not been established.^{[5][6][4]}

Argon plasma coagulation

Argon plasma coagulation (APC) is a widely available monopolar electrocautery device where argon gas is passed through a fine catheter inserted through the channel of an endoscope. As the gas leaves the catheter it passes over a high voltage electrode which electrifies the gas producing argon plasma. This plasma conducts the electrical energy to the target tissue without physical contact. The benefit of the system is that it produces superficial coagulation of the target tissue without injuring deeper layers of the gut wall. APC has been shown to effectively ablate Barrett's mucosa and mucosal eradication of greater than 95% has been reported in the majority of subjects (97% of treated patients).^{[7][8][9][10]} Randomised controlled studies show that both medically treated patients and those with prior successful fundoplication can be cleared of Barrett's mucosa whereas control patients do not show significant regression.^{[7][8][9]} Long term data to >84 months shows some relapse of Barrett's mucosa but 65% of patients have no evidence of Barrett's mucosa.^[11] APC has been compared to PDT^{[5][6]} and multipolar electrocoagulation therapy,^{[12][13]} but no significant differences have been identified. APC is safe but isolated reports of oesophageal stricture formation and oesophageal perforation have been reported. The majority of studies examining APC have treated non-dysplastic Barrett's mucosa.

Multipolar electrocoagulation

Multipolar electrocoagulation (MPEC) is a bipolar technique using a catheter passed through the channel of an endoscope. The catheter has a number of electrodes on its tip. Electrical current is passed between the electrodes through the adjacent target tissue causing thermal coagulation of the tissue. The current is confined to the mucosal surface and therefore only mucosal destruction is seen with sparing of the deeper layers. The type of mucosal effect is similar to that of APC. MPEC has been compared to APC and these two techniques have been found to have comparable efficacy in ablation of Barrett's mucosa.^[12] MPEC may require slightly fewer treatment sessions than APC and be quicker to perform. Safety of MPEC therapy appears to be good and long term follow up suggests the results are similar to that seen in patients treated with APC. The majority of studies examining MPEC have treated non-dysplastic Barrett's mucosa.

Cryotherapy

Cryotherapy for Barrett's mucosal ablation involves spraying the oesophageal mucosa with either liquid nitrogen or pressurised CO₂ gas. The mucosa is ablated by freezing the superficial layers. The equipment required is bulky, expensive and highly specialised and at this stage not readily available outside research centres. Initial studies were performed using liquid nitrogen but this is relatively hazardous equipment to use as catheter dysfunction could cause injury to staff and equipment. More recent studies use pressurised CO₂ which is technically easier to administer. Reported safety seems good but significant treatment side effects include chest pain, dysphagia and odynophagia. These symptoms can last a number of days. Studies have been performed only for dysplastic Barrett's mucosa.^[1]

Radiofrequency ablation

Radiofrequency ablation (RFA) of Barrett's mucosa has received the most rigorous study of all the ablation techniques. RFA involves placement of a balloon catheter in the oesophagus. Around the circumference of the balloon are fine electrodes through which radiofrequency energy is delivered allowing treatment of a 3cm circumferential segment of the oesophagus. Balloon position is monitored with an endoscope and treatment of the entire Barrett's segment is generally possible in one session. The procedure is relatively easy and quick to perform and is well tolerated by patients. Side effects include chest pain, dysphagia and stricture formation. Rare complications such as bleeding and perforation have been noted. The RFA catheters are single use and relatively expensive limiting broad application of this technology. Well-designed randomised sham controlled studies have shown high levels of eradication of both non-dysplastic (>90%) and dysplastic (>90%) Barrett's mucosa.^[1] Long term follow up studies show the response is durable with the majority of patients (>85%) maintaining complete eradication over a five year follow up period. RFA has been compared to PDT and has been shown to be more effective at Barrett's mucosal ablation. Studies have been performed in patients whose reflux disease was treated medically or managed with surgical fundoplication and the outcome was similar in these two groups.

Evidence summary and recommendations

Evidence summary	Level	References
There are a number of therapies that are able to ablate Barrett's mucosa but ablation is incomplete in a number of patients and relapse of the Barrett's mucosa over time means that ongoing surveillance endoscopy is still required. The prognosis of patients who have achieved complete eradication of Barrett's mucosa after ablation is not known.	I, II	[1], [3], [4], [6], [11], [12], [13]

Evidence-based recommendation?	Grade
Long term outcome studies do not yet support ablation in patients without dysplasia.	B

Issues requiring more clinical research study

- The long term outcome of ablation of non-dysplastic Barrett's mucosa needs to be studied to assess the durability of the ablation therapy and determine if there are any patients who subsequently no longer need follow up in Barrett's surveillance programs.

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What are the best modalities for accurately staging early oesophageal adenocarcinoma?

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What are the best modalities for accurately staging early oesophageal adenocarcinoma?

Introduction

The TNM staging system for oesophageal adenocarcinoma (American Joint Committee on Cancer, the International Union Against Cancer) is universally accepted and correlates with patient survival.^[1] Early oesophageal adenocarcinomas (EOA) are those defined as intra-mucosal adenocarcinoma (T1m) or superficial submucosal adenocarcinoma (T1sm1).^[2] A more comprehensive sub-classification of early oesophageal cancers has been proposed with mucosal disease and submucosal disease divided into three categories respectively (m1-3, and sm1-3) based on depth of invasion. The risk of nodal involvement correlates with the depth of invasion with tumour invasion deeper than the muscularis mucosa associated with a significant increase in prevalence of lymph node metastases.^{[3][4]} Cancers that are confined to the mucosa have a low risk of nodal involvement (0% in most series) and can be managed successfully with endoscopic resection (ER). When the cancer has invaded the superficial third of the submucosa (T1sm1), if the tumour is well differentiated with no lymphovascular invasion and of low histological grade, some studies suggest the risk of positive lymph nodes

remains low (<1%).^{[5][6]} Other studies have shown superficial (sm1) submucosal invasion in oesophageal carcinoma is associated with a low but not negligible rate of lymph node metastasis of 12.9%.^[7] However, if there is deeper submucosal invasion (T1sm2, T1sm3) or these other criteria are not met, then the risk of lymph node involvement increases to 44%.^[6] There are a range of management options for EOA, including endoscopic resection, surgical oesophagectomy, radiation therapy and chemotherapy and their appropriateness is dependent on accurate staging.

Options for staging of EOA include:

1. Endoscopic biopsy
2. Endoscopic resection (ER) (also known as endoscopic mucosal resection or EMR)
3. Endoscopic ultrasound (EUS) with or without fine needle aspirate (FNA)
4. Positron emission tomography-computerised tomography (PET-CT)

Endoscopic biopsy

Diagnostic accuracy of high grade dysplasia and EOA has improved due to advances in endoscopic technology including high-definition white light endoscopy, digital chromoendoscopy and systematic biopsy protocols. However, the potential for diagnostic inaccuracy persists due to biopsy sampling error and variability in histopathologic interpretation. Studies have reported the presence of occult adenocarcinoma at oesophagectomy in patients with Barrett's Oesophagus with HGD after endoscopic surveillance with systematic biopsies.^[8] The use of jumbo biopsy forceps still misses unsuspected adenocarcinoma in Barrett's Oesophagus with HGD.^[9] In comparison to systematic biopsy protocols, endoscopic resection (ER) together with expert pathological review, alters the histological grade or T-stage in the majority of patients with Barrett's-associated neoplasia.^{[10][11]}

Endoscopic resection (ER)

Endoscopic resection (ER, also known as endoscopic mucosal resection EMR) involves local snare excision of the lesion down to the level of the submucosa and has been increasingly used as both a staging tool and a therapeutic treatment option for management of dysplastic Barrett's Oesophagus and EOA.^{[12][13]} ER is recommended for dysplasia associated with any visible lesions within Barrett's segment as it allows more accurate assessment of the severity of dysplasia and local T-staging, particularly for the assessment of submucosal invasion, compared with targeted biopsies alone. It may also be curative in intramucosal (T1a) adenocarcinoma. In a multicentre cohort study, ER resulted in a change of diagnosis for approximately 30% of Barrett's Oesophagus patients with early neoplasia (with and without visible lesions).^[14] In other series, ER results in a change of pre-treatment histopathologic diagnosis in 25-55%.^{[10][15][16]} In a prospective series of 75 patients at two Australian tertiary centres, ER histology resulted in altered grading or staging in 48% of patients (down 28%, up 20%) and complete Barrett's excision was successful in 94% with no metachronous lesions detected after a mean follow-up of 31 months.^[11] In nodular lesions, ER with histological examination provides greater utility than staging by EUS.^{[17][18]}

ER does carry risks of perforation, bleeding and anaesthetic-associated risk although rates of these adverse events were low in most series.^{[11][18][19]} Strictureing is an additional risk, particularly where long segment circumferential ER is performed. Contraindications to ER may include ulcerated or depressed lesions, coagulopathy, strictureing or poor endoscopic access to the lesion. If ER is performed with curative intent in EOA, it is important to enrol patients into a strict surveillance program with high-definition white light endoscopy and digital chromoendoscopy, due to the risk of developing metachronous lesions.

Endoscopic ultrasound (EUS)

EUS has been used as a staging tool in EOA to determine depth of infiltration and the presence of lymph node metastases prior to referral for endoscopic therapy or oesophagectomy. Studies have shown that EUS is superior to computed tomography (CT) for delineating tumour depth staging and the presence of pathological lymph nodes.^[20] The T-staging accuracy of EUS for EOA and high grade dysplasia in the setting of Barrett's Oesophagus has been questioned. A systematic review of 12 studies with data on 292 patients with oesophageal high grade dysplasia or EOA comparing EUS with surgery or ER pathology staging found a T-stage concordance of 65% across all studies and 56% concordance in 8 studies with individual patient level data.^[21] In another meta-analysis of patients with either superficial oesophageal squamous cell carcinoma (SCC) or adenocarcinoma, a subgroup analysis found the overall EUS accuracy for differentiating mucosal (T1a) from submucosal (T1b) oesophageal adenocarcinoma was 143 of 170 lesions (84%).^[22] Other studies confirm a significant false positive rate for diagnosis of submucosal invasion (up to 84%) which may lead to unnecessary oesophagectomy in patients that could be successfully treated with ER.^{[23][24]} High frequency miniprobe EUS, with improved image resolution, still has limited accuracy in the detection of submucosal invasion of early oesophageal cancers.^[24] Chemaly et al demonstrated in their study of 91 patients with superficial Barrett's adenocarcinoma or SCC, that the overall accuracy of miniprobe EUS was 73.5%. In the same study, a statistically significant difference in the accuracy rate of EUS was noted, dependant on lesion location within the oesophagus, with 87.1% of proximal and mid oesophagus lesions staged accurately compared with 47.6% of distal oesophagus lesions. The endoscopic morphology of visible lesions within Barrett's Oesophagus may also be useful for predicting the histologic T-stage, with one series demonstrating that Paris type 0-IIb (flat) lesions were always confined to the mucosal layer, whereas Paris type 0-IIc (depressed) lesions almost invariably had submucosal invasion.^[25] EUS evaluation before ER therefore appears to have limited value in the absence of suspicious endoscopic features.

It is important to differentiate the relatively poor performance of EUS in staging EOA, as distinct from staging for more advanced lesions ($\geq T2$) and lymph node metastasis. In a study of 100 consecutive patients with Barrett's Oesophagus and EOA, EUS proved to be highly accurate in differentiating T1 from $>T1$ lesions (sensitivity, specificity, PPV, and NPV all 100%) but not sufficiently reliable at differentiating T1m and T1sm (sensitivity 89% and 27% respectively).^[20] In a meta-analysis of patients with oesophageal cancer (SCC and adenocarcinoma) undergoing staging EUS, CT or 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), EUS had the highest sensitivity at 80% but also the lowest specificity 70% for detection of regional lymph node metastases.^[26] EUS with fine-needle aspirate (FNA) increases specificity by allowing sampling of suspicious mediastinal or coeliac axis lymph nodes, which may significantly impact treatment decisions.^[27] EUS-FNA has been shown to be superior to EUS alone and CT for nodal staging.^{[20][28]}

Positron Emission Tomography/Computed Tomography (PET/CT)

FDG-PET and CT have a limited role in staging EOA due to small tumour size in many cases and infrequent regional lymph node and distant metastases. In a retrospective series of 58 patients with superficial oesophageal adenocarcinoma, FDG-PET could not differentiate high grade dysplasia (Tis) from invasive T1 cancer, with 45% of Tis tumours having FDG uptake compared with 55% of T1 tumours.^[29] For the evaluation of distant metastases, FDG-PET probably has a higher sensitivity than CT although its combined use allows more precise anatomical location of metastases.^[26] In a prospective series of 139 patients with oesophageal cancer (85 adenocarcinoma, 53 SCC), PET/CT changed the stage group in 40% and resulted in a change in management in one third of patients, and had powerful prognostic stratification.^[30] CT has also been found to be inferior to EUS for T-staging and detection of locoregional lymph node metastases^[20] and should be reserved for staging of distant metastases in combination with FDG-PET or alone when PET is unavailable. However, in patients where surgery is being considered (for example due to submucosal invasion in the ER specimen), a PET-CT scan would usually be requested by the surgeon prior to proceeding with surgery.

Evidence summary and recommendations

Evidence summary	Level	References
Endoscopic resection (ER) results in a change in pre-treatment diagnosis after systematic biopsies in patients with Barrett's-related dysplasia or adenocarcinoma.	IV	[10], [14], [15], [16]
ER allows improved pathological staging of high grade dysplasia and T1m and T1sm adenocarcinoma as compared with biopsy and endoscopic ultrasound (EUS).	IV	[16], [18]
Rates of adverse events following ER performed at expert centres are low.	IV	[11], [18], [19]

Evidence-based recommendation?	Grade
Endoscopic resection is the most accurate staging modality for early oesophageal adenocarcinoma for suitable lesions and where appropriate expertise is available.	D

Evidence summary	Level	References
Endoscopic ultrasound has inadequate accuracy in determining the stage of early oesophageal adenocarcinoma, especially distinguishing T1m from T1sm tumours. In contrast, EUS is effective for differentiating between T1 and >T1 stages.	IV	[21], [24]
Endoscopic ultrasound and EUS-guide fine-needle aspiration (EUS-FNA) are superior to computed tomography (CT) for locoregional lymph node staging	IV	[20], [28]

Evidence-based recommendation?	Grade
Endoscopic ultrasound can be used prior to endoscopic resection for the identification of deeply invasive adenocarcinoma ($\geq T2$) and locoregional lymph node metastasis, particularly for lesions with ulcerated or depressed morphology.	D

Evidence summary	Level	References
FDG-PET cannot reliably differentiate oesophageal high grade dysplasia from invasive T1 adenocarcinoma.	IV	[29]
For the evaluation of distant metastases, FDG-PET probably has a higher sensitivity than CT although its combined use allows more precise determination of location of metastases.	IV	[26] , [30]

Evidence-based recommendation?	Grade
FDG-PET or PET/CT is not routinely indicated in staging early oesophageal adenocarcinoma. It is best used for the staging of distant metastases or in cases of suspected more advanced local disease.	D

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What are the endoscopic features of neoplasia (dysplasia and early cancer) within a BO segment?

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What are the endoscopic features of neoplasia (dysplasia and early cancer) within a BO segment?

Introduction

Dysplasia and early cancer in Barrett's Oesophagus (BO) can be inconspicuous. This is the premise behind the present recommended strategy of performing random four quadrant biopsies in every two centimetres of the BO segment. This approach has been frequently described as "hit and miss" and is fraught with problems such as adherence where only 41-56% of endoscopist follow the recommended guideline.^{[1][2]} Newer endoscopic imaging modalities have been proposed to improve the detection of dysplasia. Numerous studies have been performed on chromoendoscopy techniques (Methylene Blue, Indigo Carmine and Acetic Acid), electronic image enhancement technologies (Narrow Band Imaging, I Scan, Fujinon Intelligent Chromo Endoscopy) and high magnification platforms (Confocal Endomicroscopy, Endocytoscopy). Although promising, the data appears to have been limited mostly to tertiary referral and research centres with experience and interest in endoscopic imaging. There is lack of information if these methods can ultimately impact patient management. At the present moment, high resolution white light endoscopy (HR-WLE) remains the gold standard in evaluating patients with BO although the modalities described above can be used in addition to HR-WLE to improve characterisation of lesions.^[3] Thus, it is important to understand the gross morphological features of dysplasia and early cancer and if available, apply some of the more advanced imaging methods.

How should surveillance be performed?

For purposes of standardisation, the Prague's C & M criteria has been proposed. The criteria includes the assessment of the circumferential (C) and maximum (M) extent of the endoscopically visualised BO segment, as well as endoscopic landmarks, such as the upper end of the gastric folds^[4] (see also [What is the endoscopic definition of BO and how is it described?](#)). These findings have been validated in two large studies to date and has been found to be not only practical but reproducible.^{[5][6]} It also enables accurate identification of a lesion on repeat endoscopy for endoscopic resection especially if biopsies which have been performed previously on an inconspicuous area reveal dysplasia or early cancer.

Dysplasia in BO can be patchy.^[7] Thus examination of any patient with BO should be meticulous. Debris and mucous should be washed off. If there is extensive peristalsis, antispasmodic agents can be used. A recent study from Kansas described spending longer times inspecting the BO segment (1cm/minute) which led to a significant increase in the yield of detecting dysplastic lesions.^[8]

Gross features of dysplasia and early cancer which should be looked for

There is some evidence that cancer preferentially occurs in the distal Barrett's segment. A study of 213 patients with esophageal adenocarcinoma reported that in over 80% of cases, the tumor was located at the distal margin of the columnar-lined segment.^[9] It is also important to pay special attention to the two to five o'clock position in patients with shorter segments of BO (<5cm) as there is evidence that these areas could harbor more dysplasia.^[10] It may be worthwhile to retroflex the endoscope in a hiatal hernia segment and carefully examine this area.

All ulcers in BO should be monitored closely for carcinoma. In a large case series that reported endoscopic characteristics of mucosal cancers, depressed or excavated lesions were found in 49 of 349 patients (14%).^[11] Biopsies should always be taken in depressed regions and if negative; repeated after a course of proton pump inhibitor therapy.

Visible lumps or nodules consisting of high grade dysplasia (HGD) suggest a more advanced lesion where more sinister pathology may be present. Studies have shown that endoscopic resection of visible lumps or nodules consisting of HGD in biopsies result in an upgrade to a final diagnosis of cancer in almost 40% of cases.^{[12][13]} In a surgical series of esophagectomies performed for presumed HGD in biopsies, coexisting cancer was found in 78% of patients with a visible lesion compared to 32% without a visible lesion ($p = 0.019$).^[14] The importance of careful examination for synchronous and more advanced pathology cannot be underestimated.

Interrogating suspicious areas

Suspicious lesions visualised on 'white light overview' can be interrogated further with any of the enhanced imaging techniques described above. Digital or optical magnification endoscopes have been utilised using Methylene Blue (MB), Acetic Acid (AA) or Narrow Band Imaging (NBI). A meta-analysis by Ngamruengphong et al of 450 patients with BO in nine studies concluded that MB chromoendoscopy was comparable and not superior to conventional four-quadrant random biopsies.^[15] AA and NBI appear to be more promising. Areas harboring dysplasia or early cancer appear to lose the aceto-whitening reaction when AA is used.^{[16][17]} With NBI and magnification, an irregular microvasculature and/or microstructure can be visualised in areas harbouring dysplasia or cancer.^{[18][19][20][21]} A few studies have looked at even higher levels of magnification (>450X) using Confocal Endomicroscopy^{[22][23][24][25][26]} or Endocytoscopy^{[27][28]} where histology can be visualised in real time. Irregularity of the cellular structure remains the key feature in differentiating dysplastic from non dysplastic tissue.

It is, however, not yet clear at this stage whether these modalities can replace biopsies. Some of them are expensive, time consuming, technically difficult and requires additional knowledge in interpreting images. Given its high negative predictive value, there could be a role where normal areas which do not harbour any dysplasia (based on various criteria advocated by various investigators) could be 'left alone' and simply not sampled.^[29]^{[30][31]} Only abnormal or suspicious areas should be subjected to biopsies or resection. This practice could potentially lead to a paradigm shift of how patients are surveyed presently and warrants further assessment.

Conclusion

Given the inconspicuous nature of dysplasia in BO, meticulous inspection and attention to subtle endoscopic anomalies using the best available equipment and endoscopes are warranted. At the present moment, after careful interrogation of the BO mucosa; random four quadrant biopsies according to the Seattle protocol should be undertaken (see also [What is the histological definition and grading of dysplasia in patients with BO?](#) and [What are the histological features of early adenocarcinoma of the oesophagus?](#)).

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What are the goals of treatment of high grade dysplasia in patients with BO?

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What are the goals of treatment of high grade dysplasia in patients with BO?

Introduction

There is no high level research evidence which directly answers this question. Therefore, the following is based on the evidence regarding various management strategies used in high grade dysplasia (HGD) and the risk of continued surveillance with no intervention.

There is a histologic progression from non-dysplastic Barrett's metaplasia to low grade dysplasia, high grade dysplasia, intramucosal cancer and invasive malignancy. Due to the rich lymphatic supply to the oesophagus, even early invasive malignancy has a significant chance of metastasis.^[1] For this reason, as well as the possibility of sampling error, high grade dysplasia has traditionally been the trigger for therapeutic intervention in Barrett's Oesophagus. Furthermore, the risk of progression to adenocarcinoma appears to accelerate with increasing dysplastic change (see also [What is the appropriate management of low grade dysplasia in patients with BO?](#) and [What endoscopic surveillance protocol should be followed for patients with BO and high grade dysplasia?](#)).

High grade dysplasia is prone to both over and under-staging. Therefore, given the importance of this diagnosis, the first goal of managing the patient with HGD is to confirm the diagnosis.

Confirmation of HGD diagnosis

Histologic Confirmation (overstaging)

The intra-observer agreement for dysplasia staging of BO is poor. This is particularly so in the presence of reflux oesophagitis, where inflammatory atypia may be misinterpreted as HGD (ie: overstaging). Even amongst gastrointestinal pathologists inter-observer error for grading dysplasia is only moderate, with a kappa 0.43.^[2] It is therefore recommended that all BO specimens reported as HGD should be accompanied by a corroborating opinion by a second histopathologist.

Endoscopic Confirmation (understaging)

Surgical literature suggests that a significant proportion of patients operated on for "HGD" in fact had adenocarcinoma in the excised specimen. In the older surgical literature this was up to 20-40%^[3] but in a more recent study only 5% of those operated on for "HGD" had submucosal invasive disease at resection.^[4] It is, therefore, important to be as careful as possible in assessing the other mucosa for irregularities or nodules which may suggest more advanced disease. This should be done at the time of the index procedure. However, if the endoscopic appearance is not concerning, and the histological diagnosis of HGD is received subsequently, then it is suggested to repeat the endoscopy for further careful endoscopic assessment and biopsy. This detailed review of the patient's Barrett's segment may include the use of imaging enhancement techniques and should include biopsy strategy according to the Seattle protocol. It may be reasonable to consider referring patients to a centre with expertise in the management of Barrett's Oesophagus for this detailed endoscopic review.^[5] Furthermore, any suspicious areas (irregularities, nodules or ulcerations) should be removed by endoscopic mucosal resection in order to permit full histologic assessment prior to determining management and particularly prior to undergoing ablative therapy (which does not afford further histologic review).

Goals of treatment

Once the severity of neoplastic progression has been confirmed as being HGD (as far as practicable), the goal of treatment is to prevent the progression to malignancy through the removal of dysplastic tissue. More specifically the goals of treatment are:

- The removal of all dysplastic tissue^[6]
- The removal of all Barrett's metaplasia if possible^[6]
- Preservation of normal swallowing/nutrition
- Minimisation of morbidity due to the eradication technique
- Confirmation of the diagnosis of HGD (ie: exclusion of malignancy) through examination of resected tissue (endoscopically or surgically), where possible
- Continued follow up in patients who have had endoscopic therapy^[6]

There is no management strategy which perfectly fulfils all these criteria. There continues to be debate as to the most appropriate management of good surgical candidates.

Endoscopic mucosal resection may be used in four settings:

- as definitive treatment to remove all Barrett's in patients with short segment disease,
- to allow adequate histologic staging of nodular lesions (ie: acting as a "big biopsy"),
- to remove nodular lesions prior to confluent ablative therapy (eg: radiofrequency ablation which has a limited depth of approximately 500µm), or
- to remove suspicious lesions in poor health status patients as definitive therapy.

Confluent ablative therapies include photodynamic therapy (PDT), radiofrequency ablation (RFA), argon plasma coagulation and cryotherapy. In 2013 RFA has largely replaced PDT as the standard ablative treatment for high grade dysplasia. The primary aim of treatment is to remove all Barrett's tissue. With RFA, eradication of dysplasia is achieved in 86% of patients.^[7] Eradication of all Barrett's tissue is more difficult, achieved in 77% of patients.^[7] Of those patients undergoing successful eradication of all Barrett's tissue, 5-25% will have recurrence of Barrett's Oesophagus at 12 month follow-up.^{[8][9]} Therefore, even in cases where all Barrett's appears to have been eliminated, both by endoscopic visualisation as well as Seattle protocol biopsies of the neosquamous segment there is a need for continued long-term surveillance.^[6]

Surgical resection has the advantage of certainty – cancer can be excluded with certainty and the Barrett's segment is completely removed. This comes at a significant burden of morbidity (up to 40% in expert centres)^{[10][11]} and mortality (approximately 2.5% in experienced centres),^[12] but is still an option which should be discussed, particularly in the setting of relatively young patients.

Evidence summary and recommendations

Practice point?

The confirmation of high grade dysplasia should act as a trigger for definitive treatment.

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What are the histological features of early adenocarcinoma of the oesophagus?

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What are the histological features of early adenocarcinoma of the oesophagus?

Introduction

Barrett's Oesophagus

For more information see [What is the histological definition of BO?](#)

Histologic features and grades of dysplasia

For more information see [What is the histological definition and grading of dysplasia in patients with BO?](#)

Oesophageal adenocarcinoma

Although there are a great variety of structural manifestations of the development of adenocarcinoma, the key feature that allows a biopsy specimen to be classified as Oesophageal adenocarcinoma is the evidence of invasion of epithelial cells into the connective tissue matrix of the lamina propria. In neoplastic glands, the basal membrane is interrupted, which results in the invasion of epithelial cells into the lamina propria connective tissue matrix. Degrees of differentiation of neoplastic cells vary markedly and thus, histologic grading can describe tumours as being (i) well differentiated, (ii) moderately differentiated, (iii) poorly differentiated, or (iv) undifferentiated.

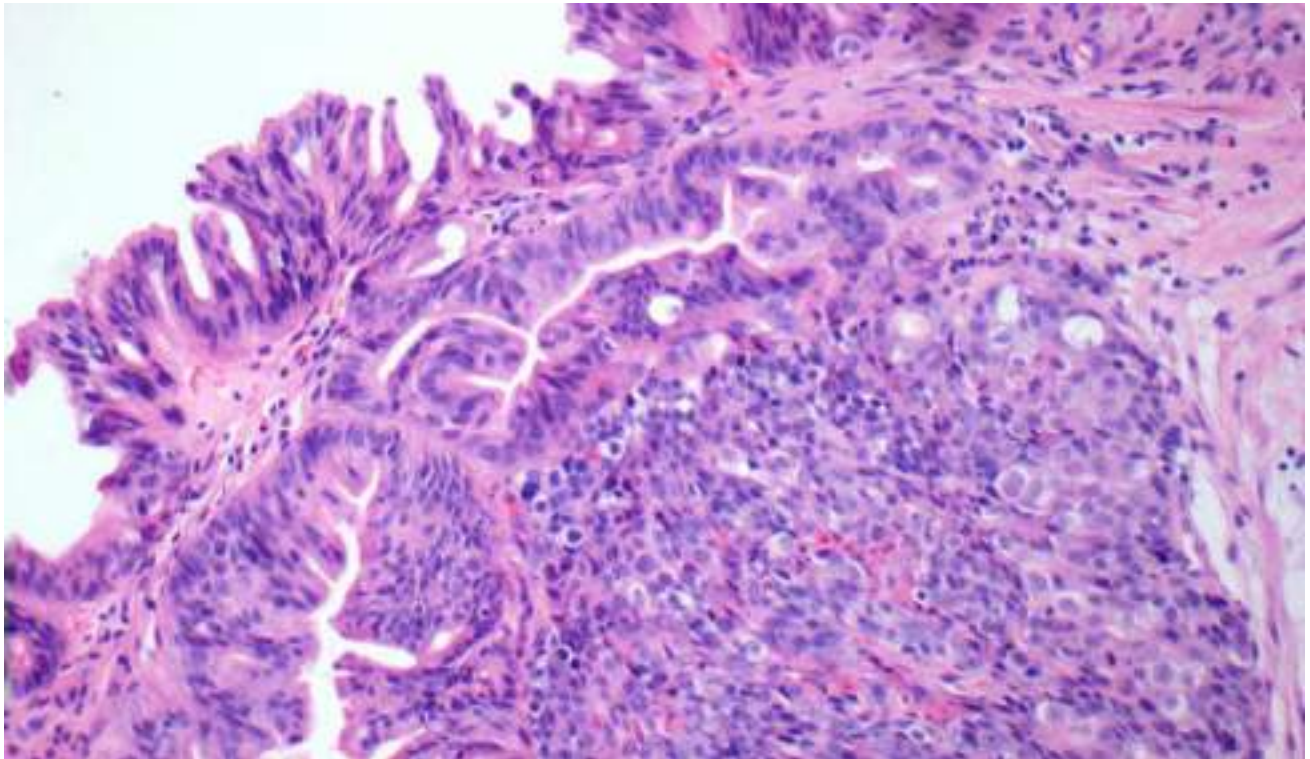
Pathologist's perspective

Early adenocarcinoma in Barrett's Oesophagus refers to invasion into mucosa or superficial submucosa, but not deeper in the oesophageal wall. These tumours are stage T1 in the current TNM staging system.

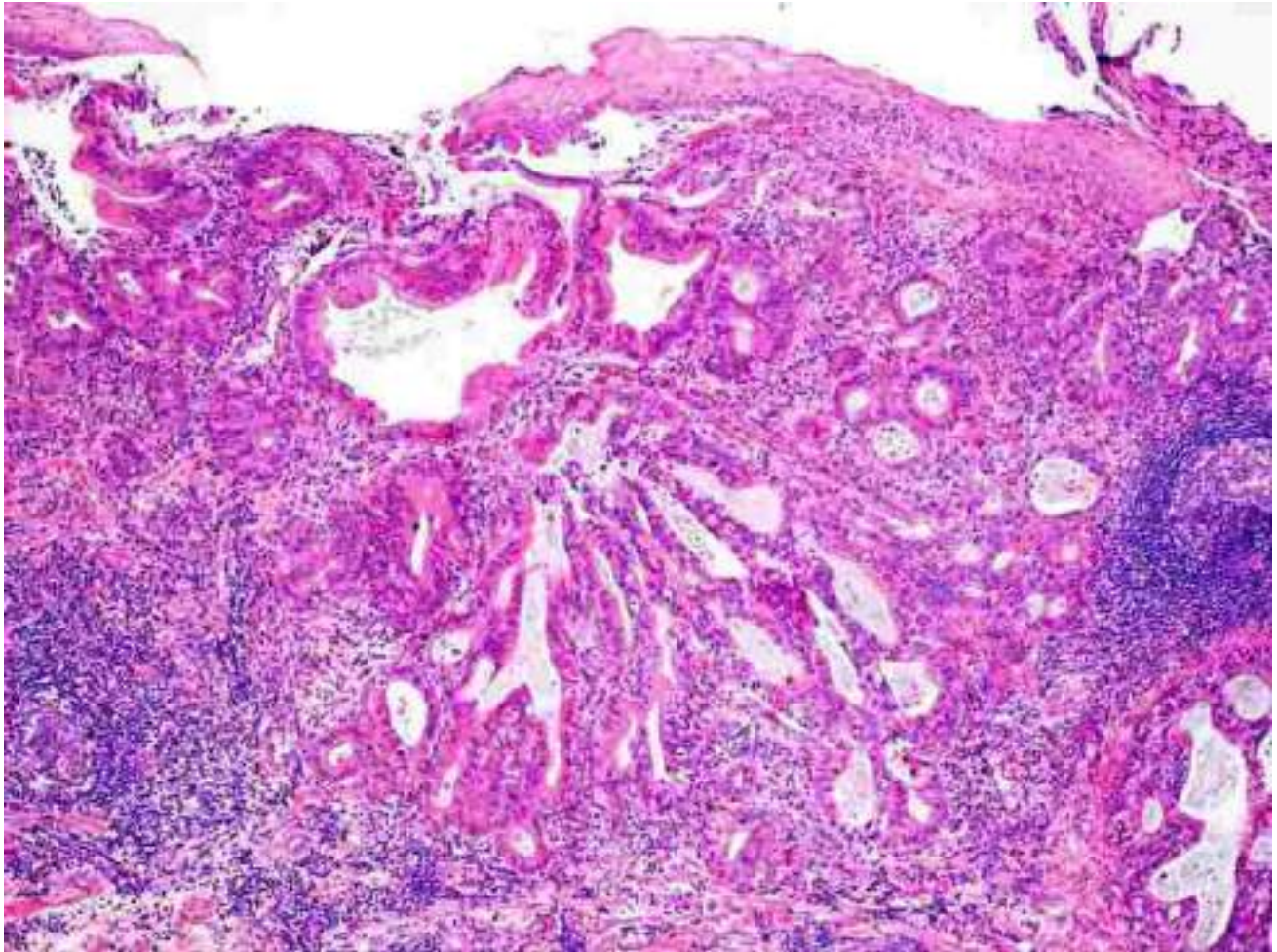
Adenocarcinoma exists when there is invasion of neoplastic cells beyond the basement membrane of the epithelium. The histological features identifying that invasion has occurred include:^{[1][2]}

1. Single neoplastic cells or small clusters of neoplastic cells in the lamina propria.

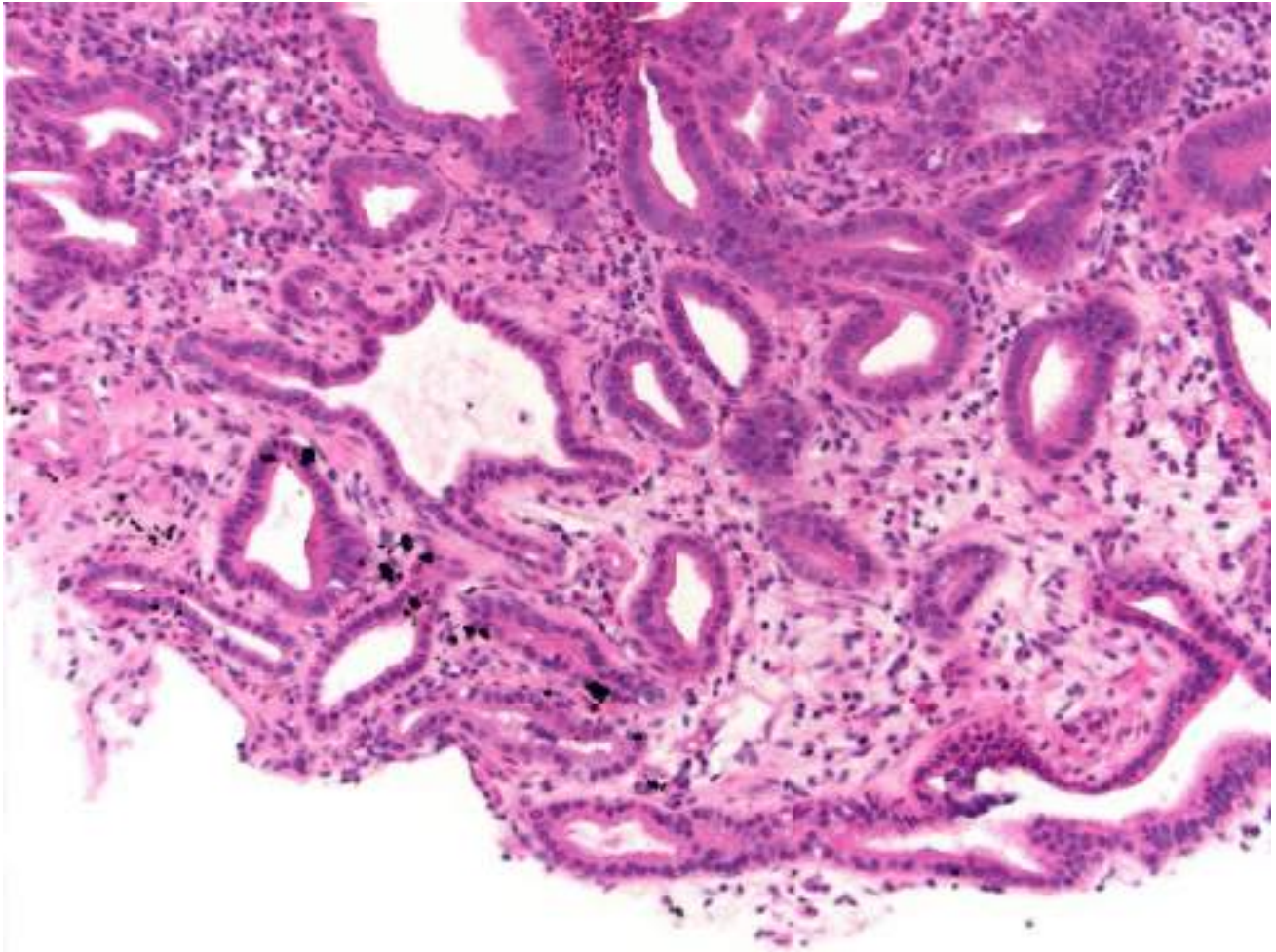
2. Complex architectural patterns characterised by solid growth patterns, tight cribriform growth pattern, glands with acute angulation in at least one part of their outline, and a pattern of anastomosing fusion of small glands. Most of these architectural patterns are common to invasive adenocarcinoma in other organs e.g. prostate and endometrium, and are familiar to histopathologists.
3. Neoplastic cells invading overlying squamous epithelium.
4. Desmoplastic stromal reaction. This is useful when present, however, it is recognised that early invasive adenocarcinoma of the oesophagus can invade without eliciting a histologically identifiable stromal reaction.



Solid and tight cribriform growth pattern diagnostic of intramucosal adenocarcinoma



Fused gland pattern of intramucosal adenocarcinoma



Angulated gland pattern of intramucosal adenocarcinoma

Features that predict the presence of invasive adenocarcinoma in biopsies diagnosed as high grade dysplasia ('suspicious high grade dysplasia').

It has been well recognised that significant interobserver variability exists between pathologists in the separation of high grade dysplasia from early invasive adenocarcinoma in biopsy specimens.^[3] Recent studies have identified a variety of histological patterns that predict a high likelihood of associated invasive adenocarcinoma (in subsequent specimens) in biopsies with high grade dysplasia. These are summarised below:

1. Zhu et al^[4]

- solid or cribriform growth patterns
- ulceration of dysplastic epithelium
- abundant neutrophils within dysplastic epithelium
- dilated neoplastic glands containing necrotic debris
- dysplastic glandular epithelium being incorporated into squamous epithelium

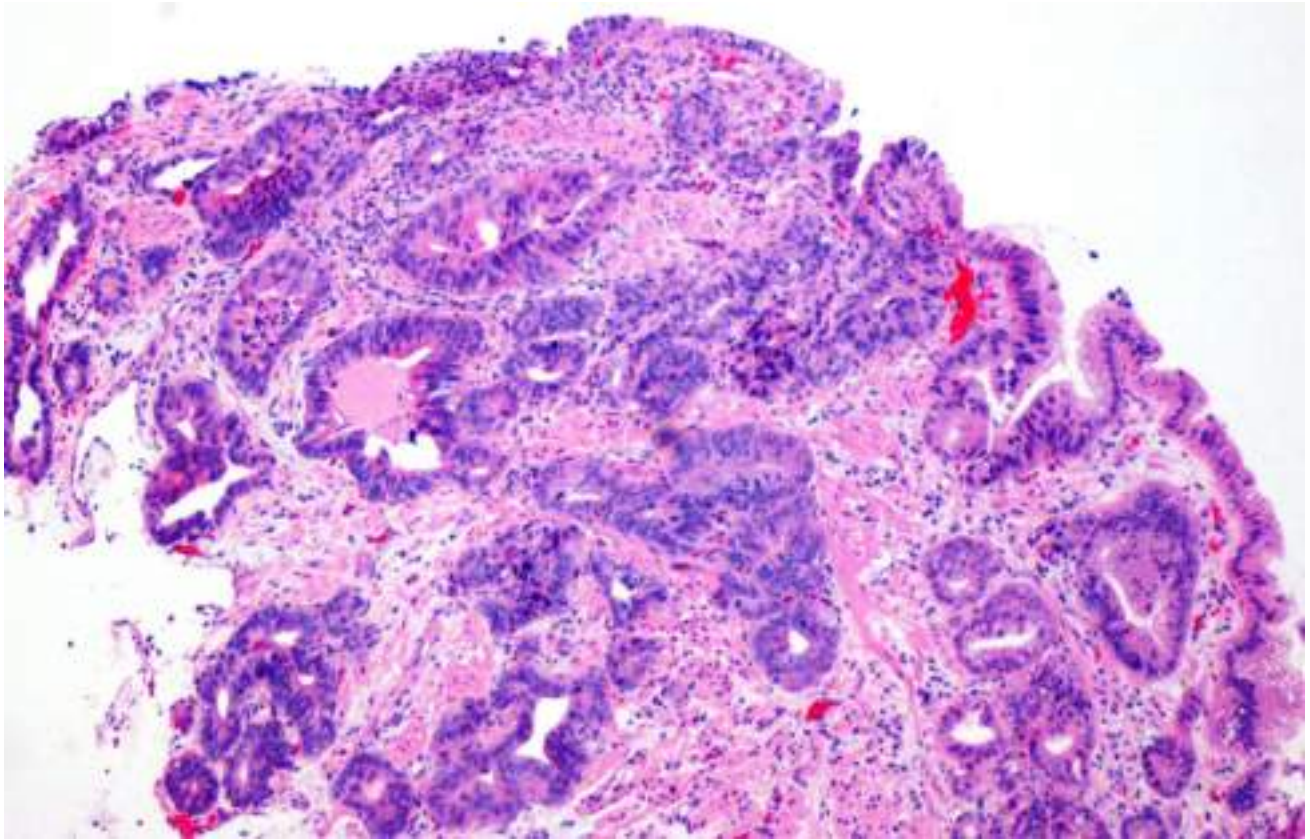
The risk of identifying adenocarcinoma in subsequent resection specimens in this study was: 0 features - 5%; 1 feature - 40%; ≥ 2 features - 80%.

2. Patil et al^[5]

- Presence of an endoscopic lesion
- 'never ending' glandular pattern
- Sheet like growth
- Angulated glands
- ≥ 3 glands with intraluminal debris
- ≥ 1 focus of single cell infiltration

The last two features were, in particular, highly predictive for the presence of adenocarcinoma.

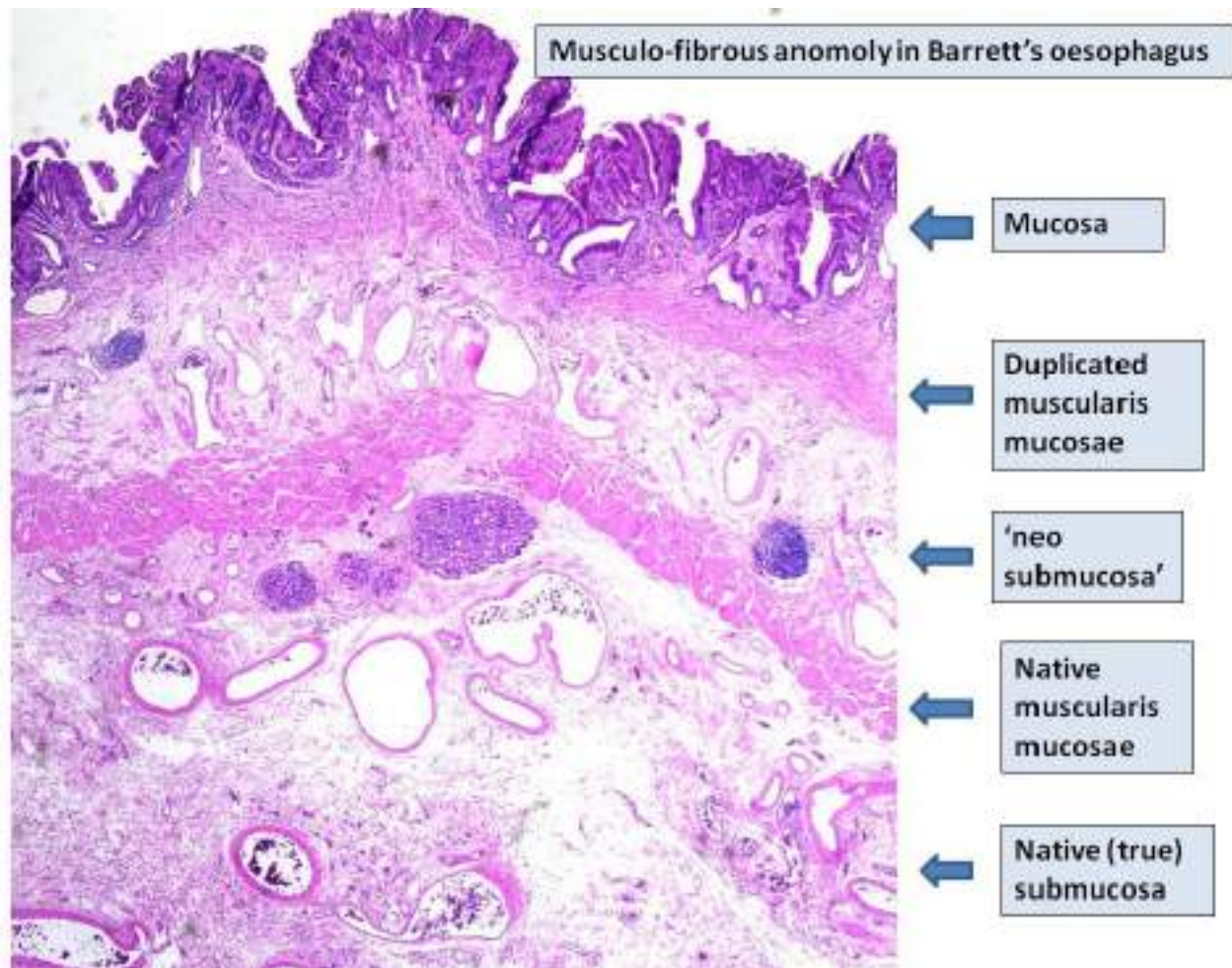
At present there is no mandated requirement for pathologists to specifically qualify or quantify the features presented in these studies. However, it would be regarded as good practice for pathologists to communicate concern that invasive adenocarcinoma may exist when one or more of these features exist.



High grade dysplasia with an area suspicious for intramucosal carcinoma - necrotic debris in glands and a developing pattern of gland fusion

The issue of duplication of the muscularis mucosae in Barrett's Oesophagus and its implication for sub staging early adenocarcinoma.

The muscularis mucosae is consistently thickened in Barrett's Oesophagus. In at least two thirds of cases there is reduplication with the formation of an intervening fibrovascular stroma between the deeper native muscularis mucosae and the superficial new muscle layer. The intervening fibrovascular stroma is sometimes referred to as the 'neo-submucosa' while the entire reduplication process is called the 'musculo-fibrous anomaly'.^{[6][7]} The native submucosa resides beneath the deep native muscularis layer. In mucosal biopsies, adenocarcinoma may appear to invade through a muscle layer, however, because of the musculo-fibrous anomaly, it is not possible for pathologists to determine if invasion is into neo-submucosa or true submucosa. This distinction is prognostically important because invasion of neo-submucosa has a risk for metastasis approximately the same as intramucosal adenocarcinoma (<10%), while the risk for true submucosal invasion is higher (approximately 30%).^[8] Correct assessment can be made on endomucosal resection specimens or formal resections.



The AJCC (2010) staging of early oesophageal adenocarcinoma subdivides both mucosal invasion (T1a) and submucosal invasion (T1b) into three levels.

T1a is sub-divided as M1-M3 as follows:

- m1 - In situ (pTis = high grade dysplasia)
- m2 - into the lamina propria
- m3 - into the muscularis mucosae

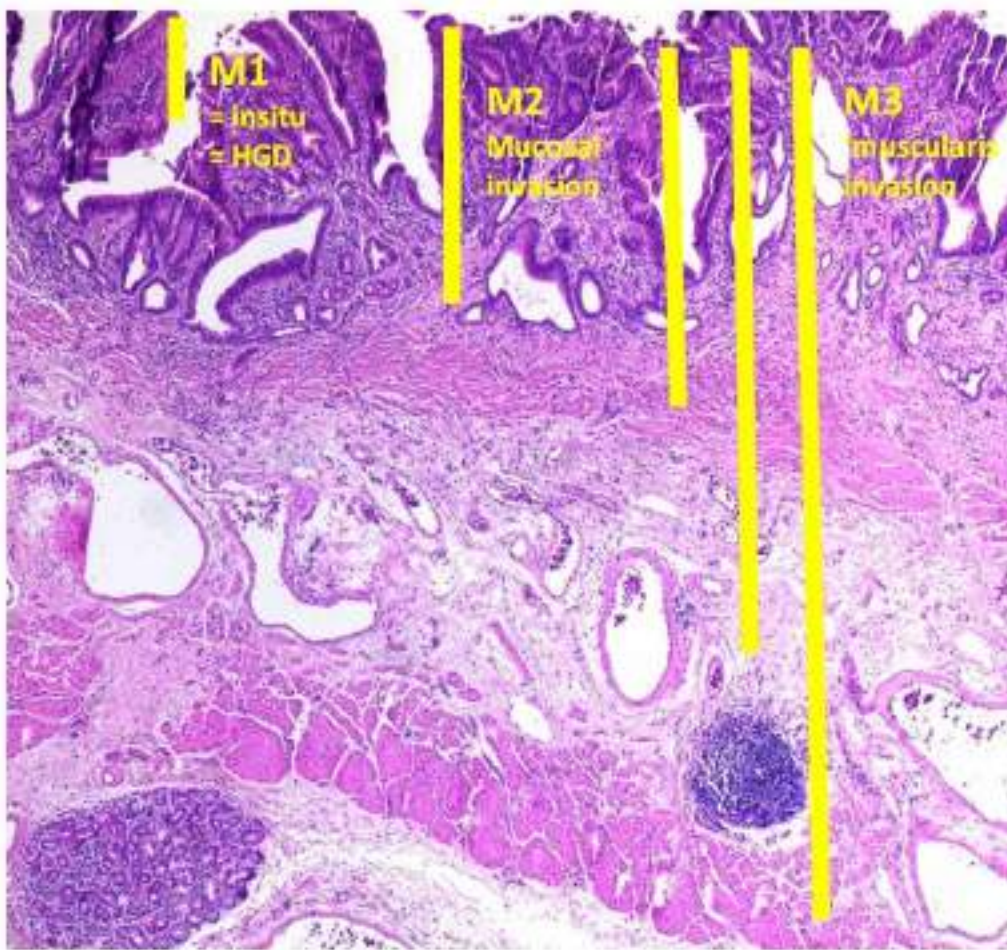
T1b is sub-divided as SM1-3 as follows:

- sm1 - superficial 1/3 submucosa
- sm2 - intermediate one third of submucosa
- sm3 - outer one third of submucosa

AJCC staging system (mucosa)

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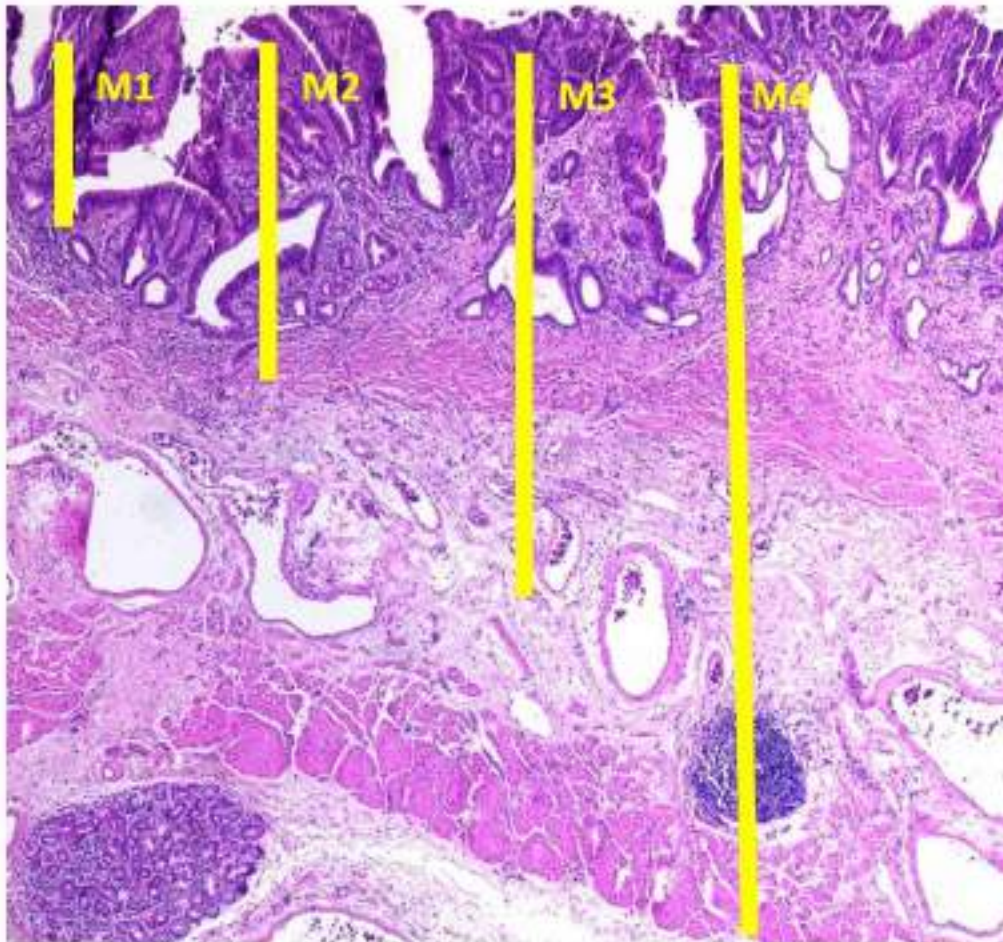
AJCC
m1 - In situ
m2 - into the lamina propria
m3 - into the muscularis mucosae

Since the AJCC system does not account for the musculo-fibrous anomaly, a second four tiered system has been recommended by Vieth & Stolte to better define mucosal invasion of adenocarcinomas.^[9] In the Stolte sub staging system, T1a is sub-divided as M1-M4 as follows:

- m1 - into the lamina propria
- m2 - into the superficial/inner muscularis mucosae
- m3 - into the space between the layers of the muscularis mucosae
- m4 - into the outer/true muscularis mucosae

Pathologists are encouraged to report the sub stage of early adenocarcinoma using both systems and it forms part of the structured reporting guidelines for endomucosal resection specimens developed by the Royal College of Pathologists of Australasia.^[10]

Stolte staging system (mucosa)



Stolte

m1 - into the lamina propria

m2 - into the superficial/inner muscularis mucosae

m3 - into the space between the layers of the muscularis mucosae

m4 - into the outer/true muscularis mucosae

Pathological reporting of endoscopic resection specimens

The histological report of endoscopic mucosal resections should include data that are important for clinical management, particularly the identification of patients who should be considered for oesophagectomy. These are discussed in greater detail in the guidelines for reporting oesophageal and gastro-oesophageal carcinomas provided by the Royal College of Pathologists of Australasia.^[11]

The histological features for reporting include the following:

- Tumour type
- Grade
- Tumour size
- Level of invasion
- Lymphovascular invasion
- Perineural invasion
- Tumour budding

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■ Distance of clearance to deep margin

Intramucosal adenocarcinomas without adverse histological features can be managed conservatively by endoscopic resection.^{[12][13]} Additionally, low-risk tumours invading the upper submucosa (SM1, <500µm invasion of submucosa; no poorly differentiated areas; no lymphovascular invasion; clearance to deep margin >1mm) may be amenable to conservative management by endoscopic resection alone after careful histological assessment.^{[14][15]}

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What are the risk factors for progression from non-dysplastic BO to high-grade dysplasia or adenocarcinoma?

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What are the risk factors for progression from non-dysplastic BO to high-grade dysplasia or adenocarcinoma?

Introduction

Many observational studies have attempted to define the rate of progression from non-dysplastic Barrett's Oesophagus to states of low- or high-grade dysplasia, or adenocarcinoma. There is emerging consensus from large-scale, population-based cohort studies and meta-analyses that the rate of progression to cancer among patients with non-dysplastic Barrett's Oesophagus is in the range of 1 to 5 per 1000 per year (i.e. 0.1% to 0.5%).^{[1][2]} A subset of studies has further attempted to identify those factors which modify the rate of progression to dysplasia or cancer. The quality of these 'modifying factor studies' has been uneven, with the majority of studies suffering from one or more of the following limitations: small sample sizes and low statistical power; retrospective exposure assessment; high rates of loss to follow-up; selection bias (single institution referral centres); inadequate confounder control. To date, no randomised controlled trials have been published which have tested whether any factors modify the rate of progression to cancer, although at least one is in the field.^[3] These elements of study quality must be borne in mind when assessing the evidence base. Wherever possible, estimates from higher quality studies have been used in the summaries below.

Patient factors associated with rate of progression from BO to high-grade dysplasia or adenocarcinoma

Some studies^{[4][5][6]} but not all^{[7][8]} report significantly increased rates of progression with increasing age. There is consistent evidence that the rates of progression to cancer are significantly higher in men than women, with most estimates converging on two-fold higher rates among men.^{[6][8][9]} Rates of progression appear to be about two-fold higher among ever smokers than never smokers.^{[6][10]} A number of studies have assessed whether progression rates are modified by measures of obesity with no evidence of an effect. One study has assessed biochemical analytes, and reported significantly higher rates of progression to cancer among those with higher HOMA scores and higher leptin levels.^[11]

Endoscopic factors associated with rate of progression from non-dysplastic BO to high-grade dysplasia or adenocarcinoma

Longer segments of columnar mucosa in Barrett’s Oesophagus have been consistently associated with higher rates of progression to cancer.^{[7][9][10][12][13][14][15][16]} Endoscopic features that have been associated with significantly increased rates of progression in some studies include the presence of nodules,^{[13][15]} ulceration^[17] and strictures.^{[8][17]} Such areas of abnormality are likely to harbour high-grade dysplasia or adenocarcinoma, and as such require further investigation (see also [What are the endoscopic features of neoplasia \(dysplasia and early cancer\) within a BO segment?](#))

Histologic factors associated with rate of progression from non-dysplastic BO to high-grade dysplasia or adenocarcinoma

For non-dysplastic Barrett’s Oesophagus, there are no histological features that have been reliably associated with risk of progression. Markers of cellular atypia such as aneuploidy appear to confer higher risks of progression to cancer,^[18] although these are frequently associated with dysplasia.

Pharmacologic factors associated with rate of progression from non-dysplastic BO to high-grade dysplasia or adenocarcinoma

There is evidence from observational studies that several classes of medications significantly reduce the rate of progression to cancer among patients with Barrett’s Oesophagus, including non-steroidal anti-inflammatory drugs (NSAIDs),^{[12][19][20]} proton-pump inhibitors (acid suppressant medications)^{[19][21][22]} and statins (HMG co-A reductase inhibitors which act to lower serum cholesterol).^{[12][23][24]} However, it is important to note that no randomised trials have yet reported on these associations, although at least one such trial is currently underway.^[25]

Evidence summary and recommendations

Evidence summary	Level	References
Factors that have been associated with an increased rate of progression from non-dysplastic BO to high-grade dysplasia or adenocarcinoma in observational studies include those relating to the patient (age, sex, smoking), endoscopic appearance (greater segment length), and histology (aneuploidy).	III-2	[9], [10], [17], [18], [26]
There is observational evidence that regular users of proton-pump inhibitors, non-steroidal anti-inflammatory drugs, and statins, may have lower rates of progression from BO to neoplasia. These findings await confirmation from randomised controlled trials.	II, III-2, III-3	[12], [19], [22], [23], [24]

Evidence-based recommendation?	Grade
<p>A clinical assessment of a patient's future risk of high-grade dysplasia or adenocarcinoma in the setting of non-dysplastic Barrett's Oesophagus should consider their:</p> <ul style="list-style-type: none"> ■ Age ■ Sex ■ Smoking history ■ Endoscopic findings 	C

Issues requiring more clinical research study

- Do medications reduce the rate of progression to cancer? Is chemoprevention possible?
- Are there any dietary factors that reduce the rate of progression from BO to cancer?
- Does obesity modify the rate of progression to cancer?

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What endoscopic surveillance protocol should be followed for patients with BO and high grade dysplasia?

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What endoscopic surveillance protocol should be followed for patients with BO and high grade dysplasia?

Introduction

High Grade Dysplasia (HGD) or early neoplasia (defined here as intramucosal cancer - IMC) in Barrett's Oesophagus (BO) has traditionally led to consideration of oesophagectomy. In recent years, endoscopic therapy has become an effective alternative in treating these conditions^{[1][2]} (see also [What is the best endoscopic treatment for high grade dysplasia in patients with BO?](#) and [What is the best endoscopic management of early oesophageal adenocarcinoma?](#)). The most recent international guidelines now recommend endoscopic intervention once HGD or IMC is diagnosed, although surgery can still be considered in young and fit patients or in the presence of extensive dysplasia.^{[3][4]} As far as we know, surveillance for IMC has not been suggested. Surveillance in the setting of HGD used to be a reasonable alternative to oesophagectomy before the advent of effective endoscopic therapy, as not all cases of HGD progress to invasive cancer, and such patients might be spared the risks of major surgery. However, with safe endoscopic therapy now available it is less clear if or when surveillance is still reasonable in patients with HGD (for endoscopic surveillance after endoscopic treatment for BO neoplasia, see [After successful endoscopic treatment for BO neoplasia, how frequently should patients undergo endoscopy?](#)).

If contemplating endoscopic surveillance for HGD rather than intervention, the following issues should be considered: How accurately can invasive cancer be excluded with endoscopic surveillance?; what is the risk of progression from HGD to invasive cancer?; and what other clinical factors might shift the balance between the risk of complications of endoscopic therapy and the risk of missing a potentially advanced cancer on surveillance.

Risk of undiagnosed cancer

The accuracy of a pre-operative diagnosis of HGD is imperfect and the concern over undiagnosed invasive malignancy has traditionally been an argument for intervention. The reported rates of unsuspected cancer found at surgery in patients with a preoperative diagnosis of HGD vary greatly, mostly between 7%^[5] and 36%.

^{[6][7]} The need for careful inspection with high resolution endoscopes and sampling according to rigorous biopsy protocols has been recognised. Narrow band imaging (NBI) has been widely studied in the assessment of Barrett's epithelium, and there are some data that suggest that it may be superior to white light endoscopy (WLE) for the detection of dysplasia in Barrett's.^{[8][9]} In a more recent prospective study it was shown that, in expert hands, high resolution WLE was sufficient to detect all areas of IMC, while the accuracy for detecting HGD was improved with additional NBI examination.^[10]

In summary, the risk of undiagnosed cancer is difficult to determine. More recent studies appear to be more accurate in determining the degree of dysplasia, presumably due to improved visualisation with high resolution endoscopy.

Risk of progression from HGD to cancer

Progression from HGD to invasive cancer is common, albeit not universal. A meta-analysis published in 2008 sought to determine the cancer incidence in patients with HGD in BO who underwent endoscopic surveillance. Four studies and 236 patients were included, with follow-up totalling 1241 patient-years. Sixty-nine cancers developed, resulting in a weighted incidence rate of 6.6 per 100 patient years.^[11] A more recent retrospective population-based study from the Netherlands identified a cohort of 326 patients who underwent endoscopic surveillance after diagnosis of HGD in BO. After excluding prevalent cancers (diagnosed within the first six months after diagnosis of HGD), the rate of progression to cancer was 14.4 per 100 patient years.^[12] Some of the risk factors identified included older age and multifocal (rather than unifocal) HGD. All of the findings in this study were taken from a pathology database and no endoscopic and only limited clinical data were available, raising the possibility of confounding by indication. Despite this, these findings support the notion that the risk of progression to cancer is substantial. Risk factors for progression to cancer previously identified have again included multifocal (rather than unifocal) HGD,^[8] and nodular (rather than flat) disease.^{[13][14]}

In summary, the risk of progression is at least 6.6% per year, with some data pointing to much higher rates.

In what situations may surveillance be reasonable?

The guidelines of the US-based Society of Thoracic Surgeons, published in 2009, state that surveillance may be considered for patients with flat and unifocal HGD, due to their relatively low rate of progression.^[15] As mentioned above, the more recent guidelines by gastroenterological societies differ on this.^{[3][4]} The risk of serious complications with endoscopic therapy is very low,^[1] and we need to consider the situations when one would not intervene with endoscopic therapy once HGD is diagnosed. For instance, there may be situations where safe endoscopic treatment is unable to be delivered, due to anatomical reasons like oesophageal strictures or diverticula, or due to systemic issues like chemotherapy or inability to safely stop antithrombotic therapy. Thus there may be instances where either the only therapeutic option is surgery, or where the timing of endoscopic therapy is best delayed to increase the safety of the procedure. The balance between risk of intervention and risk of being on surveillance may shift in these certain circumstances, and surveillance may be preferable.

Some authors have reported apparent regression of dysplasia^[14] although it is impossible to exclude sampling error, histologic misclassification, or removal of a single focus of HGD with the biopsy forceps, and therefore it is unclear whether HGD can truly regress. Nevertheless, in cases of a single finding of unifocal HGD that cannot be reproduced on subsequent endoscopies, especially in an elderly or frail person, it could be argued that surveillance may be reasonable due to a lower risk of progression.^[14]

Therefore, surveillance for HGD is not advisable except for uncommon instances where surgical treatment may be the only therapeutic option; where endoscopic therapy has to be delayed in order to optimise other clinical conditions; or possibly where HGD cannot be seen on subsequent examinations in elderly or frail patients.

What surveillance protocol should be followed for HGD?

Evidence on how best to perform surveillance for HGD is scant. The endoscopic surveillance protocol used by the authors of one of the largest prospective study on surveillance in HGD called for three-monthly endoscopies in the first year.^[14] If no HGD was found on two consecutive endoscopies in the first year, then the frequency of endoscopy was decreased to six-monthly for the second year. After the second year, repeat at yearly intervals was implemented if no HGD was found. Persistent HGD was managed on an individual basis, with ongoing three-monthly endoscopies, or lesser frequency as per patient wishes or comorbidities. The biopsy protocol described targeted biopsies for visible lesions plus quadrantic biopsies every 2cm.

The AGA guidelines recommend three-monthly endoscopy with quadrantic biopsies every 1cm plus targeted biopsies of visible lesions, while the British guidelines do not make any recommendations.^{[3][4]} An expert consensus statement, formed by a large number of expert participants in a Delphi process and published in 2012, recommended quadrantic biopsies every 1-2cm plus targeted biopsies, for surveillance of HGD.^[16] One study directly assessed the yield of quadrantic biopsies taken at 2cm intervals compared with biopsies taken every 1cm, in the setting of known HGD. Biopsies taken every 1cm led to a significantly higher cancer detection rate.^[17]

In summary, the biopsy protocol for endoscopic surveillance for HGD should be three-monthly endoscopy with high resolution WLE, with optional additional examination with virtual chromoendoscopy such as NBI. Targeted biopsies of visible lesions plus quadrantic biopsies taken every 1cm throughout the segment of Barrett's mucosa should be taken.

Summary

The role of surveillance in the setting of HGD has shifted with the advent of effective endoscopic therapy. Since the risk of progression from HGD to cancer is substantial and the risk of complications with endoscopic therapy is low, endoscopic intervention is indicated in most instances of HGD, with surveillance reserved for uncommon situations where endoscopic therapy is either not feasible or has to be delayed; or possibly, in older or frail patients, where persistence of HGD cannot be confirmed.

If surveillance is performed for HGD, endoscopy using high resolution endoscopes with targeted and random quadrantic biopsies every 1cm throughout the Barrett's segment should be performed. No comparative data on different intervals between endoscopic surveillance is available and no evidence-based recommendations can be made regarding this, but expert consensus is that it should be performed every three months.

Evidence summary and recommendations

Practice point?

Surveillance is generally not indicated for patients with high grade dysplasia, and therapeutic intervention must be considered instead.

Practice point?

Targeted biopsies of visible lesions plus quadrantic biopsies every 1cm throughout the segment of Barrett's mucosa should be taken.

Practice point?

High resolution endoscopes should be used, with optional use of virtual chromoendoscopy such as narrow band imaging (NBI).

Practice point?

If endoscopic surveillance is performed, intervals of three months may be appropriate.

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What is appropriate medical systemic therapy for symptoms associated with BO?

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What is appropriate medical systemic therapy for symptoms associated with BO?

Introduction

Medical systemic therapy for patients with Barrett's Oesophagus aims to control symptoms and reduce the risk of complications, including those related to peptic damage and (potentially) progression to adenocarcinoma. Uncomplicated Barrett's Oesophagus itself is not a cause of symptoms, indeed patients with Barrett's Oesophagus may have reduced sensitivity to oesophageal acidification, rather these are due to the effects of gastrooesophageal reflux on the squamous mucosa above the Barrett's Oesophagus and to regurgitation of refluxate.^[1] As a group, patients with Barrett's Oesophagus have greater acid exposure than patients with less endoscopically severe reflux disease.^{[2][3]} The general principles of medical systemic therapy for symptoms are essentially identical to treatment of the more severe forms of reflux oesophagitis without evidence of Barrett's Oesophagus. The quality of evidence in the assessment of the control of symptoms specifically in patients with Barrett's Oesophagus is poor, with few comparative randomised trials. Most information is derived from observational studies and medical treatment arms of comparative studies with surgical therapy or studies into other aspects of therapy (eg regression of metaplasia or control of intraoesophageal pH).

Asymptomatic Barrett's Oesophagus

A subpopulation of patients with Barrett's Oesophagus have minimal or no typical reflux symptoms, but may still be at risk of complications. The value of medical systemic treatment in currently asymptomatic patients with Barrett's Oesophagus and no macroscopic evidence of peptic oesophagitis diagnosed incidentally has not been examined. Patients with evidence of peptic oesophagitis should be treated to prevent the development of stricture.

H2 Receptor Antagonist therapy

In the pre Proton Pump Inhibitor Therapy (PPI) era the use of cimetidine and ranitidine (+ antacid/other antisecretory agents) was shown to be effective in treating symptoms due to reflux in patients with Barrett's Oesophagus.^{[4][5][6]} These studies were small and selection of patients was not described. Up to 43% of patients may require higher doses than standard therapy to control symptoms,^[7] but on an escalating dose regimen most patients' symptoms can be controlled.^[8]

Proton Pump Inhibitor Therapy

Largely observational studies (sometimes the medical arm of a randomised study) show that most patients can be adequately controlled from a symptomatic point of view on PPI therapy,^{[6][9][10][11][12][13][14][15]} although in a significant proportion treatment with higher doses of PPI is required.^{[16][17][18]} Control of symptoms does not, however, equate to control of oesophageal acidification.^{[19][20][21]}

Patients who achieve control of symptoms have a durable response over a period of years.^{[13][22][23][24]}

Comparison of PPIs has not shown any PPI to be consistently superior to another in the control of symptoms in patients with Barrett's Oesophagus.^[25]

In patients with symptoms controlled on Ranitidine, changing to omeprazole did not result in better control.^[26] Comparison of PPI to H2RA in a single trial showed that PPIs were superior in controlling symptoms.^[6]

Prokinetic Therapy

No studies have been performed to demonstrate that either prokinetic therapy alone, or its addition to acid suppression therapy has therapeutic value in the treatment of symptoms in patients with Barrett's Oesophagus.

Evidence summary and recommendations

Evidence summary	Level	References
Acid suppression with PPI is the most effective systemic therapy for reflux symptoms in patients with Barrett's Oesophagus and can be expected to control symptoms in most patients with a durable effect over years	II, IV	[9], [6], [10], [11], [12], [13], [14], [15], [22], [23], [24]
Higher than standard doses of PPI may be required to control symptoms in a proportion of patients.	IV	[16], [17], [18]

Evidence-based recommendation?	Grade
Symptomatic patients with Barrett's Oesophagus should be treated with Proton Pump Inhibitor therapy (PPI), with the dose titrated to control symptoms.	C

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What is the appropriate management of low grade dysplasia in patients with BO?

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What is the appropriate management of low grade dysplasia in patients with BO?

Introduction

Low grade dysplasia (LGD) has long been regarded as a condition associated with only a modest increase in the risk of oesophageal adenocarcinoma development, compared to non-dysplastic Barrett's. Published guidelines recommend increased frequency of surveillance.^{[1][2]} Until recently there has been no strong evidence to indicate that ablation therapy reduces neoplasia development in LGD. However, recent European studies have suggested that when individuals have confirmed low grade dysplasia that is agreed on by expert pathologists, the risk of progression to neoplasia is higher than previously thought.^{[3][4][5]} This information, combined with more robust evidence regarding the efficacy of radiofrequency ablation (RFA) have led to increased use of ablation therapy for LGD. A recent randomised controlled trial supports this approach.^[5]

Uncertainty regarding risk of low grade dysplasia progression

The management of patients diagnosed with Barrett's oesophagus with low grade dysplasia (LGD) is currently uncertain, as there is considerable debate about the risks of progression to high grade dysplasia (HGD) or cancer in this group. Population-based studies which have followed Barrett's oesophagus patients diagnosed with LGD in the community have reported rates of progression to cancer of ~0.5% p.a. (Hvid-Jensen et al 2011). In contrast, studies undertaken in academic centres in which diagnoses of LGD are made only after review by expert gastrointestinal pathologists report rates of progression as high as 13% p.a. (Curvers et al 2010). Importantly, in those studies, about 85%

The decision to advise intensified surveillance or endoscopic ablation for LGD needs to take into account the features of the Barrett's segment and histology as well as patient age, fitness and preference.

No strong evidence exists for surgical antireflux procedures or chemoprevention as interventions for LGD.

of patients diagnosed originally with LGD were down-staged to non-dysplastic Barrett's oesophagus upon expert review. In the group of down-staged patients, the rate of progression was ~0.5% p.a – about the same as the rate observed in the community-based studies. These apparently conflicting data have implications for [how LGD is diagnosed](#), [how patients are managed](#) and [frequency of surveillance](#).

Management strategies for low grade dysplasia in Barrett's Oesophagus

Diagnosis of LGD

The histological diagnosis of LGD is subject to poor inter-observer agreement between pathologists^{[2][3]} (see also [What is the histological definition and grading of dysplasia in patients with BO?](#)). When the diagnosis of LGD is confirmed by two or more pathologists, the incidence of progression is substantially higher than when pathologists disagree on the diagnosis.^[3] Therefore, confirmation of the diagnosis of LGD by a second pathologist, ideally an expert gastrointestinal pathologist, is essential in estimating the risk of progression and deciding on management.

Surveillance for LGD and risk of progression to HGD and cancer

Continued surveillance but at shorter intervals of 6-12 months has been the standard of care for LGD in Barrett's (see also [How Frequently Should Patients with Barrett's Oesophagus Undergo Endoscopy?](#)). However, recent studies have suggested a rate of progression higher than previously estimated, leading some experts to advocate ablation for LGD.

a. Progression of LGD to cancer

The reported incidence of cancer arising in patients with LGD has varied greatly from no greater than in non-dysplastic Barrett's to much higher rates. A systematic review was conducted in 2009^[6] assessing the rate of progression to cancer of LGD, high grade dysplasia (HGD) and non-dysplastic Barrett's Oesophagus. The weighted average incidence rate for progression to cancer from LGD was 17/1000 patient years. This compared with 6/1000 patient years for non-dysplastic Barrett's and 66/1000 patient years for HGD.

b. Progression to HGD or cancer

Three recent European studies have evaluated the incidence of progression from LGD to either HGD or cancer and found surprisingly high progression rates. A German study derived from community based practices demonstrated 19% progression over two years.^[4] A Dutch study of 147 individuals diagnosed with LGD from

non-university hospitals found that when the slides were reviewed by two expert pathologists, only 15% (22) were still considered LGD, with 85% downstaged to non-dysplastic or indefinite. Among those considered to have true LGD, 85% were found to have cancer (two patients) or HGD (six patients) over 109 months follow-up (progression rate 13.4% per year).^[3] The same researchers along with other European groups performed a RCT of RFA versus surveillance and found progression to HGD or cancer in 26.5% of the surveillance group at three years.^[5]

c. Endoscopic surveillance of LGD and detection of HGD and cancer

The purpose of surveillance in LGD is to detect HGD and cancer in order to intervene with endoscopic ablation or surgery. High definition endoscopes with narrow band imaging can be used in expert centres to detect visible mucosal abnormalities in most individuals with HGD or cancer.^[7] In a study of 50 consecutive patients referred to an expert tertiary referral centre for assessment of dysplastic BO, all patients with HGD or cancers were found to have endoscopically visible lesions, with no additional cancers or patients with HGD found on 4 quadrant biopsies every 1cm from flat mucosa. Many of these individuals had only LGD as their worst prior pathology. This raises the possibility that some individuals in other studies considered to have progression from LGD to HGD or cancer may have had potentially visible lesions that were missed on initial assessment. In individuals found to have confirmed LGD, very careful endoscopic assessment is mandatory and referral to an expert centre should be considered. (see also [What are the endoscopic features of neoplasia \(dysplasia and early cancer\) within a BO segment?](#)).

Ablation therapies

The principle of ablation therapies is that neosquamous mucosa will replace the ablated area provided effective antireflux treatment is provided. There is a large literature on several forms of ablation for dysplastic Barrett's Oesophagus: argon plasma coagulation (APC), photodynamic therapy (PDT), radiofrequency ablation (RFA), multipolar electrocautery (MPEC), Nd-YAG laser and cryotherapy. Most of these studies are uncontrolled case series. A systematic review of rates of progression to adenocarcinoma after ablation therapy with any of the modalities above, found a significantly reduced cancer incidence rate of 1.6/1000 patient years after ablation for LGD compared to 17/1000 patient years derived from surveillance studies.^[6]

Randomised controlled studies of RFA and PDT compared to surveillance have included significant numbers of individuals with LGD, but the number of cancers developing in LGD patients has been small, making it difficult to draw conclusions regarding efficacy for LGD. The randomised studies are described in more detail below.

a. Photodynamic therapy

Although six RCT's of PDT for Barrett's have been performed, only one of these provides useful data regarding individuals with LGD. Ackroyd et al.^[8] performed a RCT of PDT versus surveillance in 36 individuals with LGD. Sixteen out of eighteen in the treatment group showed a reduction in the area of Barrett's of median 30% compared to 2/16 in the placebo group. There was regression of LGD to non-dysplastic Barrett's in all 18 subjects treated with PDT compared to 4/16 in the placebo group ($p < 0.001$). There were no cases of progression in either group. This study used the oral photosensitiser aminolevulinic acid, which is less likely to cause strictures than intravenous sensitising agents. No dysphagia or strictures were reported. Despite this positive study, PDT is currently not widely used, probably because the delivery system is somewhat more complex than other forms of ablation and the perceived risk of strictures. PDT has not been directly compared with RFA.

b. *Radiofrequency ablation*

- i. Shaheen et al^[9] performed a multicentre, randomised, sham-controlled trial (AIM dysplasia trial) of RFA using the Barrx Halo system, initially with the Halo 360 balloon device and subsequently with the Halo 90 focal ablation device until all visible Barrett's was ablated. 127 subjects were enrolled, including 64 with LGD who were randomised in 2:1 ratio to RFA or sham procedure. The primary outcome measures were complete eradication of dysplasia (CRD) and intestinal metaplasia (CRIM) and were reported at 12 months to be 90% and 80% respectively in the RFA-treated LGD patients compared to 2% and 23% respectively in the control group. Progression from LGD to HGD occurred in 5% of the treatment group and 14% of the sham group at 12 months, but no cancers occurred. Strictures occurred in 6% of RFA-treated individuals.
- ii. RFA was also compared to surveillance in a European multicentre RCT involving only subjects with LGD.^[5] One hundred and thirty six subjects were randomised 1:1 to RFA or surveillance. The follow-up period was three years, at which point progression to cancer was reported in 8.8% of controls versus 1.5% in RFA treated subjects (p=0.03). 26.5% of control patients had progressed to HGD or cancer compared to 1.5% in the RFA group. Although this data appears compelling, the progression rate in the control group is high and occurred within 12 months of randomisation in many cases, suggesting prevalent lesions may have been missed at initial assessment. The pathological criteria for LGD were very stringent, potentially leading to exclusion of some individuals who may have been considered to have LGD by some pathologists. Corroborating evidence is needed to confirm the generalisability of these findings and also to determine whether particular subgroups with LGD are at higher risk than others.
- iii. Durability of RFA. Shaheen et al^[10] reported on two and three year follow-up data from subjects who took part in the AIM dysplasia trial described above.^[9] Among LGD patients, 51/52 (98%) had eradication of dysplasia and intestinal metaplasia at two years. However, three subjects with initial LGD progressed to HGD despite RFA, but were successfully treated with RFA and /or EMR. Another patient progressed from LGD to adenocarcinoma that was successfully treated with EMR. These data demonstrate that ongoing careful surveillance is needed even after apparently successful ablation for LGD. Shaheen reported that 5.1% of RFA treated subjects had subsquamous intestinal metaplasia, compared 40% of controls, though the significance of this finding remains uncertain.^[9] Much longer term data are still needed to determine the longterm efficacy of RFA.

c. *Economic analyses of radiofrequency ablation for LGD*

A cost effectiveness analysis^[11] compared different strategies for managing LGD: A. surveillance six monthly for the first year after diagnosis then annually; RFA if HGD developed and oesophagectomy for cancer; B. RFA when LGD diagnosed then surveillance annually once eradicated. Although option A was less costly, there was considered to be an improved outcome in terms of quality-adjusted life years (QALY) using option B, with an incremental cost effectiveness ratio (ICER) of US\$18,231 per QALY, which is considered cost-effective. Option B remained cost-effective across a range of values for the relevant variables, such as risk of progression, efficacy, cost and durability of RFA, and quality of life after surgery. The major shortcoming of this model is that all cancer was treated with oesophagectomy and the potential to successfully treat many early cancers with endoscopic mucosal resection was not considered.

Surgical therapies

Conventional antireflux surgery and also biliary diversion procedures have been studied in case series and have shown apparent regression of LGD in small numbers of patients. However, these series are uncontrolled and do not provide strong evidence of efficacy.^{[12][13]}

Medical therapies

There are no randomised trials that have specifically addressed the question of whether acid suppression with proton pump inhibitors reduces progression rate of dysplasia. Pharmacological therapy (chemoprevention) with celecoxib 200mg for 48 weeks for dysplastic Barrett's has been studied in a randomised, placebo-controlled study. This study included 64 individuals with LGD, but did not show any benefit in rates of regression or progression of dysplasia.^[14] Chemoprevention with aspirin is being studied, but there is no evidence at this stage to indicate an overall benefit in LGD.

Summary

There are several areas of uncertainty relating to the LGD. Recent evidence suggests that when LGD is confirmed by agreement of at least two pathologists, there is a much higher incidence of progression to HGD or cancer than previously demonstrated. However, this information needs to be confirmed by other researchers and the reason for the differences from other estimates still needs to be clarified. RCT's support the use of ablation with both PDT and RFA for LGD. For RFA, reduced progression to HGD and cancer has been demonstrated following RFA. On the other hand, ablation therapy is expensive, often uncomfortable and inconvenient for the patient and the long term efficacy of ablation is not known. Given that most individuals with LGD will probably not progress, the option of intensified surveillance continues to be a valid approach, though surveillance must be performed in a rigorous manner and referral to an expert centre should be considered. The decision to advise intensified surveillance or endoscopic ablation for LGD needs to take into account the features of the Barrett's segment and histology as well as patient age, fitness and preference. Where LGD is confirmed by two pathologists and is present on repeat endoscopies, ablation should be considered, especially in a relatively young and fit patient. RFA is the form of ablation with the strongest evidence.

Evidence summary and recommendations

Evidence summary	Level	References
The histological diagnosis of LGD is subject to poor inter-observer agreement between pathologists. Confirmation of LGD by agreement between at least two pathologists predicts a higher risk of progression to HGD or cancer.	III-2	[3]
The average incidence rate for progression to cancer from LGD is 17/1000 patient years, which is approximately three times the risk for non-dysplastic Barrett's, though there is a broad range of progression rates reported from individual studies.	III-2, IV	[3], [6]
In individuals with confirmed LGD, more advanced lesions may be visualised by rigorous high definition endoscopy performed in an expert centre.	III-1	[7]
Endoscopic ablation of with a range of methods is associated with lower rates of	IV	

Evidence summary	Level	References
progression to cancer.		[6]
RFA is the form of ablation with the strongest evidence for benefit in confirmed LGD, with an RCT demonstrating reduced progression to cancer or HGD. There is no evidence to indicate that ablation for confirmed LGD results in reduced mortality compared to surveillance.	II	[5]

Evidence-based recommendation?	Grade
The diagnosis of low grade dysplasia should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist.	C

Evidence-based recommendation?	Grade
In patients with confirmed low grade dysplasia, it is advised to perform rigorous high definition endoscopy or refer to an expert centre for assessment.	C

Evidence-based recommendation?	Grade
In patients with confirmed low grade dysplasia, intensified endoscopic surveillance is required. Endoscopic ablation may be considered especially where low grade dysplasia is definite, multifocal and present on more than one occasion. This decision needs to be individualised, based on discussion of risk and benefits with the patient.	B

Issues requiring more clinical research study

- Are the high rates of progression of low grade dysplasia (LGD) shown in recent European studies replicated in studies from other regions?
- Exploration of potential reasons for high rates of progression – are prevalent lesions missed on initial endoscopy in studies from community centres?
- What are the long-term outcomes after ablation for Barrett’s with LGD? Is there significant risk of recurrent dysplasia and neoplasia from recurrent intestinal metaplasia and buried Barrett’s? How do the long-term outcomes compare with surveillance for LGD?
- Is it possible to identify a subgroup of LGD patients at higher or lower risk of progression?

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What is the best endoscopic management of early oesophageal adenocarcinoma?

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What is the best endoscopic management of early oesophageal adenocarcinoma?

Introduction

Early oesophageal adenocarcinoma (EOA) comprises the histological tumour classification of T1a (invasion into the mucosa) and T1b (invasion into submucosa but not muscularis propria). The depth of invasion can be further stratified based on which mucosal (m1-m3) or submucosal (sm1-sm3) layer is involved^{[1][2]} (see also [What are](#)

the histological features of early adenocarcinoma of the oesophagus?). EOA represents 6-12% of patients presenting with oesophageal adenocarcinoma.^{[3][4]} The risk of lymph node involvement with T1a and T1b EOA is 1.3-2.5% and 12-31% respectively.^{[4][5][6][7]} Unlike locally advanced or node-involving disease, EOA can often be cured with surgical or endoscopic approaches. Compared to oesophagectomy, endoscopic treatment is less morbid, less expensive and organ preserving.^[8] Over the past 10 years endoscopic treatment has been increasingly used for EOA.^[9] In general endoscopic treatment methods can be divided into tissue resection and tissue ablation. Tissue resection methods are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Tissue ablation comprises radiofrequency ablation (RFA), argon plasma coagulation (APC), photodynamic therapy (PDT) or cryotherapy. There are no randomised control trials that compare the efficacy of any endoscopic therapy to oesophagectomy for EOA.^[10] Careful interrogation of all Barrett's mucosa is recommended as a longer inspection time leads to a higher likelihood of detecting suspicious lesions.^[11] There may be a spatial predisposition for HGD and EOA to be located between the 12 o'clock and 3 o'clock arc. Several studies have found advanced histology to be within this region in over 50% of cases.^{[12][13][14]} Confirmation of the histology by an experienced gastrointestinal pathologist is recommended prior to further therapy.

Staging

Endoscopic resection enables accurate histological T staging, particularly the depth of invasion. It is considered the most accurate means of T staging for EOA and can alter pre-resection histological grade.^{[15][16]} Endoscopic ultrasound is no longer considered useful EOA staging and is generally not employed.^[17] All visible abnormalities within the Barrett's segment should be described based on the revised Paris classification of superficial neoplastic lesions in the gastrointestinal tract^[18] (e.g. Paris 0-Is or 0-Ilc, see Figure 1)^[19] and resected to establish a complete histological staging and potential cure.

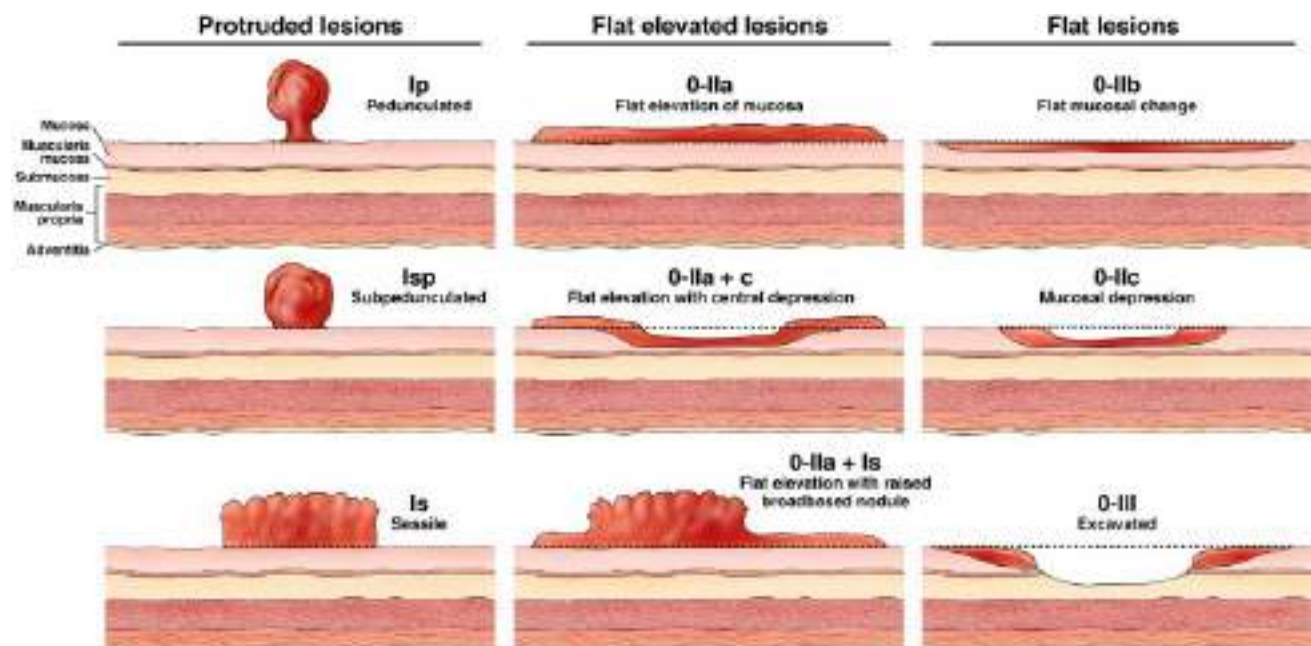


Figure 1. Schematic representation of the Paris classification for mucosal neoplasia. Lesion morphology assists with evaluating the risk of invasive disease and guides the approach to endoscopic resection. AMN are broadly divided into protruded, flat elevated, and flat morphologies. Protruded lesions rise > 2.5 mm above the surrounding mucosa and include pedunculated (0-Ip), subpedunculated (0-Isp), and sessile (0-Is) types. Flat elevated lesions (0-IIa) rise < 2.5 mm above the surrounding mucosa, and features such as central depression (0-IIa + c) or a broad based nodule (0-IIa + Is) are described. Flat lesions include 0-IIb (barely perceptible elevation), 0-IIc (depressed), and 0-III (excavated) types. Source from Holt, Bronte A., Bourke, Michael J. - Clinical Gastroenterology and Hepatology - Volume 10, Issue 9, 969-979 © 2012 AGA Institute

Endoscopic Resection

Provided the histology is favourable (T1a, size <2cm, well differentiated, no lymphovascular invasion, clear resection margins), further endoscopic treatment for the remaining Barrett's can be planned. Options include close endoscopic surveillance, complete Barrett's excision or complete Barrett's ablation. In those who are medically fit some form of endoscopic treatment of the residual Barrett's segment is generally advocated due to the risk of metachronous neoplasia. This is believed to be approximately 20-30% in the next five years.^{[20][21]} Endoscopic resection may not be possible in cases of refractory oesophageal stricture. Following endoscopic resection of EOA and complete elimination of the residual Barrett's segment patients require regular surveillance to exclude recurrent or metachronous Barrett's metaplasia or neoplasia. Endoscopic resection of EOA should be performed in referral centres that have integrated expertise in endoscopy, imaging, surgery, and histopathology.

Endoscopic Mucosal Resection (EMR)

The commonly utilised techniques for EMR include multi-band mucosectomy (MBM) and the cap based lift, suck and cut approach. In randomised control trials comparing these two modalities, procedure time and cost were lower with the MBM technique without a significant difference in primary efficacy, complications or maximum thickness of specimens.^{[22][23]} In the largest series of EMR of T1a adenocarcinoma followed by APC of the remaining Barrett's segment, involving 1000 patients with median follow up exceeding 4.5 years, the long term complete remission rate was 94%, recurrence of high-grade dysplasia or adenocarcinoma was 14.5% and five year overall survival 92%.^[24] There were only two EOA related deaths. The rate of treatment failure was 4.2% and major complications occurred in 1.5%. In other series with shorter follow up complete remission from cancer was achieved in 96-99% with recurrence rates of 2-11%.^{[25][26]} Without adjuvant therapy of the remaining Barrett's segment the rate of metachronous lesions exceeds 20%.^{[20][21]} Subsequent stepwise resection or radiofrequency ablation reduces this risk significantly.^{[27][28]} The rates of oesophageal stricture are proportional to resection extent.^[29] While symptomatic stricture rates approach 13%-20%^{[24][25]} for focal resections and can exceed 50% in <5cm circumferential Barrett's excision,^{[28][29]} endoscopic management of strictures is effective in most cases. There is a low risk of significant complications, which include perforation and bleeding.^{[15][24][25]}^[26] Although in most instances these are endoscopically manageable, EMR should be carried out in a centre with multidisciplinary support encompassing advanced surgical, medical and radiological care.

Endoscopic Submucosal Dissection

ESD allows en-bloc resection of the relevant pathology which is favourable from an oncological perspective. In a Japanese series of ESD for EOA the endoscopic and pathologic (R0) en-bloc resection rates were 100% and 85%, respectively.^[12] Metachronous lesions were found in 4%. Significant bleeding occurred in 4% and this was managed endoscopically in all cases. Stenosis occurred in 15%. In a European series of 30 patients undergoing ESD of EOA or HGD followed by RFA in those with residual Barrett's mucosa, the en bloc and R0 resection rate was 90% and 39%, respectively.^[30] Minor bleeding occurred in 7%. At median follow up of 17 months 96% were free from neoplasia. In a small series of ESD for T1 GOJ adenocarcinoma the rate of curative resection was 72-79% with no local or distant recurrence at median follow up of three years.^{[31][32]} Both EMR and ESD require advanced skills and tertiary level support, however, ESD requires mandatory overnight admission, is more resource and time consuming.

ESD versus EMR

In a pooled analysis of a systematic review of endoscopic treatment of all types of oesophageal T1 cancers there were no significant differences between EMR and ESD in procedural complications, patients undergoing surgery, positive specimen margins, lymph node positivity, local recurrence and metachronous cancer development. ESD had significantly lower resection pieces and lower local recurrence rates.^[33] In a subanalysis of a meta-analysis comprising non-randomised trials of ESD vs EMR for superficial neoplasms of the gastrointestinal tract, ESD had higher en-bloc and curative resection rates. Operative time, bleeding and perforation rates were higher in the ESD group for all gastrointestinal lesions, however, no sub-analysis of oesophageal lesions was performed for these parameters.^[34] The low R0 resection rate of lateral margins, requirement for specialised expertise and increased procedure time of ESD favours EMR as the mainstay of endoscopic resection of EOA. However, focal lesions with a strong suspicion of submucosal invasion or those >2cm should be considered for en-bloc ESD to help with accurate histological staging and a possible organ sparing curative resection.

Radiofrequency ablation

RFA has no role in the treatment of proven, suspected or possible EOA. All visible abnormalities within a given Barrett's segment must be removed by EMR before RFA is considered. It is used to treat flat dysplasia or residual non-dysplastic Barrett's mucosa after focal EMR of a visible abnormality. In a multicentre randomised trial of focal EMR followed by RFA of the residual segment versus stepwise complete resection in Barrett's segments \leq M5 with HGD and T1a/T1sm1, the rates of remission from neoplasia at median follow up of 24 months were comparably high at 95% and 100%, respectively. There was a significantly increased rate of stenosis in the stepwise resection arm of 88% compared to 14%.^[28] In a large systemic review of RFA in dysplastic Barrett's Oesophagus medium term follow-up showed a durable response to treatment.^[35] However, buried metaplasia has been reported within neosquamous epithelium biopsy specimens and this may predispose to the development of subneoplastic cancer. Adenocarcinoma has been reported following RFA.^[36] Thus, following RFA of dysplastic Barrett's Oesophagus caution is recommended. After clearance of neoplasia, dysplasia and Barrett's mucosa is achieved, six-monthly endoscopic surveillance for one year followed by annual surveillance is advised.

Cryotherapy

This treatment has no role as a primary therapy of EOA, however, may be an option in patients that are failing or refusing to have conventional treatment. In a retrospective multicentre series of localised EOA in patients failing or unsuitable for conventional therapies the complete intraluminal response to spray cryotherapy was 72% in patients with T1 lesions at 10 month follow up.^[37]

Argon Plasma Coagulation

Like other ablative strategies, argon plasma coagulation (APC) has no role for the treatment of visible or suspected EOA. It can be used as an adjunctive to complete endoscopic Barrett's resection or destruction of small islands that are not feasible for resection. In the largest series of EMR for T1a EOA APC was used as adjuvant therapy for the remaining Barrett's segment with encouraging long-term results.^[24]

Photodynamic Therapy

Photodynamic Therapy (PDT) has largely been replaced by other ablative modalities. It has no role in primary therapy of EOA. In a retrospective review of 24 patients with T1 EOA, EMR with PDT resulted in a neoplasia remission rate of 83% at 12 months.^[38]

T1a versus T1b approach

T1a EOA can be effectively managed with endoscopic resection. Patients should be counselled about the benefits of organ preservation, reduced morbidity and mortality compared to surgery. They also need to be informed of the minor risk of untreated lymph node spread and the need for ongoing endoscopic surveillance. Due to the high risk of lymph node involvement, surgically fit patients with T1b EOA should be offered oesophagectomy as a potentially curative treatment. Selected T1b lesions can be endoscopically resected with the understanding that there is a higher risk of lymph node metastasis. It may be considered in patients not willing or unfit to undergo surgery. Treatment decisions should be made in the context of a multidisciplinary management team comprising endoscopists, surgeons, oncologists, histopathologists and radiologists. In a retrospective review comparing surgery and endoscopic therapy with adjuvant ablation or chemoradiotherapy in 68 T1b patients there was no significant difference in survival at median follow up of 40 months.^[39] In a retrospective series of 21 patients with SM1 disease treated with endoscopic resection, complete remission from cancer was achieved in 95% of patients, however recurrent or metachronous carcinoma was found in 28% at median follow up 62 months. The calculated five-year survival was 66% and no Barrett's cancer related deaths occurred.^[40] In addition to endoscopic therapy for EOA, adjuvant chemoradiotherapy appears a logical treatment option. However, there is no data to support this approach.^[39]

Recurrence

Recurrence has been described in 6-30% of patients undergoing endoscopic therapy for EOA.^{[20][24][25][41]} Risk factors include larger lesion diameter, long-segment disease, piecemeal removal of the lesion, failure to perform adjunctive ablative therapy, presence of multifocal neoplasia, and an elapsed time of more than 10 months prior to achieving complete remission. In most cases, recurrences can be successfully managed endoscopically. The gastro-oesophageal junction (GOJ) appears to be a common site of neoplasia recurrence and should be assessed in follow up very carefully.^{[27][28]}

Evidence summary and recommendations

Evidence summary	Level	References
Endoscopic resection is the most accurate T staging modality for early adenocarcinoma.	IV	[15] , [16]

Evidence-based recommendation?	Grade
All lesions and visible abnormalities should be staged by focal endoscopic resection.	D

Evidence summary	Level	References
Endoscopic mucosal resection is effective and safe for T1a early oesophageal adenocarcinoma when performed in experienced centres.	II, III-2, IV	[24] , [25] , [39] , [38] , [23]
Selected patients with T1b early oesophageal adenocarcinoma may benefit from endoscopic resection if oesophagectomy is not indicated.		

Evidence-based recommendation?	Grade
Patients with T1a on endoscopic work-up should be offered endoscopic resection as a less morbid and potentially equally effective treatment option in comparison to oesophagectomy.	D
Selected patients with T1b early oesophageal adenocarcinoma may be offered endoscopic resection if oesophagectomy is not indicated.	

Evidence summary	Level	References
Endoscopic submucosal dissection does not offer a significant advantage over endoscopic mucosal resection for most early oesophageal adenocarcinoma.	III-2, IV	[33] , [34] , [12] , [30]

Evidence-based recommendation?	Grade
If endoscopic resection of early oesophageal adenocarcinoma is planned, endoscopic	C

Evidence-based recommendation?	Grade
mucosal resection is appropriate in most cases.	

Evidence summary	Level	References
Following resection of early oesophageal adenocarcinoma the remaining untreated Barrett's mucosa remains at significant risk for metachronous neoplastic disease.	III-2, IV	[20] , [21] , [24] , [25]

Evidence-based recommendation?	Grade
<p>Following resection of early oesophageal adenocarcinoma the remaining Barrett's mucosa should be eradicated.</p> <p>Following resection of early oesophageal adenocarcinoma, Barrett's eradication options include complete Barrett's endoscopic resection, radiofrequency ablation, cryotherapy and argon plasma coagulation.</p> <p>Following resection of early oesophageal adenocarcinoma the patient should undergo regular and careful surveillance examinations.</p>	C

Evidence summary	Level	References
Ablative therapies such as RFA, cryotherapy, APC and PDT have no role as primary therapy for early oesophageal adenocarcinoma.	II, III-2, IV	[28] , [37] , [38]

Evidence-based recommendation?	Grade
Ablative therapies should not be used as primary endoscopic therapy for early oesophageal adenocarcinoma.	C

Practice point?

Endoscopic resection of early oesophageal adenocarcinoma should be performed in referral centres that have integrated expertise in endoscopy, imaging, surgery, and histopathology.

Practice point?

Careful and dedicated interrogation of all Barrett's mucosa is advised.

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What is the best endoscopic treatment for high grade dysplasia in patients with BO?

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What is the best endoscopic treatment for high grade dysplasia in patients with BO?

Introduction

Patients with high grade dysplasia (whereby the glandular crypts are significantly distorted and may include branching which is not present in LGD) are at highest risk for progression to cancer. Therefore, this epithelium should be eradicated provided the biopsies have been independently reviewed by two expert histopathologists preferably one with special expertise in oesophageal diseases (see also [What is the histological definition and grading of dysplasia in patients with BO?](#)). Elimination of metaplastic/dysplastic tissue can be achieved by endoscopic means [ablation/endoscopic mucosal resection (EMR)] or via surgery. Historically, the gold standard for treatment of high grade dysplasia (HGD) and intramucosal cancer was oesophagectomy especially given the risk of a synchronous cancer in the former. Another advantage of oesophagectomy is that the entire segment is removed including occult adenocarcinoma and local lymph nodes although endoscopic surveillance may still be required post-surgery.^[1]

Current worldwide practice favours endotherapy (endoscopic mucosal resection or ablation) over surveillance or esophagectomy for HGD/intramucosal cancer though there are no randomised control trials comparing endoscopic treatment versus oesophagectomy. All such patients should be discussed at a multidisciplinary meeting involving the GI pathologist (preferably with an interest in oesophageal diseases), interventional endoscopist, upper GI surgeon and medical oncologist/radiotherapist.

Endoscopic Mucosal Resection (EMR)

EMR is the removal of affected mucosa and submucosa by resection through the middle or deeper part of the submucosa. Unlike other ablative methods, EMR permits histological assessment of the whole lesion permitting definition of lateral extent and depth. EMR is considered appropriate for visible/nodular lesions whereas radio-frequency ablation (RFA) is currently the choice of ablative therapy for flat dysplastic/neoplastic epithelium. All visible nodular lesions should undergo EMR. Mucosally confined oesophageal carcinoma has a very low risk of metastatic lymphadenopathy (1-2%) which makes endoscopic resection feasible.^[2] If the neoplasia has breached the muscularis mucosae, then by definition the submucosa is involved and lymph node metastases are in the order of 10-20% for sm1/sm2 and up to 55% in sm3 cancers. Oesophagectomy (distal or subtotal) should be considered.^{[3][4][5][6][7][8]} Reported complications of EMR include early bleeding (within 12-24 hours), perforation (0.06-5%) and stricture formation particularly after circumferential resection (30-40%)^[9] (see also [What is the best endoscopic management of early oesophageal adenocarcinoma?](#)).

Endoscopic ablation methods

Ablation can take the form of heat injury [multipolar electrocautery (MPEC), argon plasma coagulation (APC), laser; neodymium-doped yttrium aluminium garnet (Nd-YAG), radio-frequency ablation (RFA), cold injury (cryotherapy) and photochemical injury (PDT). Post ablation/EMR, anti-secretory therapy in the form of PPI's is prescribed, so the oesophageal mucosa heals with the growth of new squamous epithelium (neo-squamous epithelium).

Radio-frequency ablation

RFA is currently the choice of ablative therapy for flat dysplastic/neoplastic epithelium. The landmark AIM Dysplasia Trial randomised 127 patients (64 LGD, 63 HGD) in a 2:1 ratio into RFA and endoscopic surveillance or endoscopic surveillance alone.^[10] A hundred and seventeen completed a year's follow-up. At one year, complete eradication of HGD (intention to treat) occurred in 81% of those in the ablation group as compared with 19% in the control group ($p < 0.001$). Moreover, two and three year outcomes of the trial confirmed durability of the treatment effect after allowing for focal touch up RFA.^[11] In the HGD group, complete eradication of dysplasia (CE-D) was achieved in 50/54 patients (95%) at two years and 23/24 (96%) at three years.

Reported complications with RFA include transient fever, mild dysphagia, odynophagia, oesophageal stricture (9%) and rarely perforation.^[12] Buried metaplasia appears to occur infrequently after RFA.^[10] It is therefore a durable, well tolerated and relatively safe procedure and at the very least as efficacious as PDT in the treatment of HGD.^[13]

Photodynamic therapy (PDT)

This eradication therapy involves the use of a photosensitising agent delivered either intravenously or orally i.e. porfimer sodium (approved for use in the USA) or 5-aminolevulinic acid (5-ALA, rest of the world) followed 48 hours later by delivery of laser light to the Barrett's epithelium. Upon contact with laser light, cells containing the photosensitizer form highly reactive oxygen metabolites that destroy tissue.

In a long-term randomised multicentre trial, Overholt et al assessed the safety and efficacy of PDT treatment plus omeprazole compared to omeprazole alone. At five year follow-up, HGD was eradicated in 77% of those treated with PDT and omeprazole versus 37% on proton pump inhibitor (PPI) alone. Cancer progression which was a secondary outcome was lower in the PDT group (15%) as compared with the omeprazole group (29%) [p=0.004].^[14]

PDT achieves a relatively uniform depth of ablation and a significantly greater depth of penetration (with tissue necrosis >5mm) as compared with other ablative techniques.^[15] In addition, longer segments of tissue can be treated because it is a non-contact ablative technique. Efficacy rates of 57-100% have been achieved with porfimer sodium (deeper tissue penetration than 5-ALA) with mean follow-up intervals of 10-51 months.^[16] It has been reported that a third of patients treated with PDT develop oesophageal strictures.^[17] Cutaneous phototoxicity is also common, occurring in 30-69% of patients.^{[18][17]} The drawbacks of PDT are its high cost, complications and limited availability.

Cryotherapy

Endoscopic spray cryotherapy ablation uses liquid nitrogen (-196°C, CSA system) (or rapidly expanding carbon dioxide gas (-78° C at flow temperature of 6-8L/min, Polar Wand) to produce rapid freezing and slow thawing of a defined volume of tissue causing injury. Non-randomised and uncontrolled studies show success rates comparable to other ablative modalities for the treatment of Barrett's HGD, with complete eradication of dysplasia seen in 87-96% and complete elimination of intestinal metaplasia in 57-96% of treated patients.^{[19][20]} In early-stage oesophageal cancer, spray cryotherapy eliminates mucosal cancer in 75% of patients.^[21]

Evidence summary and recommendations

Evidence summary	Level	References
Endoscopic mucosal resection alters histological grade or local T stage in 48% of patients and dramatically reduces oesophagectomy rates by providing safe and effective therapy. EMR has a high success rate (94%) for complete Barrett's excision in short segment Barrett's Oesophagus.	IV	[22]
Radiofrequency ablation has been shown to completely eradicate high grade dysplasia in 81% of patients at one year of follow-up as compared to a 19% complete eradication in patients undergoing endoscopic surveillance alone. Further positive outcomes were maintained in those undergoing radiofrequency ablation at two and three-years of follow-up with 95% and 96% complete eradication, respectively.	II	[10], [11]

Evidence-based recommendation?	Grade
Endoscopic mucosal resection should be considered for patients with intramucosal adenocarcinoma or high grade dysplasia and visible/nodular lesions.	D

Evidence-based recommendation?	Grade
Radiofrequency ablation should be considered for patients with high grade dysplasia and flat segments of Barrett's. Radiofrequency ablation may be the preferred treatment strategy over endoscopic mucosal resection for patients with long segments Barrett's Oesophagus or circumferential Barrett's due to a lower rate of stricture formation.	B

Practice point?
It is advisable to refer patients with Barrett's Oesophagus and dysplasia or early oesophageal adenocarcinoma to tertiary referral centres for management.

Issues requiring more clinical research study

- What is the long term durability and reduction of risk to progression to oesophageal cancer for patients treated with endoscopic therapy?

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What is the endoscopic definition of BO and how is it described?

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What is the endoscopic definition of BO and how is it described?

Introduction

Barrett's Oesophagus (BO) is a premalignant condition of the oesophagus defined as the presence of metaplastic columnar epithelium,^[1] which endoscopically appears as salmon pink mucosa, extending above the gastro-oesophageal junction (GOJ) and into the tubular oesophagus, thereby replacing the stratified squamous epithelium that normally lines the distal oesophagus.^{[1][2]}

The columnar type mucosa can be one of three types: gastric-fundic type, cardiac type and intestinal-type.^[3] It is the intestinal type that has been clearly shown to predispose to cancer development^[4] and therefore most experts agree that an oesophageal biopsy of columnar epithelium above the GOJ showing intestinal type is required to confirm and establish a diagnosis of BO, rather than relying on endoscopy alone. This is discussed in more detail in the section titled [What is the histological definition of BO?](#)

Intestinal metaplasia at the cardia

There has been debate in the literature as to whether or not cardiac-type epithelium should be included in the definition of BO. Hence according to the 2011 American Gastroenterological Association (AGA) Technical Review on the Management of Barrett's Oesophagus "Barrett's esophagus' presently should be used only for patients who have intestinal metaplasia in the esophagus".^[5] This differs from the definition in previous British Society of Gastroenterology^[6] in which BO was defined as "an endoscopically apparent area above the oesophagogastric junction that is suggestive of Barrett's, which is supported by the finding of columnar lined oesophagus on histology."^[6] This was based on the premise that the diagnosis of IM can be limited by sampling error in mucosal biopsies, especially were less than 8 biopsies were taken. More recently the BSG guidelines have been updated,^[7] and although admitting that 'barrett's mucosa' without IM has a lower risk of progression to cancer based on the population-based study from the Northern Ireland register,^[8] they still recommend that "the presence of IM is not a prerequisite for the definition of Barrett's oesophagus", and if cardiac type epithelium were present in two subsequent endoscopies in segments ≤ 3 cm, these patients can be discharged from further surveillance.

This issue of length of columnar segment with IM and surveillance is discussed in later chapters on recommended surveillance for patients with BO (see also [How frequently should patients with BO undergo endoscopy?](#)), however for the purposes of these guidelines, given the population-based study from the Northern Ireland register^[8] showing a significantly lower risk of progression to cancer in those patients without intestinal-type epithelium we advocate utilisation of the AGA definition provided that appropriate sampling of the columnar segment has been performed.

Endoscopic landmarks for a diagnosis of BO

A reliable endoscopic diagnosis of BO depends on the accurate endoscopic recognition of the anatomic landmarks at the GOJ and squamocolumnar junction (SCJ).^[9] To standardise the objective diagnosis of endoscopic BO, the Prague C & M Criteria were proposed by a subgroup of the International Working Group for the Classification of Oesophagitis (IWGCO).^[10] In this system, the landmark for the GOJ is the proximal end of the gastric folds. Whilst the exact definition of what constitutes the GOJ remains unresolved with no universally

accepted definition, the vast majority of published papers on BO have used the proximal extent of the gastric folds, which was first described in 1987 by McClave et.al.,^[11] and indeed the Prague C & M Criteria have been widely adopted. In the original paper, criteria were externally validated by 29 expert endoscopists and the interobserver agreement, for recognising different lengths of BO and the GOJ location position were very good. This has recently been further externally validated by another group where 16 gastroenterology trainees had similar high interobserver agreement^[12] confirming the utility of these criteria by both trainees and experts after adequate training. However recognition of ≤ 1 cm of BO using the Prague C & M Criteria was less reliable, which is the basis for the recommendation of recent BSG guidelines^[7] to "suggest that 1 cm (M of Prague criteria) should be the minimum length for an endoscopic diagnosis of Barrett's (Evidence grade IV)".

In addition, a recent study in Japan has also highlighted the importance of training on Prague criteria. Before adequate training interobserver agreement amongst a group of 25 experienced endoscopists for identification of the GOJ was poor but this improved markedly after training.^[13] It should also be noted that a criticism of the Prague criteria are that they may fail to identify short segment BO, a lesion found frequently in most Asian countries.^[9] Hence, many Japanese authors believe endoscopic BO is better defined as the most distal extent of the palisade vessels.^{[9][14][15]} Given the absence of evidence to advocate the use of one over the other, and the widespread use of Prague C & M Criteria by western endoscopists, we advocate the use of the proximal extent of the gastric folds in defining BO.

The proximal margin of BO in the Prague Criteria are based on measurement of both the circumferential (C) and maximal (M) extent of metaplasia (shown in figures 1 & 2 below).^[10] There is less debate regarding this margin and it is defined as maximum extent of columnar epithelium above the GOJ.^[10]

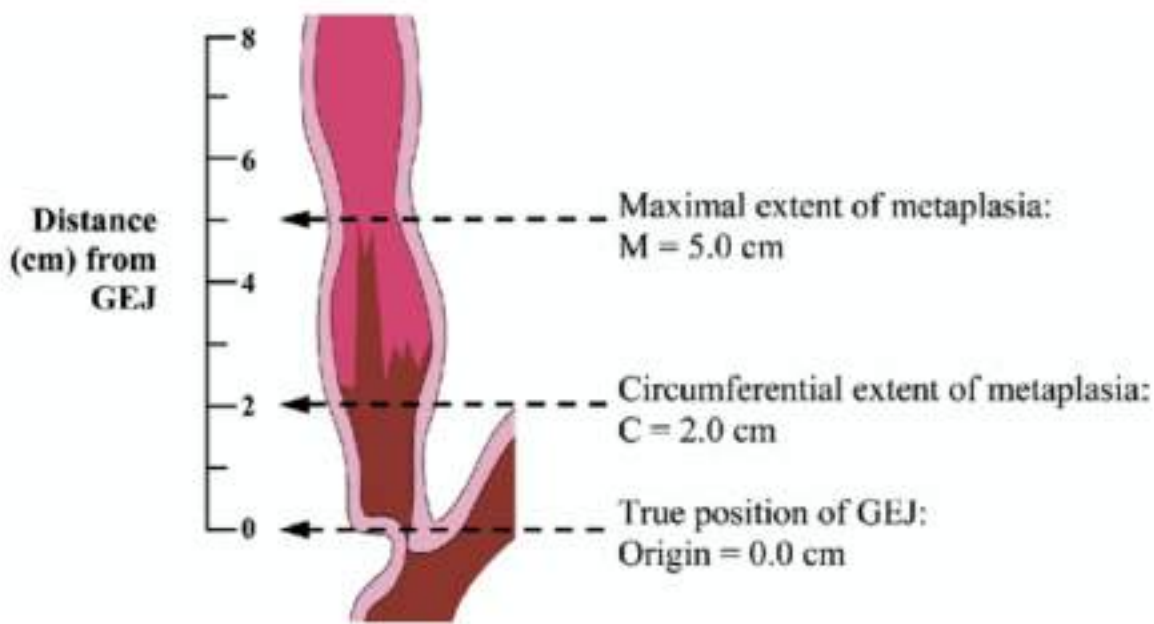


Figure 1. Diagrammatic representation of endoscopic Barrett's Oesophagus showing an area classified as C2M5. C: extent of circumferential metaplasia; M: maximal extent of the metaplasia (C plus a distal "tongue" of 3 cm); GEJ: gastroesophageal junction.

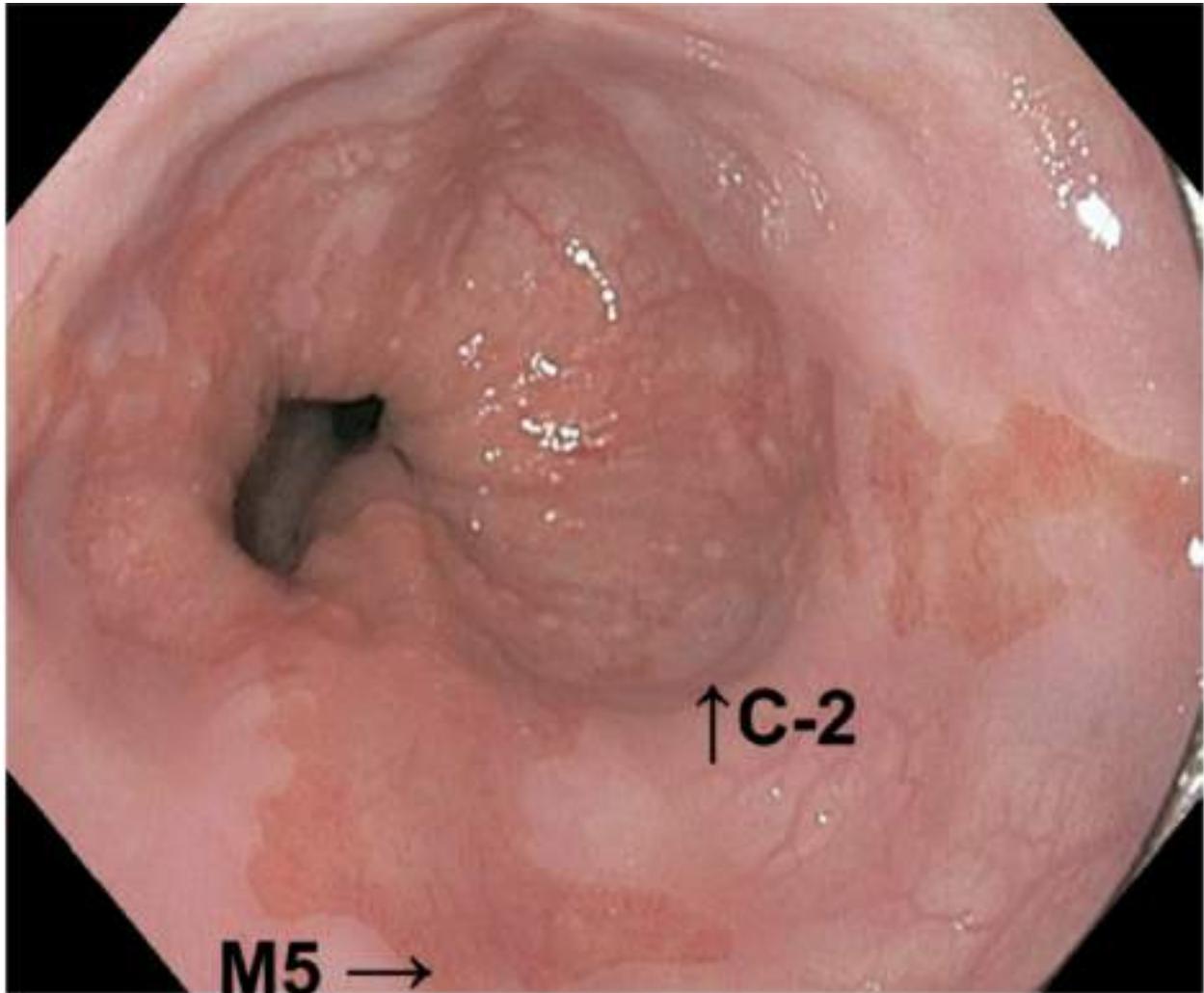


Figure 2. Video still of endoscopic Barrett's Oesophagus showing an area classified as C2M5. C: extent of circumferential metaplasia; M: maximal extent of the metaplasia (C plus a distal "tongue" of 3 cm).

Source: Images used from Publication Gastroenterology, 131(5), Prateek Sharma, John Dent, David Armstrong et. al, The Development and Validation of an Endoscopic Grading System for Barrett's Esophagus: The Prague C & M Criteria, p1395-1396, Copyright (2006), with permission from Elsevier

Practice point?

Biopsies assessing for intestinal metaplasia (columnar epithelium with goblet cells) should be performed when any length of salmon pink mucosa is seen extending above the gastro-oesophageal junction into the tubular oesophagus for a confirmed diagnosis of Barrett's Oesophagus.

Practice point?

The presence of Barrett's Oesophagus should be described using the Prague C & M Criteria.

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What is the histological definition and grading of dysplasia in patients with BO?

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What is the histological definition and grading of dysplasia in patients with BO?

Introduction

Features that characterise and are the basis for grading dysplasia arising in Barrett’s Oesophagus have not been subject to high level research evaluation. They are largely derived from clinical experience. Therefore, this review is based on information that is generally accepted, and has been published in a similar form in review papers and textbooks.

Uncertainty regarding risk of low grade dysplasia progression

The management of patients diagnosed with Barrett’s oesophagus with low grade dysplasia (LGD) is currently uncertain, as there is considerable debate about the risks of progression to high grade dysplasia (HGD) or cancer in this group. Population-based studies which have followed Barrett’s oesophagus patients diagnosed with LGD in the community have reported rates of progression to cancer of ~0.5% p.a. ([Hvid-Jensen et al 2011](#)). In contrast, studies undertaken in academic centres in which diagnoses of LGD are made only after review by expert gastrointestinal pathologists report rates of progression as high as 13% p.a. ([Curvers et al 2010](#)). Importantly, in those studies, about 85% of patients diagnosed originally with LGD were down-staged to non-dysplastic Barrett’s oesophagus upon expert review. In the group of down-staged patients, the rate of progression

was ~0.5% p.a – about the same as the rate observed in the community-based studies. These apparently conflicting data have implications for [how LGD is diagnosed](#), [how patients are managed](#) and [frequency of surveillance](#).

Definition of dysplasia in Barrett’s Oesophagus

Dysplasia is an unequivocal neoplastic transformation of the epithelial cells that is confined within the basement membrane of the metaplastic glandular tissue within which it arises. Dysplasia is a precursor lesion to invasive adenocarcinoma and, particularly in its high grade form, is a marker for the potential presence of adenocarcinoma elsewhere in oesophagus. Histological features that characterise dysplasia are best identified on standard H&E stained sections and are either a) cytological changes or b) gland architectural changes.^{[1][2]}

Cytological features involve nuclear and cytoplasmic changes. Nuclear changes are increase in size, irregular shape, increased nucleus:cytoplasmic ratio, nuclear crowding, hyperchromasia, and the presence of nucleoli. Cytoplasmic change involves mucin depletion. Dysplastic cells exhibit increased mitotic activity, including atypical forms and surface mitoses. There is typically failure of cellular maturation toward the surface of the mucosa, although this is not always the case.^[3] Goblet cell numbers are reduced and dysplastic cells may lose their normal vertical polarity.

Architectural features are irregular gland outline, variability in glandular size, gland crowding with ‘back to back’ pattern, and villiform surface contour. None of these cytological or architectural features are sufficient to diagnose dysplasia in isolation. Ancillary tests, such as p53, AMACR and Ki67 immunochemical stains, have been advocated to aid the diagnosis of dysplasia, however at present, no specific and reliable tests can replace conventional H&E examination and are therefore not recommended in routine practice.

Dysplasia arising in Barrett’s Oesophagus may be of intestinal (adenomatous) or gastric (non adenomatous) phenotype.^[4] Cases displaying hybrid features also exist. Intestinal (adenomatous) type dysplasia resembles colorectal adenoma by exhibiting glands lined by tall columnar cells with hyperchromatic, pencillate, stratified nuclei and eosinophilic cytoplasm and sharp luminal borders. The gastric (non adenomatous) dysplasia type is mostly of foveolar pattern and is characterised by cuboidal to columnar cells with pale clear to light eosinophilic cytoplasm and round to oval nuclei, sometimes with discernable small nucleoli. The glands tend to be smaller and more closely associated than in adenomatous dysplasia and the luminal borders are less distinct. At present there is no requirement for the histopathologist to document the phenotypic subtype of dysplasia since the prognostic significance of this phenotypic subdivision is not known.

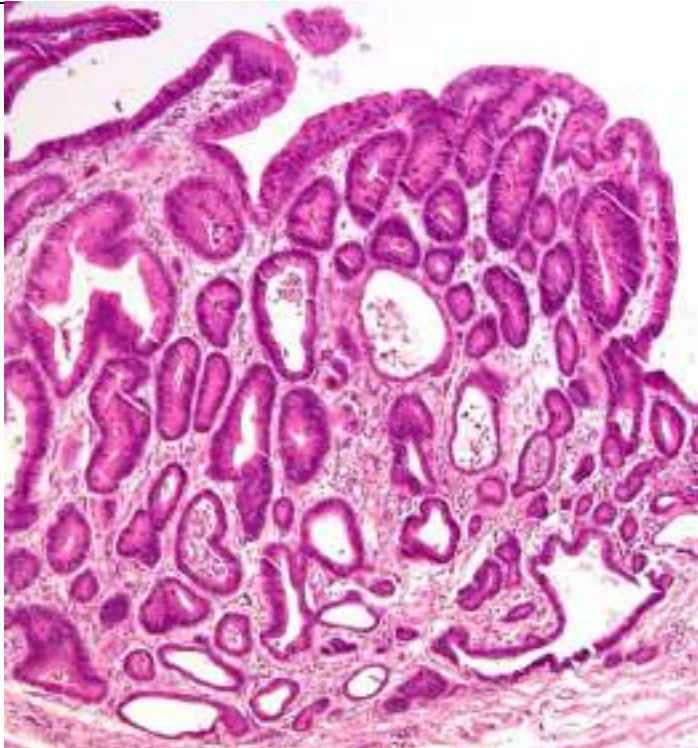


Figure 1. Low power view adenomatous dysplasia (left) and Figure 2. gastric foveolar dysplasia (right)

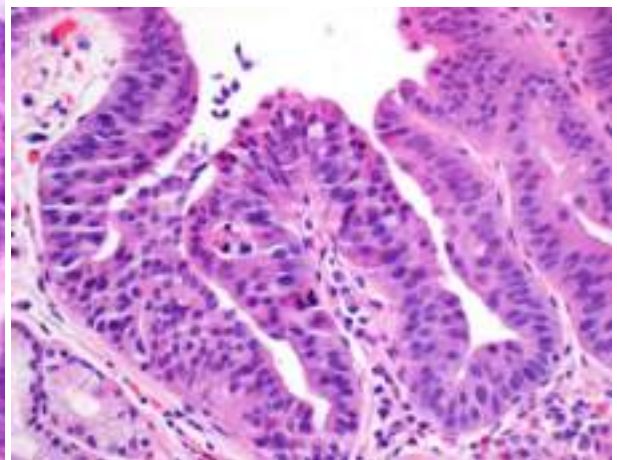


Figure 3. High power view - adenomatous dysplasia (left) and Figure 4. gastric foveolar dysplasia (right)

Grading of dysplasia in Barrett's Oesophagus

Grading of Barrett's Oesophagus dysplasia is best performed on the H&E stain. Pathologists should report Barrett's Oesophagus biopsies as fitting into one of four categories.^{[1][2][4][5][6]} The rationale for this tiered approach is to stratify patients into categories of increasing risk for development of or concurrent presence of oesophageal adenocarcinoma. Many papers have shown an increasing risk ranging from small (negative for dysplasia) to significant (high grade dysplasia).^[7]

1. Negative for dysplasia - The histological features of dysplasia are absent.

2. Indefinite for dysplasia - This term is applicable when the pathologist believes that the biopsy is displaying some of the histological features of true dysplasia but is unable to exclude a non-neoplastic process as the cause of the abnormality. In general the consideration is whether the histological features are sufficient to diagnose low grade dysplasia. However, in some situations (discussed below) the pathologist is concerned that the features may represent high grade dysplasia. Pathologists are most likely to consider a biopsy exhibiting cytological atypia as being indefinite for dysplasia if it shows active inflammation, retention of normal crypt architecture, a normal ratio of glands to lamina propria, obvious signs of surface maturation, and has nuclear atypia that is only of mild degree.^[8]

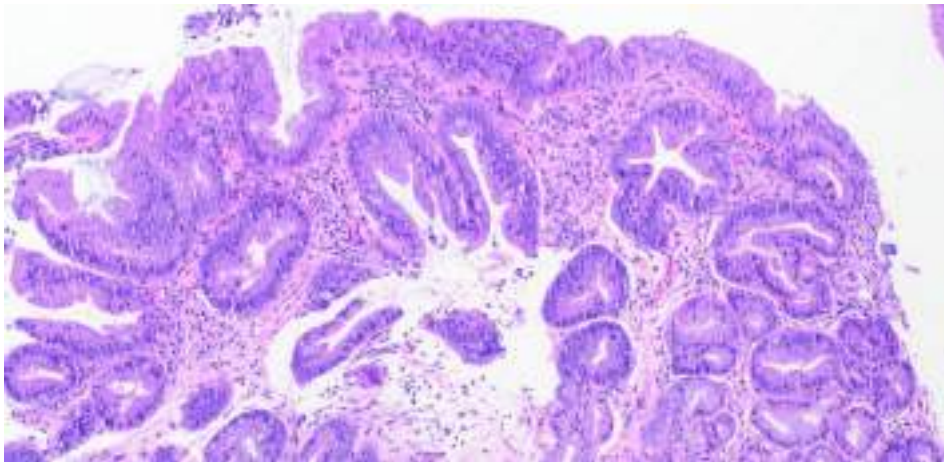


Figure 5. Indefinite for dysplasia - Cytological atypia and multilayering are present, however, there is associated acute inflammation

Indefinite for high grade dysplasia/adenocarcinoma

This concept has not been specifically studied, however, pathologists recognise a subgroup of indefinite for dysplasia, where the cytological and/or architectural abnormality is marked, however, a confident diagnosis of high grade dysplasia cannot be made. In some of these situations the concern is that invasive adenocarcinoma may exist. Reasons for not rendering a specific diagnosis include concern that the changes may be

regenerative, reactive (e.g. medication or radiotherapy induced) or inflammation related; a small amount of material, particularly if at the edge of the biopsy; and the presence of only minimal architectural abnormality in a 'very' well differentiated adenocarcinoma. Basal crypt dysplasia^[3] is a controversial pattern of high grade atypia that is restricted to the crypt base. It is associated with more conventional dysplasia in most cases. Whether this is true dysplasia remains controversial, so pathologists may apply the designation of indefinite for high grade dysplasia to this pattern.

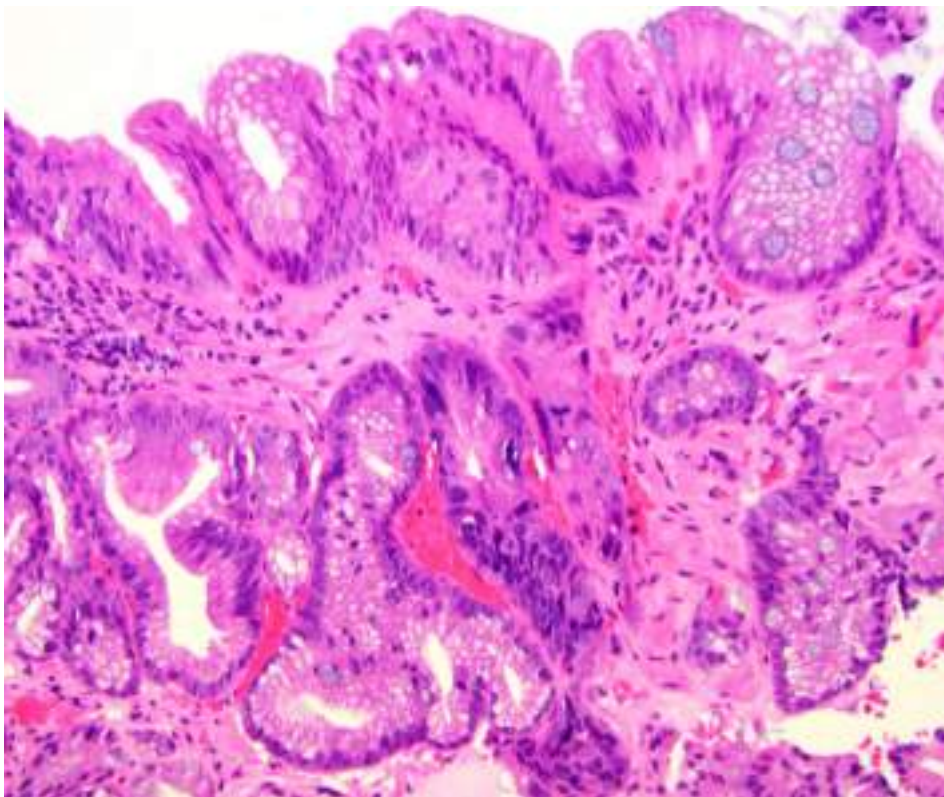


Figure 6. Basal Crypt pattern dysplasia - apparent maturation of dysplasia onto the surface

3. Low-grade dysplasia - displays mild to moderate cytologic atypia and, at most, mild disturbance of gland architecture. The neoplastic epithelial cells are crowded, elongated and hyperchromatic. The cells generally retain their vertical polarity.



Figure 7. Low grade dysplasia

4. High-grade dysplasia - typically displays both architectural abnormality and severe cytologic atypia. Aberrant architectural features include glandular crowding, branching or budding glands, villiform, cribriform, micropapillary or cystically dilated crypt patterns. Cytological features include complete loss of cell polarity, rounded enlarged nuclei with irregular thickened nuclear membranes and conspicuous nucleoli. Typical and atypical mitotic figures are readily identified at all levels within the glands, as well as on the luminal surface.

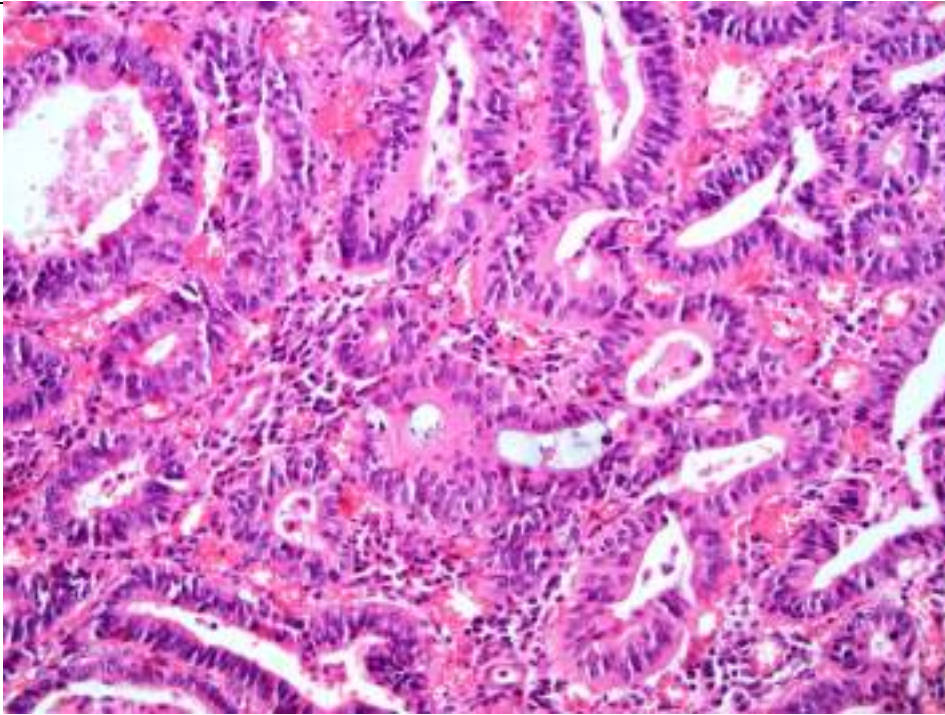


Figure 8. High grade dysplasia - architectural disturbance

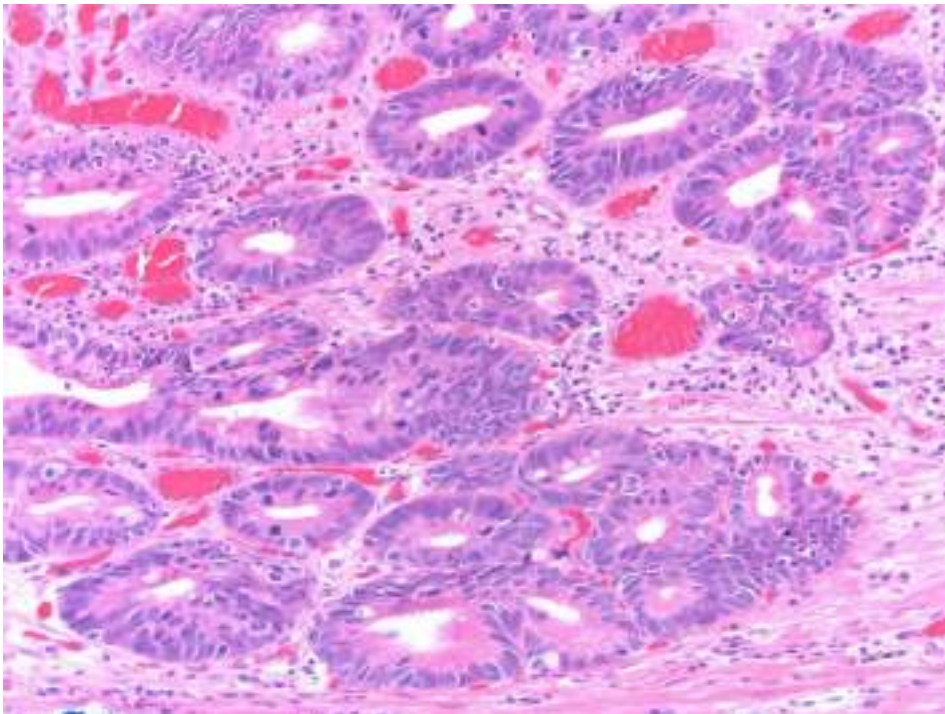


Figure 9. High grade dysplasia - cytological disturbance

Interobserver variability in the histopathological diagnosis of dysplasia

Grading of dysplasia is subject to significant interobserver variability.^{[8][9][10]} This is particularly true for the diagnosis of low grade dysplasia. Previously reported kappa values for interobserver variability among general histopathologists range from 0.14 to 0.32 (poor to fair). Specialist gastrointestinal histopathologists, particularly those with a special interest in Barrett's Oesophagus, have better agreement with kappa values of 0.48-0.69 reported (moderate to good agreement).^[11] In most cases where a diagnosis of low grade dysplasia is made by a general histopathologist and the diagnosis is subsequently changed on review by an expert panel, the effect has been to downgrade the diagnosis to 'negative for dysplasia'. In a recent study where a review of all Barrett's Oesophagus diagnosed as low grade dysplasia was undertaken by expert gastrointestinal pathologists, the cases persisting with this diagnosis had higher rates of progression to high grade dysplasia or oesophageal adenocarcinoma than those revised to negative or indefinite for dysplasia (33% vs 2% at 5 years).^[11]

No good data exists on the interobserver concordance among general histopathologists for the diagnosis of high grade dysplasia, however, in a study involving specialist gastrointestinal pathologists there was substantial diagnostic agreement with kappa = 0.65.^[12]

Interobserver concordance among pathologists has been demonstrated to be significantly higher for endomucosal resection specimens than for biopsy material in all grades of dysplasia.^[13]

These data support the notion that all cases of Barrett's Oesophagus diagnosed as dysplasia (indefinite, low or high grade) should be reviewed by at least one pathologist with a special interest in gastrointestinal tract pathology.

Traditional grading features are best applied to adenomatous type dysplasia. Appropriate criteria for grading of non adenomatous type dysplasia are still evolving.^[14]

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What is the histological definition of BO?

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What is the histological definition of BO?

Introduction

The features that should define Barrett's Oesophagus are not completely understood and this is reflected in the differing definitions given in guidelines from Europe and the USA.^{[1][2][3][4]} It is generally agreed that Barrett's Oesophagus is characterised by metaplastic columnar mucosa replacing normal oesophageal squamous mucosa, but at this time clinical studies are contradictory about whether histologically-proven intestinal metaplasia (IM) with morphologically typical goblet cells should be necessary for its diagnosis. Further studies are needed to clarify the exact definition to optimise patient screening and follow-up.

Requirement for intestinal metaplasia

It is the aim of guidelines to ensure that screening is directed to those with a significantly increased cancer risk. Because Barrett's Oesophagus is a precursor to oesophageal adenocarcinoma, a disease that is increasing in incidence, patients with this change are currently recommended to enter surveillance programmes in most clinical guidelines.

It is clear that metaplastic columnar mucosa, usually cardiac or cardio-oxynitic type, may occur in the oesophagus without IM being detected. This often reflects sampling, since longer Barrett's segments^[5] or larger numbers of biopsies^[6] are associated with increased detection of IM, as is a longer duration of follow-up with re-biopsy.^[7] It is also apparent from several studies that oesophageal adenocarcinoma may arise in a segment of metaplastic columnar mucosa without IM.^{[7][8][9]}

Since many studies of cancer risk in Barrett's Oesophagus were restricted to patients whose diagnosis of Barrett's Oesophagus required the histological identification of IM, further studies will be required to determine the relative risks of intestinalised and non-intestinalised columnar metaplasia as precursors to oesophageal

adenocarcinoma. At this time the data are conflicting. One multicentre study of 1751 patients with a median follow up of 3.5 years found a similar carcinoma incidence whether IM was present or not (3.2% and 3.1% respectively).^[7] Conversely, interrogating the Northern Ireland Barrett's Oesophagus Register of 8522 patients with a mean seven years follow-up, a study from Bhat and colleagues found that the presence of IM in the index biopsy was associated with a greater than five-fold increased risk of adenocarcinoma and combined high grade dysplasia/adenocarcinoma compared with those who did not have IM.^[8] This suggests that the presence of IM identifies a cohort at significantly increased cancer risk. A smaller multicentre study of 209 patients with oesophageal columnar mucosa under surveillance for a mean of greater than nine years also found a low malignant risk if IM was not detected.^[10] Therefore, based on current knowledge there is insufficient evidence to recommend surveillance of patients who have only metaplastic cardiac-type columnar mucosa in the oesophagus.

In routine practice, intestinal metaplasia is diagnosed by the presence of goblet cells. These cells are distended by acidic mucin, which can usually be detected in routine haematoxylin-eosin stained sections and also stains intensely with the alcian blue stain (see figures below). Columnar cells with weaker positive staining and which do not have the characteristic flask shape of goblet cells are not sufficient to diagnose IM.

Biopsies from the tubular oesophagus that have columnar mucosa without IM should be given a descriptive diagnosis (e.g. glandular mucosa without intestinal metaplasia), but it is currently recommended that these are not specifically diagnosed as Barrett's Oesophagus until the biological significance is clarified.

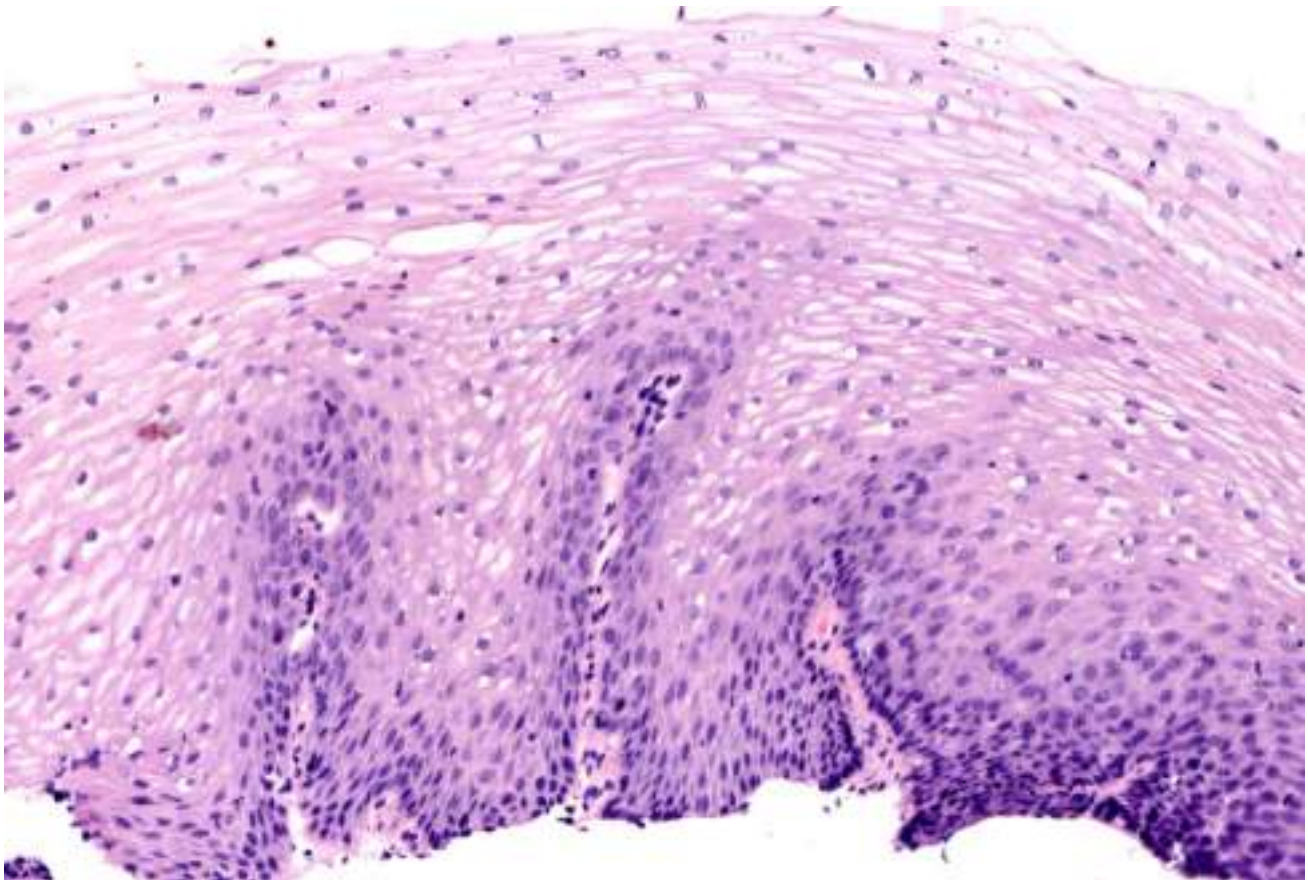


Figure 1. Normal oesophageal squamous mucosa



Figure 2. Intestinal metaplasia with goblet cells highlighted by alcian blue staining

Intestinal metaplasia at the gastro-oesophageal junction or in the gastric cardia

Intestinal metaplasia occurring in isolation at the gastro-oesophageal junction or cardia without metaplasia in the tubular oesophagus is not diagnosed as Barrett's Oesophagus. It may be a precursor to carcinoma, but the risk appears to be low and surveillance is not warranted based on current knowledge.^{[11][12]} However goblet cells noted in a GOJ biopsy can be confirmed to be IM in columnar lined oesophagus if the particular biopsy fragment shows native oesophageal structures such as submucosal glands and/or ducts.

Definitions applied by other Organisations

American Gastroenterological Association^[2]

The definition of Barrett's esophagus is the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus. Presently, intestinal metaplasia is required for the diagnosis of Barrett's esophagus because intestinal metaplasia is the only type of esophageal columnar epithelium that clearly predisposes to malignancy.

American College of Gastroenterologists^[4]

Barrett's esophagus is a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus. (Grade B recommendation).

British Society of Gastroenterology^[1]

Barrett's oesophagus is defined as an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥ 1 cm) above the GOJ and confirmed histopathologically from oesophageal biopsies (Recommendation grade C).

Evidence summary and recommendations

Practice point?

Definition of Barrett's Oesophagus

To identify patients at increased risk of neoplastic progression, Barrett's Oesophagus is defined as metaplastic columnar mucosa in the oesophagus, with intestinal metaplasia proven histologically.

Issues requiring more clinical research study

- Further studies are needed to clarify the exact definition of Barrett's Oesophagus to optimise patient screening and follow-up.
- Further studies will be required to determine the relative risks of intestinalised and non-intestinalised columnar metaplasia as precursors to oesophageal adenocarcinoma.
- The biological significance of intestinal metaplasia confined to the gastro-oesophageal junction needs to be clarified.

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What is the incidence of neoplasia in patients with BO?

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What is the incidence of neoplasia in patients with BO?

Introduction

Barrett's Oesophagus (BO) was described in the 1950's. In Barrett's Oesophagus, cells of the lower portion of the oesophagus change from normal stratified squamous epithelium to include goblet cells (which are usually found lower in the oesophageal/gastric junction). Intestinal metaplasia is sometimes reported. The medical significance of Barrett's Oesophagus is its strong association with adenocarcinoma of the oesophagus (see also [What is the histological definition of BO?](#)). The predominant form of

Uncertainty regarding risk of low grade dysplasia progression

The management of patients diagnosed with Barrett's oesophagus with low grade dysplasia (LGD) is currently uncertain, as there is considerable debate about the risks of

oesophageal cancer is the squamous cell type, however this has been declining in incidence in many developed countries. Adenocarcinoma of the oesophagus has been rising in most developed countries to the extent that now both are occurring at about a similar rate.

progression to high grade dysplasia (HGD) or cancer in this group. Population-based studies which have followed Barrett's oesophagus patients diagnosed with LGD in the community have reported rates of progression to cancer of ~0.5% p.a. ([Hvid-Jensen et al 2011](#)). In contrast, studies undertaken in academic centres in which diagnoses of LGD are made only after review by expert gastrointestinal pathologists report rates of progression as high as 13% p.a. ([Curvers et al 2010](#)). Importantly, in those studies, about 85% of patients diagnosed originally with LGD were down-staged to non-dysplastic Barrett's oesophagus upon expert review. In the group of down-staged patients, the rate of progression was ~0.5% p.a - about the same as the rate observed in the community-based studies. These apparently conflicting data have implications for [how LGD is diagnosed](#), [how patients are managed](#) and [frequency of surveillance](#).

Incidence - sources of data and factors affecting

This review will focus on high quality studies as demonstrated in the body of evidence (see Appendices below), and mainly focused on a few meta-analyses that summarised the question succinctly. Factors influencing the quality score included sufficient follow-up time, whether or not the studies were population based, versus those being undertaken in specialist centres. For noting, none of these studies are from Australia, and so local variations may be possible.

There are three main sources of data ascertaining the incidence of oesophageal adenocarcinoma (OAC) in patients with BO. First includes case series at one or several institutional endoscopy clinics where patients first assessed with BO are then followed up after a period of time, e.g. re-endoscoped after one or two years. The second is a variant of these, whereby incident cases are placed in a program to undergo regular endoscopic surveillance and the third, through population based registries, linked to follow up information, such as cancer, mortality and cause of death. Each of these data sources produces different estimates of incidence of OAC in people with BO. Sources of variation appear to depend on the definition of BO at onset (new cases versus prevalent, time of follow-up, setting (e.g. population vs. specialist centre and sample size, to some extent).

In performing this review it is important to distinguish prevalent cases from incident ones (ie. new diagnoses), and to be mindful that in a surveillance setting, the natural history of BO is interrupted by treatment of people diagnosed with high grade dysplasia. Depending on the effectiveness of this treatment, people undergoing such treatment ought to be 'censored' from follow-up as the natural history of progression would have been interrupted. Even in 'population based studies', patients with diagnosed BO may undergo intensive surveillance according to a country's 'national norm' so the incidence of cancer may be underestimated. Further, certain

studies that have focused on certain subgroups, e.g. smokers, or those with certain histological sub-types who are already at high risk of developing oesophageal cancer, may be providing estimates that may be higher than expected from a more general representative population. Size of study may influence results: Shaheen et al^[1] reviewed 554 abstracts and included 27 articles including 2590 patients with BO, of which 87 developed oesophageal adenocarcinoma. Shaheen et al^[1] suggests that in the setting of BO and oesophageal cancer incidence, there is a strong inverse relationship between the size of the study and cancer risk after BO. Finally, length of follow-up may also influence results. Studies of short duration may be picking up prevalent oesophageal cancers that may have been missed at baseline.

Incidence of OAC in patients with BO - population based studies

There are five population based studies that are pertinent here. Murray et al^[2] performed population based record linkage of cases diagnosed centrally through Northern Ireland's Pathology laboratories and linked these to cancer registration records and deaths. Overall annual incidence of oesophageal cancer six months after initial detection was 2.6/1000 person-years (py). The latest study of these series, using the BO Register^[3] suggests an annual incidence rate of OAC after at least a year of follow-up overall of 1.3/1000 py, 1.6/1000 py in OAC and gastric cardia cancer combined, and 2.2/1000 py of OAC and high grade dysplasia combined. Schouten et al^[4] in the Netherlands linked records of persons diagnosed with BO in a cohort of 120,000 individuals to the a national pathology repository 'PALGA', and estimated an overall annual incidence rate, after six months follow up of 3.3/1000 py, with 3.1 /1000 py in those followed up six months to one year and 4.3/1000 py in those diagnosed one to four years of follow up. Hvid-Jensen et al^[5] linked records of 11,121 cases of BO via national cancer registry and death records and yielded an overall incidence rate for OAC of 1.2 cases per 1000 py (but 2.3/1000 py in those aged 50-69 years of age- an age range more comparable to the other studies). Alexandropoulou et al^[6] using the UK General Practice Research Database where 398 approved general practitioner practices with a catchment population of three million patients record clinical and prescribing data on all their patients. In this study, the annual incidence of oesophageal cancer (OC), one year after documentation of BO between 1996 and 2005, was 3/1000 py.

There are indications that histological subtypes like the presence of intestinal metaplasia, high grade lesions, and length of the columnar mucosa suggesting higher risks. However, record linked studies sometimes miss out on further refinement (i.e. re-grading of lesions on follow up) once the index case has been ascertained. There is lack of censorship of possible intermediate events, e.g. treatment of high grade lesions.

Meta analyses

Thomas et al^[7] performed a meta-analysis of a review of 41 studies from 1966-2004. Overall the incidence of OAC was 7/1000 py, i.e. more than about double those found in population based studies.

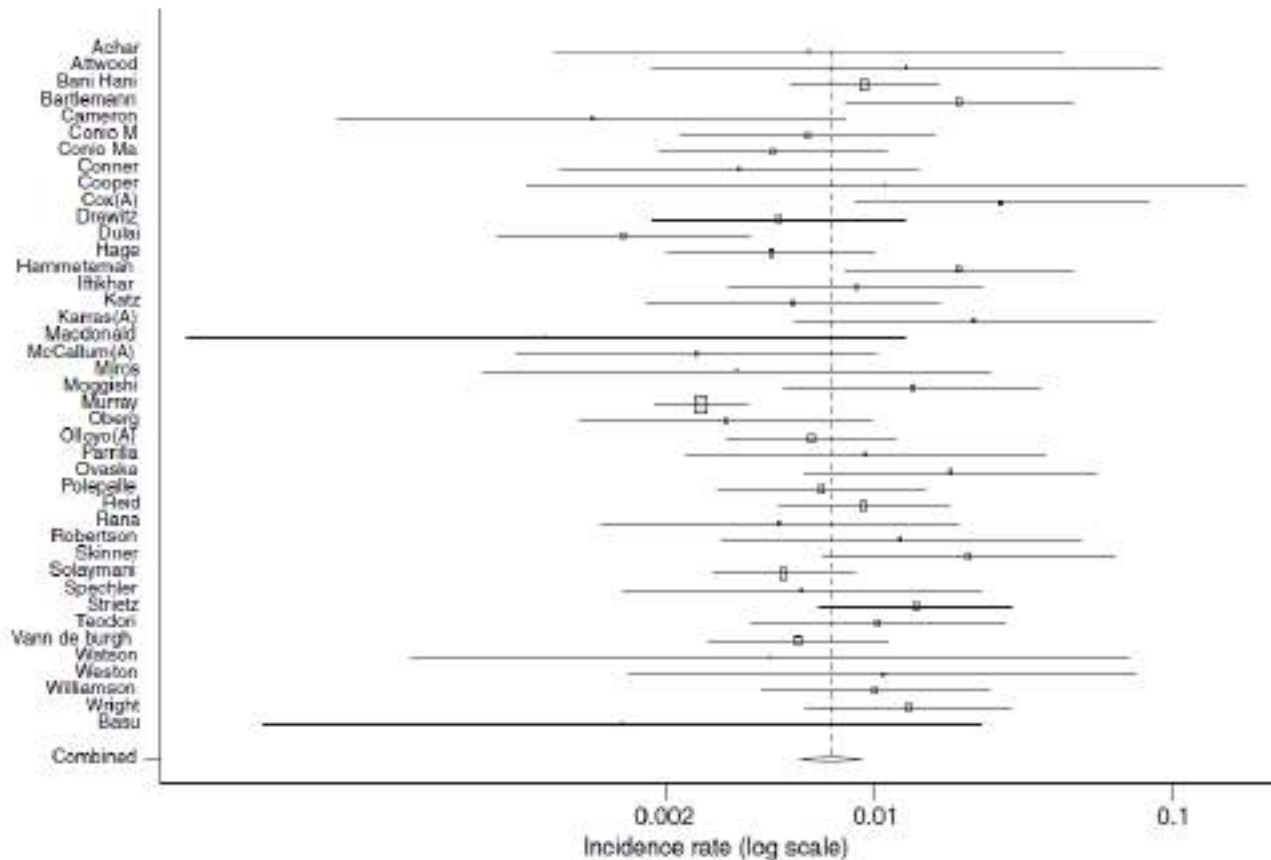
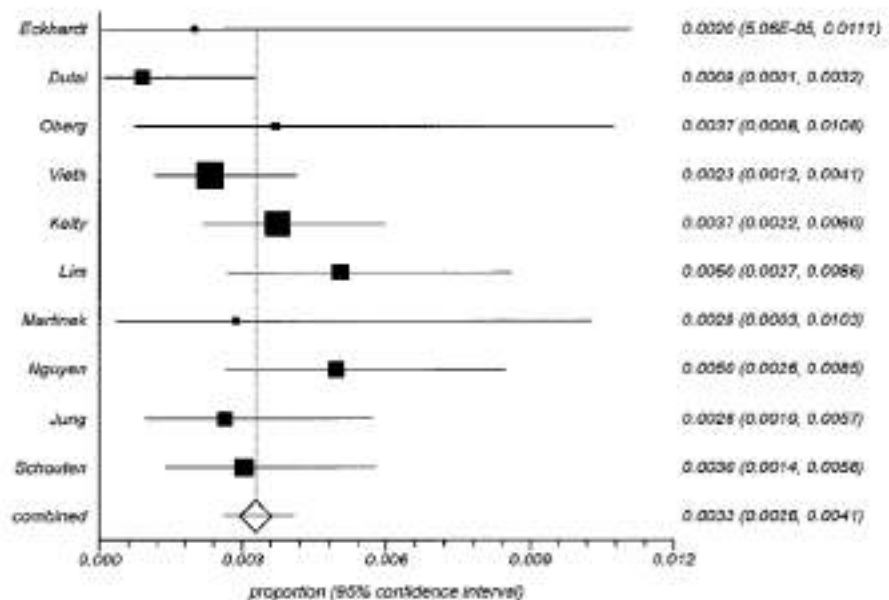


Figure 1. Forrest plot showing the overall incidence of cancer in Barrett's oesophagus in 41 studies. The cancer incidence rate is on a log scale on the x-axis (0.002, 0.01, 0.1 denotes 2/1000, 10/1000 and 100/1000 person-years duration, respectively).

From Thomas et al: Note discrepancy between overall meta-analysis and population based data from Murray et al.

Desai et al performed a meta-analysis of 57 studies from 1966-2012 identifying 10 studies of the highest methodological quality, including those without any dysplasia at baseline. Overall, the annual incidence of OAC in those with BO at baseline 3.3/1000 py. No indication was given whether potentially prevalent cases of OAC were documented six months or one year after follow-up.

Figure 2 Forest plot of the post hoc meta-analysis of the 10 studies of highest methodological quality.



From Meta analysis by Desai et al 2012

Clinical based studies

Gaddam et al^[8] followed up for an average of 5.59 years 1401 patients with non-dysplastic BO in five tertiary care referral centres in the USA with a special interest in this condition. Patients were divided according to the number of times they underwent esophagogastro-duodenoscopy (EGD). As stated "Patients in group 1 were found to have non-dysplastic BO at their first EGD. Patients in group 2 were found to have non-dysplastic BO on their first two consecutive EGDs. Similarly, patients in groups 3, 4, and 5 were found to have non-dysplastic BO on third, fourth, and fifth consecutive surveillance EGDs". Of a total of 3515 patients with BO, 1401 patients met the inclusion criteria. (7846 patient-years). The annual risk of OAC in groups 1 to 5 was 3.2/1000, 2.7/1000, 1.6 /1000, 2/1000, and 1.1/1000 py, respectively.

Jung et al^[9] assessed records of patients with BO (columnar segment > 1 cm with intestinal metaplasia) and IMGEJ (intestinal metaplasia in biopsies from the gastroesophageal junction) from 1976 to 2006 in Olmsted County, Minnesota and followed up cases for a median period of 7-8 years. Demographic and clinical data were abstracted from medical records and pathology confirmed by gastrointestinal pathologists. Excluding those diagnosed with OAC within six months of diagnosis of BO, an estimated annual rate of 2.9 oesophageal adenocarcinomas per 1000 py was found. The rate was 5.0 per 1000 person-years for high grade dysplasias, suggesting if these were untreated, the risk of OAC would have been higher. The percentage follow up is not stated, but is assumed to be at least "reasonable" as over 80% of the county population attends one of the county's two health centres annually.

Two clinically based studies from Australia and New Zealand are acknowledged.^{[10][11]} In the Australian study, an incidence rate of 1/194 py of follow-up was reported (5.15 /1000 py), in the New Zealand study an incidence rate of 10/1000 patient years was provided.

It is clear that studies among specialist centres 'yield' a higher incidence of OAC after BO than population based studies.

Summary

Australia is far more culturally diverse than the populations studied. There are no large local population based studies measuring the incidence of OAC in people with BO in the population. We have no data on the risk in relation to severity of pathology (IM, Dysplasia) nor on rates of incidence of high grade lesions and OAC. Lifestyle factors affect risk of progression and the relationship between those and outcomes would be important to unravel in a local setting.

Issues requiring more clinical research study

- Does OAC risk in Australia differ by place of birth?
- Are people with HG BO 'cured' of their condition?
- What is the local incidence of OAC in persons with BO?
- What is the local incidence of OAC in relation to histological subtypes of BO?
- What proportion of BO is related to OAC?
- What proportion of people with BO are symptomatic?
- Are there variations in risk in relation to place of birth, smoking status or BMI to guide follow-up activity?

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What is the optimal tissue sampling at endoscopy for diagnosis of BO?

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What is the optimal tissue sampling at endoscopy for diagnosis of BO?

Introduction

Barrett's Oesophagus can be suspected endoscopically but it is the histological confirmation of specialised intestinal metaplasia (SIM) that supports its diagnosis and confers an increased risk of development of neoplasia. SIM can be patchy within oesophageal columnar-lined mucosa, and may therefore not be consistently sampled with endoscopic biopsies,^[1] underlining the importance of a systematic approach to maximize the yield of biopsies.

The current standard for tissue sampling

Advancements in chromoendoscopy, endoscope digital enhancements and enhanced-magnification have not been shown to be significantly superior to the currently accepted practice of random four-quadrant biopsies at 2cm intervals.^{[2][3][4]} The diagnostic yield for SIM may be higher with increasing number of biopsies obtained.^[5] If there is concurrent erosive oesophagitis, acid suppressive therapy should be optimised before repeating the endoscopy with further biopsies in two to three months.

Prior to biopsy acquisition, adequate time must be devoted to careful endoscopic inspection using high-resolution white light endoscopy (HR-WLE) for any focal abnormality such as ulcerated or nodular lesions which should be specifically biopsied and labelled prior to random biopsies from the rest of the mucosa as minor biopsy-related bleeding is common and may impair endoscopic views. Spraying dilute adrenaline may improve visibility and efficiency during random biopsies of long-segment Barrett's^[6] but this is not routinely practised.

To maximise the size of tissue fragment biopsied, the open jaw of the biopsy forceps at the tip of the endoscope should be directed perpendicular to the targeted mucosal surface using endoscope angulation and torque, before applying endoscope suctioning and closing the forceps jaw. Jumbo biopsy forceps (jaw outer diameter 2.8 mm) are often utilised but this has not been shown to be superior to large capacity (jaw outer diameter 2.4mm) and standard capacity (jaw outer diameter 2.2mm) forceps in obtaining adequate biopsy samples.^[7]

Technological advancements

Technological advancements in chromoendoscopy (methylene-blue, indigo carmine, and acetic acid), digital enhancements (Narrow-Band Imaging, i-SCAN, Fujinon Intelligent Chromo Endoscopy) and enhanced-magnification can complement rather than replace the current practice described above for diagnosing SIM. Whilst promising, these techniques may not be superior to existing practice and may be impractical, time-consuming and costly. Ongoing studies will define their role in routine clinical practice.

Office-based unsedated transnasal endoscopy using paediatric biopsy forceps (jaw outer diameter 1.8mm) is well-tolerated and may emerge as a cost-effective screening option for the diagnosis of Barrett’s Oesophagus.^[8]
[9][10]

Evidence summary and recommendations

Evidence summary	Level	References
SIM can be patchy within oesophageal columnar-lined mucosa and may not be consistently sampled with endoscopic biopsies.	IV	[1]
Advancements in chromoendoscopy, endoscope digital enhancements and enhanced-magnification have not been shown to be significantly superior to the currently accepted practice of random four-quadrant biopsies at 2cm intervals.	I, II, IV	[2], [3], [4]
The diagnostic yield for SIM may be higher with increasing number of biopsies obtained.	IV	[5]
Jumbo biopsy forceps has not been shown to be superior to large capacity and standard capacity forceps in obtaining adequate biopsy samples	II	[7]
Office-based unsedated transnasal endoscopy using paediatric biopsy forceps is well-tolerated and may emerge as a cost-effective strategy.	II	[8], [9], [10]

Evidence-based recommendation?	Grade
The current practice of random four-quadrant biopsies at 2cm intervals remains the mainstay for tissue sampling until stronger evidence emerges for various advancements in endoscope technology and chromoendoscopy.	B

Practice point?
Focal abnormalities such as ulcerated or nodular lesions can be specifically targeted with biopsies and labelled prior to random biopsies from the rest of the mucosa as minor biopsy-related bleeding is common and may impair endoscopic views.

Practice point?

Technological advancements in chromoendoscopy, digital enhancements and enhanced-magnification can currently complement rather than replace random four-quadrant biopsies at 2cm intervals. Biopsies obtained every 2cm to be placed into separate jars which are labelled according to the distance from the incisors, while biopsies from the gastro-oesophageal junction and cardia can also be specifically labelled as such.

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What is the prevalence of BO in the Australian population in comparison with other populations?

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What is the prevalence of BO in the Australian population in comparison with other populations?

Introduction

There are a large number of studies reporting the prevalence of Barrett's Oesophagus (BO) from various countries around the world. The majority of these studies are cross-sectional in design and the sample sizes vary from less than 50 patients to more than 280,000 patients. The main limitations associated with the studies include the definition of Barrett's Oesophagus, the diagnostic criteria used with some endoscopic only and other studies including histopathologic verification, and the selection of patients. These factors and others may explain the substantial variation in the prevalence of Barrett's Oesophagus reported globally. Australian data are limited and future well designed large studies should be undertaken to improve the estimates of Barrett's Oesophagus among various population groups in Australia.

Australian prevalence of Barrett's Oesophagus

There are only three studies reporting prevalence estimates conducted in Australian populations.^{[1][2][3]} The first study reported on a consecutive sample of endoscopy patients (n=158) from a Sydney hospital (Nepean) and they specifically report the number of short segment Barrett's Oesophagus (n=46, 36%). Moreover, Barrett's Oesophagus was more common among females (65%) and those who were older (56 years versus 48 years, p=0.009).^[1] In a 2006 published study which involved a record linkage data analysis of a region of Brisbane with a population of 376,907 individuals. The analysis which assessed all oesophageal biopsies over the time frame compared rates of Barrett's oesophagus at three different time points (1990, 1998, 2002). The prevalence rates at each of the time points were 0.29% (1990), 1.44% (1998), and 1.89% (2002).^[3] The final study was conducted on 2,153 patients undergoing anti-reflux surgery found that males were twice as likely to have Barrett's Oesophagus (18.4%) compared to females (9.2%).^[2] Overall, there are no studies describing the prevalence of Barrett's Oesophagus in an asymptomatic, unselected Australian population. One small study suggests a high prevalence in specific high-risk patient populations, and two larger studies in different groups of symptomatic patients having a lower prevalence.

Barrett's Oesophagus in the Middle East

There are four studies from the Middle East reporting prevalence rates of Barrett's Oesophagus.^{[4][5][6][7]} There were no population-based studies, and the prevalence of Barrett's Oesophagus ranges were from 3.3%^[5] to 7.3%.^[6] The groups assessed included select groups such as those with chronic gastro-oesophageal reflux symptoms or dyspepsia. Prevalence varied significantly by gender with males more likely to be affected and those who were older (>50 years).^[7]

Barrett's Oesophagus in South America

There are three studies from South America reporting prevalence rates of Barrett's Oesophagus.^{[8][9][10]} There were no population-based studies, and the prevalence of Barrett's Oesophagus ranges were from 1.6%^[10] to 30.8%.^[9] All studies compared individuals with gastro-oesophageal reflux symptoms. Reflux patients had higher rates of Barrett's compared with controls.^{[10][9]}

Barrett's Oesophagus in Asia

There are 23 studies from Asia reporting prevalence rates of Barrett's Oesophagus.^{[11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33]} There were no population-based studies, however, there were several large 'health check' studies and the prevalence of Barrett's Oesophagus ranges were from 0.06%^[26] to 37.7%.^[22] The prevalence was low in Malaysia (<5%) with Barrett's patients more likely to occur in females and those of Indian ethnicity.^{[19][33]} In China, the average prevalence was around 6% with most cases likely to be male.^{[19][18]} In Taiwan, the prevalence was <2%, patients were more likely to be >60 years and were male.^{[11][26][27][30]} Japan had higher prevalence estimates (~20%) and patients were more likely to be >60 years and male.^{[12][17][22][25]} The prevalence was around 6% in Korea and patients were more likely to be older and male.^{[16][18][31][21][23][24][28]} A single study from India had a prevalence of 6% and patients were more likely to be older and male.^[13]

Barrett's Oesophagus in Europe

There are 15 studies from Europe reporting prevalence rates of Barrett's Oesophagus.^{[34][35][36][37][38][39][40][41][42][43][44][45][46][47][48]} There was only one population-based endoscopic study assessing the prevalence of Barrett's which was conducted in Finland (n=1,000), the rate was 1.6% and the majority of patients were female (69%).^[39] Other endoscopic studies reported the prevalence of Barrett's Oesophagus ranged between 0.06%^[38] and 33%.^[48] Studies from Turkey generally had low rates of Barrett's Oesophagus (<8%), and the patients were older and more likely to be male.^{[36][40][43][44]} The Netherlands produced the lowest prevalence of 0.06%^[38] and one of the largest 31%,^[41] but most studies were <5%.^[42] In the United Kingdom studies ranged from 1.4%^[35] to 33%,^[48] again mostly males affected. A German study found a 18% prevalence, with two-thirds being male.^[34] Conversely, a Swedish study reported a 4% prevalence with 69% of patients being female.^[37] Studies from Spain,^[45] Lithuania^[47] and Italy^[46] all reported a <1% prevalence of Barrett's Oesophagus.

Barrett's Oesophagus in the United States

There are 26 studies from the United States reporting prevalence rates of Barrett's Oesophagus.^{[49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73]} There were no population-based studies and the prevalence of Barrett's Oesophagus ranges from 0.25%^[61] to 28.4%.^[68] Generally the prevalence was low (<10%) for all studies in the United States. However, there were several studies comparing different ethnicities and these reported higher rates among Caucasians, followed by Hispanics, African Americans, then Asians.^{[52][67][70][71]}

Summary

The prevalence of Barrett's oesophagus varies by geography and ethnicity, however, the prevalence is generally low (<5%), except for those with gastro-oesophageal reflux symptoms or disease, older individuals (>55 years), and male gender. In certain ethnic populations, such as Asians the prevalence of Barrett's oesophagus is very low (<1%).

Evidence summary and recommendations

Practice point?

Globally, the prevalence of Barrett's Oesophagus is generally low (<5%) and only in selected groups such as those with gastro-oesophageal reflux disease is it substantially higher (>15%). Prevalence also varies significantly by different ethnicities (e.g., Asians <1% prevalence) and by gender (i.e. more common in males).

Issues requiring more clinical research study

- Is there any importance in the variation of short and long segment Barrett's Oesophagus among different populations/ethnicities?
- Australian data are limited and future well designed large studies should be undertaken to improve the estimates of Barrett's Oesophagus among various population groups in Australia.

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Which factors best predict the risk of developing BO?

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Which factors best predict the risk of developing BO?

Introduction

Risk factors for Barrett's Oesophagus (BO) have been assessed in more than 50 studies. All of the studies have been observational, and the vast majority to date have been case-control studies of varying degrees of quality. Several features of study design are likely to have contributed to differences in effect estimates between studies, particularly the ways in which BO cases and controls have been defined and selected. For example, a small number of studies have recruited only newly diagnosed BO cases, whereas others have recruited patients known to have pre-existing disease ('prevalent cases'). Similarly, important differences are likely to exist between population versus institutional controls, and between 'disease-free' versus 'reflux controls'. Other features include the quality of exposure measurements, the methods of analysis and control of potentially confounding factors. These elements of study quality must be borne in mind when assessing the evidence base. Wherever possible, estimates from higher quality studies have been used in the summaries below.

Risk factors for Barrett's Oesophagus

Reflux

There is consistent observational evidence that patients with long-segment BO are much more likely (up to ten-fold in some reports) to report a past history of frequent (more than weekly) gastro-oesophageal acid reflux (GOR) symptoms than population controls. A systematic review of six high-quality observational studies reported a summary odds ratio of 4.92 (95% CI 2.01-12.0) for long segment BO and 1.15 (95% CI 0.763-1.73) for short segment BO.^[1]

Obesity

The association between body mass index (BMI, a simple but crude measure of body mass adjusted for height) and risk of BO has been inconsistent across studies. Most studies have reported small, non-significant, positive associations. Measures of central adiposity (such as waist circumference, waist-hip ratio) and visceral obesity (such as computed tomography (CT) measures of abdominal fat) have been consistently reported to be significantly associated with moderately increased risks of BO. A pooled analysis of four population-based case-control studies comprising 1102 BO cases and 1400 population controls found no evidence of a significant association between BMI and the risk of BO. In contrast, that pooled analysis observed that persons in the highest versus the lowest quartiles of waist circumference had approximately 125% and 275% increases in the odds of BO among men and women, respectively (men OR 2.24, 95% CI 1.08 - 4.65; women OR 3.75, 95% CI 1.47 to 9.56). The associations with measures of central obesity persisted after adjusting for the confounding effects of BMI and gastro-oesophageal reflux.^[2] Similarly, a meta-analysis of 15 studies reported a summary OR of 1.98 (95% CI 1.52-2.57) for measures of central adiposity associated with BO.^[3]

Smoking

Data from case-control studies consistently report risks of BO among smokers to be about 50-60% higher than non-smokers, after adjusting for other potentially confounding factors. A pooled analysis using primary data from five case-control studies (1059 BO cases, 1332 gastro-oesophageal reflux disease (GORD) controls, 1143 population controls) reported a summary odds ratio of 1.67 (95% CI 1.04-2.67) for ever versus never smoking when comparing BO cases to population controls, and OR 1.61 (95% CI 1.33-1.96) when compared to GORD controls.^[4] Similarly, a systematic review and meta-analysis of 39 studies comprising 7069 BO patients reported a summary odds ratio of 1.42 (95% CI 1.15-1.76) for ever versus never smoking when comparing BO cases to population controls.^[5]

Male sex

A systematic review and meta-analysis of 32 studies providing a sex ratio for Barrett's Oesophagus reported a summary ratio of 1.96 (95% CI 1.77-2.17). Although there was considerable heterogeneity in the magnitude of the ratio across studies (ratio ranges 1.08-4.43), all studies observed a male excess of BO.^[6]

Age

Population studies suggest that the probability of a new diagnosis of Barrett's Oesophagus increases with age. A US community study reported that the incidence of new Barrett's Oesophagus was 7 per 100,000 person-years for people 21-30 years and 31 per 100,000 person-years for people aged 61-70 years (adjusted for the different endoscopy rates at different ages).^[7] Case-control studies estimate that the relative risk of diagnosis of Barrett's Oesophagus increases by about 30% per decade above 40 years when compared against patients with a diagnosis of gastro-oesophageal reflux disease.^[8]

Helicobacter pylori

A limited number of case-control studies have conducted serological assays comparing the prevalence of anti-H pylori antibodies between BO cases and controls. These studies have typically reported risk reductions of about 50% for persons with evidence of past infection with H pylori.^[9]^[10]

Alcohol

There is no evidence that alcohol consumption increases the risk of BO. At least three high-quality case-control studies^{[11][12][13]} and one cohort study^[14] have examined this factor in detail and all reported null findings.

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)

A very small number of observational studies have investigated possible associations between self-reported use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) and risks of BO.^{[15][16]} There was no evidence that regular users of aspirin or NSAIDs differed in their risks of BO from never users.

Diet

There is no consistent evidence implicating any dietary or nutritional factors in altering a person's risk of BO, however studies are few.

Metabolic factors

A small number of observational studies have investigated possible associations between metabolic factors and risks of BO. Some studies have reported modest positive associations with high levels of insulin and leptin,^[17]^[18] although findings are inconsistent across studies. Data for other factors (such as insulin-like growth factors) are scarce.

Hiatal hernia

Hiatal hernias have been reported more frequently among patients with BO when compared against both patients with gastro-oesophageal reflux disease (GORD) (about a three-fold increased relative risk) and non-GORD controls (about a 13-fold increased relative risk).^[19]

Family history

A small number of studies has investigated the family history of patients with Barrett's Oesophagus. These studies estimate that about 7% of patients with Barrett's Oesophagus have a confirmed history of Barrett's Oesophagus or oesophageal adenocarcinoma occurring in a first- or second-degree relative,^[20] equating to a relative risk about 12-fold higher than GORD controls.

Risk prediction tools for Barrett's Oesophagus

One study has developed a prediction tool to estimate the probability that a person has BO.^[21] The tool included terms for age, sex, smoking status, body mass index, education, and frequency of use of acid suppressant medications (area under the ROC curve, 0.70; 95%CI, 0.66–0.74). The model had moderate discrimination in an external dataset (area under the ROC curve, 0.61; 95%CI, 0.56–0.66).

Other factors

Clinical studies have identified associations with obstructive sleep apnoea, although associations have been inconsistent across studies and residual confounding by other factors (notably obesity) cannot be excluded.^[22]
^[23]

Evidence summary and recommendations

Evidence summary	Level	References
Major risk factors for Barrett's Oesophagus have been well characterised in population-based studies, and include age, male sex, history of frequent gastro-oesophageal acid reflux, abdominal obesity, smoking and family history.	III-3, IV	[1], [2], [3], [4], [6], [8], [20]

Evidence-based recommendation?	Grade
Clinical assessment of a person's future risk of Barrett's Oesophagus should consider: <ul style="list-style-type: none"> • Age • Person's sex • History of gastro-oesophageal acid reflux • Waist-hip ratio or other measures of central adiposity • Smoking history • Family history of oesophageal adenocarcinoma and/or Barrett's Oesophagus 	B

Issues requiring more clinical research study

- What is the role of aspirin/NSAIDs in the development of BO, and is chemoprevention possible?
- Are there any dietary factors that reduce the risk of BO?
- Is the apparent protective effect of Helicobacter infection causal? If so, what are the implications for clinical management?

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Abbreviations

Abbreviations

AA	Acetic acid
AGA	American Gastroenterological Association
APC	Argon plasma coagulation
BMI	Body mass index
BO	Barrett's Oesophagus
BSG	British Society of Gastroenterology
CI	Confidence interval
CLO	Columnar lined oesophagus
CT	Computed tomography
EGD	esophagogastroduodenoscopy
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
EOA	Early oesophageal adenocarcinoma
ER	Endoscopic resection
EUS	Endoscopic ultrasound
EUS-FNA	EUS-guide fine-needle aspiration
FDG-PET	F-fluoro-2-deoxy-D-glucose positron emission tomography
FFPE	Formalin-fixed, paraffin-embedded
FNA	Fine needle aspirate

GOJ	Gastro-oesophageal junction
GOR	Gastro-oesophageal acid reflux
GORD	Gastro-oesophageal reflux disease
H&E	Haematoxylin & Eosin
HGD	High grade dysplasia
HR-WLE	High resolution white light endoscopy
ICER	Incremental cost effectiveness ratio
IM	Intestinal metaplasia
IMC	Intramucosal cancer
IMCa	Intramucosal adenocarcinoma
IMGEJ	Intestinal metaplasia in biopsies from gastroesophageal junction
IWGCO	International Working Group for the Classification of Oesophagitis
LGD	Low grade dysplasia
LYS	Life-years saved
MB	Methylene blue
MBM	Multi-band mucosectomy
MPEC	Multipolar electrocoagulation/electrocautery
MUC	Mucin immunostaining
NBI	Narrow band imaging
Nd-YAG	Neodymium-doped yttrium aluminium garnet
NSAIDs	Aspirin or non-steroidal anti-inflammatory drugs
OAC	Oesophageal adenocarcinoma
OC	Oesophageal cancer
OR	Odds ratio
PDT	Photodynamic therapy
PET	Positron emission tomography
PPI	Proton Pump Inhibitor therapy
PY	Person-years
QALY	Quality-adjusted life year
RFA	Radiofrequency ablation
ROC / (ROC curve)	Receiver operating characteristic
SCC	Squamous cell carcinoma

SIM	Specialised intestinal metaplasia
TFF3	Trefoil factor 3

Competing interest declarations and management

Competing interest declarations and management

Working Party Members were asked to declare in writing, any interests relevant to the guideline development, prior to commencement. Members were asked to update their information if they became aware of any changes to their interests.

All declarations were added to a register of interests as listed below. The register was made available to the Working Party throughout the development of the guideline, allowing members to take any potential conflicts of interest into consideration during discussions, decision making and formulation of recommendations.

If Working Party Members were identified as having a significant real or perceived conflict of interest, the Chair could decide that the member either leave the discussion whilst the specific area they were conflicted in was discussed or the member could remain present but not participate in the discussion, or decision making on the specific area where they were conflicted. There were no instances where this occurred during the development of this guideline.

Guideline working party members are responsible to update their conflict of interest statements if a new interest arises. The members will receive a formal reminder to review their statements and ensure it is up-to-date prior to the yearly meetings that will be scheduled to review all updates.

Working party member	Competing interest declaration
Angelique Levert	No competing interest to declare.
Associate Professor Alan Moss MBBS (Hons) MD, FRACP	No competing interest to declare.
Associate Professor Bernard Mark Smithers	National Advisory Board for Novartis on the management of GIST. No payment received for this service at this time.
Associate Professor Christophe Rosty, MD PhD FRCPA	No competing interest to declare.
Associate Professor Freddy Sitas	No competing interest to declare.

Working party member	Competing interest declaration
Associate Professor Geoffrey Hebbard	<p>Has received Research Support, Travel Grants and sponsorship of educational activities from the manufacturers and local distributors of all PPIs, H2Receptor Antagonists and Prokinetics. Has had, but has no current consultancies with any of those companies.</p> <p>Has received support for sponsorship of educational activities from medical device manufacturers with products relevant to the diagnosis and management of patients with Barrett’s Oesophagus. Has no shares or other financial links with the manufacturer or distributors of any of the relevant pharmaceutical or device manufacturing companies. Owns shares in The Gut Shop, a company that distributes equipment used in the assessment of patients with gastrooesophageal reflux disease, including patients with Barrett’s Oesophagus.</p>
Associate Professor Guy Eslick	No competing interest to declare.
Associate Professor Ian Norton MBBS, PhD, FRACP	<p>From 2008-2013 was a member of a steering committee for an Astra Zeneca sponsored educational meeting. Honorarium payment involved.</p> <p>Currently member of Advisory Board for Olympus Australia.</p>
Associate Professor Jurgen Stahl FRCPA	No competing interest to declare.
Associate Professor Neil Walker MD, FRCPA	No competing interest to declare.
Associate Professor Sarah J (Sally) Lord MBBS MSc (Applied Biostatistics and Epidemiology)	Married to Working Party member Reginald Lord.
Clinical Professor Marian Priyanthi Kumarasinghe	No competing interest to declare
David Whiteman	No competing interest to declare.
Dr Adrian Chung MBBS, BMed Sci, FRACP	No competing interest to declare.
Dr Andrew Clouston MBBS PhD FRCPA	No competing interest to declare.
	<p>No direct competing interest.</p> <p>Previous recipient of Victorian State Department of Health New Technology Grant to establish endoscopic treatment programme for dysplastic Barrett’s</p>

Working party member	Competing interest declaration
Dr Andrew Taylor MBBS MD FRACP	oesophagus statewide programme at St Vincent's Hospital and in conjunction with Prof Finlay Macrae, Royal Melbourne Hospital. This funding enabled purchase of Halo Radiofrequency Ablation equipment for three years 2009-2011. No specific further funding since then.
Dr Bradley Kendall MBBS, FRACP	No competing interest to declare.
Dr Catherine Campbell MBBS, FRCPA	No competing interest to declare.
Dr Darren A. Pavey MBBS FRACP	No competing interest to declare.
Dr Eric Y Lee BSc(Med) MBBS Hons FRACP	No competing interest to declare
Dr Farzan Fahrtash Bahin, MBBS (Hons), MPhil (Med)	No competing interest to declare.
Dr Florian Grimpén, MD, FRACP	No competing interest to declare.
Dr Henry To	No competing interest to declare.
Dr Iain Thomson MBBS, FRACS	No competing interest to declare.
Dr Ian Brown FRCPA	No competing interest to declare.
Dr Ian Faud Yusoff MBBS, FRACP	No competing interest to declare
Dr Jeremy Dwyer MBBS (Hons)	No competing interest to declare.
Dr Louisa Gordon	No competing interest to declare.
Dr Luke Hourigan MBBS FRACP	Member of ANZELF research group and has received sponsorship to attend annual scientific meeting sponsored by Olympus Australia
Dr Mark Appleyard MD FRACP MRCP MBBS BSc	Has received financial support from Olympus to attend educational conferences; equipment support for clinical research and financial support for clinical research staff.
Dr Mark Schoeman MBBS, PhD, FRACP, AGAF	No competing interest to declare.
Dr Oliver Maximilian Fisher, MD	Supported by a grant from the Swiss Cancer League (BIL KLS-3133-02-2013).
Dr Spiro Raftopoulos	No competing interest to declare.
Dr Sutharshan Kannuthurai	No competing interest to declare.
Dr W Bastiaan de Boer MBBS, BMedSci, FRCPA	No competing interest to declare.
Dr Yuri Veniaminovich Bobryshev PhD	No competing interest to declare
Erfan Jaberianfar	No competing interest to declare.
Melissa Thomas	No competing interest to declare.
Ms Qingwei Luo	No competing interest to declare.

Working party member	Competing interest declaration
Peter Sarich	No competing interest to declare.
Professor David Watson MBBS, MD, FRACS	No competing interest to declare.
Professor James Kench	No competing interest to declare.
Professor Jon Emery MA, MBBCh, FRACGP, MRCGP, DPhil	Chief investigator on a research project investigating a non-endoscopic approach to screening for Barrett's oesophagus in primary care. No pecuniary interest in the associated cytosponge screening test.
Professor Michael Bourke MBBS, FRACP	No competing interest to declare.
Professor Prithi S Bhathal, MBBS PhD FRCPA	No competing interest to declare.
Professor Rajvinder Singh MBBS MRCP MPhil FRACP AM FRCP	No competing interest to declare.
Professor Reginald V Lord MBBS MD FRACS	Married to Working Party member Sarah (Sally) Lord
Professor Shan Rajendra MBBCh, MSc, MRCP, MD, FRCP, FRCPE, FRACP	Member of Medical Advisory Committee, GI Dynamics, Australia.
Sonali Munot	No competing interest to declare.

Derek Maule - No competing interest to declare.

Foreword

Foreword

Barrett's Oesophagus is a condition in which the normal squamous mucosa in the distal oesophagus is transformed to a metaplastic columnar mucosa. Barrett's Oesophagus is important clinically because it is the only known precursor to oesophageal adenocarcinoma ('OAC'), a cancer which has had the fastest rising incidence in Australia and other industrialised nations during the past three decades. Survival from advanced OAC is very poor, hence the focus on diagnosing and treating people with precancerous and early cancerous lesions. Because patients with Barrett's Oesophagus have up to 50-fold higher risks of OAC than people without the condition, they are typically placed on surveillance programs requiring regular endoscopies. Despite their greatly increased relative risk of cancer, 95% of people with Barrett's Oesophagus never develop OAC and 95% of patients diagnosed with OAC have no preceding diagnosis of Barrett's Oesophagus. Thus, there is clinical uncertainty about the best way to manage this condition, both at the individual level and across the population.

These Guidelines therefore seek to assist Australian doctors and patients by providing up-to-date, evidence-based information about Barrett's Oesophagus and early oesophageal adenocarcinoma. The development process was extensive, involving a large working group who systematically reviewed the literature to address pertinent clinical questions. Through consensus, a set of recommendations was developed which have been

rated according to the underlying quality and applicability of the evidence. The Guidelines are aimed at gastroenterologists, pathologists and physicians, as well as members of teams in multi-disciplinary clinics to which patients with Barrett's Oesophagus and OAC are referred (including surgeons, radiologists, nurse practitioners etc). As an open resource, we anticipate that the Guidelines will also be relevant and informative to primary care practitioners and their patients who may be diagnosed with this condition.

Information covered by the Guidelines includes:

1. Prevalence, incidence, natural history and risk factors for Barrett's Oesophagus
2. Endoscopic and histologic definitions of Barrett's Oesophagus and early oesophageal adenocarcinoma
3. Management of Barrett's Oesophagus and early oesophageal adenocarcinoma, including modification of lifestyle factors, screening, surveillance, as well as medical, endoscopic and surgical interventions.

Importantly, these Guidelines do not extend to the management of invasive adenocarcinoma of the oesophagus.

Terminology used in the Guidelines

A recurring theme throughout the Guidelines development process has been the importance of using consistent and precise terminology to ensure that recommendations accord with the published evidence. For example, there are several histological classification schemes used internationally for describing neoplastic changes in Barrett's Oesophagus, including the WHO scheme ('intraepithelial neoplasia') and the Vienna Classification ('dysplasia'). For these Guidelines, we have followed the Vienna Classification. Another example is the use of terms such as 'screening' and 'surveillance' applied to different types of early detection activities. In line with accepted epidemiologic practice, we have reserved 'screening' to describe the process of identifying new cases of disease in an unselected population, whereas 'surveillance' describes the systematic follow-up of patients with known disease at periodic intervals as part of an early detection strategy to prevent progression to cancer.

Recently, there have been numerous developments in the field of Barrett's Oesophagus, including new (lower) estimates of the rate of progression to cancer, new information about factors associated with progression to cancer, new ablation and resection modalities for treating dysplastic lesions, and new cost-effectiveness studies that seek to understand the impact of policy changes at a societal level. All of these have a bearing on clinical practice. That said, much uncertainty remains about key aspects of clinical management for this condition, as high-quality evidence is lacking. For this reason, we have often had to use lower quality evidence when making recommendations; this has been highlighted wherever it has occurred. Further, we have carefully reviewed comparable guidelines from international agencies to calibrate the recommendations in the light of those made elsewhere. The aim of these Guidelines is to ensure the optimal management of patients with Barrett's Oesophagus so as to prevent (or minimise) the development of cancers among this group, balanced against the potential harms of over-investigating or over-treating those at very low risk of disease progression. While the recommendations contained herein are not prescriptive and should not override good clinical judgement, they do represent consensus views of expert practitioners and accord with international practices. Finally, the field is moving very quickly, with a number of large-scale chemoprevention trials and management trials expected to report findings in the foreseeable future, and so we envisage regular updates to the Guidelines. The Wiki environment provides an excellent platform for doing so.

Congratulations to the large team who worked so hard to bring this long-term project to fruition. Their efforts will, it is hoped, improve the management of Australians with Barrett's Oesophagus.

Professor David Whiteman

Chair, Barrett's Oesophagus Guidelines Working Party

Head, Cancer Control Group

QIMR Berghofer Medical Research Institute

Guideline development process

Guideline development process

Introduction

The need to develop guidelines for detection, assessment and management of Barrett's oesophagus and oesophageal adenocarcinoma was identified as a priority arising from the strategic research partnership between ProbeNet and Cancer Council NSW. Cancer Council Australia was approached to collaborate in developing and establishing these Clinical Practice Guidelines for the Management of Barrett's Oesophagus and Early Oesophageal Adenocarcinoma for the Australian community and healthcare setting. No external funding has been received to develop these guidelines.

The guidelines were developed by a multidisciplinary working group (see [Guideline Working Party members](#)). Topic leaders from the Working Party membership were designated to address topics in their areas of expertise, with other Working Group members contributing as co-authors. The literature assessed for these guidelines focuses on the diagnosis and management of patients with Barrett's Oesophagus and early oesophageal adenocarcinoma.

The guideline development process, conducting the literature searches, appraising the literature and formulating and grading recommendations, followed the guideline development process outlined below.

Steps in preparing clinical practice guidelines

Clinical practice guidelines are based on a systematic review where possible. The Working Party developed clinical questions which determined the scope for the guidelines. The search strategy and literature search was conducted by the Project Officer, who distributed the search results to the Working Party authors. Topic groups were assigned to review and synthesise the relevant literature and to formulate evidence-based recommendations where possible. Each topic author followed a clear strategy and the appropriate steps in preparing their guideline sections.

The strategic steps followed are outlined below:

1. Structure the research questions
2. Develop a search strategy
3. Search the literature
4. Critically appraise the literature
5. Formulate and grade recommendations

Structure the research questions

The Working Party discussed the most important aspects for diagnosing and managing Barrett's Oesophagus and Early Oesophageal Adenocarcinoma and developed clinically focused key questions. These clinical questions were developed and approved by Working Party members. The clinical questions asked for the Barrett's Oesophagus and Early Oesophageal Adenocarcinoma Guidelines are as follows:

Barrett's Oesophagus without Dysplasia

Natural History

- What is the prevalence of BO in the Australian population in comparison with other populations?
- Which factors best predict the risk of developing BO?
- What is the incidence of neoplasia in patients with BO?
- What are the risk factors for progression from non-dysplastic BO to high-grade dysplasia or adenocarcinoma?

Referral

- For which populations is screening for BO cost-effective?

Diagnosis/Definition

- What is the endoscopic definition of BO and how is it described?
- What is the optimal tissue sampling at endoscopy for diagnosis of BO?
- What is the histological definition of BO?

Management

- Are there any medical or surgical interventions that cause regression of BO?
- Are there any treatments that prevent progression of BO to cancer?
- What is appropriate medical systemic therapy for symptoms associated with BO?
- Is there a role for ablative therapy to treat BO?

Surveillance and Follow-up

- How frequently should patients with BO undergo endoscopy?

-
- Are there groups of patients with non-dysplastic BO that require more frequent surveillance?
 - Are there groups of patients with BO that can be discharged from surveillance?
 - Is surveillance cost-effective for follow-up of patients with BO?

Barrett's Oesophagus with Dysplasia and/or Adenocarcinoma

Definition and Diagnosis

- What are the endoscopic features of neoplasia (dysplasia and early cancer) within a BO segment?
- What is the histological definition and grading of dysplasia in patients with BO?
- What are the histological features of early adenocarcinoma of the oesophagus?
- What are the best modalities for accurately staging early oesophageal adenocarcinoma?

Biomarkers

- Are there biomarkers for the diagnosis (presence) of BO?

Management

Low grade dysplasia

- What is the appropriate management of low grade dysplasia in patients with BO?

High grade dysplasia and early cancer

- What are the goals of treatment of high grade dysplasia in patients with BO?
- What is the best endoscopic treatment for high grade dysplasia in patients with BO?
- After successful endoscopic treatment for BO neoplasia, how frequently should patients undergo endoscopy?
- What is the best endoscopic management of early oesophageal adenocarcinoma?
- What endoscopic surveillance protocol should be followed for patients with BO and high grade dysplasia?
- How effective is endoscopic management compared with surgical management for high grade dysplasia in patients with BO?

Develop a search strategy

Appropriate search strategies were constructed for each clinical question. MeSH terms were agreed by the Working Party members and were expanded by the Project Officer after conducting pilot searches and searching the MeSH vocabulary. MeSH index terms were translated to Emtree terms for the Embase database to ensure that appropriate index terms unique to each database were used. When there was no appropriate MeSH or Emtree index term available a combination of free text words were used in order to capture the relevant data.

The following exclusion criteria was applied: studies published pre 1980, languages other than English, conference abstracts and the following study designs: non-systematic reviews, case reports, letters, editorials, comments, animal, in vitro and laboratory studies. This exclusion criteria was then refined as per individual clinical question. The search strategy was approved by the members of the Working Party.

Search the literature

A range of medical databases, guideline clearinghouses and clinical trial portals were searched. These included The Cochrane Library, PubMed, Embase, Trip Database, Econlit, NHS Economic Evaluation Database, the National Guideline Clearinghouse, the National Comprehensive Cancer Network and the National Institute for health and clinical excellence, Scottish Intercollegiate Guidelines Network and Canadian Medical Association. Search results were screened for relevance by the Project Officer and relevant literature was collated, the full text articles obtained and sent to Working Party topic authors to critically appraise, synthesise and use as the evidence base for their topic questions. To view the complete search yield and more detailed information about the literature search such as inclusion and exclusion criteria, please go to each clinical question page. The information can be found in the Appendices on each question page.

Critically appraise the literature

Relevant articles selected from the literature search were reviewed by the clinical question authors and each article was critically appraised with respect to level of evidence, quality of the evidence, size of the effect and clinical importance and relevance. Level of evidence was assigned according to the following criteria from the NHMRC Evidence Hierarchy:

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
III-1	A pseudo-randomised controlled trial (i. e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i. e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study ■ Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ■ Historical control study ■ Two or more single arm study ■ Interrupted time series without a parallel control group 	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> ■ Historical control study ■ Two or more single arm study

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.^[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

Formulate and grade recommendations

The body of literature was assessed by each topic author and recommendation grades were assigned using the following criteria adapted from the NHMRC body of evidence matrix:

Component of Recommendation	Recommendation Grade			
	A Excellent	B Good	C Satisfactory	D Poor
Volume of evidence ^{1**}	one or more level I studies with a low risk of bias or several level II studies with a low risk of bias	one or two level II studies with a low risk of bias or a systematic review /several level III studies with a low risk of bias	one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level IV studies, or level I to III studies /systematic reviews with a high risk of bias
Consistency ^{2**}	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population ³	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
	directly applicable to Australian	applicable to Australian healthcare context	probably applicable to Australian healthcare context with some	

These guidelines have been developed as web-based guidelines and the pdf serves as a reference copy only. Please note that this material is only current to the date and time stamped on this document.

Component of Recommendation	Recommendation Grade			
	A Excellent	B Good	C Satisfactory	D Poor
Applicability	healthcare context	with few caveats	caveats	not applicable to Australian healthcare context

¹ Level of evidence determined from level of evidence criteria

² If there is only one study, rank this component as 'not applicable'

³ For example results in adults that are clinically sensible to apply children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.

** For a recommendation to be graded A or B, the volume and consistency of evidence must also be graded either A or B!

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.^[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

Recommendation grades are indicated below:

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP (practice point)	Where no good-quality evidence is available but there is consensus among Guideline committee members, consensus-based guidance points are given, these are called "Practice points"

Adapted from: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.^[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

Write the topic

Topic authors were asked to write the content for their guideline question topic using the following format:

- background
- review of the evidence
- evidence summary with levels of evidence and numbered references

-
- recommendation(s) and corresponding grade(s)
 - references

Review of the question topics

The body of evidence and recommendations for each question topic were reviewed by the Guidelines Working Party and final recommendations agreed to, based on the evidence.

Public consultation

The draft guidelines were released for public consultation to all interested parties in Australia for the period from 11 June to 11 July 2014. The consultation process involved soliciting public review of the draft guidelines through posting onto the Cancer Council Australia Cancer Guidelines Wiki and alerting professional societies and other interest groups via link to the site. All feedback on the draft received during the consultation period in Australia was reviewed by the topic authors and Guidelines Working Party. Subsequent changes to the draft was agreed by consensus of the Guideline Working Party, based on consideration of the evidence.

References

<references>

1. ↑ [1.0](#) [1.1](#) [1.2](#) National Health and Medical Research Council. *NHMRC Australian Guidelines to reduce health risks from drinking alcohol*. Commonwealth of Australia: National Health and Medical Research Council; 2009 Jan 1 Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/ds10-alcohol.pdf.

Summary of recommendations

Summary of recommendations

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

For explanation of levels of evidence and grades for recommendations, see [Levels of evidence and grades for recommendations](#) below. You may also like to refer to the Appendix - [Guideline Development Process](#)

Recommendations

Barrett's Oesophagus and Mucosal Neoplasia


Natural History

What is the prevalence of BO in the Australian population in comparison with other populations?


Point(s)

Globally, the prevalence of Barrett's Oesophagus is generally low (<5%) and only in selected groups such as those with gastro-oesophageal reflux disease is it substantially higher (>15%). Prevalence also varies significantly by different ethnicities (e.g., Asians <1% prevalence) and by gender (i.e. more common in males).

Which factors best predict the risk of developing BO?

Recommendation	Grade
<p> Clinical assessment of a person's future risk of Barrett's Oesophagus should consider:</p> <ul style="list-style-type: none"> • Age • Person's sex • History of gastro-oesophageal acid reflux • Waist-hip ratio or other measures of central adiposity • Smoking history • Family history of oesophageal adenocarcinoma and/or Barrett's Oesophagus 	<p>B</p>

What are the risk factors for progression from non-dysplastic BO to high-grade dysplasia or adenocarcinoma?

Recommendation	Grade
<p> A clinical assessment of a patient’s future risk of high-grade dysplasia or adenocarcinoma in the setting of non-dysplastic Barrett’s Oesophagus should consider their:</p> <ul style="list-style-type: none"> ▪ Age ▪ Sex ▪ Smoking history ▪ Endoscopic findings 	<p>C</p>

Referral

For which populations is screening for BO cost-effective?


Point(s)
<p>There is no evidence to support general population screening for Barrett’s Oesophagus.</p>
<p>In the absence of Randomised Controlled Trial evidence of effectiveness, screening for Barrett’s Oesophagus would be most cost-effective if limited to 50-year old men with gastro-oesophageal reflux disease.</p>

Diagnosis Definition

What is the endoscopic definition of BO and how is it described?

Point(s)
Biopsies assessing for intestinal metaplasia (columnar epithelium with goblet cells) should be performed when any length of salmon pink mucosa is seen extending above the gastro-oesophageal junction into the tubular oesophagus for a confirmed diagnosis of Barrett's Oesophagus.
The presence of Barrett's Oesophagus should be described using the Prague C & M Criteria.

What is the optimal tissue sampling at endoscopy for diagnosis of BO?

Recommendation	Grade
 The current practice of random four-quadrant biopsies at 2cm intervals remains the mainstay for tissue sampling until stronger evidence emerges for various advancements in endoscope technology and chromoendoscopy.	B

Point(s)
Focal abnormalities such as ulcerated or nodular lesions can be specifically targeted with biopsies and labelled prior to random biopsies from the rest of the mucosa as minor biopsy-related bleeding is common and may impair endoscopic views.
Technological advancements in chromoendoscopy, digital enhancements and enhanced-magnification can currently complement rather than replace random four-quadrant biopsies at 2cm intervals. Biopsies obtained every 2cm to be placed into separate jars which are labelled according to the distance from the incisors, while biopsies from the gastro-oesophageal junction and cardia can also be specifically labelled as such.

What is the histological definition of BO?

Point(s)
Definition of Barrett's Oesophagus
To identify patients at increased risk of neoplastic progression, Barrett's Oesophagus is defined as metaplastic columnar mucosa in the oesophagus, with intestinal metaplasia proven histologically.

Management

Are there any medical or surgical interventions that cause regression of BO?

Recommendation	Grade
<ul style="list-style-type: none"> There is insufficient evidence to recommend the use of acid suppressive therapy for the regression of Barrett's Oesophagus. 	B
<ul style="list-style-type: none"> Insufficient evidence exists to routinely recommend anti-reflux surgery for the regression of Barrett's Oesophagus. 	C

Point(s)
<p>Acid suppressive therapy and anti-reflux surgery can be used to control symptoms and heal reflux oesophagitis in patients with Barrett's Oesophagus. There is insufficient evidence to recommend high dose (twice daily) acid suppressive therapy when symptom control or mucosal healing is achieved with standard dosing.</p>

Are there any treatments that prevent progression of BO to cancer?

Recommendation	Grade
<ul style="list-style-type: none"> Ablation of Barrett's Oesophagus should remain limited to individuals with high grade dysplasia in Barrett's Oesophagus who are at imminent risk of developing oesophageal adenocarcinoma. 	B

Point(s)
<p>The treatment of gastro-oesophageal reflux with either proton pump inhibitors or antireflux surgery has not been shown to influence progression to oesophageal adenocarcinoma.</p>
<p>There is currently no good evidence supporting the use of COX inhibitors for prevention of oesophageal adenocarcinoma.</p>

What is appropriate medical systemic therapy for symptoms associated with BO?

Recommendation	Grade
<p>★ Symptomatic patients with Barrett’s Oesophagus should be treated with Proton Pump Inhibitor therapy (PPI), with the dose titrated to control symptoms.</p>	<p>C</p>

Is there a role for ablative therapy to treat BO?

Recommendation	Grade
<p>★ Long term outcome studies do not yet support ablation in patients without dysplasia.</p>	<p>B</p>

Surveillance and Follow-up

How frequently should patients with BO undergo endoscopy?

Point(s)
<p>In the absence of any randomised trial evidence, the frequency of surveillance endoscopy in Barrett’s Oesophagus can be guided by currently available practice guidelines.</p>
<p>It is advisable to undertake endoscopic surveillance in suitable patients with Barrett’s Oesophagus. The frequency of surveillance is based on the presence or absence of dysplasia on previous Seattle protocol biopsies and length of Barrett’s Oesophagus.</p>
<p>A diagnosis of dysplasia (indefinite, low and high grade) should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist.</p>
<p>It is recommended that oesophageal biopsies at the time of endoscopic surveillance of Barrett’s Oesophagus be taken according to the "UNIQ-item-31077-QINU".</p>

Are there groups of patients with non-dysplastic BO that require more frequent surveillance?

Recommendation	Grade
<ul style="list-style-type: none"> ★ Patients with Barrett's Oesophagus length equal to or greater than 3cm may have intensive surveillance, possibly every two to three years following the "UNIQ--item-53415--QINU`" 	C
<ul style="list-style-type: none"> ★ Patients with one or more modifiable risk factors for progression to oesophageal adenocarcinoma (such as smoking) should be encouraged to make lifestyle changes. 	D

Point(s)
Patients with Barrett's Oesophagus length equal to or greater than 3cm may have more frequent surveillance than those less than 3cm.

Are there groups of patients with BO that can be discharged from surveillance?

Recommendation	Grade
<ul style="list-style-type: none"> ★ For patients with < 1cm of columnar lined oesophagus that do not have evidence of intestinal metaplasia or dysplasia on "UNIQ--item-53488--QINU`" biopsy of the segment, endoscopic surveillance is not recommended 	C
<ul style="list-style-type: none"> ★ Patients with one or more modifiable risk factors for progression from Barrett's Oesophagus to oesophageal adenocarcinoma (such as smoking or obesity) should be encouraged to make lifestyle changes. 	D

Point(s)
Patients with evidence of "regression" of Barrett's Oesophagus i.e. reduced Barrett's Oesophagus length or absence of intestinal metaplasia, can still continue surveillance.
Patients with significant co-morbidities, or those whom are unable to tolerate procedural intervention for dysplasia/oesophageal adenocarcinoma may be considered to be discharged from surveillance.

Barrett's Oesophagus and Neoplasia

Definition and Diagnosis

What are the best modalities for accurately staging early oesophageal adenocarcinoma?

Recommendation	Grade
★ Endoscopic resection is the most accurate staging modality for early oesophageal adenocarcinoma for suitable lesions and where appropriate expertise is available.	D
★ Endoscopic ultrasound can be used prior to endoscopic resection for the identification of deeply invasive adenocarcinoma ($\geq T2$) and locoregional lymph node metastasis, particularly for lesions with ulcerated or depressed morphology.	D
★ FDG-PET or PET/CT is not routinely indicated in staging early oesophageal adenocarcinoma. It is best used for the staging of distant metastases or in cases of suspected more advanced local disease.	D

Biomarkers

Are there biomarkers for the diagnosis (presence) of BO?

Recommendation	Grade
★ Insufficient evidence exists to recommend cytokeratin staining to aid in the diagnosis of Barrett's Oesophagus.	D
★ Insufficient evidence exists to recommend the implementation of immunohistochemistry biomarkers to aid in the diagnosis of Barrett's Oesophagus.	D
★ Insufficient evidence exists to recommend mucin (MUC) expression immunostaining in formalin-fixed, paraffin-embedded tissue to aid in the diagnosis of Barrett's Oesophagus.	D

Recommendation	Grade
★ Insufficient high quality evidence exists to recommend the non-endoscopic capsule sponge device coupled with immunohistochemistry for trefoil factor 3 (TFF3) to replace the current clinical standard for the diagnosis of Barrett's Oesophagus.	C
★ Insufficient evidence exists to recommend the implementation of serum G17 for the diagnosis of Barret's Oesophagus.	D
★ Insufficient evidence exists to recommend evaluation of AG2 expression as a protein biomarker in fresh tissue to aid in the diagnosis of Barrett's Oesophagus.	D
★ Insufficient evidence exists to recommend magnifying endoscopy to aid in the diagnosis of Barrett's Oesophagus.	D

Point(s)
Thorough endoscopic sampling (""`UNIQ--item-45012--QINU`""") coupled with H&E staining of sections and interpretation by trained, expert pathologists is advised for the diagnosis of Barrett's Oesophagus. More clinical research is required before biomarkers for Barrett's Oesophagus can be implemented as standard clinical practice.

Management

Low grade dysplasia

What is the appropriate management of low grade dysplasia in patients with BO?

Recommendation	Grade
★ The diagnosis of low grade dysplasia should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist.	C
★ In patients with confirmed low grade dysplasia, it is advised to perform rigorous high definition endoscopy or refer to an expert centre for assessment.	C
★ In patients with confirmed low grade dysplasia, intensified endoscopic surveillance is required. Endoscopic ablation may be considered especially where low grade dysplasia is definite, multifocal and present on more than one occasion. This	B

Recommendation	Grade
decision needs to be individualised, based on discussion of risk and benefits with the patient.	

High grade dysplasia and early cancer

What are the goals of treatment of high grade dysplasia in patients with BO?

Point(s)
The confirmation of high grade dysplasia should act as a trigger for definitive treatment.

What is the best endoscopic treatment for high grade dysplasia in patients with BO?

Recommendation	Grade
★ Endoscopic mucosal resection should be considered for patients with intramucosal adenocarcinoma or high grade dysplasia and visible/nodular lesions.	D
★ Radiofrequency ablation should be considered for patients with high grade dysplasia and flat segments of Barrett's. Radiofrequency ablation may be the preferred treatment strategy over endoscopic mucosal resection for patients with long segments Barrett's Oesophagus or circumferential Barrett's due to a lower rate of stricture formation.	B

Point(s)
It is advisable to refer patients with Barrett's Oesophagus and dysplasia or early oesophageal adenocarcinoma to tertiary referral centres for management.

After successful endoscopic treatment for BO neoplasia, how frequently should patients undergo endoscopy?

Point(s)
Consider three monthly surveillance gastroscopy with "UNIQ--item-52107--QINU" during the endoscopic treatment phase to confirm clearance of intramucosal adenocarcinoma (IMCa) and residual Barrett's. Once clearance has been achieved, consider 6 monthly endoscopic surveillance

Point(s)

for one year, then annually. Higher risk patients (as outlined above) may require closer surveillance gastroscopy after clearance of Barrett's Oesophagus neoplasia is achieved (i.e. initially 3 monthly for a year). Endoscopic resection of any nodularity in the squamous epithelium should be considered to clarify possible recurrent or metachronous IMCa from subsquamous glands.

What is the best endoscopic management of early oesophageal adenocarcinoma?

Recommendation	Grade
<p>★ All lesions and visible abnormalities should be staged by focal endoscopic resection.</p>	D
<p>★ Patients with T1a on endoscopic work-up should be offered endoscopic resection as a less morbid and potentially equally effective treatment option in comparison to oesophagectomy.</p> <p>Selected patients with T1b early oesophageal adenocarcinoma may be offered endoscopic resection if oesophagectomy is not indicated.</p>	D
<p>★ If endoscopic resection of early oesophageal adenocarcinoma is planned, endoscopic mucosal resection is appropriate in most cases.</p>	C
<p>★ Following resection of early oesophageal adenocarcinoma the remaining Barrett's mucosa should be eradicated.</p> <p>Following resection of early oesophageal adenocarcinoma, Barrett's eradication options include complete Barrett's endoscopic resection, radiofrequency ablation, cryotherapy and argon plasma coagulation.</p> <p>Following resection of early oesophageal adenocarcinoma the patient should undergo regular and careful surveillance examinations.</p>	C
<p>★ Ablative therapies should not be used as primary endoscopic therapy for early oesophageal adenocarcinoma.</p>	C

Point(s)

Endoscopic resection of early oesophageal adenocarcinoma should be performed in referral centres that have integrated expertise in endoscopy, imaging, surgery, and histopathology.

Point(s)

Careful and dedicated interrogation of all Barrett's mucosa is advised.

What endoscopic surveillance protocol should be followed for patients with BO and high grade dysplasia?

Point(s)

Surveillance is generally not indicated for patients with high grade dysplasia, and therapeutic intervention must be considered instead.

Targeted biopsies of visible lesions plus quadrantic biopsies every 1cm throughout the segment of Barrett's mucosa should be taken.

High resolution endoscopes should be used, with optional use of virtual chromoendoscopy such as narrow band imaging (NBI).

If endoscopic surveillance is performed, intervals of three months may be appropriate.

How effective is endoscopic management compared with surgical management for high grade dysplasia in patients with BO?

Recommendation

Grade

★ It is recommended that patients with high grade dysplasia in Barrett's Oesophagus be managed in centres with high volume experience of the condition. The treatment and follow-up should occur in those specialist centres.

C

Point(s)

Patients with high grade dysplasia in Barrett's Oesophagus can be discussed at a multidisciplinary team meeting at a specialist centre.

Endoscopic treatment will be the first line treatment option for the majority of patients with high grade dysplasia in Barrett's Oesophagus. There will be a group of patients for whom endoscopic treatment is not appropriate or successful and will be best treated with surgery in a specialist centre.

Levels of evidence and grades for recommendations

The following table provides a list of the evidence-based recommendations detailed in the content of each topic question. The table below provides details on the highest level of evidence identified to support each recommendation (I-IV). The Summary of Recommendations table includes the grade for each recommendation (A-D). The key references that underpin the recommendation are provided in the last column. Individual levels of evidence can be found in the Evidence Summaries for each recommendation in each question.

Each recommendation was assigned a grade by the expert working group taking into account the volume, consistency, generalisability, applicability and clinical impact of the body of evidence supporting each recommendation. When no Level I or II evidence was available and in some areas, in particular where there was insufficient evidence in the literature to make a specific evidence-based recommendation, but also strong and unanimous expert opinion amongst the working group members about both the advisability of making a clinically relevant statement and its content, recommended best practice points were generated. Thus, the practice points relate to the evidence in each question, but are more expert opinion-based than evidence-based. These can be identified throughout the guidelines with the following: Practice point (PP).

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP (practice point)	Where no good-quality evidence is available but there is consensus among Guideline committee members, consensus-based guidance points are given, these are called "Practice points"

Adapted from: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.^[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

Level of evidence was assigned according to the following criteria from the NHMRC Evidence Hierarchy^[1]:

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
		A study of test accuracy with: an independent, blinded comparison with a valid		A	

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
II	A randomised controlled trial	reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	<p>A comparative study with concurrent controls:</p> <ul style="list-style-type: none"> ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study ■ Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	<p>A comparative study with concurrent controls:</p> <ul style="list-style-type: none"> ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study
III-3	<p>A comparative study without concurrent controls:</p> <ul style="list-style-type: none"> ■ Historical control study ■ Two or more single arm study ■ Interrupted time series without a parallel control group 	Diagnostic case-control study	A retrospective cohort study	A case-control study	<p>A comparative study without concurrent controls:</p> <ul style="list-style-type: none"> ■ Historical control study ■ Two or more single arm study

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

References

- ↑ ^{1.0} ^{1.1} National Health and Medical Research Council. *NHMRC levels of evidence and grades for recommendations for guideline developers*. Canberra: National Health and Medical Research Council; 2009 Available from: https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf.

Working party members and contributors

Working party members and contributors

Working party member	Clinical questions
Angelique Levert	
Associate Professor Alan Moss MBBS (Hons) MD, FRACP	
Associate Professor Bernard Mark Smithers	
Associate Professor Christophe Rosty, MD PhD FRCPA	
Associate Professor Freddy Sitas	
Associate Professor Geoffrey Hebbard	

Working party member	Clinical questions
Associate Professor Guy Eslick	
Associate Professor Ian Norton MBBS, PhD, FRACP	
Associate Professor Jurgen Stahl FRCPA	
Associate Professor Neil Walker MD, FRCPA	
Associate Professor Sarah J (Sally) Lord MBBS MSc (Applied Biostatistics and Epidemiology)	
Clinical Professor Marian Priyanthi Kumarasinghe	
David Whiteman	
Dr Adrian Chung MBBS, BMed Sci, FRACP	
Dr Andrew Clouston MBBS PhD FRCPA	
Dr Andrew Taylor MBBS MD FRACP	
Dr Bradley Kendall MBBS, FRACP	
Dr Catherine Campbell MBBS, FRCPA	
Dr Darren A. Pavey MBBS FRACP	
Dr Eric Y Lee BSc(Med) MBBS Hons FRACP	
Dr Farzan Fahrtash Bahin, MBBS (Hons), MPhil (Med)	
Dr Florian Grimpen, MD, FRACP	
Dr Henry To	
Dr Iain Thomson MBBS, FRACS	
Dr Ian Brown FRCPA	

Working party member	Clinical questions
Dr Ian Faud Yusoff MBBS, FRACP	
Dr Jeremy Dwyer MBBS (Hons)	
Dr Louisa Gordon	
Dr Luke Hourigan MBBS FRACP	
Dr Mark Appleyard MD FRACP MRCP MBBS BSc	
Dr Mark Schoeman MBBS, PhD, FRACP, AGAF	
Dr Oliver Maximilian Fisher, MD	
Dr Spiro Raftopoulos	
Dr Sutharshan Kannuthurai	
Dr W Bastiaan de Boer MBBS, BMedSci, FRCPA	
Dr Yuri Veniaminovich Bobryshev PhD	
Erfan Jaberianfar	
Melissa Thomas	
Ms Qingwei Luo	
Peter Sarich	
Professor David Watson MBBS, MD, FRACS	
Professor James Kench	
Professor Jon Emery MA, MBBCh, FRACGP, MRCGP, DPhil	
Professor Michael Bourke MBBS, FRACP	

Working party member	Clinical questions
Professor Prithi S Bhathal, MBBS PhD FRCPA	
Professor Rajvinder Singh MBBS MRCP MPhil FRACP AM FRCP	
Professor Reginald V Lord MBBS MD FRACS	
Professor Shan Rajendra MBBCh, MSc, MRCP. MD, FRCP, FRCPE, FRACP	
Sonali Munot	

Name	Affiliation
Prof Ian Olver AM	Working Party Convener, CEO, Cancer Council Australia
Derek Maule	Consumer representative to the Working Party
Cancer Council Australia Guideline Project and Technical Team	
Christine Vuletich	Manager, Clinical guidelines Network, Cancer Council Australia until 3 July 2014
Jutta von Dincklage	Head, Clinical Guidelines Network 4 July 2014 - present Product Manager, Wiki Development, Cancer Council Australia 2010 - until 3 July 2014
Laura Wuellner	Project Manager, Clinical Guidelines Network Sept 2014- present
Laura Holliday	Project Officer, Systematic Literature Review, Clinical Guidelines Network, Cancer Council Australia 2012-2014
Emma Dickins	Project Officer, Systematic Literature Review, Clinical Guidelines Network, Cancer Council Australia 2014-present