Clinical practice guidelines for the diagnosis and management of Barrett's Oesophagus and Early Oesophageal Adenocarcinoma

1 Clinical practice guidelines for the diagnosis and management of Barrett's Oesophagus and Mucosal Neoplasia

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2.1 Summary of recommendations

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

2.2 Recommendations

2.2.1 Barrett's Oesophagus and Mucosal Neoplasia

2.2.1.1 Natural History

2.2.2 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).

2.2.3 Which factors best predict the risk of developing BO?

Recommendation	Grade
Clinical assessment of a person's future risk of Barrett's Oesophagus should consider: • 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**

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

Recommendation	Grade
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: ▪ Age ▪ Sex ▪ Smoking history ▪ Endoscopic findings	C

2.2.4.1 Referral

2.2.4.2 Diagnosis Definition

2.2.5 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.

2.2.6 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.

2.2.7 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.

2.2.7.1 Management

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

Recommendation	Grade
There is insufficient evidence to recommend the use of acid suppressive therapy for	

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Recommendation	Grade
the regression of Barrett's Oesophagus.	B
Insufficient evidence exists to routinely recommend anti-reflux surgery for the regression of Barrett's Oesophagus.	C

Point(s)
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.

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

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

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

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

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

2.2.11 Is there a role for ablative therapy to treat BO?

Recommendation	Grade
Long term outcome studies do not yet support ablation in patients without dysplasia.	**B**

2.2.11.1 Surveillance and Follow-up

2.2.12 How frequently should patients with BO undergo endoscopy?

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

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

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 '"`UNIQ--item-53415--QINU`"'	**C**
Patients with one or more modifiable risk factors for progression to oesophageal adenocarcinoma (such as smoking) should be encouraged to make lifestyle changes.	**D**

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

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

Recommendation	Grade
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
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/oesphageal adenocarcinoma may be considered to be discharged from surveillance.

2.2.15 Barrett's Oesophagus and Neoplasia

2.2.15.1 Definition and Diagnosis

2.2.16 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 (≥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

2.2.16.1 Biomarkers

2.2.17 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
Insufficient high quality evidence exists to recommend the non-endoscopic capsule sponge device coupled with immunohistochemistry for trefoil factor 3 (TFF3) to	C

Recommendation	Grade
replace the current clinical standard for the diagnosis of Barrett's Oesophagus.	
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.

2.2.17.1 Management

Low grade dysplasia

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

High grade dysplasia and early cancer

2.2.19 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.

2.2.20 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.

2.2.21 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 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.

2.2.22 What is the best endoscopic management of early oesophageal adenocarcinoma?

Recommendation	Grade
All lesions and visible abnormalities should be staged by focal endoscopic resection.	D
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. Selected patients with T1b early oesophageal adenocarcinoma may be offered endoscopic resection if oesophagectomy is not indicated.	D
If endoscopic resection of early oesophageal adenocarincoma is planned, endoscopic mucosal resection is appropriate in most cases.	C
Following resection of early oesophageal adenocarcinoma the remaining Barrett's mucosa should be eradicated. Following resection of early oesophageal adenocarcinoma, Barrett's eradication options include complete Barrett's endoscopic resection, radiofrequency ablation, cryotherapy and argon plasma coagulation. Following resection of early oesophageal adenocarcinoma the patient should undergo regular and careful surveillance examinations.	C
Ablative therapies should not be used as primary endoscopic therapy for early oesophageal adenocarcinoma.	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.
Careful and dedicated interrogation of all Barrett's mucosa is advised.

2.2.23 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.

2.2.24 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.

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2.3 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			

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	A 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	A comparative study with concurrent controls: ▪ 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: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ 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: ▪ 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)

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2.1.1 Prevalence of BO in Australia

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2.1.2 Risk factors

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2.1.2.1 Which factors best predict the risk of developing BO?

2.1.2.1.1 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.

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2.1.2.1.2 Risk factors for Barrett's Oesophagus

2.1.2.1.2.1 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) than population controls. A systematic review of six 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]

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2.1.2.1.2.2 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]

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2.1.2.1.2.3 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]

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2.1.2.1.2.4 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]

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2.1.2.1.2.5 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.[7].[8]

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2.1.2.1.2.6 Alcohol

There is no evidence that alcohol consumption increases the risk of BO. At least three high-quality case-control studies[9][10][11] and one cohort study[12] have examined this factor in detail and all reported null findings.

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2.1.2.1.2.7 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.[13][14] There was no evidence that regular users of aspirin or NSAIDs differed in their risks of BO from never users.

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2.1.2.1.2.8 Diet

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

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2.1.2.1.2.9 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,[15] [16] although findings are inconsistent across studies. Data for other factors (such as insulin-like growth factors) are scarce.

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2.1.2.1.2.10 Hiatal hernia

Hiatal hernias have been reported more frequently among patients with BO.[17]

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2.1.2.1.3 Risk prediction tools for Barrett's Oesophagus

One study has developed a prediction tool to estimate the probability that a person has BO.[18] 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).

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2.1.2.2 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 male sex, history of frequent gastro-oesophageal acid reflux, abdominal obesity and smoking.	III-3, IV	[1], [2], [3], [4], [6]

Evidence-based recommendation	Grade
Clinical assessment of a person's future risk of Barrett's Oesophagus should consider: • Person's sex	B

Evidence-based recommendation	Grade
• History of gastro-oesophageal acid reflux • Waist-hip ratio or other measures of central adiposity • Smoking history	

Practice point
For overweight/obese, male patients who suffer frequent symptoms of gastro-oesophageal reflux, it is advisable to take a smoking history. In such patients, counselling and clinical follow-up may be warranted.

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2.1.2.3 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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2.1.2.4 References

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

Barrett's Oesophagus (BO) is a premalignant condition of the oesophagus defined as the presence of metaplastic columnar epithelium 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.

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 2005 definition from the British Society of Gastroenterology in which BO is 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] A recent large population based study has shown a significantly lower risk of progression to cancer in those patients without intestinal-type epithelium and therefore we advocate utilisation of the AGA definition.

A reliable endoscopic diagnosis of BO depends on the accurate endoscopic recognition of the anatomic landmarks at the GOJ and squamocolumnar junction (SCJ).[7] 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).[8] 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.,[9] 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. Recognition of ≤ 1 cm of BO was, less reliable. Recently, criteria have also been validated by 16 gastroenterology trainees and interobserver agreement were similarly high[10] confirming the utility of these criteria by both trainees and experts after adequate training.

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.[11] 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.[7] Hence, many Japanese authors believe endoscopic BO is better defined as the most distal extent of the palisade vessels.[7][12][13] Given the absence of evidence to advocate the use of one over the other, and the widespread use of Praque 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).[8] There is less debate regarding this margin and it is defined as maximum extent of columnar epithelium above the GOJ.[8]

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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

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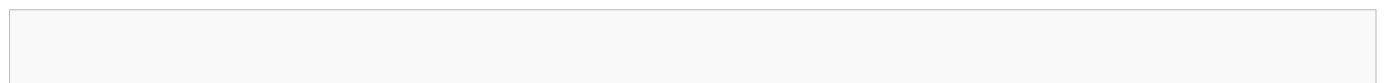
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2.1.7 Optimal tissue sampling

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

2.1.9.1.1 Introduction

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.

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2.1.9.1.2 Medical therapies

Randomised trials have 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]

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2.1.9.1.3 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.

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2.1.9.2 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 regression of Barrett's oesophagus	B

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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 should 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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2.1.16 Cost-effectiveness of surveillance for follow-up

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

2.1.16.1.1 Background

Australia's health system faces increasing pressure to contain health care costs, while still maintaining high quality and optimal care. Cost-effectiveness analysis is a process that systematically compares the relative health care 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
- 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]

2.1.16.1.2 Review of the evidence

A recent systematic review assessed the evidence for cost-effectiveness of endoscopic surveillance of non-dysplastic Barrett's oesophagus.[5] Seven studies met the inclusion criteria[6][7][8][9][10][11][12] which involved a comparison of surveillance for individuals with Barrett's oesophagus versus no surveillance, an outcome of either quality-adjusted life year (QALY) or life-years saved (LYS) and inclusion of both costs and health benefits in the analysis. Figure 1 summarises the key results for the studies included in the review in terms of the incremental cost per QALY/LYS ratios of endoscopic surveillance versus no surveillance strategy. Two studies by Sonnnberg 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]

Studies were published during 1999-2009, and with the exception of one UK study[7] the remaining studies were based on US populations. All studies undertook decision-analytic Markov modelling with health state transitions to reflect disease progression over 25-30 years or until death (i.e., lifetime models). 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.

2.1.16.1.3 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.

2.1.16.1.4 Current directions – surveillance of high-risk individuals

Targeting surveillance to high-risk individuals might maximise benefits and minimise unnecessary use of hospital resources. Intuitively, cost-effectiveness of selected populations for screening or surveillance should be achieved where QALYs gained are relatively high and their costs are potentially lower than strategies directed at 'any-risk' populations.

Two cost-effectiveness studies were identified that involve a hypothetical biomarker testing option[16][2] Rubenstein's JH et al. approach was to determine how sensitive and specific a biomarker test would need to be, and how cheap, to be cost-effective in surveillance. In Gordon LG et al. 2013, the cost-effectiveness of surveillance was markedly improved under the hypothetical scenario of biomarker testing strategy was favourable if patients testing negative for biomarkers did not receive surveillance in the following five years and received two-yearly surveillance thereafter. In addition, cost-effectiveness was greatly improved if endoscopy surveillance of patients with non-dysplastic Barrett's oesophagus was scheduled less frequently, either three- or five-yearly and/or annually for low-grade dysplasia. However, the model assumed that no cancers progress to advanced stage disease under such modified surveillance protocols, and there is only limited evidence available to support this.[17]

Presently, the appropriateness of biomarker testing, its efficacy within a surveillance program, its feasibility and its acceptance are yet to be determined. Further research involving patients with positive biomarkers and additional high-risk clinical factors such as being male, the presence of oesophagitis, length of Barrett's oesophagus, and length of time with Barrett's oesophagus[18] is warranted on economic and efficacy grounds to elicit outcomes from a more targeted high-risk surveillance population.

2.1.16.1.5 Conclusion

Economic evaluations are designed to assist with efficiently allocating scarce health care resources, that is, to minimise costs for given health outputs. The cost-effectiveness of appropriate management strategies for patients with Barrett's oesophagus must be considered. Using current estimates of the malignant potential of Barrett's oesophagus in the wider population versus those reported in surveillance program audits, surveillance of all patients with non-dysplastic Barrett's oesophagus may not be cost-effective. However, further work to identify high-risk individuals, perhaps in the future using a biomarker based strategy, appears promising to improve the economic acceptability of endoscopy-based surveillance of Barrett's oesophagus.

2.1.16.1.6 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.

2.1.16.1.7 Further research is required on

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

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2.1.17 Endoscopic features of neoplasia

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

2.1.17.1.1 Introduction

Dysplasia and early cancer in Barrett's Oesophagus (BO) can be inconspicuous. Most BO neoplasia are flat and small (<1cm2). 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), technologies involving image enhancement devices without chromoendoscopy (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. 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.

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2.1.17.1.2 How should surveillance be performed?

For purposes of standardisation, the Prague's C & M criteria should be used. The criteria includes the assessment of the circumferential (C) and maximum (M) extent of the endoscopically visualized BO segment, as well as endoscopic landmarks, such as the upper end of the gastric folds.[3] These findings have been validated in two large studies to date and has been found to be not only practical but reproducible.[4][5] 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 lesion reveal an area harbouring dysplasia or early cancer.

Dysplasia in BO can be patchy.[6] 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.[7]

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2.1.17.1.3 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.[8] 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.[9] 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%).[10] 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.[11][12] 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).[13]

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2.1.17.1.4 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.[14] 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.[15][16] With NBI and magnification, areas with dysplasia or early cancer appear to have an irregular microvasculature and/or irregular microstructure.[17][18][19][20] A few studies have looked at even higher levels of magnification (>450X) using Confocal Endomicroscopy[21][22][23][24][25] or Endocytoscopy[26][27] 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 however could be a role where normal areas which do not harbor any dysplasia (based on various criteria advocated by various investigators) could be 'left alone' and simply not sampled.[28][29][30] Only abnormal or suspicious areas could be biopsied or resected. This practice could potentially lead to a paradigm shift of how patients are surveyed presently and warrants further assessment.

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2.1.17.1.5 Conclusion

Given the inconspicuous nature of dysplasia in BO, careful, meticulous inspection and attention to subtle endoscopic anomalies using the best available equipment and endoscopes are warranted. At the present moment, targeted and random four quadrant biopsies are recommended.

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2.1.18 Histological definition and grading of dysplasia in BO

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2.1.19 Histological features of early oesophageal adenocarcinoma

Contents

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

2.1.19.1.1 Introduction

Oesophageal adenocarcinoma originates in glandular (epithelial) tissue of the distal part of the oesophagus. Before the development of adenocarcinoma, simple columnar epithelium replaces a section of squamous stratified epithelium. This pre-cancerous event relates to the formation of so called Barrett's oesophagus.

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2.1.19.1.2 Barrett's Oesophagus

According to the American Gastroenterological Association (2011),[1] Barrett's oesophagus is defined as "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 oesophagus". Although three types of simple columnar epithelium (including (i) cardiac type, (ii) gastric-fundic type, and (iii) intestinal-type) can be identified in the setting of the simple columnar epithelium which replaces stratified squamous epithelium, only the intestinal-type with goblet cells (Figure 1), known as Barrett's metaplasia, has been proved to be associated with an increased risk of neoplastic progression.[1][2][3][4][5][6][7][8][9][10][11][12][13] It is established that annual risk of esophageal adenocarcinoma is about 0.5% per year in patients with intestinal metaplasia (Barrett's metaplasia).[1][2] The cellular origin of Barrett's oesophagus remains controversial.[3][4][5][6][7][8][9][10][11][12][13][14] Even though a number of recent reports indicate that stem cells might be involved in the formation of Barrett's oesophagus, the most commonly accepted view is that that in Barrett's metaplasia, the differentiated cells from the stratified squamous epithelium directly convert to a simple columnar epithelial phenotype which is present in the intestine.[3][4][5][6][7][8][9][10][11][12][13][14]

Figure 1. Barrett's metaplasia (synonymous with Barrett's oesophagus). The most distinctive feature of Barrett's oesophagus relates to the presence of glands which are formed by simple columnar epithelium that contains so called goblet cells. Goblet cells are glandular simple columnar epithelial cells, the main function of which is to secrete mucin. In histological sections a goblet cell can be easily identified by the presence of a very large cytoplasmic vacuole filled with mucin; such vacuole appears a transparent or slightly bluish-stained space in Haematoxylin & Eosin (H&E) stained sections. Magnification: x200.

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2.1.19.1.3 Histologic features and grades of dysplasia

According to the current "metaplasia-dysplasia-adenocarcinoma sequence" paradigm, the formation of esophageal adenocarcinoma occurs as a result of dysplastic changes of Barrett's metaplastic epithelium that eventually lead to unregulated cell growth.[2][3][4][5][6][7][8][9][10][11][12][13][14] One of the key histologic manifistations of the development of dysplastic alterations is the progressive disappearance of goblet cells from simple columnar epithelium .[2][3][4][5][6][7][8][9][10][11][12][13]. Although there are several classifications of dysplastic changes that occur in the Barrett's oesophagus, dysplastic changes are most commonly classified into four clinically significant categories (groups of tissue specimens)[2]:

- Negative for dysplasia;

- Indefinite for dysplasia;

- Low grade dysplasia;

- High grade dysplasia.

In order to determine a degree of dysplasia, the cytologic and histologic characteristics and peculiarities of tissue specimens are examined with specific attention to the following parameters: (i) nuclear and cytoplasmic features; (ii) degree of "surface maturation" (comparison between nuclear size within crypts and nuclear size at the mucosal surface) and (iii) tissue "architecture" (relationship between glands and lamina propria).[2] The histologic features of each category of dysplasia are presented below in Figures 2-5.

Figure 2. Negative for dysplasia. These tissue specimens (biopsies) that are classified into the *Negative for dysplasia* category are characterised by a minimal amount of cytologic atypia as well as by a low nuclear /cytoplasmic ratio in epithelial cells. The nuclei in epithelial cells are typically regular and are basally located. It is essential to noting here that, in the presence of signs of inflammation (an increased amount of immune inflammatory cells in the the surrounding matrix of the lamina propria), increased cytologic atypia is allowed for the classification of a specimen into the *Negative for dysplasia* category. In *Negative for dysplasia* specimens, normal tissue architecture with abundant amount of connective tissue (lamina propria matrix) between glands is preserved. Magnification: x200.

Figure 3. Indefinite for dysplasia. This category is used to define tissue specimens, in which histologic changes cannot be definitively described as dysplastic or neoplastic. Although signs of cytologic atypia can be noted in some glands, the most of the epithelium is typically free of atypia. In this category, the tissue architecture is normal with minimal gland crowding. This category is often used to describe either tissue specimens that display the evidence of pronounced inflammation (in areas of slightly altered glands) or tissue specimens, in which the surface epithelium is lost. Magnification: x200.

Figure 4. Low grade dysplasia. The key feature of tissue specimens classified into the *Low grade dysplasia* category is the presence of cytologic atypia. Severe architectural alterations of glands are not a typical feature of these tissue specimens, even though mild gland crowding is allowed to be present. It is important to noting that, although cytologic atypia is a key feature of this specimen category, nuclear polarity is preserved. Magnification: x200.

Figure 5. High grade dysplasia. The key feature in the tissue specimens of this category is loss of polarity of nuclei in the epithelium. The cytologic changes are profound. Typically, the nuclei are rounded and often they are situated horizontal to the basement membrane. Surface maturation is lost as well. The distortion of glandular architecture is a typical in this specimen category. Glands are typically crowded. However, it is important to noting here that there should be no evidence of the invasion of epithelial cells into the lamina propria. If *High grade dysplasia* is found, additional biopsies should be evaluated for the presence of neoplastic glands. Magnification: x200.

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Patients with dysplastic alterations have been shown to have significantly increased risk of progression to adenocarcinoma.[2][3][4][5][6][7][8][9][10][11][12][13] Although there are concerns about intra- and interobserver reproducibility of the evaluation of the degree of dysplasia,[5] histologic evaluation plays an important role in the surveillance of patients with Barrett's oesophagus.[2][3] It is worth to noting also that dysplasia can be described as "carcinoma in situ" reflecting the fact that cells within glands have undergone neoplastic alterations even though the basal membrane is still intact.[15] It is important to stress that there is no commonly accepted classification of dysplasia; especially, there is no common agreement that the *Indefinite for dysplasia* category should be used for grading of oesophageal tissue specimens.

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2.1.19.1.4 Oesophageal adenocarcinoma

Figure 6. Oesophageal adenocarcinoma. Although there are a great variety of the structural manifestations of the development of adenocarcinoma, the most key feature that allows the classification of a biopsy specimen as an *Oesophageal adenocarcinoma* specimen 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 markedly vary and thus, histologic grading can refer tumours as (i) well differentiated, (ii) moderately differentiated, (iii) poorly differentiated, and (iv) undifferentiated tumours. The specimen shown in Figure 6 represents a moderately differentiated tumour.

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2.3.1 Treatment goals of high grade dysplasia BO patients

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    1.2 Confirmation of HGD diagnosis
        1.2.1 Histologic Confirmation (overstaging)
        1.2.2 Endoscopic Confirmation (understaging)
    1.3 Goals of treatment
2 References
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2.3.1.1 What are the goals of treatment of high grade dysplasia in patients with BO?

2.3.1.1.1 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, such that, the risk of progression to malignancy over one year is 0.5% per year for non-dysplastic BO,[2] 1.5% per year for LGD,[2] but as high as 6.5% for HGD.[3]

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.

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2.3.1.1.2 Confirmation of HGD diagnosis

2.3.1.1.2.1 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 intra-observer error for grading dysplasia is only moderate, with a kappa 0.43. Inter-observer agreement for HGD is somewhat better, with a kappa of 0.65[4] It is therefore recommended that all BO specimens reported as HGD should be accompanied by a corroborating opinion by a second histopathologist.

2.3.1.1.2.2 Endoscopic Confirmation (understaging)

Surgical literature suggests that up to 30-40% of patients operated on for "HGD" in fact had adenocarcinoma in the excised specimen.[5] 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 recommended 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. 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).

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2.3.1.1.3 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. 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 and mortality (approximately 2.5% in experienced centres),[7] but is still an option which should be discussed, particularly in the setting of relatively young patients.

Endoscopic mucosal resection may be used in three settings:

- as definitive treatment to remove all Barrett's in patients with short segment disease,
- to remove nodular lesions prior to confluent ablative therapy (eg: radiofrequency ablation), 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.[8] Eradication of all Barrett's tissue is more difficult, achieved in 77% of patients.[8] 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.[9][10] 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]

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2.3.1.2 References

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2.4 Guideline development process

2.4.1 Guideline development process

2.4.1.1 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 guidelines for the Australian community and healthcare setting.

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 mucosal neoplasia.

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

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2.4.1.2 Steps in preparing clinical practice guidelines

A clear strategy was developed and each topic author followed the appropriate steps in preparing their guideline sections. The Working Party developed clinical questions and topic groups were assigned to review and synthesise the relevant literature and to formulate evidence-based recommendations. The search strategy and literature search was conducted by the Project Officer, who distributed the search results to the Working Party authors. 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

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2.4.1.3 Structure the research questions

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

2.4.1.4 Barrett's Oesophagus and Mucosal Neoplasia

- 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 BO to neoplasia?

2.4.1.4.1 Referral

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

2.4.1.4.2 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?

2.4.1.4.3 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?
- Are there any ablative therapies which lead to the regression of BO?

2.4.1.4.4 Surveillance and Follow-up

- How frequently should patients with BO undergo endoscopy?
- Are there high risk groups of patients with BO that require more frequent surveillance?
- Are there low risk groups of patients with BO that can be discharged from surveillance?
- Is surveillance cost-effective for follow-up of patients with BO?

2.4.1.5 Barrett's Oesophagus and Neoplasia

2.4.1.5.1 Definition and Diagnosis

- What are the best endoscopic techniques to detect and assess neoplasia within BO?
- 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?

2.4.1.5.2 Biomarkers

- Are there biomarkers for the diagnosis (presence) of BO?
- Are there useful biomarkers to detect and improve the diagnosis of neoplasia in patients with or without BO?
- Are there biomarkers that predict more accurately the risk of progression from BO to neoplasia?

2.4.1.5.3 Management

2.4.1.5.3.1 Low grade dysplasia

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

2.4.1.5.3.2 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 optimal endoscopic management of early oesophageal adenocarcinoma?
- What endoscopic surveillance protocol should be followed for patients with BO and high grade dysplasia or early neoplasia?
- How effective is endoscopic management compared with surgical management for high grade dysplasia in patients with BO?

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2.4.1.6 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.

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2.4.1.7 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.

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2.4.1.8 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
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)

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
III-2	A comparative study with concurrent controls: ▪ 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: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ 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: ▪ Historical control study ▪ Two or more single arm study
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

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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)

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2.4.1.9 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
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some 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)

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2.4.1.10 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

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2.4.1.11 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.

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2.4.1.12 Public consultation

The draft guidelines were released for public consultation to all interested parties in Australia for the period from to 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.

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<references>

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2.5 Working party members and contributors

Working party members and contributors

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Associate Professor Bernard Mark Smithers	
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Working party member	Clinical questions
Sonali Munot	

2.6 Competing interest register

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.

The guidelines have now entered the updating phase. 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	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. 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.
Associate Professor Guy Eslick	No competing interest to declare.
Associate Professor Ian Norton MBBS, PhD, FRACP	From 2008-2013 was a member of a steering committee for an Astra Zeneca sponsored educational meeting. Honorarium payment involved. Currently member of Advisory Board for Olympus Australia.
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.
	No direct competing interest. Previous recipient of Victorian State Department of Health New Technology Grant to establish endoscopic treatment programme for dysplastic Barrett's

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 Grimpen, 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 Jaberiyanfar	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.

2.7 Abbreviations

Abbreviations

AA	Acetic acid
AGA	American Gastroenterological Association
BMI	Body mass index
BO	Barrett's Oesophagus
CI	Confidence interval
CT	Computed tomography
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
IWGCO	International Working Group for the Classification of Oesophagitis

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LGD	Low grade dysplasia
LYS	Life-years saved
MB	Methylene blue
NBI	Narrow band imaging
NSAIDs	Aspirin or non-steroidal anti-inflammatory drugs
OR	Odds ratio
PDT	Photodynamic therapy
QALY	Quality-adjusted life year
RFA	Radiofrequency ablation
ROC / (ROC curve)	Receiver operating characteristic

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