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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1.4 Barrett's Oesophagus and Neoplasia

1.4.1 Definition and Diagnosis

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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

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2.2 Recommendations

2.2.1 Barrett's Oesophagus and Mucosal Neoplasia

2.2.1.1 Natural History

Expression error: Unrecognized word "span".

2.2.2 Multidisciplinary Treatment

2.2.3 What is the role of prognostic factors in management of BSTTs?

Recommendation	Grade
Statistical models assessing the influence of prognostic factors can be used to counsel patients and to stratify their need for adjuvant therapies or entry into clinical trials.	**D**

Point(s)
Accurate data collection will facilitate further study in this area. Tissue banking will allow further assessment of tumours as new diagnostic and therapeutic modalities emerge.

2.2.4 What is the outcome of a second opinion in BSTT pathology?

Recommendation	Grade
Whenever a primary diagnosis of bone or soft tissue sarcoma is made outside the context of a specialist sarcoma unit, wherever possible, referral to an expert pathologist (within a specialist sarcoma unit) for review of the diagnosis and grade should be undertaken before definitive management is instituted.	**D**

2.2.5 Does referral to a specialist centre improve outcomes?

Recommendation	Grade
Patients with suspected sarcoma to be referred to a specialist sarcoma unit prior to diagnosis in order to reduce the rates of incomplete excision, reoperation, local recurrence and to improve survival.	**C**

2.2.6 Chemotherapy (systemic therapies)

2.2.7 What is the role for adjuvant systemic therapy for adults with BSTT?

Recommendation	Grade
Curative treatment of high-grade osteosarcoma comprises chemotherapy and surgery.	**B**
Pre-operative chemotherapy for high-grade osteosarcoma including cisplatin, doxorubicin and in selected patients high-dose methotrexate, improves outcomes compared to regimens omitting high-dose methotrexate.	**C**
As for osteosarcoma, doxorubicin and cisplatin are indicated for malignant fibrous histiocytoma of bone.	**D**
As for osteosarcoma, doxorubicin and cisplatin are indicated for high-grade spindle cell sarcomas of bone and malignant fibrous histiocytoma.	**D**
Curative treatment of Ewings sarcoma comprises of a combination of chemotherapy and surgery and/or radiotherapy.	**B**
The use of post-operative chemotherapy in adult type soft tissue sarcomas is not the current standard of care.	**D**
The use of pre-operative chemotherapy in adult type soft tissue sarcomas is not the standard of care.	**D**

Point(s)
Patients considered for chemotherapy should be referred for clinical trial participation.

2.2.8 What is the role for systemic therapy in advanced soft-tissue sarcoma?

Recommendation	Grade
There is no evidence to support combination chemotherapy regimens over sequential single agent regimens in the first-line treatment of advanced soft-tissue sarcomas.	**B**
Single agent ifosfamide can be considered as second-line treatment for patients who have not received ifosfamide as first-line.	**B**
Dacarbazine with or without gemcitabine is reasonable third-line therapy after exposure to doxorubicin and ifosfamide in advanced soft tissue sarcoma.	**B**
Systemic therapy with paclitaxel is reasonable in all patients with angiosarcoma, given the palliation that can be offered by these agents.	**D**

Point(s)
Clinical trial participation should be considered for patients with soft tissue sarcomas.

2.2.9 Radiotherapy

2.2.10 What is the evidence for radiotherapy in limb and extremity soft tissue sarcoma in terms of local recurrence, survival and limb salvage?

Recommendation	Grade
All patients with large, localised, high-grade extremity soft tissue tumours should be offered radiotherapy.	**B**
Omission of radiotherapy may be considered in select patients with small, superficial, extremity soft tissue tumours.	**D**

Point(s)
Radiotherapy does not compensate for inadequate surgery.

2.2.11 What is the evidence that pre-operative radiotherapy is superior to post-operative radiotherapy in limb and extremity soft tissue sarcoma in terms of local recurrence, survival and limb salvage and morbidity?

Recommendation	Grade
The timing of radiotherapy needs to be individualised dependent upon resection and reconstructive considerations.	**B**

Point(s)
Pre-operative radiotherapy may be the preferred approach in certain situations such as: A tumour of borderline resectability, and pre-operative radiotherapy may render it resectable. Radiosensitive histology (eg., myxoid liposarcoma), where tumour downstaging may be advantageous. Where adjacent critical structures (eg., brachial plexus) may limit the total dose of post-operative radiotherapy.

2.2.12 What is the evidence that radiotherapy, either pre-operative or post-operative, decreases local recurrence or improves survival in truncal sarcomas?

Recommendation	Grade
In patients with non-metastatic truncal sarcomas, adding radiotherapy to surgery is appropriate to further improve local control. When offered, pre-operative radiotherapy is preferable to post-operative radiotherapy.	**C**

2.2.13 What is the evidence that radiotherapy, either pre-operative or post-operative, decreases local recurrence or improves survival in retroperitoneal sarcomas?

Recommendation	Grade
In patients with non-metastatic retroperitoneal sarcomas, adding radiotherapy to surgery is appropriate to further improve local control. When offered, pre-operative radiotherapy is preferable to post-operative radiotherapy.	**C**

2.2.14 What are the indications for IMRT, brachytherapy, intraoperative radiotherapy (IORT), extra-corporeal radiotherapy and particle therapy in the management of BSTTs?

Recommendation	Grade
Brachytherapy (as an alternate or as a boost to external beam radiation) improves local control over surgery alone for high grade sarcomas for the limb and trunk.	**B**
IORT boost to external radiation could be considered in combination with surgery for management of retroperitoneal sarcomas.	**B**
It maybe reasonable to consider IMRT for patients with retroperitoneal and extremity/truncal sarcomas as adjuvant to surgery, if resource permits, for potential advantages in reduction of radiation dose to normal tissues.	**D**
Reconstruction using the patients own resected bone (previously bearing the sarcoma) fragment after a large extra-corporeal dose of radiation is a possible option reported to have satisfactory to good functional outcomes.	**D**
Particle beam therapy appears to offer good local control with acceptable toxicity.	**D**

2.2.15 Surgery

2.2.16 What are the factors influencing the extent of surgery in BSTTs?

Recommendation	Grade
It is important that wide surgical margin is achieved to prevent local recurrence and poor survival outcomes.	**B**
Musculoskeletal tumours are best managed in a specialist sarcoma unit by a multidisciplinary team.	**C**
Soft tissue sarcomas initially excised with residual disease and/or positive margins will require re-excision, preferably in a specialist sarcoma unit. These tumours should be re-excised with wide margins and usually require adjuvant radiotherapy.	**C**

Recommendation	Grade
Retroperitoneal sarcomas are best managed in a specialised tumour centre by a multidisciplinary unit.	**C**
Limb salvage surgery is an acceptable treatment in the management of osteosarcoma.	**C**
Pre-operative radiation therapy may allow preservation of vital structures without compromising local control.	**C**
Pre or post-operative radiation therapy should be considered in the management of soft tissue sarcoma. Decision should be made in the setting of a multidisciplinary team.	**A**
Isolated limb perfusion should be considered in patients with extensive soft tissue sarcoma where there is doubt whether limb salvage surgery can be achieved. Decision should be made in the setting of a multidisciplinary team.	**C**
Grade 1 Chondrosarcoma can be safely managed with intralesional excision with cementation. Distinction between this and other grades requires correlation of clinical and radiological features.	**C**

Point(s)
Any lump greater than 5 cm or deep to the deep fascia should be considered a sarcoma until proven otherwise.
Persistent and unremitting pain, not responsive to oral analgesics and nocturnal in occurrence should stimulate investigation for a bone tumour.
Complete imaging (anatomic and functional including XR, CT, MRI, nuclear scan) should be undertaken of a bone and soft tissue tumour prior to surgical manipulation.
Biopsy should be performed under image guidance to determine the track of the biopsy, and the target of the biopsy to confirm representativeness. Computed tomographic guidance is recommended. Biopsy should be performed after all imaging modalities have been completed to minimise the impact of biopsy induced image artifact.
Sarcomas are best managed at a specialist sarcoma unit.
Local recurrence is related to the adequacy of surgical margins. Wide surgical margins should be employed for bone and soft tissue sarcomas except when close margins are planned and adjuvant radiotherapy/chemotherapy is employed.
Tissues of different resistance to tumour invasion that surround a tumour may be used to

Point(s)
calculate the quality of surgical margins. In this way, more careful planning of surgical margins may be undertaken when contemplating limb-sparing surgery.
Combination therapy is required to adequately manage bone and soft tissue sarcomas. Radiotherapy and wide margin surgery are used for soft tissue sarcomas. Chemotherapy and wide margin surgery are used for bone sarcomas.
Radiotherapy is recommended for low grade soft tissue sarcomas particularly if these tumours are large and excised with marginal margins.
Adequacy of surgical margins achieved should be assessed by a expert musculoskeletal pathologist. Refer to the Royal College of Pathologists of Australasia Soft Tumour Resection Structured Reporting Protocol 1st Edition 2011

2.2.17 What are the factors that impact on the choice of reconstructive options in BSTTs?

Recommendation	Grade
Provision of education and psychological support is an important component in holistic care of the sarcoma patient.	**C**
Referral to specialist hand and upper limb surgical team to be sought when surgical resection and reconstruction is required for sarcoma in the hand and forearm area.	**D**
Consider incorporation of thoracoplastic techniques with mesh and vascularised flap coverage in management of chest wall defects following sarcoma resection.	**C**
The decisions for reconstruction of skeletal elements are ideally made at a specialist sarcoma unit.	**D**
Sarcomas are better managed in a specialist sarcoma unit with planning of primary resection, reconstruction and timing of radiotherapy (where required) for optimal outcome.	**D**
Consider vascularised tissue coverage in management of soft tissue sarcomas, particularly when large resections or radiotherapy expected, and in children.	**C**
Recognise that pre-operative radiotherapy leads to a higher wound complication profile than (i) no radiotherapy, and (ii) post-operative radiotherapy.	**B**
Consider vascularised flap coverage (including free tissue transfer) in	**B**

Recommendation	Grade
reconstruction of sarcoma defects following pre-operative radiotherapy.	
Consider vascularised flap coverage (including free tissue transfer) in reconstruction of sarcoma defects when post-operative radiotherapy is anticipated.	**D**
When restoration of vascularity to a limb is required following sarcoma resection, prioritise arterial reconstruction and consider the need for venous reconstruction.	**D**
Consider vascularised tissue in reconstruction of bone and soft tissue in lower extremity sarcoma.	**D**
Consider vascularised tissue in reconstruction of bone and soft tissue in upper extremity sarcoma.	**D**

Point(s)
The nature of reconstruction of defects following sarcoma resection is often complex due to the required size of resection, likelihood of need for perioperative radiotherapy with associated surgical challenges, and variation in involved tissue types. Specialist Multidisciplinary Team management is advised for all cases for optimal outcome.
Optimisation of general patient factors, both physical (including diabetic control, nutrition, minimising smoking and avoiding preventable perioperative morbidity) and psychological, will provide benefits to patient outcome. Patient education regarding the disease process and treatment options is also important in achieving the best holistic outcome.
Radiotherapy (in any form) reduces vascularity and impairs wound healing. Reconstructive options are affected by choice and timing of radiotherapy. A treatment plan for each case should be discussed at commencement of treatment to determine best timing and choice of surgical resection, surgical reconstruction and radiotherapy. This will allow best outcome with minimisation of surgical-related and radiotherapy-related morbidity.
When limb-preserving surgery is undertaken, care should be taken to reconstruct all resected tissues. This includes skeletal stability in bony reconstruction, reconstruction of neurovascular structures and functional muscle groups, and overlying soft tissue coverage.
In all resection defects requiring soft tissue coverage, vascularised tissue is the preferred reconstruction. This may be in the form of locoregional flap transfer, or free flap tissue transfer with reconstruction of the tissue vascularity using micro-surgical anastamoses of blood vessels. This enables best healing of underlying structures, reduces infection and other complication risks relating to skeletal implants, and provides greatest resilience to radiotherapy.

Point(s)
Restoration of function is the priority in reconstruction of the bony skeleton. Many options are available for reconstruction in metadiaphyseal areas, with preference for biological reconstruction where possible. Endoprosthetic reconstruction is commonly used in periarticular reconstruction.
Limb salvage procedures result in better functional outcomes, but do not necessarily result in greater quality of life.

2.2.18 What preoperative optimisation strategies improve outcomes in BSTTs?

Recommendation	Grade
Pre-operative embolisation may be considered in selected cases.	**D**
Pre-operative imatinib mesylate may be considered in selected patients with DFSP when surgery is difficult or potentially mutilating.	**D**

Point(s)
It is advisable to consider the suitability and applicability of pre-operative optimisation strategies, such as embolisation, prior to surgery for large or complex BSSTs.

2.2.19 What is the role of regional chemotherapy in BSTTs?

Recommendation	Grade
Isolated limb perfusion (ILP) may be considered as a palliative alternative to amputation in patients with extremity soft tissue sarcoma.	**D**

Point(s)
The toxicity of isolated limb perfusion (ILP) with melphalan is increased when combined with TNFα.
ILP may be considered to downstage extremity soft tissue sarcoma when primary amputation would otherwise be considered.

2.2.20 Follow-up

2.2.21 What are the measures to assess treatment response in BSSTs?

Recommendation	Grade
Functional imaging may assist standard methods of evaluating response to pre-operative chemotherapy or radiation therapy.	**D**

2.2.22 What is the ideal duration, frequency and modality of follow-up for BSTTs?

Recommendation	Grade
Regular clinical examination is part of routine surveillance for local recurrence.	**D**
High risk patients in whom pulmonary metastasectomy would be considered, are advised to undergo three to six month CT chest until five years.	**D**

Point(s)
Where the primary site is difficult to examine, for example the retroperitoneum or following complex/flap reconstructions routine imaging may be appropriate.
Follow-up intervals recommended in current multinational guidelines are each three to four months in years one and two after diagnosis, six monthly in years three to four and annual thereafter. Late metastases may occur >10 years after diagnosis and there is no universally accepted stopping point for tumour surveillance. By contrast, the incidence of late effects of treatment increases with time. For patients enrolled in clinical trials, the above recommendations may vary in accordance with the follow-up protocols of these trials.
For patients considered suitable for pulmonary metastasectomy, low dose protocol non- contrast CT chest is the modality of choice for pulmonary surveillance.

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		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	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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2.1.6 Endoscopic definition

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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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2.1.6.2 References

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2.1.9 Medical or surgical inverventions to regress BO

Contents

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**

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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2.1.9.3 References

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2.1.10 Treatments that prevent progression of BO to cancer

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2.1.11 Medical systemic therapy for symptoms of BO

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2.1.12 Role of ablative therapy

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2.1.14 Frequency of surveillance

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2.1.15 Discharge from surveillance

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2.1.16 Cost-effectiveness of surveillance for follow-up

Contents

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

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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.

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

Contents

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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2.4 Guideline development process

2.4.1 Guideline development process

2.4.1.1 Introduction

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?
- What endoscopic protocol should be followed for 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 where 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 1990, languages other than English, 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, the National Guideline Clearinghouse, the National Comprehensive Cancer Network, ClinicalTrials.gov, and the National Institute for health and clinical excellence. 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
		A study of test accuracy with:			

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
II	A randomised controlled trial	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)
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	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ■ Historical control study

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
	■ Interrupted time series without a parallel control group				■ 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

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
	population/s		population/s studied in	population/s studied in

Component of Recommendation	Recommendation Grade			
	A Excellent	B Good	C Satisfactory	D Poor
Generalisability	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	body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	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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2.4.2 References

<references>

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1. ↑ [1.0] [1.1] [1.2] 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.

2.5 Working party members and contributors

Working party members and contributors

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Associate Professor Freddy Sitas	
Associate Professor Geoffrey Hebbard	
Associate Professor Guy Eslick	
Associate Professor Ian Norton MBBS, PhD, FRACP	
Associate Professor Jurgen Stahl FRCPA	
Associate Professor Neil Walker MD, FRCPA	
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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.
	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

Working party member	Competing interest declaration
Associate Professor Geoffrey Hebbard	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.
Dr Andrew Taylor MBBS MD FRACP	No direct competing interest. Previous recipient of Victorian State Department of Health New Technology Grant to establish endoscopic treatment programme for dysplastic Barrett's 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

Working party member	Competing interest declaration
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.
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.

Working party member	Competing interest declaration
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
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