Oesophageal cancer

Don't miss the early signs

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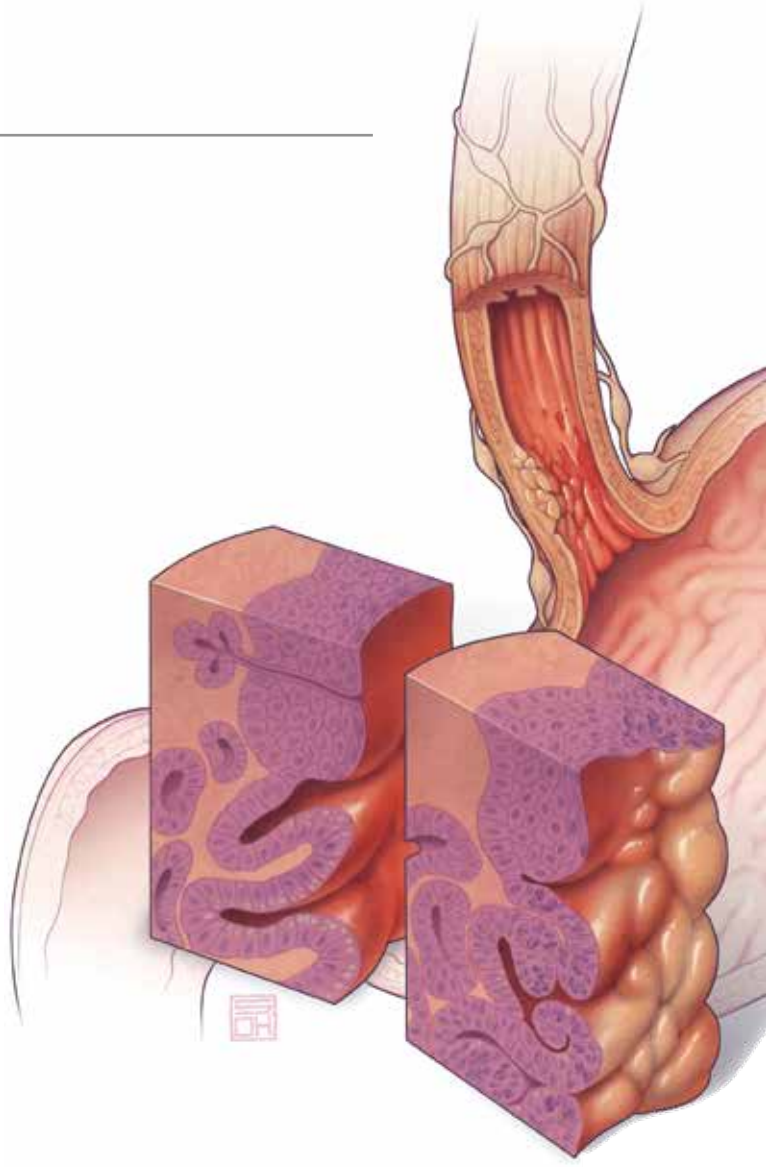
Oesophageal adenocarcinoma is becoming the more common of the two main types of oesophageal cancer with the increasing incidence mirroring the obesity epidemic. Risk factors include Barrett's oesophagus and gastro-oesophageal reflux disease, which can be recognised early and managed to prevent progression to cancer.



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KEY POINTS

- Oesophageal cancer is the most rapidly increasing cancer diagnosis in Western countries.
- Some of the major risk factors for oesophageal cancer are preventable.
- Barrett's oesophagus with high-grade dysplasia is a premalignant lesion.
- Identifying patients who require upper gastrointestinal endoscopy and interpreting a histological diagnosis of Barrett's oesophagus can be complex.
- Red flags for oesophageal cancer are dysphagia, especially with weight loss, a significant family history, male sex or age older than 50 years.

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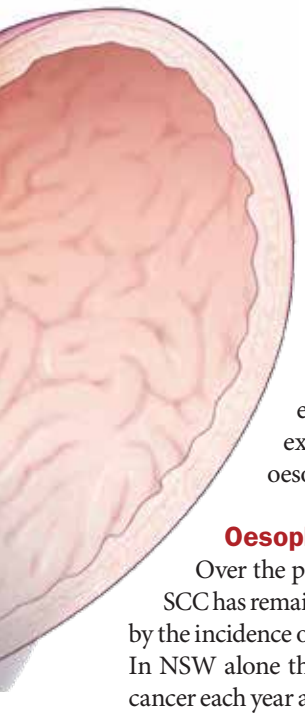
Oesophageal cancer is the most rapidly increasing cancer diagnosed in Western countries, and worldwide is the eighth most common cancer and the sixth most common cause of cancer-related death.[1,2] There are two distinct main types of oesophageal cancer: squamous cell carcinoma (SCC) and oesophageal adenocarcinoma (OAC).

SCC is classically a disease of lower socioeconomic groups where risk factors such as smoking, alcohol intake, malnutrition and diets high in N-nitroso compounds (found in processed and cured meats) are prevalent. Regions such as east Asia, east Africa and South Africa make up much of the global burden of disease.[3]

OAC, on the other hand, is in many respects a disease of more affluent Western countries. Major risk factors for OAC include Barrett's oesophagus, obesity and gastro-oesophageal reflux disease (GORD). The incidence of OAC is increasing in Western countries including Australia, mirroring the obesity epidemic facing healthcare providers in those countries.

GPs can play a major role in decreasing the mortality from oesophageal cancer. The main risk factors for both oesophageal SCC and OAC are largely preventable. Furthermore, there is a



clear pathway of progression from Barrett's oesophagus to OAC, which in theory should allow at-risk individuals to undergo a program of surveillance and receive early treatment. Unfortunately, most cases present at a late stage. However, with early recognition and treatment, there can be a significant improvement in the otherwise dismal overall five-year survival rate of 14%.[4-6] Therefore, GPs have a key role in the prevention of oesophageal cancer as well as its early recognition in at-risk patients with 'red-flag' symptoms.

This review will outline those 'red flags', the evidence for screening and surveillance endoscopy and the management a GP might expect for a patient with a new diagnosis of oesophageal cancer.

Oesophageal cancer in Australia

Over the past few decades, the incidence of oesophageal SCC has remained unchanged but notably has been overtaken by the incidence of OAC, which is expected to continue to grow. In NSW alone there are about 400 new cases of oesophageal cancer each year and the incidence has increased 2% per year for the past 10 years.[7] Most of this rise is attributable to cases of OAC, which is more than twice as common among men than women and more common in people older than 50 years of age and those living in regional areas.[5]

Risk factors for oesophageal cancer

The risk factors for both oesophageal SCC and OAC are well defined (Box 1).[8-14] The most important association to note is the relation between the rising incidence of OAC and those of obesity and GORD. It is proposed that obesity increases the intra-abdominal pressure resulting in incompetence of the lower oesophageal sphincter, leading to reflux of acid into the lower oesophagus. This chronic insult results in an adaptive response and intestinal metaplasia (Barrett's oesophagus), dysplasia and then carcinoma. The observation that infection with *Helicobacter pylori*, which reduces gastric acidity, actually decreases the risk of OAC may also support this theory.[15] Infection with human papilloma virus (HPV) is significantly associated with oesophageal SCC, particularly in high-risk regions such as China.[16-18]

Barrett's oesophagus

Barrett's oesophagus is currently defined as metaplastic columnar epithelium of the lower oesophagus.[19] The presence of goblet cells that denote intestinal metaplasia is an additional requirement for diagnosis according to the American Gastroenterological Association and Cancer Council Australia guidelines for the management of patients with Barrett's oesophagus.[20,21] It has been recommended that at least one expert pathologist is required to make a diagnosis of Barrett's oesophagus and certainly to qualify the presence of low-grade dysplasia (LGD) or high-grade dysplasia (HGD). HGD in particular needs extensive biopsy and specialist review to ensure that no evidence of invasive cancer is present. Barrett's oesophagus is clearly the strongest risk factor for OAC; however, it still cannot accurately be predicted who will progress from GORD to Barrett's oesophagus and then go on to develop OAC.

The presence of GORD with erosive oesophagitis increases a patient's risk of developing Barrett's oesophagus fivefold over five years.[22] However, only 7.5% of patients with OAC have a previous diagnosis of Barrett's oesophagus and the risk of Barrett's oesophagus without dysplasia progressing to HGD or cancer is as little as 0.4% and 0.12% per year, respectively.[23]

Once a diagnosis of Barrett's oesophagus with HGD has been made, however, the patient's risk of neoplastic progression significantly increases, reportedly up to 59% over five years in one study.[24] In fact, in oesophagectomy specimens tested for

1. RISK FACTORS FOR OESOPHAGEAL CANCER[8-14]

Oesophageal squamous cell carcinoma

- Smoking (RR, 5 to 10; dose response and duration)
- Alcohol intake (RR, 2.9 to 7.4; dose response, synergistic with smoking, abstinence decreases risk)
- High intake of very hot beverages
- Low intake of fresh fruit and vegetables
- Vitamin C and E deficiency
- Caustic injury (20 to 40-year latency)
- Lower socioeconomic status
- Achalasia
- Palmar hyperkeratosis
- Family history of oesophageal cancer

Oesophageal adenocarcinoma

- Barrett's oesophagus (RR, 50 to 100)
- GORD (OR, 8 to 43.5 depending on severity and duration)
- Obesity
- Smoking (less association than for SCC)
- Family history of Barrett's oesophagus or oesophageal cancer
- Low intake of fresh fruit and vegetables
- Lower socioeconomic status (less association than for SCC)
- Vitamin C and E deficiency

Protective factors

- *Helicobacter pylori* (OAC)
- Long-term NSAID use (SCC and OAC)

Abbreviations: GORD = gastro-oesophageal reflux disease; OAC = oesophageal adenocarcinoma; OR = odds ratio; RR = risk ratio; SCC = squamous cell carcinoma.

Barrett's oesophagus with HGD, up to 35% of cases demonstrate invasive adenocarcinoma on pathological examination.[25] Therefore, HGD should be considered an imminently premalignant lesion that requires either endoscopic or surgical treatment.

The significance of Barrett's oesophagus with LGD is less clear. It is confounded by subjective variations in reporting between pathologists and conflicting study results finding rates of progression to adenocarcinoma ranging from zero (within 6.2 years of follow up in one study) to a relative risk of 9.7.[26] The presence of LGD at least mandates acid suppression with a high-dose proton pump inhibitor, followed by repeat endoscopy to exclude the presence of missed HGD. The role of endoscopic treatment for LGD is not clear and remains an area of controversy given the potentially high number needed to treat to prevent one progression to OAC.

A range of pharmacological, endoscopic and surgical treatments are available for patients with Barrett's oesophagus without dysplasia, depending on local expertise. There is evidence that aggressive acid suppression with proton pump inhibitors slightly decreases the risk of progression from Barrett's oesophagus to OAC.[27] Regression of LGD has also been noted after antireflux surgery.[28] At present a phase III randomised controlled trial (a Phase III, Randomized, Study of Aspirin and Esomeprazole Chemoprevention in Barrett's Metaplasia [AspECT]) is examining the observation that NSAIDs significantly lower the five-year risk of progression to OAC in patients with Barrett's oesophagus. One prospective study found that the risk was lowered by 7.7%.[29]

The evidence for various treatments for patients with Barrett's oesophagus has been extensively discussed in a recent Cochrane review.[6] The critical points of note were that antireflux therapies do not eradicate Barrett's oesophagus but may regress the development of LGD or prevent de novo dysplasia. Furthermore, endoscopic and ablative therapies are effective in treating patients with Barrett's oesophagus and HGD and even early oesophageal cancer. However, there are no randomised controlled trials comparing outcomes in oesophagectomy versus endoscopic therapy.[26]

New techniques are emerging to stratify the risk of a patient with Barrett's oesophagus progressing to adenocarcinoma, including immunohistochemical staining of p53-positive cells.[14] This will hopefully allow better identification of at-risk individuals and selection for early intervention.

In general, the patient with a new diagnosis of Barrett's oesophagus without dysplasia can be reassured that the risk of progression to adenocarcinoma is low, and effective endoscopic therapies exist for those with LGD or HGD.

Summary points

- Barrett's oesophagus is the strongest risk factor for OAC, but without dysplasia, the risk is low.
- LGD requires high-dose acid suppression and close surveillance endoscopy.
- Barrett's oesophagus with HGD is an imminently premalignant lesion that requires endoscopic or surgical treatment.
- NSAIDs are currently being investigated as possible chemopreventive agents for progression from Barrett's oesophagus to OAC.

Presenting symptoms and 'red flags' – who needs an urgent endoscopy?

Dysphagia is the cardinal presenting symptom of oesophageal cancer. In one Australian study, more than 70% of patients diagnosed with oesophageal cancer admitted on direct questioning to having dysphagia.[30] Additionally, a family history of Barrett's oesophagus or oesophageal cancer,[14] or a personal history of significant unintentional weight loss, especially in males over the age of 50 years, mandates urgent endoscopy.

Overall, however, weight loss, as well as odynophagia or epigastric pain are uncommon presenting symptoms of oesophageal cancer. Odynophagia is more prevalent among patients with oesophageal SCC than among those with OAC.

Interestingly, in the Australian study, only 7 to 9% of patients reported reflux symptoms at presentation, but on direct questioning up to 46% said they had reflux symptoms.[30] Another study found that of those patients with recurrent reflux, the odds ratio (OR) of developing OAC was 7.7, but if they had more severe and longer-lasting symptoms, especially at night, the OR increased to 44.[10]

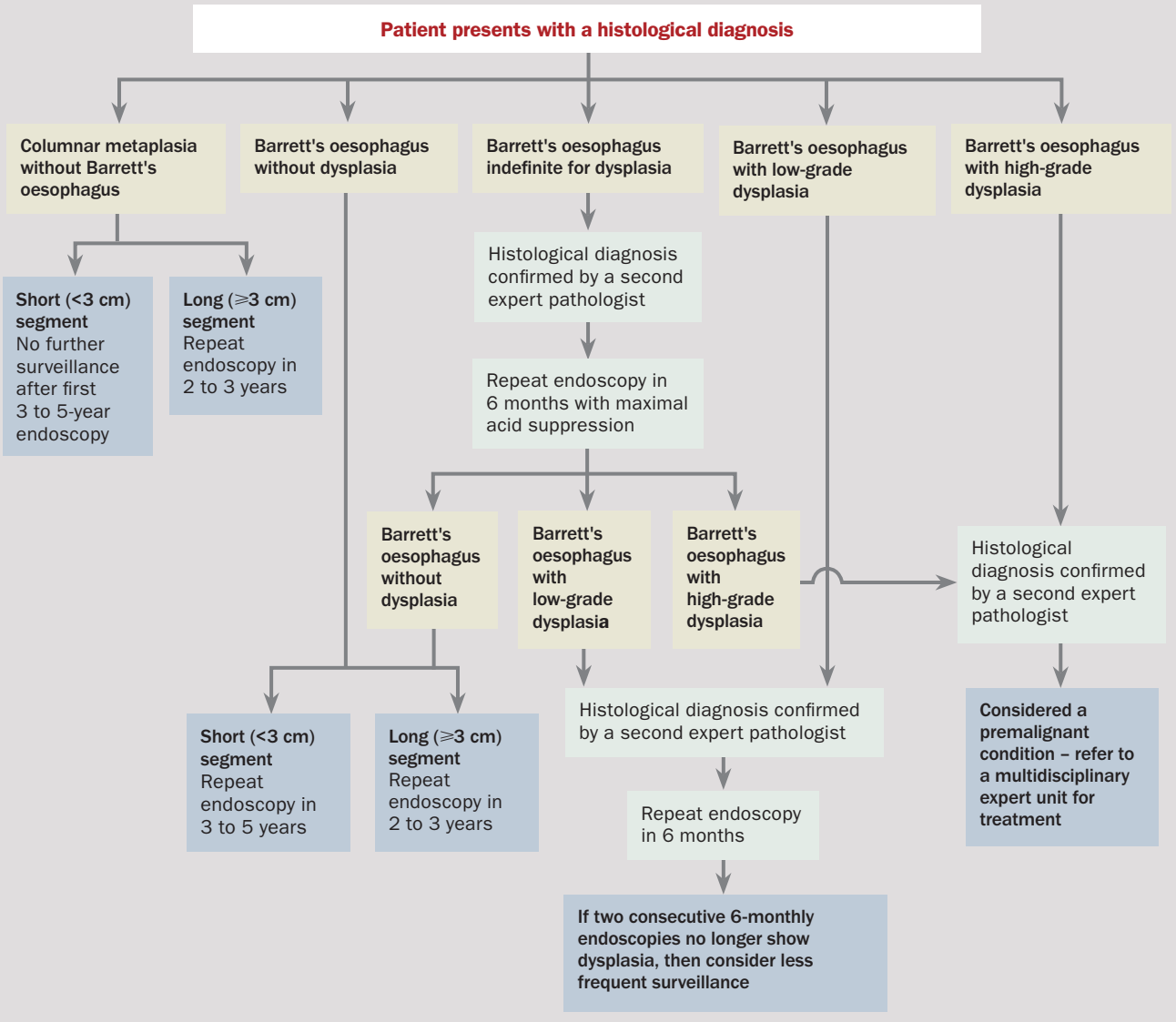
Summary point

- Patients with dysphagia, especially those with weight loss or a significant family history, or of male sex or age older than 50 years, should be referred for urgent endoscopy (within two weeks of presentation).

What about screening and surveillance?

It seems logical that a screening program for OAC might be beneficial as there is a relatively well-defined metaplasia–dysplasia–carcinoma sequence and, with early detection, there are effective endoscopic treatments available that improve survival. However, patient selection for an effective screening program remains problematic. Although there is no doubt that GORD is a major risk factor for Barrett's oesophagus and OAC, the prevalence of GORD in Western countries is up to 20%.[31] Only a small proportion of patients with GORD will have Barrett's oesophagus and, furthermore, up to 45% of patients with Barrett's oesophagus will not have symptomatic GORD.[14] Most importantly, endoscopically monitoring patients with chronic GORD symptoms has not been shown to diminish the risk of cancer.[32] Therefore, referring each patient with GORD for endoscopy will

SIMPLIFIED SURVEILLANCE GUIDELINES FOR BARRETT'S OESOPHAGUS[21]



likely miss many patients with Barrett's oesophagus and is not cost-effective because of the number of endoscopies in patients who do not have Barrett's oesophagus.[33] Rather, selective endoscopy on the basis of refractory GORD on maximal medical treatment, or clearly abnormal 'red flag' symptoms such as dysphagia or haematemesis, is advised.

These findings have been reflected in the position statements of the Gastroenterological Society of Australia, the British Society of Gastroenterology and the American Gastroenterological Association, as well as a 2014 Cochrane review that concluded there is no evidence to support endoscopic screening for oesophageal cancer.[33-37] Asian countries with a higher incidence of oesophageal cancer, such as Korea and China, do have more liberal screening policies. Therefore, Asian patients with significant GORD could reasonably be referred for endoscopy, especially if a trial of proton pump inhibition fails to control their symptoms.[38]

Patients with an established diagnosis of Barrett's oesophagus or Barrett's oesophagus with LGD or HGD are entered into a program of endoscopic surveillance, sometimes after an early repeat endoscope with further biopsies to ensure the correct histological diagnosis or to rule out an occult cancer. There is

2. T STAGE DEFINITIONS FOR OESOPHAGEAL CANCER (BOTH SQUAMOUS CELL CARCINOMA AND OESOPHAGEAL ADENOCARCINOMA)[39]

Tx = Primary tumour cannot be assessed
T0 = No evidence of primary tumour
Tis = High-grade dysplasia
T1 = Tumour invades lamina propria, muscularis mucosae or submucosa
T1a = Tumour invades lamina propria or muscularis mucosae
T1b = Tumour invades submucosa
T2 = Tumour invades muscularis propria
T3 = Tumour invades adventitia
T4 = Tumour invades adjacent structures
T4a = Resectable tumour invading pleura, pericardium or diaphragm
T4b = Unresectable tumour invading other adjacent structures, such as aorta, vertebral body, trachea, etc.

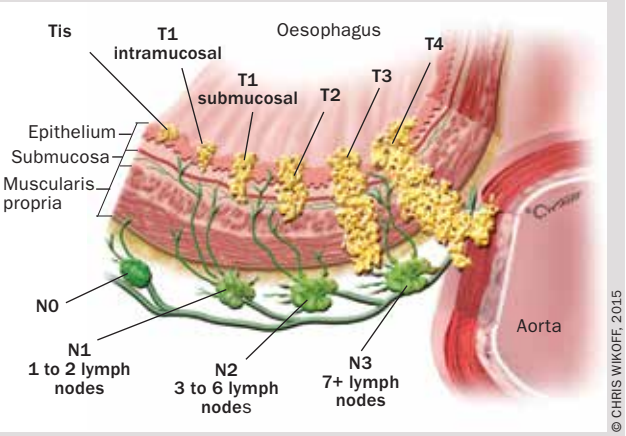


Figure 1. Staging of oesophageal cancer.

very little direct evidence to support the rationale for surveillance of Barrett's oesophagus with or without dysplasia. Australian guidelines for surveillance are outlined in the flowchart.

Summary point

- Most patients with reflux will not have Barrett's oesophagus, and many patients with Barrett's oesophagus will not have a history of reflux. Currently, there is no evidence for routine screening endoscopy in patients with GORD symptoms. Only patients with dysphagia, haematemesis or GORD symptoms that persist or progress on maximal medical treatment should be referred for endoscopy.

What happens after a diagnosis of oesophageal cancer?

A diagnosis of OAC is almost always made at endoscopy and, therefore, after referral of the patient to a specialist.

TABLE 1. STAGING OF OESOPHAGEAL ADENOCARCINOMA: ANATOMICAL STAGE/PROGNOSTIC GROUPS[39]

Stage	T	N	M	Grade
0	Tis	N0	M0	Well differentiated
IA	T1	N0	M0	Moderately differentiated
IIB	T1	N0	M0	Poorly differentiated
	T2	N0	M0	Moderately differentiated
IIA	T2	N0	M0	Poorly differentiated
IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

ABBREVIATIONS: M = metastasis; N = lymph nodes; T = tumour.

A gastroenterologist who makes the diagnosis will generally refer the patient on to an upper gastrointestinal surgeon or oncologist. After counselling the patient, the clinician will want to find out two key pieces of information: the stage of the tumour and the patient's fitness for surgery (Box 2, Figure 1 and Table 1).[39] The involvement of a multidisciplinary team of surgeons, oncologists, gastroenterologists, anaesthetists, nurses and allied health professionals is critical at an early stage to guide the workup process and to determine an individualised management plan.

Routine investigations to determine the stage of the cancer include basic blood tests and a contrast-enhanced CT scan of the thorax, abdomen and pelvis to look for local invasion and metastatic disease; the CT scan also provides a baseline for determining the patient's response to neoadjuvant treatment. There is currently no proven or widely available serum tumour marker. Positron emission tomography (PET) can be used at the discretion of the multidisciplinary team to pick up metastatic disease or better define inconclusive lesions noted on the initial staging CT scans (Figure 2). Most units will also recommend a staging laparoscopy to look for low-volume peritoneal metastatic

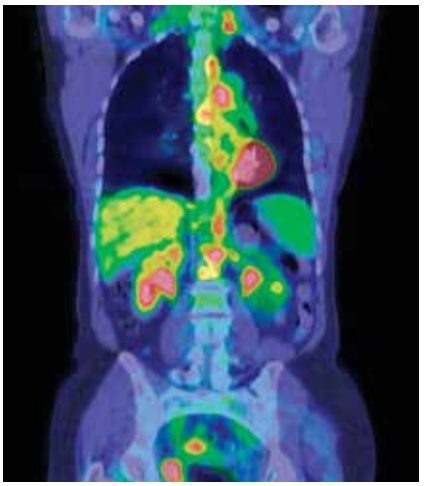


Figure 2. A positron emission tomography (PET) scan showing metastatic disease.

disease that is too small to be seen on PET or CT scans.

Laparoscopic ultrasound and MRI are modalities occasionally used on an individual basis. Some centres will perform an endoscopic ultrasound as a more sensitive tool for identifying early-stage disease or local lymph node involvement (Figure 3), depending on local experience.[40,41] This is critical if endoscopic surgical resection is to be contemplated.

All patients need to undergo cardiorespiratory assessment. Most oesophagectomies in Australia are performed using an abdominal and thoracic approach, either open or using minimally invasive techniques. Both require single lung ventilation and patients with a history of chronic airways disease or morbid obesity may not tolerate such an anaesthetic.

Management

Neoadjuvant treatment

Over the past decade, several major clinical trials have examined the role of neoadjuvant chemotherapy or chemoradiotherapy in patients with oesophageal cancer. In 2006, the Medical Research Council Adjuvant Gastric Infusion Chemotherapy (MAGIC) trial concluded that preoperative chemotherapy increased five-year survival by 13%, and reduced the risk of death by 25% without any difference in postoperative complications.[42] In 2012, the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) randomised a group of patients with oesophageal cancer (75% with OAC) and found that preoperative chemoradiotherapy increased the likelihood of clear resection margins by 23%, more than doubled the median overall survival compared with surgery alone and decreased the risk of death by 34% during follow up.[43]

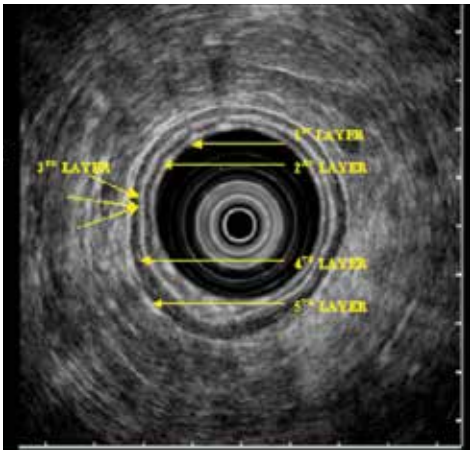
A Cochrane review in 2013 confirmed these results, concluding that preoperative chemotherapy, with or without radiotherapy, conferred a 9% survival benefit at five years.[44] The review recognised that the addition of radiotherapy probably did confer a further benefit, although trials had provided mixed results with incomparable groups and the CROSS trial was not considered in the meta-analysis.

There are few studies comparing adjuvant chemotherapy to chemoradiotherapy. A meta-analysis in 2011 concluded that the addition of radiotherapy conferred a survival benefit, but exactly how much and to which subgroup is unclear.[45] It is now standard practice to offer neoadjuvant treatment to patients with oesophageal cancer. The specific chemotherapy regimen offered, and the addition of radiotherapy, is dependent on patient comorbidities and local protocols.

Treatment of early oesophageal adenocarcinoma

Early oesophageal cancer is defined by the American Joint Committee on Cancer stages T0 to T1a (Box 2, Figure 1 and Table 1).[39] With increasing T stage there is increasing risk of lymphatic invasion and lymph node metastases. Oesophageal SCC is thought to metastasise at an earlier depth of invasion than OAC.

In some expert units, endoscopic resection has been demonstrated to be an effective treatment for patients with early OAC that has not penetrated the lymphatic-rich submucosa (i.e. stage T1a). Although the overall morbidity and mortality rates are much lower than for oesophagectomy, there is still a significant risk of oesophageal stricture formation with endoscopic resection.



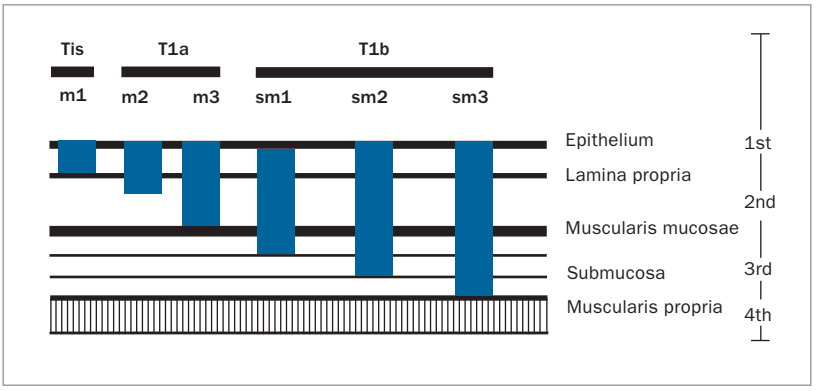


Figure 3. Endoscopic ultrasound and staging of early oesophageal cancer.

ABBREVIATIONS: m = mucosa; sm = submucosa.

© FIGURE 2: ISM/SPL

TABLE 2. STAGE-SPECIFIC FIVE-YEAR SURVIVAL RATES[51]

Stage of tumour	5-year survival
0 to IA	80%
IB	64%
IIA	50%
IIB	40%

A recent case-controlled study comparing oesophagectomy with endoscopic resection and ablation in patients with stage T1a OAC found no tumour recurrence in those undergoing resection.[46] However, 6.6% of the endoscopic therapy group required further local treatment within the first 3.7 months. It may also be appropriate to perform endoscopic resection in patients with stage T1b cancers that have favourable histological features or in poor surgical candidates.

Although endoscopic resection is certainly possible and deserves consideration in certain cases, oesophagectomy remains the gold standard even in the management of patients with early oesophageal cancer. This is because it removes the primary lesion with a margin of normal tissue as well as the draining lymph nodes, to provide the most accurate staging possible.

Treatment of squamous cell cancer of the oesophagus

It has been noted in the literature examining patients receiving neoadjuvant chemoradiotherapy that the long-term survival of patients with oesophageal SCC who do not progress to surgery has appeared comparable with survival rates in patients undergoing surgery alone. Three notable studies have specifically examined this question, and none were able to show a survival benefit of surgery with adjuvant chemoradiotherapy over definitive chemoradiotherapy alone.[47-49] This is similar to the results in patients with head or neck SCC and those with anal SCC, where definitive chemoradiotherapy has replaced surgery as the mainstay of treatment in most cases.

Although this challenges the necessity of surgery for patients with oesophageal SCC, these studies did show a significant improvement in locoregional control with the addition of surgery, including a decreased likelihood of palliative treatment for dysphagia.[47-49] Furthermore, initial quality of life scores were lower in patients who had undergone surgery than in those who had not, but at two years there was no difference in the scores. Some patients may not be suitable for radiotherapy, for example those with long-segment oesophageal SCC or concomitant lung disease.

Overall, neoadjuvant chemotherapy or chemoradiotherapy followed by surgery is still considered the standard treatment for patients with oesophageal SCC. Nonoperative management is a legitimate consideration to offset the risks and morbidity of surgery; however, it must be balanced with the long-term risk of significant dysphagia and odynophagia at end-stage disease.

Treatment of locally advanced oesophageal adenocarcinoma

The definitive treatment for patients with OAC is oesophagectomy. This is a difficult procedure for patients, with a significant 30-day all-cause morbidity of about 30% depending on patient and institutional factors. The most significant complications of oesophagectomy is anastomotic leakage and mediastinitis, affecting less than 5% of patients. Other complications include anastomotic stricture, chyle leak, pulmonary complications such as pneumonia and cardiac complications such as atrial fibrillation. Fortunately, in experienced units the 30-day mortality of oesophagectomy is similarly low at less than 5%.[50] The five-year stage-specific survivals with complete resection of the primary tumour, without any neoadjuvant or adjuvant treatment are outlined in Table 2.[51] Despite modern surgical and anaesthetic techniques, overall five-year survival remains low, ranging from 17.6 to 36% depending on which study is quoted.[52-54]

Most oesophagectomies in Australia are performed via an open technique involving a laparotomy and thoracotomy and using a gastric conduit, although colonic and jejeunal conduits are occasionally required. Minimally invasive laparoscopic/thoracoscopic techniques are becoming more commonplace but have the disadvantage of lower lymph node yield. Robotic oesophagectomy has been suggested to be at least as safe as laparoscopic/thoracoscopic or open oesophagectomy but no comparative oncological data exist.[55,56]

Most patients can expect a hospital admission of seven to 14 days depending on their comorbidities, and will be referred for further adjuvant chemotherapy. On discharge, patients are to be maintained on a soft diet for up to four weeks. The most common reasons for patients to present to their GP in the postoperative period are wound pain (especially after a thoracotomy), diarrhoea or dysphagia. Chronic neuropathic pain after a thoracotomy is not uncommon and can be managed with adjuvant analgesics, ideally started in the immediate postoperative period with the assistance of a pain medicine specialist. Diarrhoea is common in the first weeks postoperatively and is usually self-limiting. Dysphagia mandates early review by the operating surgeon for consideration for endoscopy to exclude anastomotic stricture in the early postoperative period, and later to exclude cancer recurrence.

Problems with dysphagia, breathlessness, diarrhoea, reflux, fatigue and odynophagia can occur after an oesophagectomy and will potentially have a significant impact on the quality of life of patients, even in those without cancer recurrence. Patients typically continue to lose weight in the postoperative period for up to four weeks, and dietitian input during this period is invaluable.

Palliative treatment

Palliative treatment is appropriate for patients with unresectable locally advanced or metastatic oesophageal cancer and is often considered in frail elderly patients with significant comorbidities.

Outcomes for unresectable disease are very poor and the complications can be devastating. These can include severe dysphagia, odynophagia and tracheo-oesophageal fistula. The broad aims of the palliative management of patients with oesophageal cancer can be categorised as optimising local control of the cancer, symptom control and social support. These can be achieved with systemic chemotherapeutic agents, targeted radiotherapy and endoscopic thermal techniques. Oesophageal stents have an evolving role as a palliative treatment but are usually reserved as a last resort due to the risk of erosion, migration and intractable acid reflux.

Being unable to eat is often a source of significant emotional distress for patients and enteral feeding via a feeding tube may be considered. The most critical element of the palliative treatment of patients with oesophageal carcinoma is the multidisciplinary team of surgeons, medical and radiation oncologists, palliative care specialists, pain medicine specialists, nurses, dietitians, social workers and counsellors.

Conclusion

Oesophageal cancer is an important and growing problem in Australia. Heterogeneity in guidelines as to which patients should undergo endoscopy and how to manage those with Barrett's oesophagus reflects the complexity of the disease and our evolving understanding of it. GPs need to have an understanding of the significance of the histological subtypes of Barrett's oesophagus so they can counsel their patients. GPs can help to identify the most at-risk patients by probing for 'red flag' symptoms and also help to minimise preventable lifestyle risk factors. MT

References

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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