PALLIATIVE CARE OF PEOPLE WITH OESOPHAGEAL CANCER

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Abstract

Palliative management of patients with incurable oesophageal cancer necessitates a broad spectrum of measures to relieve symptoms. Symptoms include those generated by the direct effects of disease (dysphagia due to local tumour burden) and the systemic effects of advanced cancer. Aggressive surgical treatments are rarely indicated for locally advanced disease because of the high associated morbidity and mortality. Interventions are aimed at eliminating dysphagia with options including stenting and tumour-specific treatments. Likewise, systemic disease responds in a limited way to aggressive therapy. The aim of all therapy (disease-modifying or direct symptom measures) is to optimise levels of function and comfort in the face of advancing disease. The choice of interventions depends upon the symptoms experienced, the overall functional status of the person, the estimated prognosis of the person, the sites of disease spread and the patient's preference. Palliative management requires a multidisciplinary approach including the active engagement of the patient's general practitioner.

In Australia, oesophageal cancer accounts for 1.2% of all cancer diagnoses, with this figure likely to continue to increase.[1] There are two main types of oesophageal cancer: adenocarcinoma and squamous cell carcinoma. The two main risk factors for adenocarcinoma of the oesophagus are gastro-oesophageal reflux and obesity.[2] In contrast, the main risk factors for squamous cell carcinoma of the oesophagus are tobacco smoking and high alcohol consumption, with the risk amplified when both factors are present simultaneously. Australia reflects the trend noted in many countries with the incidence of oesophageal cancer rising. It is of note that rates of squamous cell carcinoma of the oesophagus are remaining reasonably stable, while the number of people, particularly men, diagnosed with adenocarcinoma of the oesophagus is increasing.[3] Unless diagnosed early, the prognosis of people with oesophageal cancer is poor. Estimates suggest that up to 75% of people will not be suitable for surgical resections when resection is the only curative treatment option.[4]

Like many cancers, people with incurable oesophageal cancers are at risk of multiple symptoms, both physical and psychological. Symptoms suggestive of locally extensive disease include dysphagia, the development of a hoarse voice secondary to laryngeal nerve palsy and cough secondary to aspiration or fistula formation. Uncontrolled disease is likely to manifest with weight loss, anorexia and fatigue independent of dysphagia. The problems of metastatic disease include pain (often chest or back pain when swallowing), anxiety, depression, ascites and breathlessness.[2,5] Optimal care for people requires support from comprehensive cancer teams specialised in the delivery of palliative options. The aim of this paper is to discuss the palliative management of the main problems likely to be associated with locally advanced or metastatic oesophageal cancer.

Dysphagia

Between 80% and 90% of people with oesophageal cancer will develop dysphagia at some point in their disease trajectory.[6] This is often a distressing problem that requires palliation appropriate to the person's capacity to tolerate the different treatment modalities. Options to palliate dysphagia are summarised in table 1.

Vomiting

In patients with oesophageal cancer, vomiting is likely to be multifactorial, with numerous processes occurring simultaneously. This may include stimulation of gastrointestinal tract mechanoreceptors and/or chemoreceptors on vagal, or glossopharyngeal afferents may occur through local mucosal irritants such as the tumour or, the presence of a stent. Other causes include radiotherapy, chemotherapy, and acid reflux due to delayed gastric emptying as a result of medications, ascites and malignant infiltration of the stomach.

The optimal palliation of the problem requires an assessment to define as clearly as possible, the cause of the problem. While people are undergoing tumour-modifying treatments with chemotherapy or radiotherapy, the anti-emetics of choice are 5-HT3 antagonists, alone or in combination with other anti-emetics such as metoclopramide. In refractory nausea, agents such as aprepitant may be considered.[8] In later stages of disease, the evidence is less clear. The anti-emetic that has the most robust evidence base is metoclopramide,[9] and this should be the first choice except when cramping abdominal pain is present. In this situation, clinical guidelines suggest avoiding metoclopramide. The reason for this is that metoclopramide increases the activity of the stomach antrum and may exacerbate cramping pain.[10]

Table 1: *Palliative strategies to improve dysphagia.*[7]

Intervention	Indication	Frequently encountered or serious complications
Laser ablation	Tumours at high risk of bleeding Tumours that have re-obstructed when other approaches to palliation have been used In people who are not well enough for surgical resection with otherwise operable tumours.	Stricture Local reactions
Phototherapy	Provides a more definitive response, but with an increased likelihood of a stricture developing.	Stricture formation
Self-expanding metallic stents	When combined with brachytherapy, the need for repeat interventions seems to be reduced.	Increased risk of migration compared to plastic stents Bleeding Pain Fistula formation
Plastic stents	Dysphagia treated with a palliative intent.	Re-obstruction secondary to tumour re-growth Migration Bleeding Fistula formation
Dilatation without stenting	Dysphagia treated with palliative intent.	Re-obstruction Perforation

Depending upon the local factors (the position of the tumour, stent or level of surgical resection), the gastro-oesophageal sphincter may be damaged. When this happens, there is a high likelihood of acid reflux which is sometimes persistent and debilitating. Both pharmacological and non-pharmacological approaches to this problem should be adopted. Regular proton pump inhibitors or H2-antagonists at maximal doses, sometimes with rescue doses of antacids, are recommended. Although there is little evidence to describe which agent is best, there is a meta-analysis to support the use of H2-antagonists to reduce the volume of gastric secretions, to a greater extent than proton pump inhibitors, potentially delivering better symptom control.[11] Other non-pharmacological approaches include elevation of the head of the bed and avoiding fatty foods which delay gastric emptying. Early referral to a dietician should be considered.

Cough and breathlessness

There are numerous reasons why people with advanced oesophageal cancer may develop cough including reflux, laryngeal nerve palsy and oesophago-bronchial fistula. The management of cough thus depends upon the cause. Although rare, oesophago-bronchial fistulas are amongst the most devastating complications. In addition to cough, recurrent or persistent respiratory tract infections and a high risk of bleeding may occur. Optimally, fistulae are treated with parallel stenting of both the oesophagus and trachea. [12]

When it is not possible to reverse the underlying cause, other approaches to palliation may be considered with the knowledge that the evidence bases supporting such recommendations are limited. However, clinical guidelines suggest the use of both peripheral and central cough suppressants. Peripheral antitussive agents (eg. sodium cromoglicate) suppress the afferent receptors that mediate cough, whereas central agents (eg. dextromethorphan) suppress receptors in the brain stem. Opioids may be effective although there is no data to support the efficacy of one opioid over another.[13]

Breathlessness accompanying advanced cancer is a poor prognostic sign and when unrelieved, significantly impairs quality of life. Regardless of life expectancy, it is reasonable to explore whether there are any easily reversible causes contributing to the problem. The evidence that supports palliation of dyspnoea is improving. Morphine is an effective medication to relieve dyspnoea which, when prescribed at low doses regularly (10-20mg/24 hours orally), is associated with few harmful effects. The number needed to treat is as low as 1.6.[14] Oxygen rarely improves the sensation of dyspnoea in people with normal partial pressures of oxygen, except in very small numbers of people.[15] If oxygen is commenced, a timely review of the benefits must be undertaken.[15] Non-pharmacological strategies must always be considered such as positioning, activity pacing, relaxation exercises (when people are well enough to tolerate the training), breathing exercises and psychological support, again highlighting the importance of the multidisciplinary team in the management of these patients.[16]

Pain

Pain is an expected complication for many people with cancer, both at diagnosis and as disease progresses. At diagnosis, 30% of people with oesophageal cancer report pain.[3] There are fewer data to describe the scope of the problem as disease progresses. However, given the magnitude for the problem of pain associated with advanced cancer overall, it is reasonable to conclude that, like other cancers, patients with oesophageal cancer are likely to be at risk of significant pain and discomfort as the disease progresses.

Pain, like other symptoms, is optimally managed by ensuring, as far as possible, that the aetiology of the pain is understood and evidence-based interventions to manage the pain are tailored appropriately.[17] Optimal results require structured and comprehensive assessments. At the time of presentation, an assessment should be made of the pain severity, character, likely aetiology, timing and location, and exacerbating/relieving factors. It is also necessary to check for associated symptoms.

The assessment of pain severity is best summarised using a validated screening tool, allowing not only communication around the severity of pain, but also ongoing tracking of pain trajectory. The management of pain requires knowledgeable prescription of analgesia with medications tailored to the severity of pain. However, the majority of people with advanced cancer will have pain that is of sufficient severity to warrant opioid analgesia. Within current guidelines, the initial opioid of choice remains morphine.[18] However, it is expected that the imminent publication of the revised European Association for Palliative Care pain guidelines is likely to recommend alternative opioids such as oxycodone and hydromorphone to be equally good first choices when commencing strong analgesics.[19] When commencing opioids, the aim must be to prescribe the lowest regular possible dose that affords the person relief. Analgesia is best prescribed on a regular rather than an "as needed" basis with concomitant use of appropriate targeted co-analgesics. The adverse effects of analgesia must be pre-empted with advice and strategies provided to the person and their carers around problems such as nausea and constipation.[18]

Weight loss

Significant weight loss is common in advanced oesophageal cancer, as in other cancers of the upper gastrointestinal tract. This problem may occur as a result of inability to take in sufficient calories to maintain weight or as part of cancer-related cachexia. Whatever the cause, weight loss has been identified as a major issue, with the presence of significant weight loss reducing people's capacity to tolerate tumour-modifying treatments and increasing the number of adverse effects people may suffer as a result of treatments.[20] As a result, weight loss has been identified as a poor prognostic factor with detrimental effects on people's quality of life, not only physically but psychologically.[21]

It is acknowledged that at present, it may be difficult to identify whether the weight loss is due to cancer cachexia or starvation secondary to dysphagia. There is no reliable biological marker of cancer-related cachexia, which is increasingly recognised as a complex inflammatory state. This is characterised by skeletal muscle wasting and loss of subcutaneous fat.[22] When it is unclear whether the weight loss is due to the cancer itself or other aetiologies, a trial of enteral or parenteral feeding is warranted. This is particularly in early stage cancers when, without adequate nutrition, people are unlikely to tolerate cancer treatments. The other group who will benefit from supplemental feeding are those who become unable to swallow because of complications of treatment such as mucositis secondary to radiotherapy. However, in the presence of clearly advancing disease with few therapeutic options to change disease behaviours, the potential complications associated with instituting parenteral feeding are such that groups such as the American Society of Parenteral Nutrition and the European Guidelines on Parenteral Nutrition have published recommendations against instituting parenteral nutrition in people with cachexia in advanced disease alone.[23]

Aside from the physical implications, there is a significant amount of existential suffering experienced by people with advanced cancer who lose significant amounts of weight. Contributing problems include changes in self-esteem, body image, anxiety and distress.[21] Furthermore, weight loss may lead to family conflict with identified themes underpinning this, namely caregiver grief, anger towards health professionals for perceived neglect and pressure to eat, leaving the patient feeling angry, frustrated, isolated or upset.[24] Identification of strategies to prevent or arrest the physical problems that underlie cancer cachexia is paramount. However, concurrent strategies to help palliate the consequences of this problem are needed. Until such a time that this problem can be reversed, a greater focus on patient and family-related distress is needed.

Hiccups

While identified as distressing, the actual incidence and prevalence of hiccups in advanced oesophageal cancer is unknown. Hiccups are repeated spasms of the diaphragm followed by sudden closure of the glottis which, when intractable, can be very distressing. Prolonged episodes of hiccups lead to worsening anorexia, weight loss, disabling sleep deprivation, anxiety and depression.[25] Hiccups in the situation of advanced oesophageal cancer are most likely due to stimulation or irritation of the afferent limb of the vagus nerve, or of the centres that control the diaphragm. Irritants may include distension or irritation of the oesophagus, direct stimulation of the vagus nerve, phrenic nerves or the diaphragm by tumour. Other causes such as electrolyte disturbances and medications are summarised in table 2. Not surprisingly, given how poorly the scope of the problem is summarised, there are limited data to support the optimal approach to palliating hiccups. Most of the recommendations are based on case reports only.[26] (See table 3) While this is not optimal, there are clear difficulties with improving the evidence-base for this symptom.

Fatigue

Fatigue is a commonly reported problem in cancer with multiple contributing factors, both physical and

Table 2: *Causes of hiccups in advanced cancer.*[26]

Malignancy
Oesophagogastric cancer
Colon cancer
Hepatoma
Leukemia
Lung cancer
Lymphoma
Pancreatic cancer
Renal cancer
Liver metastasis
Metabolic Derangements
Hyponatremia, hypokalemia, hypocalcemia
Renal failure
Uremia
Uncontrolled diabetes mellitus
Hypoadrenalism
CNS Pathology
Brain tumours (eg. gliomas, metastatic tumours)
Stroke
Hematoma/cerebral haemorrhage
Encephalitis/meningitis
Brain abscess/toxoplasmosis
Cardiovascular Disorders
Myocardial ischemia/infarction
Pericardial effusion/pericarditis
Thoracic/Pulmonary Disorders
Pneumonia
Pleural effusion/pleuritis
Thoracic herpes zoster
Mechanical ventilation
Gastrointestinal Disorders
Erosive esophagitis
Infectious oesophagitis (eg. herpes simplex, Candida species)
Peptic ulcer disease
Gastric distension from food, liquid, air, endoscopy
Gastric outlet or small bowel obstruction
Pancreatitis
Ascites
Cholecystitis
Subdiaphragmatic abscess
Psychogenic

Table 3: *Suggested strategies to improve hiccups.*[26]

Pharmacologic therapy
Baclofen
Carvedilol
Chlorpromazine*
Gabapentin*
Haloperidol
Ketamine
Lidocaine infusion
Methylphenidate
Metoclopramide*
Nebulized saline or lidocaine
Nefopam
Nifedipine/nimodipine
Olanzapine
Phenytoin
Valproic acid
Digital rectal stimulation
Phrenic nerve block with local anaesthesia*
Acupuncture

** Interventions with better evidence for palliation of hiccups.*

psychological. As with all cancer-related symptoms, the initial assessment must include a search for reversible factors. Cancer-related fatigue is most remarkable for the fact it fails to improve with rest.[27] There are a number of agents under investigation to better manage cancer-related fatigue, but no specific agent yet carries a sufficient evidence-base to be recommended.[28]

Psychological symptoms

Patient distress is often characterised by anxiety, "a diffuse, unpleasant, often vague feeling of apprehension, often associated with bodily sensations of pounding of the heart or sweating", or depression, "a pervasive and sustained lowering of mood, often associated with tearfulness, guilt or irritability, and loss of pleasure or interest in usual activities".[29] Depression has frequently been reported as one of the top 10 most common symptoms,[30] and as the most persistent symptom in people with advanced cancer.[31] A Swedish prospective, longitudinal study reported that 42% of patients (n=94) with oesophageal cancer had Hospital Anxiety and Depression Scale scores indicating possible or probable anxiety disorder and/or depression at one month post-diagnosis.[32] These high levels of morbidity persisted over the 12 months of the study, regardless of the cancer therapy given.

Psychological morbidity often goes undetected in people with cancer. Patients themselves may contribute to this because of their reluctance to disclose psychological or social concerns.[33,34] A diagnosis of depression may be complicated by the presence of physical symptoms and may be missed in situations in which depression is presumed to be a normal response to the situation.[35,36] There is now ample evidence to support interventions to improve psychosocial outcomes. Furthermore, recognition and treatment of psychological morbidity in patients may not only improve patients' quality of life, but also have implications for the long-term psychological morbidity of surviving partners. Unrelieved psychological symptoms of the patient appear to increase the risk of caregivers' psychological morbidity.[37]

A number of studies of the impact of illness perception on psychological distress suggest that cognition-based interventions and encouraging a positive focus as a coping strategy may be most effective in minimising emotional distress and improving the psychological health of survivors of oesophageal cancer.[38]

Anxiety can affect the ability to retain information.[39] Audio-taping consultations can lead to significant improvements in oesophageal cancer survivors' information retention (compared to a control group), without adverse psychological outcomes, as measured by the Hospital Anxiety and Depression Scale.[40] This practice should be encouraged as part of routine care.

Conclusion

Oesophageal cancer is associated with a significant physical symptom burden and psychological morbidity, especially as disease progresses. Active, prospective assessment at each clinical encounter of these potential symptoms will improve rates of recognition and the ability to respond with appropriate supportive measures.

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