



Controversies in oesophagogastric cancer

OVERVIEW OF CONTROVERSIES IN OESOPHAGOGASTRIC CANCER

Andrew Cameron,¹ Katrin M Sjoquist¹ and John R Zalberg²

1. National Health and Medical Research Council Clinical Trials Centre, University of Sydney, New South Wales.

2. Peter MacCallum Cancer Centre, Victoria and Department of Medicine, University of Melbourne, Victoria,

Email: Andrew.Cameron@ctc.usyd.edu.au.

The management of oesophagogastric cancer has undoubtedly improved over the past decades, although there remains a number of significant challenges for all clinicians involved in caring for patients with these diseases. The incidence of oesophagogastric cancer in Western countries continues to increase, driven mainly by a rise in adenocarcinomas of the distal oesophagus and gastro-oesophageal junction.¹ Consequently, the need to improve outcomes for patients with oesophagogastric cancer will continue to be an area of concern. As discussed by a number of leaders in the field, this issue of *Cancer Forum* highlights challenges and current areas of controversy in the management of patients with oesophagogastric cancer.

In Australia, there are about 3400 new diagnoses of gastric and oesophageal cancer each year, with 2400 deaths.¹ Oesophageal squamous cell carcinoma remains the most common type of oesophageal cancer, although its incidence continues to decrease and is mainly caused by smoking.² Barrett's Oesophagus remains the main risk factor for distal oesophageal and gastro-oesophageal junction cancers.³ Early diagnosis of malignant change and screening of patients at high risk presents a potential opportunity to increase the chances of cure, but provides a number of challenges for interventional gastroenterologists and surgeons alike. Increased understanding of the histological features defining the steps in progression from dysplasia to carcinoma has improved the ability to predict the progression to invasive disease. In this issue of *Cancer Forum*, Macrae, Tan and Smithers discuss the current understanding of the progression of premalignant lesions, and the risks and benefits of a tailored treatment approach utilising minimally invasive techniques and ablative therapies.⁴

Unfortunately, the majority of patients present with locally advanced or metastatic disease. For patients with resectable tumours, there is increasing evidence that neoadjuvant treatments can improve outcomes and increase the chance of cure over surgery alone. Both chemotherapy and chemo-radiotherapy before surgery have been shown to improve survival compared to surgery alone, without significantly increasing 30-day perioperative mortality.⁵ The optimal treatment regimen

is yet to be defined, although indirect evidence suggests that chemoradiotherapy may be the optimal strategy for patients who are fit. Bishnoi and Price and Deb, Ferraro, Tebbutt and Fox discuss the role of cytotoxic and targeted therapies,^{6,7} while Lee reviews the role of radiotherapy in oesophagogastric cancer.⁸

Improved staging methods, such as endoscopic ultrasound and PET, have shown utility in identifying patients who are not curable. The ability to identify those patients who will not benefit from standard neoadjuvant therapy, or for whom more aggressive treatments are warranted in order to aim at cure, would assist in optimising treatment outcomes. Current areas of research include the role of molecular imaging using F-18 flurodeoxyglucose (FDG) PET scans to help determine prognosis and identify patients who may respond to neoadjuvant chemotherapy. One such example is the Australasian Gastro-Intestinal Trials Group 'DOCTOR' trial, which examines the role of early (14-day) FDG PET response to platinum based neoadjuvant chemotherapy in predicting pathological response, and the potential utility of an alternative treatment regimen in non-responders.⁹

Other areas of ongoing research include the identification and validation of molecular biomarkers to help predict the benefit of treatment or determine prognosis. Candidate biomarkers and their potential uses are discussed in the article by Cameron, Barbour, Wayte and Akhurst.¹⁰ The evolution of patient pathways towards a more individualised treatment strategy strongly suggests that pathologists and radiologists will likely have an increasing stake in the multidisciplinary team of the future.

Surgical excision of the primary tumour however, remains the principal basis of cure. Complete microscopic resection remains a key prognostic factor for both oesophageal and gastric primary tumours. The varying location of tumours, from the thoracic oesophagus to distal stomach, requires an individualised surgical approach as discussed by Duong and Spillane.¹¹ The balance between optimising oncologic outcomes and minimising treatment related morbidity and mortality is the basis of current controversy within the surgical community. The choice of approach (open versus laparoscopic), the extent of lymphadenectomy and the issue of how to consider gastro-oesophageal junction tumours remain

areas of debate within the current literature. An extensive dissection is likely to remove all cancerous tissue, but at the expense of morbidity and mortality.

Many of these questions can only be best answered in clinical trials preferably with Australian participation. It is recognised that there are often patient and tumour related characteristics that relate to variable outcomes between ethnic groups, no more so than in oesophagogastric cancers. Consequently, it is vital that participation in clinical research relevant to the Australasian context continue to be embraced by the upper gastrointestinal surgical community as a means to providing answers to many of these important questions.

A patient's nutritional and physical fitness may be key determinants in the outcomes of surgery in any one individual. Multidisciplinary assessments and management before and after surgery are increasingly being utilised. Patients with locally advanced oesophagogastric cancer are often malnourished and require nutritional screening. Biochemical measures remain insufficient but there are guidelines to implement nutritional support as required. Physiological fitness is also important in reducing perioperative complications, whether it be impacted by disease symptoms, perioperative treatments or other medical conditions. Dynamic tests of physical fitness are increasingly utilised to stratify patient risk. The increasing use of pre-operative treatments in oesophagogastric cancer has also met with an increased need to optimise patient fitness for surgery in light of the fact that there is a finite window of opportunity after which surgery will be less effective. Riedel, Ismail, Findlay and Ryan discuss a range of evaluation and intervention strategies in their article.¹²

Unfortunately, a large proportion of patients will either present with metastatic disease or will relapse after initial treatment and die as a consequence of their disease. First line therapies for advanced/metastatic disease revolve around the doublet of platinum and 5-fluorouracil (5-FU) and cisplatin. Activity has also been demonstrated with other agents including the taxanes. The REAL2 study showed that oxaliplatin could be substituted for cisplatin and capecitabine for 5-FU, such that triplet combinations are now the standard of care for medically fit patients with a good performance status.¹³ Second line therapy has a limited role for fit patients with recent evidence suggesting that irinotecan and docetaxel can be beneficial over best supportive care alone.¹⁴

Like other tumour types, targeted therapies are in various stages of investigation. The anti-Her2 agent, trastuzumab in combination with cisplatin and 5-FU is an important new development in Her2-positive gastric cancer. Bevacizumab, an antiangiogenic monoclonal antibody against VEGF-A, has failed to show a survival benefit in combination with cisplatin and capecitabine in oesophagogastric cancers. Multi-targeted tyrosine kinase inhibitors like sunitinib and sorafenib have only shown modest activity. Clearly, further evaluation of these drugs and the value they may have in addition to current

standards of care are required. As in the ToGA trial, molecular differentiation of tumours is likely to identify subgroups that will benefit from targeted therapy in the future. Deb, Ferraro, Tebbutt, and Fox describe the use of trastuzumab in treating gastric cancer and explore the role of other targeted therapies in managing these patients.⁷

As the complexity of treatment increases, the involvement of all members of the multidisciplinary team is critical to achieve the optimal care of patients in all stages of this disease. The sequelae of both the disease and its treatment require input from a broad range of professionals to achieve the best outcomes. This need to individualise treatment is increasingly recognised as an important aspect of management of a variety of cancers and oesophagogastric cancer is no exception. Nonetheless, most patients will eventually succumb to this disease. Progressive disease can give rise to symptoms such as pain, dysphagia, nausea, anorexia and fatigue. Various medical and surgical therapies are available to optimise symptoms and improve the quality of life of these patients. Significant psychological morbidity can be minimised by anticipating and intervening early in the development of symptoms. Screening for various symptoms throughout the disease trajectory and addressing the psychosocial morbidity that occurs are best handled in a multidisciplinary team approach to allow for the most appropriate supportive measures. Clark, Girgis and Currow summarise the current evidence from the literature.¹⁵

Current and future research goals are targeting multiple areas of interest. Key areas include: preventive therapies that will limit the development and progression of dysplasia and Barrett's Oesophagus; better discriminatory tools to optimise peri-operative health; targeted therapies that will offer further benefits without necessarily increasing toxicity; ongoing biomarker development to identify subgroups that are likely to respond to particular treatment regimens; and palliative treatments that will maximise the length and quality of life.

In this edition of *Cancer Forum*, we have endeavoured to outline the current controversies in the management of and research into oesophagogastric cancer. In doing so we hope it provides a basis for further research into the optimal care of patients with these diseases.

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Common abbreviations used in this forum

AT	anaerobic threshold
BO	Barrett's Oesophagus
CI	confidence intervals
CPET	cardiopulmonary exercise testing
DCF	docetaxel 75 mg/m ²
ECF	epirubicin, cisplatin and 5-fluorouracil
ECX	capecitabine
EMR	endoscopic mucosal resection
EOF	triplet therapy with epirubicin and oxaliplatin plus fluorouracil
EOX	triplet therapy with epirubicin and oxaliplatin plus capecitabine
FAMTX	high-dose 5-fluorouracil and methotrexate
FDG	F-18 flurodeoxyglucose
HGD	high grade dysplasia
HR	hazard ratio
IMC	intramucosal carcinoma
RFA	radiofrequency ablation
SUV	standardised uptake value
VMA	visual mucosal abnormalities
XP	triplet therapies containing capecitabine