

# CANCER FORUM



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FORUM: Controversies in oesophagogastric cancer

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Australian behavioural research in cancer

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Cancer Council Australia's Student Essay Competition –  
Personalised cancer treatment – fad or future?

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# CANCER FORUM



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# CANCER FORUM

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## Controversies in oesophagogastric cancer

### OVERVIEW OF CONTROVERSIES IN OESOPHAGOGASTRIC CANCER

**Andrew Cameron,<sup>1</sup> Katrin M Sjoquist<sup>1</sup> and John R Zalberg<sup>2</sup>**

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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.<sup>1</sup> 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.<sup>1</sup> Oesophageal squamous cell carcinoma remains the most common type of oesophageal cancer, although its incidence continues to decrease and is mainly caused by smoking.<sup>2</sup> Barrett's Oesophagus remains the main risk factor for distal oesophageal and gastro-oesophageal junction cancers.<sup>3</sup> 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.<sup>4</sup>

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.<sup>5</sup> 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,<sup>6,7</sup> while Lee reviews the role of radiotherapy in oesophagogastric cancer.<sup>8</sup>

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 fludeoxyglucose (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.<sup>9</sup>

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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup>

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.<sup>13</sup> 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.<sup>14</sup>

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.<sup>7</sup>

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.<sup>15</sup>

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 <sup>2</sup>
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 fludeoxyglucose
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

## LOCAL THERAPIES AND RESECTION IN BARRETT'S OESOPHAGUS AND EARLY OESOPHAGOGASTRIC CANCER

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### Abstract

Endoscopic treatment to eliminate Barrett's Oesophagus, associated dysplasia and intramucosal cancer, in order to induce squamous re-epithelialisation has been developed as a viable, oesophagus-sparing alternative for eligible patients in recent years. It has gained popularity given its less invasive nature and better tolerability relative to radical oesophagectomy. Widely used modalities include endoscopic mucosal resection, radiofrequency ablation, argon plasma coagulation, photodynamic therapy and cryotherapy, each having their own advantages and limitations. Yet invasion of dysplasia into and beyond the submucosal layer of epithelium signifies potential metastasis, rendering endoscopic intervention no longer appropriate, and surgical intervention remains the definitive treatment. This review highlights the disease process of Barrett's Oesophagus and associated dysplasia and early cancer, the various treatment options and appropriate selection of patients, indications and management considerations.

The emergence of innovative endoscopic ablative therapies has shifted the treatment of Barrett's Oesophagus (BO) with dysplasia and early intramucosal cancer in selected patients from surgical to an endoscopic approach. This strategy is considered a genuine option after careful search for invasive cancer, in both surgically-fit and unfit patients. Yet oesophagectomy remains the definitive treatment modality, ensuring the highest cure rate for any associated oesophageal adenocarcinoma

and ultimate risk reduction. Here we aim to outline the natural history and various therapeutic options, and to establish current recommendations in practice regarding the appropriate treatment selection.

BO is a condition characteristically of the Caucasian male, where normal squamous epithelium is replaced by columnar epithelium over any length in the distal oesophagus. It is thought to develop as a response to gastroesophageal reflux disease through injury to the squamous epithelium.<sup>1</sup>

Diagnosis is based on endoscopic appearance, as well as histological confirmation of specialised intestinal metaplasia, with mucin-producing goblet cells.

Latest data suggests an 8-20% prevalence rate of BO in Western countries among patients undergoing endoscopies for reflux symptoms.<sup>2</sup> This precancerous condition has potential to progress to oesophageal adenocarcinoma, one of the fastest rising malignancies, with its rate of increase being six to seven fold higher than most common cancers, including lung, breast, prostate, colorectal and melanoma.<sup>3</sup> A progression through a series of cellular changes, from intestinal metaplasia through low grade dysplasia and high grade dysplasia (HGD) to oesophageal adenocarcinoma is postulated. The degree of dysplasia is thought to be strongly associated with the risk of carcinoma in patients with BO. The conversion rate of non-dysplastic BO into oesophageal adenocarcinoma is 0.27- 0.5% per person-year,<sup>4,5</sup> and that of HGD into oesophageal adenocarcinoma being much higher at 16-60% over up to eight years of follow up.<sup>6-8</sup>

Recent evidence suggests that patients with a columnar oesophagus but, without goblet cells on histology, may be especially at risk for transition to oesophageal adenocarcinoma, thereby querying the significance of goblet cells as a precondition in the neoplastic progression of BO.<sup>9</sup>

Epidemiological observations consistently associate BO with obese Caucasian males. A focus of recent investigation has been on genetic predisposition given that there is a familial risk of BO. In a sib-pair genome wide linkage study, three loci associated with the genes MSR1, ASCC1 and CTHRC1 were identified; further, mutations were found in each of these genes, with functional up-regulation of CCND1 which is downstream to MSR1. Further studies are anticipated.<sup>10</sup>

## Current recommendations for practice

### Intestinal Metaplasia

Currently, there is no Australian guideline regarding surveillance of patients with BO without dysplasia. The British Society of Gastroenterology recommends surveillance every two years,<sup>11</sup> while the American College

of Gastroenterology recommends two endoscopies with biopsy within one year, and then follow-up with endoscopy every three years.<sup>12</sup> Although the changes seen in BO are a step towards the development of cancer, the overall progression rate to adenocarcinoma is low. Given this relatively low risk, and the restricted treatments currently available, more aggressive interventions such as ablation and resection are not advised in Australia for uncomplicated BO.

### Dysplasia

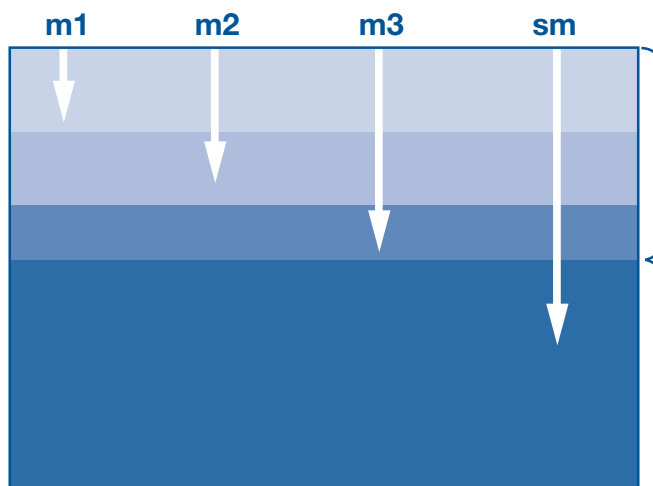
Once dysplasia has been diagnosed, there is a significant risk of progression to cancer. The progression rate of HGD has been reported to be 16-60% spanning five to eight years of follow-up.<sup>6-8</sup> Management for dysplasia is controversial and complex, especially that of HGD, with much debate surrounding the best intervention. Firstly, it is important to determine whether HGD is unifocal, multifocal, or associated with any visual mucosal abnormalities (VMA) such as nodularity, or ulceration. The presence of diffuse or multifocal HGD is associated with a higher risk (four-fold) of developing adenocarcinoma compared with focal HGD without VMA ( $p=0.02$ );<sup>13</sup> any VMA may signify the presence of underlying cancer. In our experience in Melbourne, confocal endomicroscopy which enables 1000x magnification to 250 microns into the mucosa and submucosa, has proved useful in confirming high grade dysplasia, suspecting low grade dysplasia, and defining the margins of dysplasia in VMA.

### Intramucosal versus submucosal tumor invasion

The most important factor to consider in the decision making is the depth of invasion of the cancer into the mucosal layers. Adenocarcinoma can be staged according to different depths of invasion (figure 1).<sup>14</sup>

Lymph node metastasis has not been reported in patients with HGD. Breaching the muscularis mucosa into the submucosa signifies the development of invasive cancer, where subsequent nodal involvement, distant metastasis and death can occur. In one study of 85 patients who had an oesophagectomy for mucosal or submucosal disease, there was no node involvement for any of the mucosal cancers, while 18% of submucosal cancers had a positive node, with

**Figure 1:** Subdivision of mucosal cancer according to depth of invasion.



#### Intramucosal Involvement:

- m1: carcinoma in situ, within epithelial layer
- m2: cancer invasion into lamina propria
- m3: cancer infiltration into muscularis mucosa

#### Submucosal Involvement:

- sm1: into upper third of submucosa
- sm2: into middle third
- sm3: into lower third



the rate being higher if the cancer was poorly differentiated and there was lympho-vascular invasion (46%).<sup>15</sup>

This highlights the importance of a subtle change in the depth of vertical invasion, significantly increasing the risk of lymph node metastasis; hence identification of submucosal or invasive cancer is critical. Once deemed invasive, oesophagectomy is the only treatment offering a complete resection of the tumor as well as any involved lymph nodes, providing a complete cure of the disease if localised to the region. Endoscopic ablative therapies are no longer appropriate and surgery is the preferred option, if the patient is fit.

### Endoscopic treatment of Barrett's Oesophagus and associated dysplasia

Endoscopic therapies include endoscopic mucosal resection (EMR), as well as multiple endoscopic ablative techniques developed in recent years, each differing in mechanism, efficacy, side-effects and cost effectiveness.

EMR, or mucosectomy, is the removal of affected mucosa by resection through the middle or deeper parts of the submucosa. The aim of EMR in dysplastic Barrett's and early oesophageal adenocarcinoma is to obtain a much better sample of the neoplasia for accurate pathological staging (depth of invasion) and grading (degree of differentiation). Where the lesion is focal, EMR may provide endoscopic cure so long as the lesion is confined to the mucosa, where the risk of lymph node metastasis is minimal. Both the "inject, suck, and cut" and "band and snare" techniques have been shown to yield equivalent and adequate depth of mucosa and submucosa.<sup>16</sup> EMR appears to be an effective therapy achieving curative effect similar to surgery, but avoiding the mortality and morbidity. The potential for further change in the residual BO requires the residual mucosa to be ablated or intensive long-term endoscopic surveillance undertaken, given that there are few studies reporting the long-term outcomes from focal resection of these good prognostic pathologic entities.

Multiple methods of endoscopic ablation to eliminate the metaplastic or dysplastic epithelium in the oesophagus and induce reversion to normal squamous epithelium have been developed as a viable, oesophagus-sparing alternative for eligible patients. They include but are not limited to photodynamic therapy, argon plasma coagulation, cryotherapy, and most recently, radiofrequency ablation (RFA). Successful ablation has been achieved with each of these modalities, but inherent disadvantages impede their overall success. Photodynamic therapy, one of the first techniques established, has a high (77%) complete elimination rate of HGD when combined with proton pump inhibitors.<sup>17</sup> But its drawbacks include strictures, odynophagia and cutaneous photo-toxicity. The repeated point-by-point application of argon plasma coagulation risks burying BO below neosquamous epithelium, limiting its use as a single mode therapy, but it is now often used as an adjuvant ablative therapy. Only a few uncontrolled studies have been conducted in an attempt to establish the role of cryotherapy in treatment of BO and dysplasia with promising results.<sup>18-20</sup> The HALO® RFA system (Barrx

Medical, Sunnyvale, CA, USA) has yielded consistently better results than any alternate ablative therapy. The study with the most convincing result was a randomised control trial done by Shaheen et al among patients with low grade dysplasia and HGD. The advantages include minimal complications (strictures, bleeding), higher patient tolerability and higher rates of total ablation of BO with minimal chance of developing buried BO.<sup>21</sup> Contemporarily, the results of RFA have been impressive, and a strategy of RFA with EMR for careful pre-ablative screening and staging is considered by many as the standard of endoscopic care.<sup>22,23</sup> When HGD or intramucosal carcinoma (IMC) are to be managed endoscopically, any VMA should be removed with EMR, restricting the ablative techniques to the remaining 'normal' mucosa.

### Oesophagectomy

Historically, for patients considered fit, an oesophagectomy has been considered the definitive treatment for HGD and IMC because the procedure completely eradicates the neoplastic mucosa, as well as removing the regional lymph nodes. In a review of 29 studies with 548 patients where an oesophageal resection was performed for HGD, the incidence of an occult carcinoma was 37%.<sup>24</sup> The cancer was deeper than the mucosa in more than 60% of those patients. In 2003, Korst and colleagues advocated resection for HGD as the treatment of choice unless the patient was unfit.<sup>25</sup> However, that study did not mention EMR. Since that time endoscopic techniques have evolved with better biopsy protocols and the use of directed EMR. We are now able to more carefully assess the extent of the HGD, as well as the potential for an associated area of carcinoma formation. Indeed it has been reported that in patients with HGD or early mucosal carcinoma, EMR can successfully obtain a complete resection of the disease at the time of the first treatment in 28% and up to 74% after repeated mucosal resections.<sup>26</sup>

Centres performing a high volume of oesophageal resection report operative mortalities between 2-4% but rates of 0-1% have been reported when the resection was for HGD/IMC.<sup>27</sup> With the recent trend to minimally invasive approaches for oesophageal resection it has been hoped that the morbidity and mortality from the procedure may be reduced. To date there has been no clear evidence of a major difference in operative mortality or in the general outcomes comparing open approaches with minimally invasive approaches.<sup>27,28</sup> Advocates for resection claim that the long term functional outcomes are at least equivalent to the general population.<sup>29</sup> However, patients do have higher incidences of a number of functional symptoms such as dumping syndrome, bloat, reflux and diarrhoea.<sup>30</sup>

Clearly the major disadvantage of an oesophagectomy is the potential for early operative mortality. Treatment failure from various modalities of endoscopic therapy has been reported to be 6-20%, with the development of a new metachronous cancer in the at-risk mucosa.<sup>31,32</sup> Zehetner et al compared the outcomes from patients who had an oesophageal resection for HGD/IMC (61 patients) with a cohort they treated using endoscopic therapy (40 patients).<sup>32</sup> The morbidity from resection was 39% with no

complications in the patients who had endotherapy. There were no procedure related deaths in either group. The overall survival at three years was 94% for both groups and the cancer-related survival at that time of 100% in both groups. However, the incidence of a new metachronous primary neoplastic lesion in the endotherapy group was 20%; there were no metachronous lesions after an oesophagectomy.

The group in Weisbaden, Germany, report complete resection rates from EMR for HGD and IMC to be 97%. Only a few patients had their residual Barrett's mucosa ablated (photodynamic therapy) leading to metachronous HGD or IMC in the at-risk residual Barrett's mucosa in 21%.<sup>33</sup> In this report, the risk factors for recurrence were identified to be piecemeal resection, long segment BO, no ablation of the BO, multifocal neoplasia and the time to complete removal of the identified lesion to be more than 10 months. This group highlighted the need to intensively follow patients with regular endoscopy and they have also used other imaging including EUS and CT scanning. The addition of ablative procedures such as RFA, should reduce the incidence metachronous lesions. Long-term follow-up studies after RFA will be important to establish the safety of local therapy in these carefully selected patients.

For IMC, there has been one comparative study assessing oesophagectomy compared with EMR and BO ablation. The group from Weisbaden compared the results of a cohort of patients with IMC treated with EMR and argon plasma coagulation to the non-dysplastic BO with a matched group of patients who had a resection performed in a high volume surgical unit in Cologne, during the same time period.<sup>33</sup> The major complication rate for surgery was 32% and the 90-day mortality 2.6%; with a median follow up of 4.1 years, there was no recurrence of the tumour locally or systemically. The patients who had endoscopic therapy had no major morbidity or mortality; within a median follow up of 3.7 months. 6.6% of patients needed further local therapies, with one patient not completely cleared locally because of death from an unrelated cause before total eradication of the BO was achieved.

The long-term results from the endoscopic therapies are not known and as previously stated, diligent regular follow-up endoscopy in these patients is essential. An operative death from surgery is a disaster, but equally a death from metastatic adenocarcinoma in a patient who had endoscopic therapy for a potentially curable disease is also a disaster. The decision to proceed with endoscopic therapy as the definitive treatment in a patient with HGD or IMC is not always clear-cut and should be made in a collaborative environment including the interventional endoscopist and an oesophageal surgeon. The better oesophagectomy outcomes occur in specialist high-volume centres. However, the technical expertise of the surgeon is only one component in the operative and cancer outcomes for these patients. For endoscopic therapies, it is likely the better HGD/IMC eradication figures and procedural outcomes will occur in centres that have a specific interest in this problem with strict follow-up endoscopy protocols in a multi-disciplinary clinical environment.

## Conclusion

The choice of operative versus non-operative therapy for BO with HGD/IMC has changed in the last few decades. In appropriately selected patients, endoscopic therapy is increasingly becoming the treatment of choice as it has the potential to achieve the same curative effect as surgery, with minimal invasiveness and low complication rates. Yet surgery remains the definitive choice for advanced HGD and early cancer with submucosal infiltration. Multidisciplinary assessment and planning are important to achieving optimal outcomes.

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## REVIEWING THE ROLE OF CYTOTOXICS IN OESOPHAGOGASTRIC CANCER IN THE REFRACTORY RELAPSED AND ADVANCED SETTINGS

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### Abstract

Advanced oesophagogastric cancer is an incurable disease and leading cause of cancer-specific mortality. Despite some progress in recent years, its management poses a challenge due to increasing incidence, geographical variation, histologic heterogeneity, biologic behaviour and lack of consensus on standard chemotherapy with or without biologic agents. The purpose of this review is to discuss the current controversies in selection of chemotherapy regimens. The review involves analysis of recent clinical trials to discuss the impact and implications of their results on the management of advanced oesophagogastric cancer and the planning of the next generation of clinical trials.

Small but significant improvements in survival for oesophagogastric cancer have occurred over last three decades with the five-year survival of oesophageal cancer improving from 5% to 17% and stomach cancer from 16% to 28%.<sup>1</sup> According to Australian Institute of Health and Welfare, there were a total of 3400 new stomach and oesophageal cancer cases and 2400 deaths.<sup>1</sup>

Nearly 50% of patients with a diagnosis of oesophagogastric cancer present with overt metastatic disease, and chemotherapy is the mainstay of palliative treatment. While data from clinical trials before the 1990s were largely ineffective due to the use of single-agent chemotherapies in heterogeneous, small patient populations, more recent trials with combination chemotherapy, targeted agents, and neoadjuvant chemotherapy are more promising. With the increasing use of chemotherapy as an adjunct to surgical management, systemic chemotherapy will ultimately be used to treat the majority of patients with oesophagogastric cancer.

### Basis of chemotherapy

In patients with advanced oesophagogastric cancer, chemotherapy clearly improves survival and quality of life compared with best supportive care alone, although

the evidence is more compelling in gastric cancer specifically.<sup>2-5</sup> In a meta-analysis of 35 trials with a total 5726 patients with advanced gastric cancer, systemic chemotherapy was compared with best supportive care. The main finding of this analysis was that patients undergoing chemotherapy lived for an average of six months longer than those receiving best supportive care [hazard ratio (HR) 0.37, 95% confidence intervals (CI) 0.24 to 0.55].<sup>6</sup> Furthermore, combination chemotherapy had better survival than single-agent chemotherapy (HR 0.82; 95% CI 0.74 to 0.90). However, this benefit was at the expense of increased toxicity. Therefore, in the absence of contraindications and concerns over toxicity, combination chemotherapy would be used as initial treatment in patients with good performance status.

In contrast, oesophageal cancer is more heterogeneous and evidence supporting chemotherapy alone is less compelling. The grouping of locally advanced and metastatic disease with different pathologies (ie. squamous and adenocarcinoma) makes interpretation of results difficult. Furthermore, radiotherapy is often added for local control. A multicentre randomised French study currently accruing patients with only metastatic squamous cell oesophageal carcinoma may help to ascertain if there is a benefit of chemotherapy over best supportive care.<sup>7</sup>



Similarly, Trans-Tasman Radiation Oncology Group (TROG) is conducting a randomised phase III study in advanced oesophageal carcinoma to compare palliative benefit in dysphagia in patients treated with radiotherapy versus chemo-radiotherapy (TROG 03.01 study).<sup>8</sup>

## Current options of CF versus ECF versus DCF

### Oesophageal cancer

Cisplatin and 5-Fluorouracil (5-FU) both have single agent activity in oesophagogastric cancer.<sup>9</sup> The use of the combination of cisplatin and 5-FU (CF) for the treatment of oesophageal cancer was primarily inspired by the activity of this regimen in squamous cell carcinoma of the head and neck. Cisplatin (100 mg/m<sup>2</sup>) as a single agent and cisplatin with 5-FU (1000 mg/m<sup>2</sup> by continuous intravenous infusion on days 1-5) were compared in a randomised study of 88 patients with metastatic squamous cell carcinoma of the oesophagus.<sup>10</sup> This study confirmed the superior efficacy (response rate 19% v 35%, median duration of response 28 v 33 weeks) of combination treatment over single agents at the expense of greater toxicity. Response rates to cisplatin and 5-FU are supported in other trials with response rates ranging from 35% to 40%.<sup>11,12</sup> Efforts have been made to improve upon this regimen by adding other agents but with no real progress and the true role of palliative chemotherapy remains controversial.

### Gastric cancer (including gastro-oesophageal junction)

The combination of epirubicin, cisplatin and 5-fluorouracil (ECF) was developed in the 1990s and remains the most popular regimen in Australia for advanced gastric and oesophagogastric cancer. In a pivotal Phase III trial, 274 patients were randomised to receive either ECF or Adriamycin, and high-dose 5-fluorouracil and methotrexate (FAMTX). ECF demonstrated a response rate of 45% compared with 21% for FAMTX, and a median survival of 8.9 versus 5.7 months ( $p = 0.0002$ ).<sup>14</sup> The main drawback of the regimen was the requirement of central venous access for protracted venous infusion of 5-FU. The pro-coagulant properties of the cancer and the central line led to its removal in 19% of trial patients. Toxicities were broadly comparable except that ECF caused more alopecia, nausea and vomiting, but less neutropaenia and infection.

There remains some question as to the benefit of adding an anthracycline to CF. The addition of an anthracycline to cisplatin and 5-FU has shown a trend towards benefit in three randomised phase III plus two small phase II trials. Data from these trials were pooled in a meta-analysis that reported a statistically significant benefit in favour of anthracycline/platinum-containing regimens.<sup>15</sup> The survival benefit was estimated to afford an additional two months and, of the available agents, epirubicin appeared to be the best tolerated. The meta-analysis was criticised for the small numbers of patients and for including a study that didn't address the issue of doublet versus triplet combination, but compared epirubicin with mitomycin C (M) in a triplet regimen (mitomycin C, cisplatin, and 5-FU v ECF).<sup>15</sup> An additional

but unpublished meta-analysis by Group GASTRIC has suggested no additional benefit of an anthracycline.<sup>16</sup> Therefore, it is still unclear whether ECF is more effective than doublet chemotherapy in advanced oesophagogastric cancer. Furthermore, toxicity is more severe with triplet than doublet chemotherapy. ECF, or a variation of it, is still considered to be a standard regimen in Australia and Europe based on these data.

The addition of docetaxel as a third agent added to CF in a phase III trial of gastroesophageal junction and gastric cancer has been reported. The 5-FU was dosed at 1000 mg/m<sup>2</sup> by continuous infusion over five days combined with cisplatin 100 mg/m<sup>2</sup>, compared to cisplatin 75 mg/m<sup>2</sup>, 5-FU 750 mg/m<sup>2</sup> by continuous infusion over five days, and docetaxel 75 mg/m<sup>2</sup> (DCF) in 445 patients with metastatic gastric or gastroesophageal junction adenocarcinoma.<sup>21</sup> The DCF regimen resulted in a higher response rate and longer time to progression (36% and 5.6 months, respectively) compared to 5-FU and cisplatin (26% and 3.7 months), but only a marginal median survival improvement of 0.6 months was noted. Toxicity was substantial in both treatment arms, including haematologic and gastrointestinal toxicity, with 82% of patients receiving the three-drug combination experiencing grade 3 or 4 neutropaenia. The potential superiority of DCF was underscored by a recent randomised phase II trial comparing ECF to DCF in gastric and gastroesophageal junction cancer.<sup>22</sup> The DCF regimen appeared to result in a superior response rate and time to tumour progression when compared to ECF, but toxicity, particularly rates of neutropaenia and neutropaenic fever, were substantial. The high rate of haematological toxicity has limited the regimen's use outside of American institutions. Currently in Australia, the ATTAX-3 trial is attempting to address this issue among others. It uses weekly docetaxel to reduce myelosuppression, combining it with cisplatin and 5-FU (or capecitabine – an oral prodrug of 5-FU) and then randomised to panitumumab versus placebo.<sup>23</sup> The ATTAX-3 trial is actively recruiting.

Although triplet therapy (ECF or DCF) is used by many, the toxicity trade-off does mean that CF is still used as an alternate option by many clinicians. Thus attempts to improve doublet regimens are still relevant. The combination of irinotecan and infusional 5-FU was compared head to head to conventional 5-FU and cisplatin in a recent phase III trial in gastric and gastroesophageal junction cancers.<sup>26</sup> Irinotecan 80 mg/m<sup>2</sup> in combination with 5-FU 2 g/m<sup>2</sup> over a 24-hour infusion, and leucovorin 500 mg/m<sup>2</sup> administered weekly for six weeks on and one week off, was compared to cisplatin 100 mg/m<sup>2</sup> and 5-FU 1000 mg/m<sup>2</sup> continuous infusion for five days every four weeks in 333 patients. There was no difference in response rate (26% v 32%), time to progression (4.2 v 5.0 months), or median survival (8.7 v 9.0 months). However, the toxicity profile significantly favoured the irinotecan/5-FU combination, with less neutropaenia, neutropaenic fever, stomatitis and nausea. Only the rate of grade 3 or 4 diarrhoea was greater in the irinotecan arm. This trial suggests that irinotecan/5-FU may represent a comparably active but better-tolerated alternative to 5-FU/cisplatin.

## Substitution of capecitabine and oxaliplatin in triplet and doublet regimens

Capecitabine (X) and oxaliplatin represent agents that are potential substitutes for infusion fluorouracil or cisplatin respectively. The largest clinical trial in the management of locally advanced or metastatic oesophagogastric cancer was a two-by-two design, REAL-2 trial, in which 1002 patients were randomly assigned to receive triplet therapy with epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX), or triplet therapy with epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX).<sup>27</sup> The primary endpoint was non-inferiority in overall survival for the triplet therapies containing capecitabine as compared with fluorouracil and for those containing oxaliplatin as compared with cisplatin. For the capecitabine–fluorouracil comparison, the hazard ratio for death in the CX group was 0.86 (95% CI, 0.80 to 0.99); for the oxaliplatin–cisplatin comparison, the hazard ratio for the oxaliplatin group was 0.92 (95% CI, 0.80 to 1.10). The upper limit of the confidence intervals for both hazard ratios excluded the predefined non-inferiority margin of 1.23. Median survival times in the ECF, ECX, EOF and EOX groups were 9.9 months, 9.9 months, 9.3 months and 11.2 months, respectively; and survival rates at 1 year were 37.7%, 40.8%, 40.4%, and 46.8%, respectively. In the secondary analysis, overall survival was longer with EOX than with ECF, with a hazard ratio for death of 0.80 in the EOX group (95% CI, 0.66 to 0.97;  $p = 0.02$ ). Progression-free survival and response rates did not differ significantly among the regimens. Toxic effects of capecitabine and 5-FU were similar. As compared with cisplatin, oxaliplatin was associated with lower incidences of grade 3 or 4 neutropaenia, alopecia, renal toxicity and thromboembolism but with slightly higher incidences of grade 3 or 4 diarrhoea and neuropathy.

Similar observations were made in a randomised, open-label, phase III Korean study, in which 316 patients were randomised to receive cisplatin with either Xeloda (CX) or protracted 5-FU (CF) to confirm noninferiority of CX versus CF for progression-free survival.<sup>28</sup> In the per-protocol population, median progression-free survival for CX ( $n = 139$ ) versus CF ( $n = 137$ ) was 5.6 versus 5.0 months with an unadjusted HR of 0.81 [95% CI 0.63–1.04,  $p < 0.001$  versus non-inferiority margin of 1.25]. Median overall survival was 10.5 versus 9.3 months for CX versus CF (unadjusted HR = 0.85, 95% CI 0.64–1.13,  $p = 0.008$  versus noninferiority margin of 1.25). There was no difference in treatment-related grade 3/4 adverse events in CX versus CF.

The combined data from REAL-2 and ML17032, which individually demonstrated that capecitabine is non-inferior to 5-FU, has shown a modest, but statistically significant benefit in overall survival in favour of the oral fluoropyrimidine, which was maintained on multivariate analysis.<sup>29</sup> When comparing the ECX arm in the REAL-2 study with the capecitabine and cisplatin arm in the ML17032 study, grade 3 and 4 neutropaenia were significantly higher in the triplet combination (51% v 16%) highlighting the importance of patient selection when considering doublet versus triplet chemotherapy.

## Impact of biological results on chemotherapy regimen

Finally, HER-2 positivity in metastatic gastric cancer may influence the choice of chemotherapy given the positive results of the ToGA trial, where overall survival was improved from 11.1 months with CF/X to 13.8 months with Herceptin plus CF/CX (HR 0.74, 95% CI 0.6-0.91;  $p=0.0046$ ).<sup>30</sup> We have already discussed the controversy regarding the addition of an anthracycline and although some now consider CF/CX an acceptable backbone, the EOX arm of REAL-2 trial did have a high overall survival. One logical step is combining EOX with trastuzumab. Experience from breast cancer trials however, raises the potential of high cardiotoxicity from an anthracycline combination. The dilemma may be the selection of either trastuzumab or epirubicin. The relative benefit of the addition of trastuzumab or epirubicin to cisplatin plus fluoropyrimidine is unknown, although the benefit appears to slightly favour trastuzumab (4.2 months survival gain for trastuzumab in highly HER 2 positive patient in ToGA versus 2.0 months survival gain for epirubicin in the meta-analysis) and the toxicity profile is different.

## Second line options

Data from two recent randomised phase III trials suggest that there is definite but small survival advantage from second line chemotherapy in advanced gastric cancer. Park and colleagues conducted randomised phase III Korean trials comparing second-line chemotherapy (docetaxel or irinotecan) plus best supportive care, versus best supportive care alone in patients with previously treated advanced gastric adenocarcinoma.<sup>32</sup> The addition of second-line chemotherapy to best supportive care was associated with a significant prolongation of overall survival relative to best supportive care alone (median overall survival was 5.1 months v 3.8 months) indicating a 37% reduction in the risk of death. The incidence of grade 3/4 adverse events was generally similar between treatment arms. These data confirm a previous phase III German trial that was discontinued early as a result of poor accrual, but which clearly demonstrated that patients with advanced gastric cancer benefited from second-line therapy if they had good performance status and were willing to undergo a second-line approach.<sup>33</sup> Table 1 summarises the results of potential second line options.

## Options after adjuvant chemotherapy

Recently, adjuvant chemotherapy has become a standard practice in T3 and/or node-positive gastric cancer after curative resection. Unfortunately, the majority of these patients will present with systemic disease in their follow-up. Rechallenge with cisplatin/ 5-FU if they relapsed >3 months after completing initial chemotherapy is one option addressed in a recent retrospective analysis. One hundred and six patients with oesophagogastric cancer were rechallenged with PF-based chemotherapy. The median progression-free survival and overall survival was 5.1 and 10 months respectively, for patients treated with radical intent previously.<sup>35</sup> This study demonstrated that selected patients with oesophagogastric cancer who relapse or progress >3 months after initial treatment with PF +/- epirubicin may benefit from re-introduction of PF-based



**Table 1:** Second line options after first line and after adjuvant chemotherapy failure.

Name of trial	Patient number	Treatment arms	Response rates	Survival	Gr 3-4 toxicities		
					N	D	HFS
Korean Trial <sup>32</sup>	243	Docetaxel or Irinotecan + BSC Versus BSC alone	- -	5.1 months Versus 3.8 months (P=.009) (HR – 0.63;95 % CI 0.47-0.86)	- -	- -	- -
AIO Study <sup>33</sup>	41	Irinotecan versus BSC	58% SD versus -	4 months versus 2.4 months (p=0.023) (HR=0.48; 95% CI 0.25-0.92)	10 % 0	20% 0	- -
PEP02 study <sup>34</sup>	135	Nano-Irinotecan versus Irinotecan versus Docetaxel	13.6% versus 6.8% versus 15.9%	- - -	9.1 % 13.6% 15.9%	27.3% 18.2% 2.3%	0% 6.8% 18.2%
RMH study <sup>35</sup> (retrospective)	106	Cisplatin +FU±E	-	Progression-free survival 5.1 months Overall survival 10 months	31 %	15%	-
RMH study <sup>36</sup> (phaseII)	29	Capecitabine+ Irinotecan	17%	Progression-free survival 3.1months (95% CI 2.2 – 4.1 months) Overall survival 6.5 months (95%CI 6-7.1 months)	-	-	-

Key:  
AIO - Arbeitsgemeinschaft Internistische Onkologie

SD - Stable disease  
BSC - best supportive care

chemotherapy. Similarly, in a smaller phase II study, 29 patients with oesophagogastric cancer were treated with capecitabine and irinotecan as second-line treatment after progressing on, or within three months of, platinum-based chemotherapy.<sup>36</sup> This study suggests that capecitabine and irinotecan has anti-tumour activity as second-line treatment for relapsed oesophagogastric cancer, and provides an important improvement in disease related symptoms. The second line options noted above could also be considered, in particular if relapse is within three months of adjuvant therapy. With increased perioperative ECF use, there is a need to design trials with new regimens and newer targeted drugs to give clinicians further options for this patient group.

## Conclusion

The majority of patients with oesophageal or gastric cancer will require palliative treatment at some point in the course of their disease. Cytotoxic chemotherapy can provide symptom palliation, improve quality of life and prolong survival in patients with advanced gastric cancer (including gastro-oesophageal junction), and potentially advanced oesophageal cancer although the evidence is not as robust. Despite a large number of randomised trials, there is no definite consensus as to the best agent or regimen. In general, combination chemotherapy regimens provide higher response rates than do single agents, but this translates into only modestly longer durations of disease control and survival that are measured in weeks to a few months. ECF and DCF combinations have emerged as standard regimens for first-

line treatment. A major problem with these regimens is the need for central venous access and an ambulatory infusion pump and toxicity of the third agent. Data from the REAL-2 trial suggest that outcomes are comparable if capecitabine is substituted for infusional 5-FU, and when oxaliplatin is substituted for cisplatin in the ECF regimen. The addition of a biological agent has led to a review of CF/CX as an appropriate chemotherapy backbone partly based on better tolerance, although thus far only the addition of trastuzumab has been shown to lead to a survival advantage. Importantly, there is mounting evidence that second line chemotherapy improves survival and as was seen in colorectal cancer, improvements in subsequent therapy options are likely to finally see the survival of advanced oesophagogastric cancer continue to improve. The future is likely to focus on improved targeted agents added to chemotherapy in both first and second line treatment; and some of these options are summarised in table 2.

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**Table 2:** Ongoing and future trials.

Trial name	Type	Eligibility	Treatment arms	Endpoints	Status
ATTAX-3 <sup>23</sup>	Phase II	advanced oesophago-gastric cancer	chemotherapy only (wTCF/X) chemotherapy plus panitumumab	objective tumour response rate	recruiting
LOGiC	Phase III	HER 2 positive advanced gastro-oesophageal cancer	CapOx v Capox+ Lapatinib	progression-free survival overall survival	recruiting
REAL-3	Phase III	previously untreated advanced oesophago-gastric cancer	epirubicin, oxaliplatin and capecitabine (EOX) ±Panitumumab	progression-free survival	recruiting
OXFORD-COG study	Phase III	recurrent oesophageal cancer after failure of 1st line chemotherapy	gefitinib v placebo	overall survival	recruiting
XP-Simvastatin study	Phase III	advanced gastric cancer	capecitabine+ cisplatin+ simvastatin	response rate progression-free survival overall survival	recruiting
PALIC-C study	Phase III	advanced gastro-oesophageal cancer	paclitaxel plus capecitabine with capecitabine maintenance	response rate survival	approved
RAD 001 study	Phase III	gastric carcinoma after prior chemotherapy	paclitaxel with and without RAD001	progression-free survival	not active

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## AUSTRALIAN PERSPECTIVE ON THE ROLE OF TARGETED THERAPIES IN GASTROESOPHAGEAL CANCER

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### Abstract

Oesophagogastric cancers are the fourth highest cause of cancer related deaths worldwide and the sixth most common cause of cancer related deaths in the Australian population. Their incidence has been increasing in Australia, and unlike other tumour types such as breast, there has been no significant improvement in relapse-free or overall survival rates, with five year mortality rates for gastric cancer of 25% and less than 20% for oesophageal cancers. This is partly due to patients commonly presenting with late stage disease, but significantly also due to ineffective chemotherapeutic regimens for advanced oesophagogastric cancer. However, with the promise shown by targeted therapies in other previously poor prognostic tumour streams, there is a demand for a similar application in the treatment of these tumours.

Within the Australian population, the current annual incidence for gastric cancer and oesophageal cancer is projected to be 2000 and 1400 new cases per year,<sup>1</sup> representing 1.9 and 1.2 percent of all cancers respectively.<sup>1</sup> These tumours are associated with high mortality, with projections approximately 1300 and 1100 deaths from oesophageal cancer and gastric cancer respectively, disproportionately contributing to 5.8% of all cancer related deaths in total.<sup>1</sup> The majority of cancers are either squamous cell carcinomas (SCC), occurring predominantly in the proximal and mid-third of the oesophagus and stable in incidence,<sup>2,3</sup> or adenocarcinomas,<sup>1-3</sup> which arise in the stomach and distal two thirds of the oesophagus, and which have shown a marked increase in incidence over time.

Current management of these tumours is generally poor due to a lack of well defined risk factors, non-specific symptoms and lack of biological markers, often resulting in patients presenting with regionally advanced or disseminated disease at diagnosis. Surgery is the mainstay of therapy for primary and locally advanced disease, but used alone demonstrates five-year survival rates of only

20-25%.<sup>4,5</sup> With the addition of neo-adjuvant or adjuvant chemoradiotherapy, there is some benefit with slightly improved five-year survival rates of 30-35%.<sup>6-9</sup> Treatment of metastatic disease is based on platinum based therapies with oral or intravenous fluoropyrimidine chemotherapeutic agents, with reported objective response rates of 20-50% and median overall survival universally less than 10 months.<sup>10-12</sup> However, the regimens are associated with significant toxicity, with patients reporting grade 3/4 neutropaenia and grade 3/4 diarrhoea in up to 82% and 20% of cases respectively when receiving combination of docetaxel, cisplatin, and 5-FU.<sup>11,12</sup>

Additional targets of therapy have been identified following recent advances in the molecular understanding of oncogenic pathways. These advances promise a shift from 'one treatment for all' regimens to more effective cures with minimal toxicities. Early evidence of this success is seen in HER-2 targeted treatment in breast cancer,<sup>13</sup> epidermal growth factor receptor (EGFR) inhibitors in lung cancers,<sup>14</sup> anti vascular endothelial growth factor (VEGF) therapy in renal cell carcinomas,<sup>2,15</sup> and BRAF targeted therapy in

melanoma.<sup>16</sup> The potential for the use of targeted therapies in the future treatment of these cancers is significant, with the main developments in oesophagogastric cancer focused on the use of monoclonal antibodies and small molecule-based therapies targeting signal transduction pathways, in particular EGFR, HER-2/Neu and soluble VEGF or its receptor. Within Australia, trials are currently underway in the use of panitumumab in combination with first line chemotherapeutic agents in the treatment of advanced oesophago-gastric cancers (the ATTAX-3 trial, ACTRN12609000109202).

## Targeted therapies

### Epidermal growth factor receptor

EGFR, or ErbB1, is a member of the ErbB transmembrane growth factor receptor family, which also includes ErbB2 (Her2/neu), ErbB3 and ErbB4.<sup>17</sup> Binding of the two known ligands, epidermal growth factor and transforming growth factor  $\alpha$  causes dimerisation of the receptor with any members of the ErbB family, leading to activation of the receptor's tyrosine kinase domain.<sup>18</sup> This family of receptors is a key modulator of cell cycle regulation, proliferation, survival, avoidance of apoptosis, migration and differentiation.<sup>17,18</sup>

Within oesophagogastric cancer, dysregulation of EGFR appears to be predominantly due to overexpression from gene amplification. It is detected either as increased cellular membrane staining of the protein by immunohistochemistry (IHC), or by in situ hybridisation (ISH), for the amplicon. EGFR overexpression is detected more so in SCC compared with adenocarcinoma and correlates with poorly differentiated histology, increased invasion and worse overall prognosis.<sup>19,20</sup> While there is considerable variation between studies and techniques for EGFR expression, almost all international and local studies to date have recruited patients without pretesting and following the dogma that EGFR overexpression is frequent in these tumours. Mutations of EGFR have also been identified but appear to be rare and are responsible for only a minority of the potentially treatable oesophagogastric cancer. These mutations are more commonly seen in oesophageal SCC (less than 14%)<sup>21</sup> than in adenocarcinomas (<11%).<sup>22-24</sup> The most common mutations included missense activating

mutations (G719A, S768I, L858R),<sup>21-24</sup> truncation mutations (E872 GAA-TAA),<sup>23</sup> the tyrosine kinase inhibitors (TKI) drug resistance associated T790M,<sup>22</sup> mutation and in-frame deletions (delE746-A750),<sup>22</sup> all of which have been previously characterised in non-small cell lung cancer.<sup>25-27</sup>

The development of anti-EGFR targeted therapy is well underway in several tumour streams and includes several monoclonal antibodies (cetuximab, panitumumab and matuzumab) and oral TKI (erlotinib, gefitinib). The current anti-EGFR monoclonal antibodies are partially or completely humanised IgG1 and IgG2 antibodies designed to bind EGFR and block ligand-mediated tyrosine kinase activity.<sup>28</sup> They also promote EGFR internalisation by endocytosis and may activate tumour specific immune-mediated mechanisms.<sup>29,30</sup> International trials have shown comparable response rates to other combined modality trials with relatively good toxicity.<sup>31,32</sup> Locally, the Australasian Gastrointestinal Trials Group ATTAX-3 trial, which has recently commenced recruitment, is comparing the use of docetaxel, cisplatin, fluoropyrimidine with or without panitumumab over a 24 week course for the treatment of locally recurrent or metastatic oesophagogastric cancer (table 1). The study aims to recruit 100 patients and examine for tumour response rates, overall survival, progression free survival and treatment related toxicity. The study will provide further guidelines to the use of EGFR targeted therapy for oesophagogastric cancer in Australia.

The future incorporation of EGFR based targeted therapies for oesophagogastric cancer brings with it several challenges, one of the most of which will be the management of innate or selective tumour resistance. Lessons learnt from recent studies in colorectal carcinoma have shown that acquired and innate tumour resistance through mutational activation of the K-ras protein present downstream of EGFR negates benefit from cetuximab or panitumumab.<sup>33,34</sup> Similarly, the V600E mutation of B-raf protein downstream of EGFR is also associated with a lack of response to cetuximab in colorectal carcinoma.<sup>35</sup> Currently, limited studies estimate that up to 2% of oesophageal and 6% of stomach cancers harbour the K-ras mutations and up to 11% of oesophageal and 1% of stomach cancers harbour the B-raf mutation.<sup>36</sup> The impact of these and

**Table 1:** Summary of Australian trials of targeted therapy of oesophagogastric cancers.

Trial		Recruitment status	Agents	Disease stage	Targeted sample size	Measured outcomes
ATTAX3	Randomised, Phase II	Closed	1st line - wTCF/X + panitumumab	Metastatic/ Widespread	100	Tumour response (as per Response Evaluation Criteria in Solid Tumours - RECIST v1.1), overall survival, progression-free survival, treatment related toxicity.
wTCF, docetaxel/cisplatin or capecitabine/fluoropyrimidine.						



similar mutations on EGFR-based treatments is unknown and prospective management of oesophagogastric cancer may require mutational testing or identification of responsive cohorts either at the initiation of treatment or if resistance occurs, development of combination therapies and improved efficacy of second generation agents.

### Her2/neu

The Her2/neu or ErbB2 tyrosine kinase is also a member of the ErbB growth factor receptor family, but unlike its other members, lacks an ectodomain for ligand binding.<sup>37</sup> Despite this, Her2 shares 64% homology with EGFR, with the most similar region located in its tyrosine kinase domain.<sup>38</sup> This allows heterodimeric partnering of Her2 with other family members, and within the potential combinations of homo and heterodimers that may be formed, it appears that each of the other receptors with their specific ligands prefer Her2 as their heterodimeric partner.<sup>39,40</sup> Furthermore, Her2 containing heterodimers are characterised by extremely high signalling potency, as Her2 reduces the rate of dissociation considerably, allowing more potent and prolonged activation of downstream pathways,<sup>40,41</sup> the most important appearing to involve mitogen activated protein kinase and phosphatidylinositol-3 kinase.<sup>42-44</sup> As with EGFR, Her2 activation can induce mitogenic mechanisms and progression through the cell cycle and inhibition of apoptosis.<sup>42,44</sup>

In oesophagogastric cancer, dysregulation of Her2 appears to be predominantly due to amplification and overexpression and is tested by IHC, ISH or a combination of both.<sup>45,46</sup> Clinically, in oesophageal SCC, Her2 overexpression detected by IHC correlates with extramural invasion, poor response to neoadjuvant chemotherapy and amplification detected by ISH is related to poorer survival rates.<sup>46,47</sup> In adenocarcinoma, study results have been mixed and less clear due to; a) differences in receptor testing based on IHC; b) fluorescent in situ hybridisation (FISH), silver in situ hybridisation (SISH) and chromogenic in situ hybridisation (CISH); c) use of different cut-offs to determine amplification and d) the distinction of true Her2 gene amplification and chromosome 17 polysomy. This has contributed to the wide range, between 9-34%, of reported Her2 positivity in adenocarcinomas.<sup>48,49</sup> There is also variable clinical correlation with some studies demonstrating association between Her2 amplification (defined by FISH and using a lower threshold of 4 or more signals per nucleus) and increasing tumour depth of invasion, lymph node and visceral metastasis and overall poor survival,<sup>50</sup> while others using a cut-off incorporating higher copy numbers have shown no relationship.<sup>51</sup>

Currently, Her2 targeted therapies incorporated and evaluated in treatment of oesophago-gastric cancers are the monoclonal antibodies trastuzumab and the TKI lapatinib. Formally approved in Australia for the treatment of HER2-positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease, trastuzumab is a humanised IgG1 monoclonal antibody designed to bind to the extracellular segment of the Her2 receptor. Binding of the antibody prevents receptor dimerization and activation, increases receptor endocytosis and destruction, triggers tumour specific

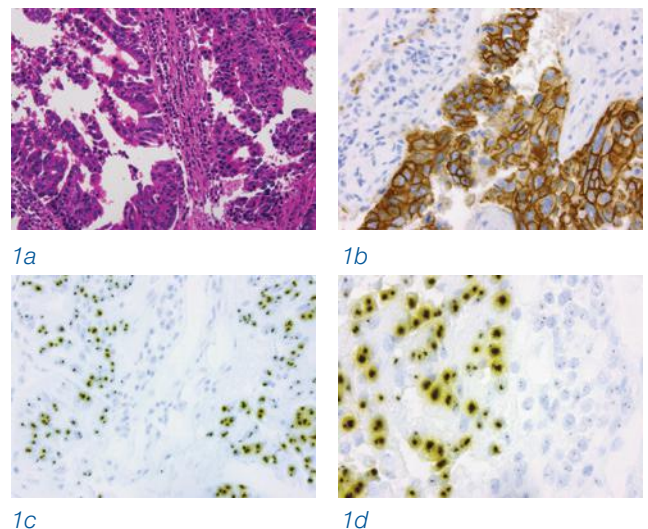
antibody dependent cytotoxicity and prevents proteolytic cleavage of Her2 from its extracellular domain, thus preventing anchor free activity.<sup>52</sup>

The evidence of Her2 directed clinical efficacy in gastric adenocarcinoma and gastro-oesophageal junction tumours comes from the recently completed multinational phase III ToGA randomised control trial comparing chemotherapy alone or in combination with trastuzumab.<sup>53</sup> Participants with histologically confirmed inoperable locally advanced, recurrent and metastatic Her2 positive gastric adenocarcinoma or gastro-oesophageal junction tumours were recruited to the study. As incorporated into current Australian Therapeutic Goods Administration guidelines, the ToGA study defined positive tumours if scoring 3+ on immunohistochemistry (defined as strong complete basolateral or lateral membranous staining in >10% of tumour cells in surgical specimens, or tumour cell clusters with a similar staining pattern in biopsy specimens irrespective of percentage) or if FISH demonstrated a Her2:CEP17 ratio > 2. The study showed an improvement in median overall survival (13.8 v 11.1 months; HR 0.74, 95% CI 0.060-0.91, p=0.0046) with no difference in rates of adverse cardiac or grades 3 or 4 adverse events between the two groups.

The Her2 TKI Lapatinib is also currently approved by the Australian Therapeutic Goods Administration for treatment of Her2 positive breast cancer, however to date it has only shown modest results as a first line treatment in patients with advanced gastric cancers with response rates <7%.<sup>54</sup> Further results from the phase III LOGiC trial, evaluating the combination of capecitabine/oxaliplatin +/- lapatinib as first line treatment of Her2 overexpressing advanced oesophago-gastric cancer therapy, are hoped to provide further direction in this area.

Current and future challenges in improving Her2 targeted therapy involve accurate identification of patients able to benefit from this treatment. While IHC and ISH based assays can theoretically identify tumours, (figure 1)

**Figure 1:** Her2 staining. 1a) Gastric adenocarcinoma, H&E x 200, 1b) IHC 3+ staining of gastric adenocarcinoma (DAB x 200), 1c) and 1d) Silver in situ hybridization staining of gastric adenocarcinoma showing high level amplification of Her2 (x200,x 400).





accuracy may be limited by tumour heterogeneity and lack of experience in the technical and interpretive aspects of molecular testing. Recently published as an abstract at American Society of Clinical Oncology meeting, the GaTHER study was performed to evaluate Her2 testing accuracy of gastric cancers in Australia.<sup>55</sup> The results demonstrated that when IHC is interpreted by appropriately trained histopathologists experienced in reviewing gastric cancers, IHC3+ samples do not need further testing and that ISH is needed to confirm amplification only in IHC 2+ tumours using current reporting protocols for breast cancers. ISH for IHC 0 and 1+ tumours was not required. The study and recommendations are currently being formulated and the forthcoming publication is hoped to provide further guidelines and standardisation for Her2 testing and assessment within Australia. Simultaneously, the Royal College of Pathologists has also initiated a quality assurance programme for Her2 testing of gastric carcinomas, further acknowledging the importance of accurate testing. Additional studies are also required to evaluate the benefit of treatment in early stage primary disease and tumours with low level amplification of Her2, which have been untested to date for efficacy to current targeted therapies.

### **Vascular endothelial growth factor**

VEGF is a potent vascular permeability and growth factor regulating normal and pathologic angiogenesis.<sup>56,57</sup> VEGF binds with several high affinity transmembrane receptors, the most notable being VEGF receptors types 1 (flt-1), and 2 (KDR, flk-1) with the main biological effects including endothelial cell mitogenesis and migration, induction of proteinases, extracellular matrix remodelling, increased vascular permeability and survival of newly formed blood vessels.<sup>56,58</sup>

Increased expression of VEGF has been measured in most tumours and patient serum, and biologically there is convincing evidence demonstrating the importance of angiogenesis with tumour growth and metastases.<sup>56,59</sup> Approximately 30-60% of patients with oesophagogastric cancer have overexpression of VEGF with relatively similar data in both SCC and adenocarcinoma showing increasing serum levels and tumour VEGF expression associated with progression from dysplasia, invasive carcinoma to metastatic disease.<sup>60-62</sup> There is also positive correlation with vascular invasion, nodal involvement, metastatic disease and worse overall survival.<sup>63-66</sup> While not examined in oesophago-gastric cancer, serum VEGF levels appear not to correlate with response to VEGF targeted therapies, possibly due to the limitation of current assays and further unknown complexities of angiogenesis and VEGF regulation.<sup>67</sup> Thus, trials to date have neither measured nor correlated VEGF with treatment decisions or outcome.

Currently, several targeted therapies have been developed for Australian Therapeutic Goods Administration approved use in other solid tumours. To date, most international phase II and III trials have evaluated the anti-VEGF humanised IgG1 monoclonal antibodies, bevacizumab, while the use of vascular endothelial growth factor receptor TKI sunitinib and sorafenib for oesophago-gastric cancer are early in development. Bevacizumab is thought to have

dual anti-tumour activity providing both anti-angiogenic effects and also possibly improving chemotherapeutic drug delivery.<sup>68,69</sup>

Due to expression of VEGF and vascular endothelial growth factor receptor in normal tissues, treatment is also associated with side-effects including hypertension, thromboembolism, proteinuria and haemorrhage.<sup>70-71</sup> Furthermore, due to reported fatal pulmonary haemorrhages in non-small-cell lung carcinoma with SCC histology, bevacizumab based trials have been limited to adenocarcinomas.<sup>70</sup> Trials to date have been encouraging and have shown improved overall survival and time to progression with similar toxicities to chemotherapy alone.<sup>73</sup> One encouraging phase II study has been led by Memorial Sloan-Kettering Cancer Centre, evaluating cisplatin/irinotecan with bevacizumab as a first-line treatment of advanced gastric and oesophagogastric junction adenocarcinomas in 47 patients.<sup>73</sup> The study reported significantly improved time to progression (8.3 months; 95% CI, 5.5 to 9.9 months) and overall survival (12.3 months; 95% CI, 11.3 to 17.2 months) compared with historic controls. Toxicity included a 6% incidence of gastric perforation or near perforation, 2% incidence of myocardial infarction, 2% rate of significant haemorrhage and 25.5% of grade 3/4 thromboembolic events, which were comparable to rates seen in patients receiving neoadjuvant cisplatin/irinotecan for advanced gastric cancer other studies.

A number of other phase 2 studies have shown benefit for the combination of chemotherapy with bevacizumab. These include trials using: oxaliplatin and docetaxel as the chemotherapy backbone (objective tumour response in 42% with median progression-free survival 6.6 months);<sup>74</sup> docetaxel, irinotecan and cisplatin (63% response rate);<sup>75</sup> and single agent docetaxel, which shows response in about one quarter of patients.<sup>76-77</sup>

Despite encouraging outcomes from these phase 2 studies, the phase 3 study AVAGAST did not meet its primary endpoint of improved overall survival.<sup>78</sup> This trial, a randomised, double blind, placebo controlled study of 774 patients, evaluated the use of cisplatin and capecitabine with either bevacizumab or placebo in the first line metastatic setting. Although there was no overall survival benefit, there was a significant improvement in progression free survival and overall response rate. The results from the AVAGAST trial also demonstrated a trend towards an overall survival benefit with the use of bevacizumab that was not statistically significant (overall survival 12.1 v 10.1 months,  $p = 0.1002$ ). There was a 1.4 month increase in progression free survival with bevacizumab use (5.3 v 6.7 months,  $p = 0.0037$ ) and statistically significant improvement in overall response rate (46 v 37%,  $p=0.0315$ ). The study did find a higher rate of haemorrhage in the group receiving bevacizumab, although this was largely grade 1 bleeding not requiring intervention. Interestingly, the rate of arterial and venous thromboembolism was similar across both treatment arms.

Of note, subgroup analysis did show regional variation in overall survival both with and without the use of bevacizumab in addition to chemotherapy. The greatest benefit was seen in those patients in the Americas who

demonstrated an overall survival hazard ratio of 0.63 with the use of bevacizumab combined with chemotherapy. In contrast, the Asian population in the study had a hazard ratio of 0.97 with the addition of an antiangiogenic agent, and essentially derived no benefit from this combination. There was also a similar trend noted for progression free survival. A number of reasons for this discrepancy have been postulated, including genetic variations in these populations, or practice differences in the approach to metastatic gastric cancer and patient selection in different geographical regions. Further evaluation of patient characteristics in the AVAGAST study compared to pooled data from patients in the United States receiving chemotherapy and bevacizumab for metastatic oesophagogastric cancer shows a significant difference in tumour location, histology and extent of disease.<sup>79</sup> Preplanned biomarker studies are ongoing to determine if there may be an identifiable subpopulation that might show benefit from the addition of bevacizumab to cytotoxic chemotherapy.

Although there would appear to be a sound biological rationale for the use of VEGF inhibitors in the setting of metastatic oesophagogastric cancer, there is currently no definitive evidence suggesting a benefit for the addition of bevacizumab to standard chemotherapy. Further research in this area may reveal a population for whom this is a beneficial addition, but the characteristics of this group are yet to be elucidated. Bevacizumab currently remains a prospect for further evaluation rather than an option for standard management of patients with metastatic gastric cancer.

## Conclusion

Despite a marginal improvement in the treatment of oesophagogastric cancers, management options for locally advanced and metastatic disease are still limited with poor overall survival. Recent advances in the use of targeted therapies have been promising, with an expanding body of both international and local experience, representing a significant shift from a 'one treatment for all' to a more tailored approach built on improving our molecular understanding of the oncogenic process.

While the survival benefits seen are significant, they are still modest and measured in months. Several challenges remain however, including the improved identification of patients most suitable for particular therapies, which is dependent on identifying and standardising the best tests for specific therapies. As with any other therapy, there will also be challenges pertaining to treatment toxicity and acquired resistance, which may be minimised with more specific biological targets identified and improved second and third generation therapies.

In the next few years, many of the current international and local trials are expected to provide further guidance in the treatment of oesophagogastric cancers. It is hoped that the initial promise will eventually lead to a wider armamentarium of target specific treatments that may be used in combination with conventional chemotherapy drugs and radiotherapy tailored specifically to the genetic profile of these tumours, with high efficacy and minimal toxicity.

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## ROLE OF RADIOTHERAPY IN OPERABLE OESOPHAGEAL CANCER

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### Abstract

External beam radiotherapy with concurrent chemotherapy has been established as one of the primary curative treatment modalities for oesophageal cancer. Technological improvements in imaging have allowed more appropriate selection of patients for curative radiotherapy. An evolving role of preoperative chemo-radiation therapy prior to surgery is being established, with more routine use in the management of operable oesophageal cancer. This article will review the current clinical approach to radiation therapy treatment of operable oesophageal cancer.

Oesophageal cancers occur throughout the oesophagus, within the cervical region beginning below the cricopharyngeal muscle and throughout the thoracic oesophagus. Gastro-oesophageal junction tumours have been included in trials treating both oesophageal cancers and gastric cancer. The most common histological subtypes are squamous cell carcinomas (SCC) and adenocarcinomas, with the former typically occurring in the upper oesophagus and the latter in the lower oesophagus. Despite the different histology, both cancers share a fairly poor five year survival rate of approximately less than 50% once the muscularis propria is involved, and less than 40% in node positive disease.

Recently the American Joint Committee on Cancer published the Cancer Staging Manual (7<sup>th</sup> edition), with a revision of the TNM staging of oesophageal cancers, differentiating the staging of SCC from adenocarcinomas.<sup>1</sup> The main changes included the sub-classification of T4 disease into operable and inoperable groups, the N stage based on the number of lymph nodes involved from cervical to celiac axis and the M stage based on distant metastases alone. Histological grade is now included in adenocarcinomas, and the staging of adenocarcinomas involving the proximal 5cm of gastric cardia and invading into the gastro-oesophageal junction (eg. Siewert III) are similarly staged as adenocarcinomas of the oesophagus. These changes reflect the changing treatment paradigm of oesophageal cancers.

The main primary curative treatment used for cervical and upper thoracic oesophageal cancers is chemo-radiation therapy, with surgery for cervical oesophageal cancers typically requiring a laryngopharyngoesophagectomy, however for lower thoracic oesophageal cancers multiple approaches to treatment are currently used in clinical practice including surgery alone, chemo-radiation therapy, preoperative chemotherapy and preoperative chemo-radiation therapy.

For early operable oesophageal cancers (eg. T1/2 N0), the main treatment modality used is surgery alone, with five year survival typically >60% at five years.<sup>1</sup> For patients with inoperable T1 or T2, node negative cancers, chemo-radiation therapy or radiation therapy alone can also be used curatively with reasonable survival rates at five years of 30-70%.<sup>2-5</sup> For more advanced disease (>T3N0) where survival rates are typically <30% at five years, chemo-radiation therapy has a definite role in the curative treatment. The following discussion in the rest of this article relates to these locally advanced operable cancers.

### Definitive radiation therapy for operable oesophageal cancer

The role of radiation therapy in oesophageal cancer has been evolving since the 1980s. In 1985, the Radiation Therapy Oncology Group 85-01 trial randomised patients to radical radiation therapy alone compared to concurrent chemo-radiation therapy (chemo-radiation therapy).<sup>6</sup> This established superior outcomes of chemo-radiation therapy over radiation therapy alone. Despite the chemo-radiation therapy arm using a lower total dose of radiation (ie. 50 Gy in 25 treatment fractions versus 64 Gy in 32 treatment fractions) there was an improved overall survival at five years of 26% and 0% for chemo-radiation therapy and radiation therapy respectively. No statistical significant differences ( $p=0.15$ ) in survival based on histology were reported after chemo-radiation therapy at five years. The benefits of chemo-radiation therapy included reduced rates of distant metastases as first site of failure (30% for radiation therapy v 16% for chemo-radiation therapy) and reduced risk of local failure (65% for radiation therapy and 46% for chemo-radiation therapy).

Although, theoretically, the use of higher doses of radiation therapy in combination with chemotherapy should improve the chance of tumour cure, the Intergroup 0123 randomised control trial showed no improvement in local control or survival when escalating radiation therapy dose to 64.4 Gy,

as compared to 50.4 Gy with cisplatin and 5-fluorouracil (5-FU) based chemo-radiation therapy.<sup>7</sup> More toxicity was observed when using higher radiotherapy doses, with 10% treatment-related deaths being observed on the high dose arms as compared to 2% on the lower dose arm. Similarly, in the cervical oesophagus a relatively large retrospective study from Canada has shown no improvements in survival when comparing radiotherapy to 70 Gy in 2 Gy fractions with high dose cisplatin, compared to lower dose radiotherapy 54 Gy in 2 Gy fractions with 5-FU and mitomycin C or cisplatin.<sup>8</sup> Location of first site of failure was loco-regional in 71% and the reported local relapse-free survival rates at two years were similar (48% v 46%). The five year survival of patients treated curatively was 28%. Currently, radiation therapy doses in the range of 50 to 66 Gy are used to treat cervical oesophagus SCC, however 50 Gy is used throughout the thoracic oesophagus due to dose limiting toxicity.

The role of histology in differentiating best treatment approaches is less clear from the published literature. In a series of 1059 surgically resected oesophageal cancers, Siewert et al analysed potential prognostic factors.<sup>9</sup> In addition to surgical margin resection status and TNM staging, the histology of adenocarcinomas was associated with a better prognosis following surgery. This translated to an overall survival of resected adenocarcinomas and SCC at five years of 42% and 30% respectively. However, adenocarcinomas more commonly occur in the distal oesophagus compared to SCC occurring usually in the mid to upper oesophagus. Cancers in the mid and upper oesophagus typically are situated closer to critical vascular and other normal structures, making surgery technically more difficult. A recent SEER database review on 4752 patients with oesophageal cancer has not shown adenocarcinomas to be a significant predictor for outcome, and this is in keeping with the randomised trials of radiation therapy for treatment of oesophageal cancer discussed previously.<sup>6,10</sup> Comparing adenocarcinomas and SCC, the respective five year survival for patients treated with radiation therapy alone were 18% and 18%, for preoperative radiation therapy 34% and 33%, for surgery alone 14% and 13%. This indicates that histological subtype does not predict for poorer response to radiation therapy and that it should not necessarily influence the decision on the most appropriate treatment modality a patient should receive. Therefore, factors such as risk of morbidity and the technical feasibility of treatment are the most important factors when considering patients for surgery and/or radiation therapy.

Currently the relatively high loco-regional failure rates with chemo-radiation therapy alone, of approximately 50%, remain suboptimal, particularly given the lack of impact higher doses of radiation have so far provided. This has led to increasing consideration of multimodality treatment approaches in operable oesophageal cancers.

### Preoperative radiotherapy

Preoperative radiation therapy alone (without chemotherapy) has had minimal impact on improving outcomes of patients with operable oesophageal cancer. A Cochrane review of 1147 patients' individual data from five randomised trials has shown that there is potentially a small (4% at five years) non-statistically significant benefit

( $p=0.06$ ) of the use of preoperative radiotherapy.<sup>11</sup> Eighty-nine percent of these patients analysed had SCC of the oesophagus. Radiotherapy doses ranged from 20 Gy in 10 fractions to 40 Gy in 10 fractions.

The use of preoperative chemo-radiation therapy has been gaining more favour recently. Individually, randomised control trials have been fairly small and inconsistently showing if there were benefits of the addition of chemo-radiation therapy to surgery.<sup>12-19</sup> In 2004, a meta-analysis of six randomised control trials showed a potential benefit of preoperative chemo-radiation therapy by improving survival at three years.<sup>20</sup> The odds ratio for survival at three years was 0.53 [95% CI 0.31-0.93], however this was at the expense of increased postoperative mortality with an odds ratio of 2.1 [95% CI 1.18-3.73]. This survival benefit was more pronounced and statistically significant in adenocarcinomas than SCC. A more recent meta-analysis has analysed both the potential benefits of preoperative chemotherapy and chemo-radiation therapy.<sup>21,22</sup> In this analysis by the Australasian Gastro-Intestinal Trials Group, 12 preoperative chemo-radiation therapy and nine preoperative chemotherapy trials were analysed, including another two trials comparing preoperative chemo-radiation therapy to chemotherapy. In total, 4188 patients with oesophageal or oesophagogastric junction carcinoma were included. Typical prescribed radiotherapy doses in the trials reported ranged from 20 Gy in 10 fractions, up to 50.4 Gy in 28 fractions, all combined a platinum compound, usually cisplatin and commonly 5-FU chemotherapy. A significant benefit in survival was seen by the addition of preoperative chemotherapy and chemo-radiation therapy. The benefit for SCC and adenocarcinomas was similar for the addition of chemo-radiation therapy (hazard ratio 0.78 [0.70-0.88] and 0.80 [0.68-0.93] respectively). Additionally, the use of preoperative chemo-radiation therapy may potentially have a larger benefit than chemotherapy alone (hazard ratio 0.88 [0.76-1.01]  $p=0.07$ ) and the 30 day perioperative mortality was not associated with the use of neoadjuvant treatment. From trials comparing preoperative chemo-radiation therapy and surgery alone, the median 30 day perioperative mortality rate was 6.9% [range 0%-17.2%] and 3.8% (range 0%-18.8%) respectively. For the trials comparing preoperative chemotherapy and surgery alone, these respective values were 6.8% [range 2.1% - 14.7%] and 5.6% [range 0%-10.0%]. The comparison of preoperative chemo-radiation therapy and chemotherapy were indirect and therefore prone to bias, however it does indicate a potential benefit for preoperative chemo-radiation therapy and the need for further randomised trials.

The optimum radiation dose in preoperative chemo-radiation therapy is not established. Concerns about using higher doses of radiation therapy relate to the potential increased risks of post-operative complications including anastomotic leaks. A recent randomised trial reported by Tepper et al, has not shown a significant increased morbidity with higher dose (50.4 Gy) radiation therapy.<sup>19</sup> An 8% v 0% anastomotic leak rate was reported for the preoperative chemo-radiation therapy arm compared to the surgery alone arm. A similar randomised trial by Urba et al, using a preoperative chemo-radiation therapy dose of 45 Gy reported an anastomotic leak rate of 15% v 8% for the chemo-radiation therapy arm



compared to surgery alone arm.<sup>16</sup> Burmeister et al reported on a randomised control trial performed within Australia using a dose of 35 Gy with a 5% anastomotic leak rate for both the preoperative chemo-radiation therapy arms and surgery arms.<sup>23</sup> Further research is required to determine the optimum radiation dose, however use of higher doses of radiation therapy offers patients a potentially curative treatment if they are unable to proceed to surgery due to a reduction in physical fitness or technical feasibility (eg. radiologically occult inoperable non metastatic disease).

Selecting which patients require trimodality surgery over definitive chemo-radiation therapy alone is unclear. The majority of evidence for preoperative chemo-radiation therapy is based on trials comparing the outcomes to a surgery alone arm. In a recent randomised control trial (FFCD 9102) there was an indication that not every patient requires trimodality therapy over chemo-radiation therapy alone.<sup>24</sup> In this trial, 444 patients were treated with two cycles of 5-FU and cisplatin, with concurrent radiotherapy of 46 Gy over four and a half weeks or two 15 Gy courses delivered over five days starting at day one and day 22 with chemotherapy. Patients who responded to treatment were then randomly assigned to further surgical resection or radiotherapy of either another 20 Gy over two weeks or 15 Gy over one week. With 250 patients randomly assigned to treatment, the two year local control rate for the surgical arm was 66% and 57% for the chemo-radiation therapy alone arms and the two year survival was 34% and 40% respectively. Additionally, the three month mortality rates were 9.3% compared to 0.8%. This reached the trial's criteria that there was a less than 95% chance that the two year survival for the chemo-radiation therapy alone arm was 10% worse than the surgery alone arms. Similar results have been reported in another randomised control trial of 172 patients treated with three cycles of induction chemotherapy followed by chemo-radiation therapy alone (65 Gy) or chemo-radiation therapy (40 Gy) and surgery.<sup>25</sup> Freedom from local progression was similarly lower in the arm with surgery as compared to chemo-radiation therapy alone arm (64% v 41%,  $p=0.003$ ). The overall survival at two years was better for the surgery alone arm (40% v 35%  $p=0.007$ ), however no statistically significant benefit was reported for patients who were responding to chemotherapy (survival at three years of 58% v 55%). These trials indicate that it may be possible to select patients who will benefit from multimodality preoperative chemo-radiation therapy and surgery based on treatment response. Use of other imaging modalities such F-18 flurodeoxyglucose (FDG) PET scans may provide a better assessment of cancer response to treatment and predict for better outcomes from chemo-radiation therapy alone. In a recently reported single institution study, patients treated with definitive chemo-radiation therapy (50.4 Gy) had a PET scan before and after chemo-radiation therapy and also before surgical resection performed in 54% of the patients.<sup>26</sup> Median survival for patients treated with chemo-radiation therapy and surgery was 23.1 months (significantly better than chemo-radiation therapy alone arm of 13.9 months,  $p<0.01$ ). Although PET complete response (31% of patients) did not predict for a better outcome in patients receiving surgery, it did predict for the chemo-radiation therapy alone arm with a median survival of 38 months v 11 months ( $P<0.01$ ). As an imaging modality, FDG PET is the most

reliable predictor of pathologic response to treatment and determinant of prognosis.<sup>27,28</sup> Further investigation of the role and utility of FDG PET as both a predictive and prognostic factor post treatment is being performed by Australian and international groups. This recent paper along with other reported studies provide an area of ongoing evolution towards optimising individualised treatment of patients with oesophageal cancer.

The growing literature on preoperative chemo-radiation therapy has resulted in a growing adoption of trimodality treatment in oesophageal cancer throughout the world. Selection of patients appropriate to this treatment approach should be performed within a multidisciplinary setting to ensure adequate patient fitness, surgical operability and the appropriate sequencing and timing of treatment.

### Post-operative radiation therapy

Adjuvant radiation therapy or chemo-radiation therapy have a role in the treatment of oesophageal cancers. A few randomised control trials have shown that radiation therapy can reduce the local recurrence risk of patients with operable oesophageal cancer, however this has not translated into a survival benefit.<sup>29,30</sup> The main benefit is mostly limited to patients with positive margins, reducing the local recurrence rate from 35-46% for surgery alone to 10-20% with adjuvant radiotherapy doses of 45 to 55 Gy. For gastro-oesophageal junction cancers, the gastric adjuvant chemo-radiation therapy study published by MacDonald et al showed both a survival and local control benefit with the addition of chemo-radiation therapy.<sup>31</sup> In this study, using adjuvant 5-FU-based chemo-radiation therapy to a dose of 45 Gy, approximately 20% of patients had adenocarcinomas involving the gastro-oesophageal junction. A 10% absolute benefit in overall survival and reduced local recurrence rate was reported at three years for the radiotherapy arm (50% v 41% and 19% v 29%, respectively). These results must be interpreted with caution and not extrapolated for all oesophageal adenocarcinomas due to the differences in prognosis and outcomes. Adjuvant chemo-radiation therapy treatment volumes are also typically large for the gastro-oesophageal junction tumours, as the oesophago-gastric anastomosis (commonly located in the mid to upper thorax) and the regional draining gastric lymph nodes need to be covered. Based on the current literature, gastro-oesophageal junction tumours can be treated with adjuvant 5-FU-based chemo-radiation therapy for stage IB or higher disease. Radiation therapy or chemo-radiation therapy can be used to improve local control for oesophageal cancers and the doses typically used are similar to definitive doses of chemo-radiation therapy therefore can be considered for patients with gross residual oesophageal cancer if the patient is appropriately fit for treatment and it is technically feasible to deliver the radiation therapy dose.

### Conclusions and future directions

Improvements in understanding of the molecular changes of oesophageal cancer will eventually allow improvements in individualisation of treatment of operable oesophageal cancer. Currently, multiple treatment approaches are available for treating operable oesophageal cancer including surgery alone, preoperative chemotherapy or chemo-

radiation therapy and definitive chemo-radiation therapy alone. The evidence is mounting that neoadjuvant therapies including chemo-radiation therapy can improve the cure rate for locally advanced operable oesophago-gastric cancers and should be considered in the current treatment paradigm of oesophago-gastric cancers. Use of molecular targeted agents may improve outcomes of patients with operable oesophageal cancer and the integration of these is currently being investigated. The current Australian led clinical trials for operable oesophageal cancers include a randomised trial comparing three cycles of preoperative epirubicin, cisplatin and 5-FU alone, or two cycles of the same chemotherapy in addition to preoperative 5-FU based chemo-radiation therapy for operable gastric and gastro-oesophageal junction cancers (TOPGEAR), and a randomised phase II trial of preoperative cisplatin, 5-FU with or without docetaxel and/or radiotherapy depending on early FDG PET response to chemotherapy for operable oesophageal or gastro-oesophageal junction cancers. These studies will help to clarify key areas of controversy in the management of gastro-oesophageal cancers.

The current approach to treating oesophageal cancer is predominantly based on the technical suitability of a patient to surgery, chemo-radiation therapy or preoperative chemo-radiation therapy. This requires a multidisciplinary assessment and discussion on the suitability of each approach. Typically oesophageal cancer in the lower third is technically easier to resect than those in the upper two thirds of the oesophagus and may determine the suitability for surgical resection. The use of functional imaging (eg. pre and post treatment FDG PET) may facilitate the determination of the optimal treatment strategy for patients with operable oesophago-gastric cancers.

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## BIOMARKERS IN OESOPHAGOGASTRIC CANCERS

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### Abstract

There is global recognition that there is an increasing need to generate predictive and prognostic biomarkers in various malignancies. Personalised medicine is progressing in certain streams of medical oncology yet remains an elusive goal in oesophagogastric cancer. This article reviews the role of F-18 fludeoxyglucose PET and various molecular methodologies in exploring potential biomarkers in the management of oesophageal and gastro-oesophageal cancers.

Biomarkers are defined as objectively measurable parameters that predict a biological state or behaviour, such as response to treatment. A prognostic biomarker is a term used to describe the likely course of disease in any one individual. This historically meant an individual who had not been treated before but this definition is increasingly complicated by the use of post-operative therapies, which alter the course of disease. Predictive biomarkers are defined as markers that can identify subpopulations of patients that are likely to respond to a given treatment. This allows for a tailoring of treatment as a specific treatment regimen is chosen for any one individual, as they are more likely to respond to it than the alternatives. Biomarkers are sought in pathology specimens, in blood collected from the affected patient and even using radiological investigations, to document changes that may predict a patient's progress.

Biomarker research has developed in an attempt to shorten clinical trial duration, but also to provide endpoints that have a biologic relevance to the clinical intervention under study. A pathologic biomarker that is often used as a surrogate endpoint in induction therapy trial design is the "percent pathologic response" in the resected primary tumour after induction therapy has been given. A major histological response to pre-operative chemotherapy or chemoradiotherapy ( $\leq 10\%$  residual tumour with the remainder of the lesion replaced by fibrosis including pathological complete response) has been shown to be an independent prognostic factor.<sup>1</sup> Several studies have shown no significant difference in survival between patients with a pathological complete response or  $<10\%$  residual tumour.<sup>2,3</sup>

In this article, we will review the current status of biomarkers in oesophagogastric cancer, reporting on the evidence to date in oesophageal adenocarcinoma and gastro-oesophageal carcinoma.

### PET as a biomarker in operable oesophagogastric cancers

There is a considerable body of PET data concerning oesophageal adenocarcinoma, particularly regarding tumours in the gastro-oesophageal junction. The only biomarker that has undergone significant investigation is F-18 fluorodeoxyglucose (FDG) PET.

FDG PET as a prognostic biomarker in the untreated patient reflects the intrinsic biology of the patient's cancer and is best examined in patients who have no induction therapy but proceed directly to surgery, because of the absence of confounding interventions. Patients with 'early stage' disease are the ones most likely to benefit from such an approach. Early stage oesophageal cancer has been defined as T1-2 N0 M0. The stage can only be truly confirmed pathologically, but defining the stage on a resected specimen prohibits the patient from potentially benefiting from an induction therapy approach followed by surgery. Rizk et al examined the utility of FDG PET in patients with surgically resected early-stage oesophageal cancer without induction therapy.<sup>4</sup> In this analysis of 50 patients, a median standardised uptake value (SUV) of FDG by the tumour (SUV=4.5) was arbitrarily selected to stratify patients as high or low risk. Those patients with a higher than median SUV<sub>max</sub> had a statistically significantly shorter three year survival of 57% compared to the 95% seen in those patients with a lower than median SUV. The patients with a low SUV ( $<4.5$ ) had a 90% chance of having a T1-2 tumour (24/25) compared to 60% (15/25) in the high SUV group. The incidence of an involved N1 or M1a node was 8% (2/25) in the low SUV group but was 48% (12/25) in the high SUV group. In the 32 patients who were classified pathologically as early stage disease (T1-2N0M0), 22/32 (69%) were in the low SUV group and 10 (31%) were in the highmax SUV group. In the 32 with pathologic T1-2N0 M0 disease, low SUV ( $<4.5$ ) had a significantly better survival ( $p=0.023$ ). The implications of this data are that patients with a high SUV should be considered at high risk of recurrence and death. This allows for further preoperative risk stratification beyond the traditional TNM staging and may allow for a more tailored approach to subsequent treatment.

### Oesophageal cancer and early FDG PET response

While histological response is a reasonable surrogate for survival in oesophageal adenocarcinoma, this end-point is obtained after the completion of the selected pre-operative therapy and surgery. Thus, non-responders to pre-operative therapy are only identified when the options to change therapy are limited and can only be given post-operatively. Given only 50-60% of patients are fit for post-operative chemotherapy,<sup>5</sup> this option has limited value. The prospective

**Table 1:** Summary of Australian trials of targeted therapy of oesophagogastric cancers.

Marker	Function	Potential biomarker role
VEGF	Involved in development and maintenance of a vascular network that may facilitate tumour growth and metastasis.	Higher VEGF index in gastro-oesophageal cancer correlates with poorer histopathological response to neoadjuvant chemoradiotherapy; <sup>2</sup> polymorphism VEGF 936C>T correlated with median disease-free survival and combined with PET scans was independent prognostic factor for clinical and histopathological response. <sup>12</sup>
COX-213-16	Rate-limiting enzymic conversion of arachidonic acid to prostaglandins, is induced by cytokines, growth factors and oncoproteins, and regulates tumour onset and progression, metastases, angiogenesis and resistance to chemotherapy. <sup>17</sup>	mRNA levels proportionate through sequence from Barrett's metaplasia to dysplasia to oesophageal adenocarcinoma; <sup>18-21</sup> higher levels associated with greater resistance to apoptosis; <sup>22</sup> high intratumoural mRNA and protein levels in oesophageal cancer (40% oesophageal adenocarcinoma) were associated with less response to neoadjuvant chemoradiotherapy. <sup>23</sup>
p53	Involved in cell cycle regulation, apoptosis and DNA repair.	Increased in progression toward oesophageal adenocarcinoma and oral squamous cell carcinoma; mutations in 40-50% oesophageal adenocarcinoma; <sup>12,24</sup> correlates with low rates of pathological complete response and worse disease-free survival and overall survival, <sup>26</sup> with after neoadjuvant chemoradiotherapy; others failed to show gene or protein levels reflecting response rates. <sup>27-30</sup>
Survivin	Plays a central role in (dys)-regulation of apoptosis; survivin has also been implicated in cell-cycle regulation and tumour angiogenesis. <sup>31</sup>	mRNA levels proportionate through sequence from Barrett's metaplasia to dysplasia to oesophageal adenocarcinoma; <sup>32</sup> levels reduced after neoadjuvant chemoradiotherapy and failure to do so was associated with worse prognosis and only minor histopathological response. <sup>33,34</sup>
NF-κβ	Sequence specific transcription factor acting as gatekeeper for cell survival, proliferation, invasion and metastasis.	Associated with aggressive pathological features when overexpressed like perineural and lymphovascular invasion, metastases <sup>35</sup> ; absence of expression associated with response to neoadjuvant chemoradiotherapy. <sup>36,37</sup>
HIF-1α	A transcription factor linked to genes involved in response to cellular hypoxia including vasculogenesis and angiogenesis, metabolism, vasodilation, cell migration, signalling and cell fate decisions.	Correlated with tumour aggressiveness and prognosis in oral squamous cell carcinoma in far eastern population <sup>38-40</sup> ; not confirmed in European population.

Key: VEGF – vascular endothelial growth factor; COX-2 – cyclo-oxygenase 2; NF-κβ – nuclear factor κβ; HIF-1α – hypoxia-inducible factor 1α.

study by Ott et al demonstrated that a ≥35% reduction in pre-treatment primary tumour SUVmax found on a second FDG PET scan on day 14 ('early metabolic response') and after the first cycle of paclitaxel, cisplatin and 5-Fluorouracil (5-FU) chemotherapy (21/56 patients received CF alone), could predict response to neoadjuvant chemotherapy and survival after resection.<sup>6</sup> All patients in the study went on to receive another two cycles of chemotherapy without radiotherapy. Early metabolic response was associated with a major histological response in 44% of patients compared with 5% for non-responders. Similarly, an early metabolic response to therapy was an independent prognostic factor for progression-free survival (PFS).<sup>6</sup> Subsequently, Lordick et al reported the only clinical study that has modified

therapy based on an early metabolic response.<sup>7</sup> The MUNICON trial studied 110 patients with oesophageal adenocarcinoma. Patients that showed an early metabolic response to the first cycle of pre-operative chemotherapy then received a further five cycles of therapy then resection with two-year survival of 75%. Metabolic non-responders on the day 14 PET scan received no further chemotherapy and went directly to surgery resulting in a two-year survival of 60% and no histological responses. MUNICON II added radiotherapy to these non-responders, using the same chemotherapy regimen.<sup>8</sup> The result was improved response rates. However, survival rates remained poor, suggesting that FDG PET has utility as a prognostic marker, but in this circumstance was a poor predictive marker.



Rizk et al reported the Memorial Sloan-Kettering Cancer Centre experience of the efficacy of a baseline FDG PET to predict response and survival in patients with gastro-oesophageal cancer undergoing chemoradiotherapy induction.<sup>9</sup> They found that although there was no difference in survival, the patients with the higher baseline SUV had higher response rates on the post-induction specimen. The finding that a high SUV at baseline predicts for pathological response rates was independently confirmed by Lordick.<sup>7</sup> The interpretation made by Rizk et al was that the patients with a low initial baseline SUV had an inherently better survival from a biological perspective, which was not altered by the addition of induction therapy.<sup>9</sup> The patients with the higher SUV initially had a worse prognosis that was improved significantly by the addition of induction therapy. Rizk et al suggests that the FDG PET can predict those high risk patients who are most likely to benefit most from induction therapy.<sup>9</sup>

The above data suggests FDG PET, when performed with due consideration of the underlying principles, including imaging on the same camera, reconstructing the data with a consistent algorithm and using a consistent time post-injection provides prognostically significant data worthy of consideration as a valid biomarker in oesophageal cancer. In Australia, the DOCTOR trial is exploring the role of adjuvant chemotherapy +/- radiotherapy based on a poor early response to neoadjuvant chemotherapy.<sup>10</sup>

## Molecular approaches for improving our understanding of oesophagogastric cancers

Research studies aimed at identifying prognostic biomarkers in oesophagogastric cancers have generally used a candidate gene or marker approach in the tumour in order to determine whether an association exists with survival, American Joint Committee on Cancer stage or response to chemotherapy or chemoradiotherapy (reviewed in Lagarde, 2007).<sup>11</sup> Although there are potential biomarkers and many demonstrate prognostic value, subsequent replication of these findings is lacking (table 1). Since several molecular alterations can act together to influence tumorigenesis, it is unlikely that a single biomarker alone can accurately predict survival. The following are various methods exploring the evidence for predictive biomarkers in oesophageal adenocarcinoma.

### Gene expression profiling

Gene expression profiling is the measurement of gene expression in a given sample, often thousands at once, to give a snapshot of cellular function. In this way, it is hoped that an individual tumour can be characterised to better target investigation of biological pathways and ultimately, facilitate drug design. This has been demonstrated in breast cancer with some signatures predicting survival and response to chemotherapy.<sup>41-43</sup> It is less well advanced in oesophagogastric cancers.

A number of studies have explored the use of mRNA expression profiling to predict survival and/or treatment response in individual oesophageal adenocarcinoma patients, with conflicting results. Real time pathological complete response on 38 pre-treatment endoscopic biopsy sections focused on expression of 5-FU, platinum and taxane related genes and found that high expression levels of MTHFR,

CALD1 and MRP1 are related to response and survival.<sup>44</sup> Langer et al have since shown that high pre-treatment levels of MRP1 and TS in oesophageal adenocarcinoma, are associated with a poor response to chemotherapy.<sup>45</sup> Chemotherapy response was also investigated in a cohort of 47 patients with oesophageal adenocarcinoma in which 86 genes were differentially expressed between responders to neoadjuvant chemoradiotherapy and non-responders.<sup>46</sup> The authors showed a significant correlation between the Ephrin B3 receptor and response, but these results are yet to be externally validated. This tyrosine kinase receptor has a role in morphogenesis, tumorigenesis and metastatic potential, angiogenesis and tumour vasculature in the gastrointestinal tract.<sup>47</sup> Similarly, Schneider et al showed that DPD, ERCC1, TS, GSPi, HER2 and EGFR mRNA expression was downregulated in response to neoadjuvant chemoradiotherapy for oesophageal cancer.<sup>48</sup>

Luthra et al reported on an oligonucleotide microarray performed on pre-treatment endoscopic biopsies from 19 patients (16 adenocarcinoma, two SCC, one adenosquamous) prior to trimodal therapy.<sup>48</sup> Unsupervised clustering was used to identify associations in the microarray according to response, however no statistically significant associations with gene expression were identified. This may be due to the underlying assumption of the unsupervised clustering method which assumes there is a pattern, even when data is truly random.

Duong et al also conducted a microarray study which analysed the expression profiles in 46 patients (25 with oesophageal adenocarcinoma).<sup>49</sup> They were able to identify a 32-gene classifier to predict chemoradiotherapy response for SCC, but a gene signature predictive for oesophageal adenocarcinoma was not identified.

Recently, Peters and colleagues have reported a four-gene prognostic signature (DCK, PAPSS2, SIRT2 and TRIM44) for oesophageal adenocarcinoma and gastro-oesophageal cancer (table 2).<sup>50</sup> The discovery phase was undertaken using a 44k cDNA microarray for 75 patients with oesophageal adenocarcinoma of varying stage, and externally validated using tissue microarrays constructed from a separate oesophageal adenocarcinoma and gastro-oesophageal patient cohort (n=371). While the mixture of stages and treatment types may confound the results, the study is of large size and is the only microarray-based biomarker investigation conducted in oesophageal adenocarcinoma that has demonstrated external validation of the prognostic signature.

**Table 2: Five-Year Survival Rates Based on the Four-Gene Signature Score.**

Number genes dysregulated (of four gene signature)	Five year survival % (95% CI) <sup>a</sup>
0	58 (36-80)
1-2	26 (20-32)
3-4	14 (4-24)

<sup>a</sup> *p* = 0.013. Key: CI = confidence interval.



## DNA copy number variations in oesophageal adenocarcinoma

Copy number variations are a form of structural variation where there is an abnormality in one or more sections of DNA within a cell. The degree of changes in chromosomal numbers within a cell,<sup>51</sup> the presence and degree of DNA damage and the proportion of flow cytometric-sorted biopsy fractions that display 4n DNA content,<sup>51,52</sup> have been proposed as markers of the progression of Barrett's Oesophagus to oesophageal adenocarcinoma to be used in conjunction with dysplasia status. Amplifications in several genomic regions can lead to the increased activity of oncogenes (eg. MYC), which promote autonomous cell growth. In order to profile whole genome DNA copy number changes in oesophageal adenocarcinoma, several groups have employed array-based comparative genome hybridisation studies or loss of heterozygosity microsatellite-based methods. The most frequently reported regions of loss are 4q, 5q, 9p, 17p, 18q and Y, while frequent gains are on 7p, 8q and 20q.

Several other studies have looked for gene-based DNA copy number changes in oesophageal adenocarcinoma and found that FHIT, CDKN2A and TP53 are frequently lost, while MYC, MYBL2 and ERBB2 are gained.<sup>53,54</sup> High resolution DNA copy number screening using SNP arrays in oesophageal adenocarcinoma tumours have found copy number events to be common, averaging 76 (range, 5-152) per tumour.<sup>55</sup> Losses and gains averaged 20 (range, 1-62) and 16 (range, 1-54) per tumour respectively, and copy neutral loss of heterozygosity events averaged 41 (range, 3-75) per oesophageal adenocarcinoma.<sup>55</sup> More high resolution studies are still required, particularly those linked to clinical trial outcomes.

## DNA methylation

Methylation of DNA within CpG islands, or sections of the genome with high levels of the DNA building blocks cytosine and guanine, are being found to occur in a growing number of genes to varying degrees in human cancers, including oesophageal adenocarcinomas.<sup>56</sup> In normally differentiated, non-neoplastic tissues these genes are mainly unmethylated. It is thought to be a critical mechanism for tumour suppressor gene silencing and inactivation.<sup>57</sup> Circulating tumour cells with methylated CpG islands have been proposed as a prognostic indicator and for tumour detection in colorectal cancer.<sup>58</sup>

A retrospective analysis of CpG island hypermethylation was assessed in 11 candidate genes in pre-treatment tumour specimens (oesophageal adenocarcinoma 23, oral squamous cell carcinoma 12).<sup>59</sup> The patients received neoadjuvant trimodal therapy. A lower number of methylated genes per patient (1.2 versus 2.4,  $p=0.026$ ) was associated with pathological complete response.

MethylLight assays have been used to identify methylation in the promoter regions of the CDKN2A, HPP1 and RUNX3 genes, and to distinguish Barrett's Oesophagus tissue at risk of progression to oesophageal adenocarcinoma.<sup>60-62</sup> Frequent differences in the methylation profiles for nine cancer related genes in oesophageal adenocarcinoma, compared with normal squamous epithelium, have also

been demonstrated,<sup>63</sup> as has aberrant methylation of the E-cadherin promoter, which seems to be a common cause of inactivation in adenocarcinomas.<sup>64</sup>

These data suggest that methylation differences may be suitable candidates for prognostic biomarkers in oesophagogastric cancers.

## DNA point mutations in oesophageal adenocarcinoma

Somatic mutations are a well recognised phenomenon in tumour biology, often in combination with changes in DNA copy number. TP53 loss of heterozygosity and mutations seem to be relatively early events in neoplastic progression in Barrett's Oesophagus and TP53 mutation frequency estimates range from 35-69% in oesophageal adenocarcinoma.<sup>55,65-68</sup> Although allelic loss of CDKN2A appears to be common, point mutations appear to be rare.<sup>69-71</sup> A number of other candidate genes have been explored for somatic mutations in oesophageal adenocarcinoma, including APC, CDH1, CTNNB1, EGFR, FHIT, BRAF, KRAS, TGFB, PIK3CA and PIK3CB.

Recently, Boonstra et al demonstrated that the CDH1 GA/GA phenotype was associated with reduced survival and conversely, the MDM2 T/G phenotype with improved disease-free survival.<sup>72</sup> They suggest that the individual differences in germ-line DNA have an impact on disease-free survival in oesophageal adenocarcinoma.

In general however, the reported frequency of somatic mutations identified in the genes studied in oesophageal adenocarcinoma appears to be low. Despite frequent allelic loss of 5q on which APC resides, a very low rate of APC mutations was described in oesophageal cancers.<sup>73-76</sup> Similarly, mutations of the E-cadherin,<sup>77</sup> FHIT,<sup>78</sup> CTNNB1,<sup>78</sup> TGFB,<sup>79</sup> and EGFR genes,<sup>80,81</sup> were rarely described in adenocarcinomas. A recent report identified activating BRAF mutations in 2/19 tumours and KRAS mutations in 4/19 tumours, suggesting that the disruption of the Raf/MEK/ERK (MAPK) kinase pathway is frequent in oesophageal adenocarcinoma,<sup>82</sup> findings supported by other studies.<sup>83,84</sup>

In summary, only a handful of selected genes have been investigated for somatic mutations in oesophageal adenocarcinoma. The majority of these genes have been selected based on evidence from other cancer types. Although the lack of somatic mutations found in these genes might suggest that the frequency of somatic mutation in oesophageal adenocarcinoma is low, an alternative hypothesis is that a different set of genes is mutated in oesophageal adenocarcinoma, which in part could account for the different disease course and poor survival. The landscape of human genetics is rapidly changing with the advent of massively parallel sequencing technologies.<sup>85</sup> The first cancer genomes to be published have revealed thousands of novel somatic mutations and implicated new genes and processes in tumour development and progression.<sup>86</sup> Next generation sequencing is particularly appealing because it can detect the full spectrum of genetic variants in cancer, which could allow for a further differentiation which reflects the phenotype. It may also allow for the identification of novel therapeutic targets for future investigation.

## Drug metabolism genes

Iqbal et al examined various genes in a cohort receiving XELOX and cetuximab as first-line treatment of gastric and gastroesophageal junction adenocarcinoma.<sup>87</sup> The genes chosen were related to 5-FU (TYMS, MTHFR) and oxaliplatin (ERCC1, XPD, GSTP1) metabolism, and human epidermal receptor signalling (EGF, HER2, COX2, FCgR2A, FCgR3A). It has shown a statistically significant association between SNPs EGF A+61G rs4444903 and GSTP1 Ile105Val rs1695 and response rate. There was a significant association with MTHFR 1298 A1298C rs1801131 and the overall survival ( $p=0.044$ ).

ERCC1 gene expression levels have been shown to be predictive of response and survival to platinum-based chemotherapy.<sup>88,89</sup> Increased ERCC-1 mRNA expression may be an indicator for non-responsiveness to neoadjuvant CDDP-based chemotherapy.<sup>90</sup> Conversely, low intratumoral expression of ERCC1 correlated significantly with better response to neoadjuvant chemoradiotherapy, even though overall survival could not be evaluated due to short follow-up.

## Conclusion

A number of biomarkers have been reported in oesophagogastric cancers. While they have been shown to be variously prognostic or predictive in response to treatment, none have been prospectively validated and most are in small patient populations. Integrating these findings into prospective trials will hopefully herald their use in everyday clinical practice and thus, improve the management of oesophagogastric cancer into the future.

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## SURGICAL APPROACHES IN RESECTABLE OESOPHAGOGASTRIC CANCER

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### Abstract

Surgery still offers the best chance of cure for patients with resectable oesophagogastric cancers. Complete tumour resection with clear margin is imperative. The role and extent of lymphadenectomy remains controversial. Operative approach is individualised according to tumour location and stage, the patient's surgical fitness and the surgeon's experience. Technological advances facilitate more accurate tumour staging and the development of minimally invasive surgical techniques. Patients with oesophagogastric cancers should be managed in the multidisciplinary setting and their tumours resected by experienced surgeons with adequate case volume.

Surgery remains the main curative treatment modality for patients with resectable oesophagogastric cancers. Optimal preoperative workup with accurate tumour staging and assessment of surgical fitness improves patient selection for appropriate therapy. Modern imaging with high resolution CT scanning, together with whole body PET scanning for oesophageal cancers and staging laparoscopy and peritoneal cytology for gastric tumours, identify the majority of patients with metastatic disease, avoiding unnecessary laparotomy. Bulky resectable primary oesophagogastric tumours with or without nodal involvement have been shown to benefit from multimodality therapy.<sup>1</sup>

Once patients with oesophagogastric cancers have been appropriately worked up, the aims of surgery are to resect the primary tumour and its draining lymph node basins with clear margin (R0 resection) and to perform a suitable reconstruction that minimises operative mortality and morbidity. This paper will concentrate on the surgical principles and the controversies regarding different surgical approaches to the treatment of oesophagogastric cancers.

### Oesophageal cancer

An R0 resection, complete removal of the tumour macroscopically and microscopically, is widely accepted as providing the best chance of cure for patients with localised resectable oesophageal cancer. At the site of the primary oesophageal tumour, longitudinal surgical margins are much easier to assess than circumferential resection margin. Meticulous dissection is required to reduce the likelihood of a positive circumferential margin, which has been shown to be a poor prognostic indicator. The median

overall survival for patients with involved circumferential margin is significantly less than those with clear margin (9.4 months versus 21.6 months).<sup>2</sup>

### Extent of lymphadenectomy

The presence of lymph node metastasis confers poor prognosis, but the role of radical lymphadenectomy in oesophageal cancer surgery remains controversial. Undoubtedly, extensive lymph node resection provides accurate tumour staging and prognostication, but its impact on patient survival is a topic for debate. Published data from clinical trials are limited and often difficult to compare due to the variable definitions used for the extent of lymphadenectomy.<sup>3</sup>

The most radical lymph node resection in oesophagectomy is a 3-field lymphadenectomy. This involves the removal of abdominal nodal stations related to the stomach (a D2 lymphadenectomy) and all draining lymph nodes associated with the oesophagus in the chest including the thoracic duct and the inferior cervical lymph nodes. The term 2-field lymphadenectomy is defined as the removal of all nodal tissues related to the stomach in the abdomen and the oesophagus in the chest, but not the cervical lymph nodes.

To date, there are only three randomised control trials examining the role of lymphadenectomy in oesophageal cancer surgery. In the only prospective randomised trial comparing 3-field lymphadenectomy versus 2-field lymphadenectomy performed by Nishihira et al, extended lymph node resection yielded a non-significant improvement in five-year overall survival rate (66% v 48%), but incurred greater operative morbidity (56% v 30%).<sup>4</sup>



In the study by Hulscher et al, there was no significant difference in overall survival for patients who had transhiatal oesophagectomy with conservative lymphadenectomy compared to those who underwent transthoracic oesophagectomy with a more extensive infracarinal lymph node resection.<sup>5</sup> Formal 2-field lymphadenectomy has been shown in a small randomised trial by Fang et al to yield better five-year survival rates than selective nodal sampling (36% v 25%) in patients undergoing thoraco-abdominal oesophagectomy.<sup>6</sup>

Conceptually extended lymphadenectomy should confer a survival benefit to patients with limited nodal spread but without distant metastatic disease. However there is no reliable tool to identify these patients pre operatively. The 7th edition of the American Joint Committee on Cancer Staging Manual staging system for oesophageal and gastroesophageal junction cancers recommends extended lymphadenectomy.<sup>7</sup> Surgeons are required to balance the risk of an aggressive surgical approach with a small potential survival benefit. Superior mediastinal or supracarinal nodal dissection, with or without cervical lymphadenectomy, is technically challenging and has significant morbidity including injury to the recurrent laryngeal nerves. Many Western oesophageal surgeons perform a more limited lymphadenectomy, involving an infracarinal lymph node resection with or without the removal of the thoracic duct and a modified D2 abdominal lymph node dissection.

### **Open surgical techniques for oesophagectomy**

There are several open surgical approaches in oesophageal cancer surgery. Combined left thoracolaparotomy through a single thoracoabdominal incision is often practiced in Asian countries. The three common techniques for oesophageal cancer resection in Western countries are the Ivor Lewis transthoracic oesophagectomy (right thoracotomy and laparotomy), the transhiatal oesophagectomy (laparotomy, blunt mediastinal dissection and left neck incision with cervical anastomosis) and the McKeown 3-phase oesophagectomy (right thoracotomy, laparotomy and left neck incision with cervical anastomosis). Although the site of the primary tumour and the degree of local invasion, and the patients' cardiorespiratory reserve can contribute to decision making, the choice of surgical techniques is often related to the surgeon's experience and preference.

There has been considerable controversy among oesophageal surgeons regarding which of the two commonly performed surgical approaches, the transthoracic or the transhiatal, yields the best short-term and long-term outcomes. The transthoracic approach allows a more thorough inspection and dissection of the oesophagus and draining lymphatic tissue under direct vision. Theoretically, this will optimise R0 resection by improving circumferential margins and the extent of lymphadenectomy, leading to an improved oncological outcome. However, a combined thoracotomy and laparotomy can adversely impact patients' recovery, many of whom may already have compromised cardiorespiratory reserve. Another disadvantage of the transthoracic approach is that a leak from an intrathoracic anastomosis can cause life threatening mediastinitis and sepsis. Proponents of the transhiatal approach emphasise

that avoidance of a thoracotomy would minimise pulmonary complications and post-operative pain, and a leak from the cervical anastomosis is much easier to manage and poses less of a threat to the patient.

There are four randomised control trials,<sup>5,8-10</sup> and two meta-analyses comparing the transthoracic versus the transhiatal approaches for oesophageal cancer resection.<sup>11,12</sup> Overall, there is no significant difference in oncological outcome between these two types of oesophagectomy. However, the transthoracic technique is associated with higher intra-operative blood loss, post-operative mortality and pulmonary complication, while the transhiatal approach had a higher incidence of anastomotic leakage and recurrent laryngeal nerve injury.

### **Minimally invasive oesophagectomy**

Advances in instrumentation together with increased experience in laparoscopic and thoracoscopic surgery have led to the development of minimally invasive oesophagectomy. The advantage of this approach is to allow surgeons to perform an optimal tumour resection under direct vision, while minimising the potential adverse impact on patients' recovery by avoiding thoracotomy and/or laparotomy incisions. The term minimally invasive oesophagectomy has been used to describe totally minimally invasive operations or hybrid procedures, where either the thoracic or abdominal component is performed endoscopically.

Since Cuschieri et al described on their initial experience in thoracoscopic mobilisation of the oesophagus in 1992,<sup>13</sup> many case control series of minimally invasive oesophagectomy have been published. In the largest known comparative study of 446 cases, Smithers et al reported longer operating time, less blood loss, shorter hospital stay and greater stricture rate for the minimally invasive surgical approach, but no significant difference in mortality or survival when compared with open transthoracic oesophagectomy.<sup>14</sup> Luketich et al showed in their series of 220 patients that a totally minimally invasive Ivor Lewis oesophagectomy can be performed successfully in 92.8% of cases with low mortality rate (1.4%) and anastomotic leak rate (11.7%), and a short hospital stay of seven days.<sup>15</sup>

There are three published meta-analyses comparing open oesophagectomy to either a totally minimally invasive oesophagectomy or to the hybrid operation.<sup>16-18</sup> These concluded that minimally invasive oesophagectomy has an equivalent oncological outcome to the open procedure, but with less operative blood loss, reduced respiratory complications, and shorter ICU and hospital length of stay. To date there is no published randomized control trial comparing minimally invasive to open oesophageal cancer resection. Thus the results of the proposed TIME trial,<sup>19</sup> randomising patients to either open transthoracic oesophagectomy or minimally invasive oesophagectomy, will be most welcome.

### **Gastroesophageal junction cancers**

There are divided opinions in the literature regarding the aetiology, classification and treatment of gastroesophageal junction cancers. Should gastroesophageal junction

tumours be managed as oesophageal or gastric cancers, or as their own entity? This is an important clinical question since there are differences in tumour biology, multimodality therapy and surgical approaches for oesophageal and gastric cancers.

To guide clinical management and facilitate comparison of data across different institutions, Siewert et al proposed a morphologically and anatomically based classification of gastroesophageal junction cancers.<sup>20</sup> Type I tumours are adenocarcinomas located within two centimetres proximal to gastroesophageal junction. Type II tumours are true cardia carcinomas or “junctional cancers” ranging two centimetres above to one centimetre below gastroesophageal junction. Type III tumours are subcardial adenocarcinomas within five centimetres of gastroesophageal junction. Epidemiological data has shown type I gastroesophageal junction tumours to resemble oesophageal adenocarcinomas, with high prevalence of Barrett’s intestinal metaplasia (81%) and gastroesophageal reflux disease (84%), and lymphatic spread occurring in both cephalad and caudal direction. Type II tumours have both gastric and oesophageal malignant features. Like gastric adenocarcinomas, intestinal metaplasia is rare in type III tumours and almost all nodal metastases are located in the abdomen.<sup>20</sup> The ability to achieve R0 resection with adequate nodal clearance is the main determinant in choice of operation for gastroesophageal junction tumours. As advocated by the Siewert’s group, most surgeons would perform oesophagectomy for type I cancers and extended total gastrectomy or proximal partial gastrectomy with radical nodal dissection for type III tumours.

The treatment of Type II gastroesophageal junction cancers, especially the bulky primaries and/or those with nodal involvement, has yet to be standardised. Apart from surgeons’ preference and experience, the extent of tumour invasion of the oesophagus and/or the presence of mediastinal nodal metastases dictates the operative approach. An extended total or proximal partial gastrectomy, with transhiatal resection of the distal oesophagus, can be performed in type II tumours with minimal or no oesophageal extension and no obvious involved mediastinal node. Oesophagectomy with proximal resection of stomach and formal mediastinal nodal dissection is recommended for patients with bulky gastroesophageal junction cancers to achieve a clear proximal surgical margin.

### Gastric cancer

The surgical approach and outcome of patients undergoing gastric cancer surgery differ significantly between Western and Asian countries. With the second highest incidence of gastric adenocarcinomas globally, Japan has a nationwide public education and screening program resulting in almost 50% of patients presenting with early stage gastric cancers.<sup>21</sup> Japanese surgeons have been advocating R0 tumour resection with radical extensive lymphadenectomy, as standard treatment because they have shown that very good long-term survival can still be achieved in gastric cancer patients with nodal metastases. In contrast, the majority of Western patients present with advanced gastric

cancers and have a poor prognosis even when treated with multimodality therapy. There is considerable variation in surgical approaches among surgeons in Western countries, as many believe nodal involvement to be a marker for systemic disease; if so extended lymph node resection would not impact on patient outcome. Given the low case volume of gastrectomy coupled with high prevalence of obese patients, many Western surgeons find radical gastrectomy with extended lymphadenectomy technically challenging, resulting in higher operative morbidity and mortality.

There are three important components to considering gastric cancer surgery. Firstly, the oncologic component of removing the cancer and its draining lymph nodes. Secondly, the extent of lymphadenectomy required to achieving a long-term disease free and overall survival. Finally, the method of reconstruction.

### Extent of lymphadenectomy

Gastric cancers spread predominately by direct extension, lymphatic, haematogenous and peritoneal spread.<sup>22</sup> The Japanese have extensively investigated the pattern of lymphatic spread and incorporated this into their approach to radical gastric surgery. They introduced the concept of lymphatic nodal stations, numbering the stomach’s named regional lymph nodes from 1-16, and then grouping these into four nodal tiers N1-4. N1 nodes are located along the lesser and greater curve, while left gastric, common hepatic, coeliac and splenic arteries nodes are N2, with N3 and N4 being more distant nodes.<sup>23</sup>

These tiers lead to the modern classification of gastric surgery into a D1 resection, encompassing the N1 tier, and the more radical D2 resection, encompassing an N1 and N2 nodal resection. Initially this included the removal of the omental bursa with spleen and distal pancreas to facilitate complete lymphadenectomy. A D2 resection is considered in Japan to be the standard of care for a patient with resectable gastric cancer.<sup>24</sup>

Controversy still exists as to what operation is appropriate in the Western setting. There have been a number of studies investigating the D1 versus D2 resection, the largest being the British Medical Research Council and the Dutch gastric cancer trials.<sup>25,26</sup> Neither trial used neoadjuvant or adjuvant therapies. The British Medical Research Council trial found no statistical difference in the five-year survival rates (35% D1 v 33% D2) but an increased complication rate (28% D1 v 46% D2) and mortality rate (6.5% D1 v 13% D2) in patients who had more extensive lymphadenectomy.<sup>26</sup> The Dutch trial initially also found no significant difference in disease-free or overall survival between the D1 and D2 groups.<sup>25</sup> Subsequent 11 year follow-up data showed improved survival for a subgroup of patients with stage II and IIIa disease who had a D2 resection.<sup>27</sup> In their 15 year follow up paper, these Dutch investigators reported the D2 patient cohort had better overall survival (21% D1 v 29% D2), and less gastric cancer related death (48% D1 v 37% D2 p=0.01) and local relapse (22% D1 v 12% D2).<sup>28</sup> The higher postoperative mortality, morbidity and reoperation rates in the D2 group in both the British Medical Research Council and Dutch trials have been attributed to splenectomy and distal pancreatectomy. Many surgeons

have now abandoned this part of a D2 gastrectomy as the high perioperative complication rate appears to outweigh any potential survival benefit.<sup>29</sup>

Japanese surgeons have assessed an even more extended resection of D2 with removal of the para-aortic nodes (D3 gastrectomy), but found no improvement over a D2 resection.<sup>30</sup> Therefore a spleen/pancreas preserving D2 resection is currently considered the operation of choice for resectable gastric cancer.

### Types of gastrectomy

The type of operation has changed little in recent years, but the method of performing it has. A distal gastric cancer that can be removed with more than a five centimetre proximal margin and leaving enough functional proximal stomach can be treated with a radical distal gastrectomy.<sup>31</sup> Otherwise, a total gastrectomy is preferred as gastric cancers can be multifocal and have submucosal spread.<sup>32</sup> For a proximal tumour, a total gastrectomy allows wider surgical margins and a more extensive lymph node dissection when compared with a proximal partial gastrectomy. However hospital morbidity, mortality and survival do not seem different.<sup>33</sup> Regarding the functional outcome, total gastrectomy is associated with less acid/bile reflux and anastomotic leak but more dumping syndrome, lipid malabsorption, anaemia and impaired bone metabolism compared to a proximal gastrectomy. Preservation of the pyloric branch of the vagal nerve may prevent much of the reflux symptoms.<sup>33</sup> Reconstruction in all cases is with the jejunum, classically via a Billroth II or a Roux-en-Y anastomosis. Various designs of jejunal pouch reconstruction have been attempted, however large trials comparing it to a traditional Roux-en-Y anastomosis are few. It appears that the major benefit of a pouch is in the early post-operative period where better food intake and increase in weight are noted. However, with prolonged follow-up these advantages seem less pronounced.<sup>34</sup>

More recently there has been a major push to perform these operations using a minimally invasive approach initially with laparoscopic surgery and more recently using a robot. Additionally endoscopic mucosal resection has been offered as an alternative to radical surgery for intramucosal early gastric cancer, as approximately 96% of early gastric cancers do not have lymph node metastases.<sup>35</sup> The procedure should be performed in a high volume centre with considerable experience in this technique, which will involve close surveillance and long term follow-up.<sup>36</sup> There are currently no randomised control trials comparing endoscopic mucosal resection to standard open surgery.<sup>37</sup>

When comparing laparoscopic with open gastrectomies, most of the studies have originated in Japan, with many of the early series utilising laparoscopic gastrectomy for early and/or distal gastric cancers.<sup>38</sup> With the advancement in laparoscopic technology and improved experience with laparoscopic surgery, more extensive surgeries, including laparoscopic assisted total gastrectomy, laparoscopic assisted D2 dissections, laparoscopic assisted proximal gastrectomy and pylorus-preserving gastrectomy, are becoming more common. The range of patients for whom laparoscopic surgery is considered appropriate

has been expanded to include overweight patients with increased co-morbidities.<sup>39</sup> When comparing laparoscopic with open gastrectomy, there is a longer operating time for laparoscopic gastrectomy in most studies, however with experience this difference is shrinking. Laparoscopic gastrectomy has a lower blood loss, a faster return of gastrointestinal function, quicker ambulation and a shorter post-operative stay. There was no significant difference in cancer related mortality and the number of dissected lymph nodes was similar between the two groups.<sup>40</sup>

As with other areas of surgery, there has been a recent push towards the use of a robot when performing a gastrectomy. A recent review of the published literature showed 10 original articles reporting 199 robotically assisted gastrectomies. It is thought that the surgery is safe, with low mortality (1.5%) and morbidity (15%).<sup>41</sup> However, due to the limited number of studies and relatively short follow-up it is too early to make conclusions regarding this new technology.

### Conclusion

Surgical approaches in resectable oesophageal and gastric cancers have evolved, with more accurate preoperative assessment of tumour stage and the development of better operative instrumentations. Operative procedure for each patient needs to be planned and individually tailored according to tumour characteristics, surgical fitness and the need for pre-operative therapy. Controversies regarding the extent of lymphadenectomy and various surgical techniques remain with more trials needed to evaluate both oncological and functional outcomes. Given the low incidence of oesophagogastric cancers in Western countries, these operations should be performed in tertiary centres with adequate case volumes and surgical experience to optimise patient outcome.

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## NUTRITIONAL STATUS AND FITNESS IN NEOADJUVANT CHEMORADIATION FOR OESOPHAGOGASTRIC CANCER

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### Abstract

Resectable oesophagogastric cancer typically requires neoadjuvant chemoradiation therapy followed by surgical resection of the primary tumour. Consideration for surgery is on the basis of the risk-benefit profile of the expected surgical and cancer survival outcomes. Major surgery such as oesophagectomy is associated with a high incidence of postoperative complications, which in turn impacts long-term survival and healthcare expenditure. A clear need exists for an objective and reliable preoperative risk assessment and perioperative optimisation strategies to improve surgical outcomes. We discuss two key preoperative risk factors – nutritional status and fitness (physiologic capacity) – that may be optimised to improve the surgical outcome in this cancer population.

Resectable oesophagogastric cancer typically requires preoperative chemotherapy or chemoradiotherapy followed by surgical resection of the primary tumour four to eight weeks later. Consideration for surgery is based on the risk-benefit profile of the expected surgical and cancer survival outcomes. The greatest surgical risk is associated

with major intra-abdominal and thoracic procedures, with an estimated 10-40% of the patients experiencing major postoperative complications after major abdominal surgery.<sup>1</sup> This impacts long-term survival and healthcare expenditure. A United States Department of Veterans Affairs study reported that postoperative complications



independently reduced the 30-day and long-term survival by 69% and increased cost five-fold.<sup>2</sup> A clear need exists for an objective and reliable preoperative risk assessment and optimisation strategies. This paper discusses two important risk factors: nutritional status and fitness (physiologic capacity) that may be optimised to improve the surgical outcome in this cancer population.

The prevalence of malnutrition in patients with cancer varies according to the tumour type but is generally reported to be as high as 20-80%.<sup>3</sup> It has a negative impact on immunocompetence, treatment tolerance and wound healing, and as such is associated with increased adverse clinical outcomes, hospital length of stay and healthcare costs.<sup>4</sup> Patients with tumours of the upper gastrointestinal tract are at particularly high risk and are frequently malnourished on presentation.<sup>5</sup> Poor baseline diet, obesity and high alcohol intake are known nutritional risk factors for developing cancers of the gastrointestinal tract.<sup>6</sup>

Nutritional status can be further significantly compromised due to the dysphagia arising from mechanical obstruction, metabolic sequelae of the disease burden itself and severe nutrition-impact symptoms associated with multi-modal treatment regimens such as neoadjuvant chemoradiotherapy. Likewise, physical conditioning (fitness) correlates with physiological capacity and is associated with improved longevity in both the surgical and non-surgical populations.<sup>7-10</sup> Lifestyle behaviours (dietary intake and physical activity), co-morbid conditions, disease state and associated multi-modal treatment regimens (eg. neoadjuvant chemoradiotherapy) can significantly impair the functional capacity (deconditioning) and have a negative physiological impact, leading to an inability to meet the metabolic demands of surgical stress.

Increasing evidence supports the role of a screening tool that identifies patients at high risk of nutritional and functional deficits who may benefit from interventional strategies for optimisation. For example, nutritional intervention may improve the recovery of functional capacity after radiotherapy,<sup>11</sup> and improve postoperative outcome after surgery,<sup>12,13</sup> while acute exercise therapy may also improve surgical outcome.<sup>14-16</sup>

### **Nutritional status: malnutrition screening and nutrition assessment**

Malnutrition screening is a simple process used to identify patients at nutritional risk who require a more detailed nutrition assessment and is considered an important adjunct in modern surgical care. Current dietetic best practice guidelines recommend that all oncology patients be screened for malnutrition and that nutrition assessment is performed on high risk patients using tools validated in the oncology population.<sup>4,11,17</sup> One such tool is the Malnutrition Screening Tool that can be easily implemented to identify patients at nutritional risk.<sup>18</sup> Subsequent detailed assessment of nutritional status is important because malnutrition is not always obvious in this patient group; for example, an obese patient may have severely depleted lean-tissue stores and poor micronutrient status. It has become more widely appreciated that in isolation, proxy measures or biochemical indices are inadequate to accurately determine

nutritional status.<sup>19</sup> A more comprehensive approach, including the scored Patient-Generated Subjective Global Assessment<sup>20</sup> or Subjective Global Assessment,<sup>21</sup> both validated for oncology patient populations, is recommended by the current guidelines. These tools are used to categorise nutritional status as either well-nourished (Subjective Global Assessment A), moderate or suspected malnutrition (Subjective Global Assessment B), or severely malnourished (Subjective Global Assessment C). Importantly, nutritional status should be differentiated from nutritional risk, as even individuals who are assessed as well-nourished at diagnosis are at high risk of decline in nutritional status during the course of treatment.

### **Fitness: screening and physiologic capacity assessment**

Consensus is lacking as to the credibility of the traditional static (performed at rest) preoperative diagnostic pulmonary or cardiac function tests as risk predictors in patients undergoing major abdominal surgery. Dynamic testing to assess functional capacity is increasingly recognised as an important adjunct in modern surgical care. Cardiopulmonary exercise testing (CPET) is a dynamic test and provides the gold standard for evaluating an individual's functional/physiologic capacity (fitness level).<sup>22</sup> CPET-derived respiratory gas exchange analysis provides a uniquely individual and objective phenotypic assessment of the metabolic response to the stress of exercise by evaluating the coupling, by the cardiovascular system, of pulmonary respiration to the end-organ cellular (mitochondrial) respiration.<sup>22</sup> Whether a patient is deconditioned due to behavioural choice, organ disease, or associated therapy eg. chemoradiotherapy, such a reduction in physiologic capacity is increasingly recognised to represent the inability to physiologically meet the metabolic demands of perioperative stress with increased risk of postoperative morbidity and mortality.<sup>23-30</sup>

### **Physiologic capacity and preoperative risk stratification**

A number of CPET-derived variables allow the objective grading of physiologic dysfunction.<sup>23,31</sup> Of these, anaerobic threshold (AT) and peak oxygen uptake have been studied as markers of physiologic capacity and as risk predictors for adverse postoperative outcomes, and are used to guide perioperative decision-making. Such decision-making includes determining suitability and timing for major surgeries, postponement of surgery for optimisation strategies, and for triage of the postoperative destination e.g. postoperative care in the ICU, for high-risk patients.

Investigators identified risk prediction value in CPET-derived anaerobic threshold, with an AT value less than 11 mL/min/kg as a critical level of physiologic capacity that predisposed elderly patients undergoing major abdominal surgeries to be at an increased risk for postoperative cardiac mortality.<sup>24,25</sup> Patients with an AT less than 11 mL/kg/min had an 18% in-hospital cardiac mortality rate, whereas patients with a higher AT value had 0.8% mortality rate. The value of AT as an objective assessment of physiologic capacity in improved risk prediction of adverse surgical outcomes has been confirmed by additional studies: Snowden et al reported that

AT values  $\leq 10$  mL/kg/min were associated with increased postoperative complications and length of hospital stay;<sup>26</sup> Smith et al confirmed that peak oxygen uptake and possibly AT, were valid predictors of postoperative morbidity and mortality after thoraco-abdominal surgery;<sup>27</sup> and Hightower et al reported an improved risk prediction using a composite measure of heart rate variability and AT (area under curve = 0.826, sensitivity = 81%, and specificity = 69%,  $p = 0.023$ ) for adverse surgical outcome after major abdominal cancer surgeries.<sup>28</sup> More specific to patients requiring oesophagectomy, investigators reported the usefulness of CPET-derived peak oxygen uptake as a predictor of postoperative morbidity,<sup>29</sup> including cardiorespiratory complications.<sup>30</sup>

These data strongly suggest the following: (1) Cancer patients can complete a maximal effort, symptom-limited cardiopulmonary exercise test prior to undergoing major cancer surgery; and (2) preoperative parameters of physiologic capacity (AT, peak oxygen uptake and heart rate parameters during exercise) associate with postoperative complications.

### **Declining physiologic capacity after neoadjuvant chemoradiotherapy**

For oesophagogastric cancer patients having neoadjuvant chemoradiotherapy, a finite window of time exists wherein surgery should be performed so that physiologic recovery from neoadjuvant chemoradiotherapy occurs without the unfavourable radiation-induced tissue changes seen if surgery is performed too early or too late. The timing of the surgery is largely empirical and not based on an objective assessment of recovery of physical function after neoadjuvant chemoradiotherapy. Accurate determination of the time to return to optimal baseline fitness would potentially have a major impact on the timing of surgery, postoperative outcome and timing of adjuvant chemoradiotherapy. This could have potentially wider implications for any cancer surgery that follow neoadjuvant chemoradiotherapy. The ability to utilise CPET to objectively evaluate recovery and interventional strategies (eg. nutrition) to expedite recovery such that physiologic function after neoadjuvant chemoradiotherapy is optimal would ensure that definitive cancer resection occurs within the most optimal timeframe.

Preliminary data demonstrate that physiologic capacity may deteriorate by as much as 20-30% following neoadjuvant chemoradiotherapy.<sup>32,33</sup> Given the increased risk of adverse postoperative outcome with poor physiologic capacity (eg. AT  $< 11$  mL/kg/min), such a decline in physiologic capacity after neoadjuvant chemoradiotherapy suggests that the previously "fit" patients may now fall below this threshold and potentially are at an increased risk of adverse postoperative outcomes. Presently, the ability to credibly identify adequate recovery from deconditioning that follows neoadjuvant chemoradiotherapy is lacking, and further studies are needed to determine if patients would benefit from postponement of surgery until they have recovered such that they are above the threshold of physiologic capacity. Whether such a waiting period would adversely impact long-term cancer outcomes and whether acute preoperative optimisation (eg. nutritional or exercise

intervention) will accelerate recovery such that patients cross this threshold and thereby show lower postoperative risk is unknown.

### **Nutrition intervention – the evidence**

There is a paucity of high-quality nutrition intervention studies specific to the upper gastrointestinal cancer population having neoadjuvant chemoradiotherapy. A prospective randomised control trial in 60 patients with gastrointestinal or head and neck cancers undergoing radiation therapy, demonstrated the benefits of early and intensive nutritional intervention in minimising weight loss and deterioration in nutritional status, with improved measures of physical function and global quality of life.<sup>34</sup> A study of 24 patients who underwent definitive chemoradiotherapy for oesophageal cancer and received nutrition intervention, demonstrated improved weight maintenance and treatment tolerance, reduced unplanned hospital admissions and better radiation-dose completion rates than historical controls.<sup>35</sup>

The timeframe between completing neoadjuvant chemoradiotherapy and undergoing surgery is a period when patients are at a significant risk of rapid nutritional decline. The inflammatory state, as well as the marked nutrition-impact symptoms, related to the accumulated acute toxicities of chemoradiotherapy, predisposes patients to severe catabolism, which is of particular clinical significance in the perioperative period. Preoperative malnutrition and weight loss is associated with an increased risk of complications following major abdominal surgeries.<sup>36,37</sup> Postoperative complications may consist of delayed wound healing, increased infection risk, wound dehiscence and development of fistulae.

### **Nutrition support options**

Early identification and management of patients demonstrating a compromised nutritional status is paramount for patients undergoing major upper gastrointestinal cancer surgeries. In recent years, there has been an increasing body of evidence suggesting that perioperative nutrition support improves the clinical outcomes for these patients. The European Society of Parenteral and Enteral Nutrition guidelines on enteral nutrition in surgery recommend nutritional support in patients with severe nutritional risk for 10-14 days prior to major surgery, even if surgery has to be delayed.<sup>38</sup> These guidelines define severe nutritional risk using parameters that are associated with increased complications: weight loss of more than 10-15% in the six months prior to surgery; body mass index of less than 18.5 kg/m<sup>2</sup>; and Subjective Global Assessment score C (severely malnourished). Similarly, the United Kingdom's National Institute for Clinical Excellence commissioned guidance document on nutrition support recommends preoperative enteral tube feeding in those patients scheduled for major abdominal procedures who are identified as malnourished and are unable to meet their nutritional requirements orally. The appropriate method of nutrition support may change according to where the patient is on the care pathway and is best determined on an individualised basis by a specialist dietitian in consultation with the patient, family and treating team. These options usually include food fortification, oral nutrition support

with specialised medical nutrition therapy formula and/or initiating supplementary tube feeding when appropriate. Total parenteral nutrition is indicated only in rare cases.

Patients undergoing neoadjuvant chemoradiotherapy raise particular issues regarding supplemental tube feeding. In definitive chemoradiotherapy, the option of prophylactic gastrostomy placement in suitable patients allows the provision of supplemental enteral nutrition to be titrated according to the level of oral intake achieved as the patient progresses throughout treatment. In the case of neoadjuvant chemoradiotherapy, this option may not be compatible with the surgical plan due to the alteration in the gastric anatomy. In these circumstances, consideration should be given to alternative supplemental tube feeding methods eg. removable naso-enteric feeding tube or surgical jejunostomy. Compared to relying on oral intake alone, this will improve both preoperative and postoperative nutritional status of the patient.<sup>39-41</sup>

### **Immunonutrition**

More recently the benefits of oral and enteral nutritional formulae enriched with conditionally essential amino acids (arginine and/or glutamine), omega-3 fatty acids and ribonucleic acids have been investigated. These substrates are proposed to play a role in modulating the immune system, leading to improved clinical outcomes such as reduced rate of infection, wound complications and duration of hospital stay.

The impact of immunonutrition on postoperative morbidity and mortality has been evaluated in numerous studies with varying and sometimes contradictory results. Earlier meta-analyses of randomised control trials suggested that perioperative immunonutrition, used for patients undergoing major abdominal surgeries, significantly reduced postoperative hospital acquired infections, length of stay,<sup>42,43</sup> and wound healing.<sup>44</sup> The use of immunonutrition for all high-risk patients undergoing major abdominal surgeries was subsequently recommended. A more recent meta-analysis acknowledges that interpretation of these earlier reviews was confounded by factors such as variation in patient populations, diverse control groups and the differences in nutritional formulae and their administration protocols.<sup>45</sup> This meta-analysis was undertaken to specifically target the gastrointestinal surgical population and concluded, on the basis of data from 2730 patients, that the use of perioperative enteral immunonutrition decreases morbidity and length of hospital stay, but not mortality, in patients undergoing major gastrointestinal surgeries, and recommended its routine use. Of the 21 studies included, only 12 were considered to be of high quality, however, the beneficial effects remained with the exclusion of low-quality studies. The use of preoperative enteral nutrition, preferably with immune-modulating substrates, in patients undergoing major abdominal cancer surgeries, including oesophagectomy and gastrectomy, is likewise supported by the European Society of Parenteral and Enteral Nutrition guidelines on enteral nutrition.<sup>38</sup>

International disease management guidelines for oesophageal and gastric cancer recommend nutritional support for both radical and palliative management. Therefore, it is essential

to ensure that patients have ready access to appropriate dietary advice.<sup>46</sup> The Australian best practice nutritional management guidelines recommend early screening and referral to and monitoring by a dietitian for patients undergoing gastrointestinal chemoradiotherapy.<sup>11</sup>

### **Exercise capacity intervention – the evidence**

Feeney et al showed that patients who developed postoperative pulmonary complications following oesophagectomy engaged in less physical activity in the pre-operative period.<sup>47</sup> This suggests that there is a potential for pre-surgical exercise training to improve cardiorespiratory fitness and to potentially improve postsurgical recovery. Mechanisms whereby exercise training may yield benefit as an effective therapy include improved endothelial function and reduced inflammatory status – factors central to postoperative morbidity.<sup>48</sup>

Although exercise regimens may be logistically harder to administer, studies have shown improved functional capacity associates with improved surgical outcomes. In patients who attended more than 80% of the prescribed exercise sessions, the training increased preoperative peak oxygen uptake by 3.3mL/kg/min.<sup>49</sup> Similarly, in a small randomised study of 30 patients awaiting abdominal aortic surgery, AT increased by 2ml/kg/min after intervention with a six week, bi-weekly, 30 min aerobic exercise program.<sup>12</sup> Greatest increase in AT can be expected in patients with poor baseline AT.<sup>13</sup> In a prospective randomised trial, Arthur et al demonstrated that a CPET-based exercise intervention eight weeks prior to cardiac surgery resulted in significant reductions in postoperative intensive care unit and hospital length of stay.<sup>14</sup> In a meta-analysis of 12 studies, preoperative exercise therapy consisting of inspiratory muscle training or exercise training, reduced hospital length of stay and complication rates in patients undergoing cardiac or abdominal surgery, but not in patients undergoing joint replacement surgery.<sup>15</sup> Specific to the cancer surgery population, a pilot study of an individually designed preoperative therapeutic exercise program in patients awaiting elective abdominal/thoracic surgery showed 84% attendance of sessions, with significant increase in cardiorespiratory fitness and muscle strength despite a relatively short period (five weeks) of training.<sup>16</sup>

It is likely that home-based programs of moderate exercise may be safe, readily administered (eg. using the Borg scale 12-14; or keeping heart rate to that below AT) and that patients will be readily motivated to exercise when they understand it may reduce their perioperative risk. As such, larger studies are required to evaluate if preoperative (prehabilitation) with exercise therapy is a logistically feasible and cost-effective strategy to reduce postoperative morbidity and mortality.

### **Summary**

The link connecting poor nutritional status and poor functional capacity with adverse surgical outcome and a reduction in quality of life is well recognised for the surgical population. Adequate assessment of nutritional



status and physiological capacity (fitness) with appropriate interventional strategies could modify this relationship. The use of CPET as an adjunct to assessment before high-risk surgery is gaining increasing acceptance. Importantly, data indicates the greatest improvement in physical function occurs when nutrition intervention and exercise therapy are combined than through either intervention alone.<sup>50</sup> This may be equally applicable to the surgical population albeit more challenging. As such multidisciplinary care in surgical oncology should include specialist anaesthesia and dietetic services to promote the assessment of functional capacity and nutritional status. Implementation of interventional strategies during neoadjuvant therapy and during the perioperative period should be considered to ensure optimal postoperative outcomes for this patient population.

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## 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup>

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.<sup>2,5</sup> 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.<sup>6</sup> 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.

**Table 1:** Palliative strategies to improve dysphagia.<sup>7</sup>

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

## 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-HT<sub>3</sub> antagonists, alone or in combination with other anti-emetics such as metoclopramide. In refractory nausea, agents such as aprepitant may be considered.<sup>8</sup> In later stages of disease, the evidence is less clear. The anti-emetic that has the most robust evidence base is metoclopramide,<sup>9</sup> 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.<sup>10</sup>

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 H<sub>2</sub>-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 H<sub>2</sub>-antagonists to reduce the volume of gastric secretions, to a greater extent than proton pump inhibitors, potentially delivering better symptom control.<sup>11</sup> 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.<sup>12</sup>

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.<sup>13</sup>

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.<sup>14</sup> Oxygen rarely improves the sensation of dyspnoea in people with normal partial pressures of oxygen, except in very small numbers of people.<sup>15</sup> If oxygen is commenced, a timely review of the benefits must be undertaken.<sup>15</sup> 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.<sup>16</sup>

## 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.<sup>3</sup> 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.<sup>17</sup> 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.<sup>18</sup> 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.<sup>19</sup> 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.<sup>18</sup>

## 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.<sup>20</sup> 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.<sup>21</sup>

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.<sup>22</sup> 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.<sup>23</sup>

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.<sup>21</sup> 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.<sup>24</sup> 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.

**Table 2:** Causes of hiccups in advanced cancer.<sup>26</sup>

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.<sup>26</sup>

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.

## 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.<sup>25</sup> 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.<sup>26</sup> (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 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.<sup>27</sup> 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.<sup>28</sup>

## 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”.<sup>29</sup> Depression has frequently been reported as one of the top 10 most common symptoms,<sup>30</sup> and as the most persistent symptom in people with advanced cancer.<sup>31</sup> 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.<sup>32</sup> 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.<sup>33,34</sup> 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.<sup>35,36</sup> 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.<sup>37</sup>

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.<sup>38</sup>

Anxiety can affect the ability to retain information.<sup>39</sup> 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.<sup>40</sup> 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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## CANCER COUNCIL AUSTRALIA'S STUDENT ESSAY COMPETITION

Cancer Council Australia's annual essay competition is open to Australian residents enrolled in a medical course in an Australian university. Students are required to submit an essay on an issue related to cancer control. In 2011, the topic was "Personalised cancer treatment - fad or future?". The essays are judged by members of Cancer Council Australia's Oncology Education Committee.

This article is the winning essay by Jillian Mellor. As the winner, Jillian attended the International Summer School on Oncology for medical students in Vienna from 13-22 July 2011.

## PERSONALISED CANCER TREATMENT – FAD OR FUTURE? A MEDICAL STUDENT'S PERSPECTIVE

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Responsible for one in eight deaths globally,<sup>1</sup> cancer is the most common human genetic disease. Last year, more than 43,000 people died from cancer in Australia,<sup>2</sup> making it one of the nation's leading causes of mortality and moreover a spur to optimise cancer treatment.

Personalising cancer treatment promises increased treatment efficacy, reduced drug side effects, early intervention based on risk factors and more accurate diagnosis. Personalised therapy, the idea of tailoring clinical therapy towards a patient's biology and pathophysiology is not new.<sup>3</sup> Oncology particularly has a long history of personalised care by stratifying patients according to their risk of developing a certain disease.<sup>4</sup> Personalised treatment can be defined in contrast to what some have called the "blockbuster" therapeutic model – large pharmaceutical companies developing drugs for mass markets, to the detriment of those who are non-responders or who respond with adverse effects.

Despite the promising potential of this new paradigm based on the genetic revolution of the past decade and subsequent fast-paced growth in cancer genomics, the clinical application of this information has been sluggish.<sup>5</sup> Currently, the clinical utility of personalised cancer treatment, in terms of assisting in management and to improve health outcomes, is limited. The question remains then whether personalised cancer treatment is a practically redundant fad or a viable and sustainable paradigm shift for clinical practice.

To answer this question, this essay will begin with an overview of the revolution in cancer genomics that ostensibly promises this new medical paradigm of

individualised cancer treatment, before moving to examine the clinical application in terms of both the benefits and limitations of such a paradigm for the patient, the healthcare team and society. It will look at the hurdles to current and future use of personalised cancer treatment.

For the purposes of this essay, the phrase "personalised treatment" means therapy based on individual biology and pathophysiology. In a more holistic sense "personalised medicine" encompasses more of the patient-doctor interaction than just biology, including but not limited to the patient's needs and wishes, their disease process and psychosocial environment.

### Promise of cancer genomics

Cancer. This simple six-letter word belies its complexity. What we think of as cancer is a heterogeneous group of over 100 distinct diseases,<sup>6</sup> currently classified according to their organ tissue of origin. Central to our understanding is the genetic basis for cancer, essentially the uncontrolled growth of cell clones caused by abnormalities such as substitutions, deletions, insertions, rearrangements and epigenetic modification in the genome, called somatic mutations. This means that human cancer genomes, or oncogenomes, can be uniquely understood in terms of the mutations that they have accumulated over time. Currently, 384 genes – almost 2% of protein-coding genes – have been found linked to mutations causing cancer.<sup>7</sup>

Hereditary mutations, located within the patient's germline, confer an increased risk of developing cancer. About 20% of the identified cancer genes have germline mutations.<sup>8</sup> Contrast this with somatic mutations that occur in genomes

of normal cells during cell division. These replication errors accumulate over decades so that thousands, in some cases hundreds of thousands of somatic mutations accumulate to cause cancer.<sup>9</sup> Approximately 90% of cancers are caused by somatic mutations (with a 10% overlap with germline mutations).<sup>8</sup>

Since the release of the sequenced human genome in 2003 with the completion of the Human Genome Project, the field of human genomics has effectively exploded. The vast terrain that is the human genome, about 25,000 genes, is being mined and catalogued systematically, using high-throughput technologies, for aberrant genes that could potentially be targeted for therapy or used as biomarkers to aid diagnosis.<sup>5</sup> Cancer genomic research is an international effort including groups such as the International Cancer Genome Consortium, through which Australian researchers are contributing by analysing mutations in ovarian and pancreatic cancer.<sup>10</sup>

The following is a brief summary of the promise of personalised cancer treatment.

**Diagnosis:** Biomarkers of a particular cancer gene, or oncogene, can be identified to specifically diagnose the cancer.

**Targeted treatment:** Designing 'smart drugs' based on genetic understanding of protein function is the basis of pharmacogenomics. Professor Michael Stratton, Director of the Cancer Genome Project, describes identified mutated cancer genes as 'Achilles' heels', ready to be exploited as targets for drug development.<sup>4</sup> Additionally, subsets of patients who are likely to respond to a particular drug can be identified for treatment. For example, trastuzumab is a monoclonal antibody developed against the amplified HER2 protein, present in 20% of breast cancers. HER2 status, either gene copy number or the protein expression level, is the best predictive marker available for assessing response to trastuzumab.<sup>11</sup>

**Limit adverse drug effects:** All patients metabolise drugs differently; patients who are genetically unable to metabolise drugs can be identified to avoid unnecessary adverse effects.

**Limit disease progression:** As an early warning for disease recurrence, cancers can be detected by monitoring for leaked DNA fragments of the oncogenome in the circulation. This technology is currently used in leukaemia surveillance.

**Risk stratification:** Some germline mutations predispose an individual to disease. These mutations can be identified to calculate the risk for the patient. For example, BRCA 1 and BRCA 2 predispose towards breast and ovarian cancer and furthermore predispose towards an increased risk of recurrence following remission.<sup>12</sup>

## Benefits and limits for the patient, the doctor and society

Some cancer patients are already benefiting from personalised treatment. The successful targeting of specific mutated oncogenes, such as the BCR-ABL fusion protein, tyrosine kinase of chronic myeloid leukaemia (CML), has transformed cancer care.<sup>6</sup> In addition, patients

with germline mutations, such as BRCA 1 and BRCA 2, have been successfully screened for these mutations and treated early to prevent the development of disease. This being said, there are limitations for patients; these can be defined as lack of accessibility in a still-developing system and the expense of specially designed drugs.

At this point in time, patient care is limited until doctors become familiar and comfortable utilising genetic information. This global problem, which occasionally hits the headlines as reported by *The Times* (England), Doctors 'lack training in genetics to cope with medical revolution', is a natural consequence of the past decade's genetics explosion.<sup>13</sup>

Finally, the Australian community is hopeful of the benefits of genetics and yet divided as to its utilisation. According to the 2003 Kirby Oration by Professor David Weisbrot, titled *The Human Genome: Lessons for Life, Love and the Law*, the concerns of the community are based to an extent on a 'genetic muddle' that blurs all things genetic, from medical genetic testing to genetic engineering, stem cell research and nuclear fall-out.<sup>14</sup> This limits public acceptance and utilisation of genetic technologies, ethical issues of privacy and discrimination. This is on top of a widening divide in the community between those who use genetic testing and those who don't; older, poorer, especially Indigenous Australians are less likely to use the 'new' genetics.<sup>15</sup>

## Moving beyond current barriers

If personalised cancer treatment is to move beyond esoteric clinical management, it must overcome many hurdles. These hurdles could be seen as teething problems in the face of a changing medical paradigm, problems that include: a still-developing regulatory framework able to promote innovation; funding of pricy genetic diagnostic tools and treatments; increasing medical genetic literacy; and the ongoing need for acceptance from the Australian community.

### Genomics regulatory framework

The idea of a rampant biotechnology industry is scary. Even ardent conservatives such as American political scientist Francis Fukuyama advance the need for strong government regulation of the biotech sector.<sup>14</sup> As the Human Genome Project was nearing completion, the Australian Law Reform Commission (ALRC) published their report, *Essentially Yours*, detailing the protection of privacy, protection against unfair discrimination and maintaining ethical standards in genetics.<sup>15</sup> With worldwide acclaim for its breadth and quality, the Commonwealth accepted the vast majority of these recommendations.<sup>15</sup> Australia therefore has a good regulatory system. And yet the reins cannot be held too tight if the industry is to be attractive to private investment and innovation, essential to its long-term viability. On this front, the ALRC explored the balance between encouraging investment and ensuring that cost-effective clinical genetic services are not compromised.<sup>16</sup>

### Increasing costs - who will pay?

The future of personalised cancer treatment in Australia depends on cost-effectiveness for the consumer and

the Commonwealth. Market fragmentation caused by the move to personalised cancer treatment is going to shake-up 'big pharma'. Instead of drugs developed for mass use (and mass profit), drugs designed through pharmacogenomics for a niche genetic market will be exceedingly expensive. Who will cover this prohibitive cost – the patient, their health insurer or Medicare? With one in two Australians not covered by private health insurance,<sup>17</sup> the gap between the haves and have-nots is wide.

### **Education for doctors and medical students**

Increased genetic literacy among clinicians will support increased clinical utility. Within the Royal Australian College of Physicians is the opportunity to sub-specialise in genetics, becoming experts in genetic interpretation and counselling. This must be supported by doctors in other specialities being comfortable handling genetic information and referring patients for genetic testing. Moreover, for personalised cancer treatment to be viable into the future, medical schools are going to have to ground their graduates in the clinical aspects of genetics. This issue was raised as a recommendation by the Australian Law Reform Council, that is, that all future doctors should be trained in the use of relevant genetic counselling and genetic services.<sup>15</sup>

### **Public acceptance and genetic literacy**

There is an underlying unease in the Australian community about the pace of change. These worries range from loss of control, fears about the beginnings of 'genetic determinism' and qualms about the ability of public authorities to effectively regulate this area in the interest of the public.<sup>15</sup> These are understandable concerns. The social and ethical implications of genetic knowledge and development is profound. In fact 3% of the budget for the Human Genome Project was invested in the social and ethical issues that would arise from genetics. Another concern regarding predictive genetic testing is discrimination. For example, if a person is predisposed with an increased risk of developing disease, there is the concern that employers may discriminate or that insurance companies may refuse health insurance on this basis. On this latter issue, the Investment and Financial Services Association has a policy on genetic testing and life insurance that states that no applicant will be required to undergo a predictive genetic test.<sup>18</sup>

### **Conclusion**

Personalised treatment promises much for cancer care, although the current clinical utility is unrealised. These hurdles can be and must be surpassed to take clinical advantage of the ongoing genetic revolution. Clinical sequencing of patient's genomes will be an addition to the clinical examination of the patient, not a replacement for it, providing a necessary aid in diagnostic, therapeutic and prognostic decisions. Personalised cancer treatment is a viable, sustainable and necessary paradigm shift for clinical practice.

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## CANCER RESEARCH AND FUNDING IN WESTERN AUSTRALIA: AN OVERVIEW FROM 2008 TO 2010

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### Abstract

Funding for cancer research plays a vital role in improving all aspects of cancer care and, thus, cancer-related outcomes. To identify strengths and gaps in current cancer research activities in Western Australia, an audit of all competitive funding for cancer research undertaken in Western Australia during 2008-2010 was conducted. The Commonwealth Government was identified as the most significant contributor to competitive cancer research funding, however the amount received by Western Australian researchers was much less than by other states such as New South Wales and Victoria. These states also attract larger amounts of international funding. The broad research areas that received the most funding were biology and treatment. Most cancer research projects focused on multiple tumour sites or were basic science projects. Relative to their burden of disease, some tumour types such as liver, oesophageal, ovarian and pancreatic cancer may be underfunded. To increase the success of Western Australian cancer researchers at a national and international level, support and capacity building is needed at a local level. Identified research priorities with targeted support should be integrated into cancer planning to ensure the development of research capacity in areas of most need.

Cancer research is essential to increase understanding of how to improve all aspects of cancer control and care. By supporting the discovery of mechanisms underlying cancer and the development of risk-reducing behavioural interventions, better diagnostic techniques and treatments, and improved services and support for cancer patients, funding for cancer research plays a vital role in improving care for people diagnosed with cancer and, thus, cancer-related health outcomes.

As the burden of cancer on society and healthcare budgets rise, investment in cancer research has become a priority worldwide.<sup>1</sup> In 2004, €2.0 billion (AUD\$3.2 billion) was spent on publicly funded cancer research in Europe – a 38% increase in spending from two years previously.<sup>2</sup> In the United States, the National Cancer Institute spent over USD \$4.7 billion (AUD \$5.2 billion) per year on cancer research during 2004-2006, representing a 14% increase from 2002.<sup>3</sup> In Australia, cancer research funding from the National Health and Medical Research Council (NHMRC), an Australian Government body, increased by 174% from \$68 million in 2004 to \$118.6 million in 2007.<sup>4</sup>

In 2007, Cancer Australia conducted an audit of funded cancer research undertaken in Australia during 2003-2005.<sup>5</sup> A total of \$291.5 million in cancer research funding was identified, 6% of which was awarded to researchers in Western Australia (WA). It was found that 66% of identified funding was provided by the Commonwealth Government, largely through the NHMRC and the Australian Research Council. State and territory governments supplied approximately 2% of funding, and state and territory Cancer Councils contributed 9%. As

this was the first national audit of its type, it could not be determined how the amount or distribution of cancer research funding changed from previous years. However, an audit conducted for New South Wales (NSW) indicated that from 2001-2003 to 2004-2006, Commonwealth Government funding for cancer research in NSW increased by 169% (\$40 million to \$67.7 million).<sup>1</sup> Across the same period, State Government funding increased by 1289% from \$1.8 million to \$25 million. This considerable increase in State Government funding was related to the establishment of the NSW Cancer Research Institute, a statewide, government-funded cancer control agency. Charitable and non-profit organisations funding remained relatively stable and industry and foreign government funding decreased during this time.

Recent audits in Australia have classified cancer research according to broad research areas (using the Common Scientific Outline classification system; see [www.cancerportfolio.org/cso.jsp](http://www.cancerportfolio.org/cso.jsp)) and tumour sites being investigated.<sup>1,5,6</sup> In the absence of any state or national level coordination of cancer research, such information is useful in guiding the funding policies and priorities of organisations that award funding for cancer research. As detailed information on the types of cancer research currently funded in WA specifically is not available, the WA Cancer and Palliative Care Network and Cancer Council WA commissioned an audit of cancer research funding in WA for 2008-2010.

The importance of cancer research and the potential value of a cancer research audit was recognised during a recent forum conducted by the WA Cancer and Palliative Care

Network to develop a WA State Cancer Control Plan.<sup>7</sup> Research was identified as a priority area for inclusion in the plan. To build capacity in this area it was suggested that the benefits of research be promoted to funders and health professionals, that collaboration between researchers and clinicians should be encouraged and supported, and that the number of clinical academic positions should be increased. A cancer research audit was proposed as a way to identify current strengths and gaps in cancer research in WA and, therefore, those areas of cancer research that should be considered as priorities during the development of the WA State Cancer Control Plan.

The aim of the audit was to obtain an overview of competitive cancer research funding in WA for the years 2008-2010. The specific objectives were to:

1. Determine the funding sources of cancer research
2. Determine how cancer research funding is used
3. Determine the broad research areas studied, using the Common Scientific Outline classification system
4. Determine the tumour sites researched.

## Method

Data was collected from September to November 2010. Information was sought for cancer research projects that received competitive cancer research funding and that were conducted during 2008-2010. Ethical approval for the audit was obtained from The University of Western Australia Human Research Ethics Committee (RA/4/1/14428).

### **Approaches to data collection and responses**

#### **'Top-down' approach**

Cancer research and competitive funding information (see table 1) was requested from organisations that provide cancer-related research funding (eg. NHMRC, Australian Research Council, Cancer Council WA and other non-profit organisations) and that administer cancer-related research funding (eg. universities and hospitals in WA).

The desired information was available online from some institutions. For other institutions, we invited research offices to provide details of cancer-related research grants administered by them during 2008-2010. Research offices that did not respond were contacted again two and four weeks after the initial request.

All five WA universities provided details of cancer research funded at their institution between 2008-2010. The three major public hospitals and two large private hospitals in WA were also contacted. Two public hospitals responded – one with the requested information and another with information from two oncology departments only. One private hospital reported it did not receive direct cancer research funding and the other provided names of researchers involved in cancer research at their institution. These researchers were then followed up directly.

For projects identified through the 'top-down' approach, information on Common Scientific Outline codes, main tumour site studied and type of grant was not provided by the institutions. Audit researchers were, however, able to determine the Common Scientific Outline code and

tumour site studied from the project title, and the grant type from the project title and type of institution that provided the funding. For projects where the amount of funding received was unclear or not provided, the chief investigator was contacted for clarification.

#### **'Bottom-up' approach**

Two hundred and eighty five individuals thought to be working in cancer-related research in WA were identified from annual reports or lists of successfully funded projects published on funding organisations' websites, and from the programs of cancer conferences held in Perth during the past four years. Prominent researchers in WA were also asked to provide names of individuals they knew were likely to be involved in cancer research. In addition, the Australian New Zealand Clinical Trials Registry was asked for names of chief investigators of all WA cancer-related trials registered during 2008-2010. Researchers were asked directly for information for each of their cancer research projects conducted during 2008-2010.<sup>8</sup>

Individuals were contacted via phone and/or email, and asked to provide the data by either completing a provided information template (which listed the variables and response options in table 1), or by providing their CV or another document containing a list of their funded research grants. Non-responders were contacted again after four weeks. Before finalising data collection, the research team reviewed the list of remaining non-responders and followed up with those thought to be involved in cancer research. In total, ninety-two individuals (32%) responded to the request for data. Fourteen respondents reported they were not involved in funded cancer research during 2008-2010 and two declined to participate.

#### **Variables and coding**

Table 1 shows the information sought for each cancer research project funded from January 2008 to December 2010 and how the variables were coded.

#### **Data exclusions**

Clinical trials funding was excluded from this analysis due to a poor response in this area. Researchers who conducted clinical trials expressed concerns regarding confidentiality and difficulties in estimating the amount of funding their involvement in a particular trial attracted.

## Results

Overview of competitive cancer research funding in WA for 2008-2010

Data was collected for 218 distinct cancer research projects. Four projects received two grants and one attracted three grants, resulting in a total of 224 competitive grants identified for the audit period. The amount awarded per grant for the three year audit period ranged from \$1058 to \$900,000. Table 2 shows the total competitive funding awarded in each calendar year.

#### **Sources of funding**

The distribution of competitive cancer research funding across different sources is shown in figure 1. The Commonwealth Government made the largest contribution

**Table 1:** Information sought for each cancer research project conducted in WA during 2008-2010.

Variable	Coding details
Area of research	<p>Broad area of research for each project was classified using the following internationally recognised Common Scientific Outline codes:</p> <ul style="list-style-type: none"> <li>• biology</li> <li>• etiology</li> <li>• prevention</li> <li>• early detection, diagnosis and prognosis</li> <li>• treatment</li> <li>• cancer control, survivorship and outcomes</li> <li>• scientific model systems</li> </ul> <p>More information on the Common Scientific Outline can be found at: <a href="http://www.cancerportfolio.org/cso.jsp">www.cancerportfolio.org/cso.jsp</a></p> <p>Projects were classified by either the researchers who provided information on each of their own studies, or, if this information was unavailable, by the audit investigators.</p>
Disease site	Defined by either the researchers who provided information on each of their own studies, or if this information was unavailable, by the audit investigators.
Amount of funding for 2008-2010	Where a total amount of funding was provided for a project funded over a number of years and yearly amounts were not able to be identified, the total amount was divided by three to give an estimated amount of funding per calendar year.
Source of funding	<p>Source of funding for each grant was classified as one of the following:</p> <ul style="list-style-type: none"> <li>• NHMRC</li> <li>• Other Australian Government body</li> <li>• State/Territory Government body</li> <li>• Cancer Council</li> <li>• Other non-profit/charitable organisation</li> <li>• University</li> <li>• Public hospital</li> <li>• Pharmaceutical company</li> <li>• Overseas organisation</li> <li>• Other</li> </ul>
Type of funding	<p>The funding received for each project was classified as one of the following:</p> <ul style="list-style-type: none"> <li>• research grant</li> <li>• tender</li> <li>• non-competitive funding</li> <li>• infrastructure funding</li> <li>• equipment funding</li> <li>• training and people support (eg scholarships and fellowships)</li> </ul>

**Table 2:** Annual funding to cancer research projects in WA 2008-2010.\*

Year	Total funding
2008	\$7,579,383
2009	\$9,990,017
2010	\$10,925,259

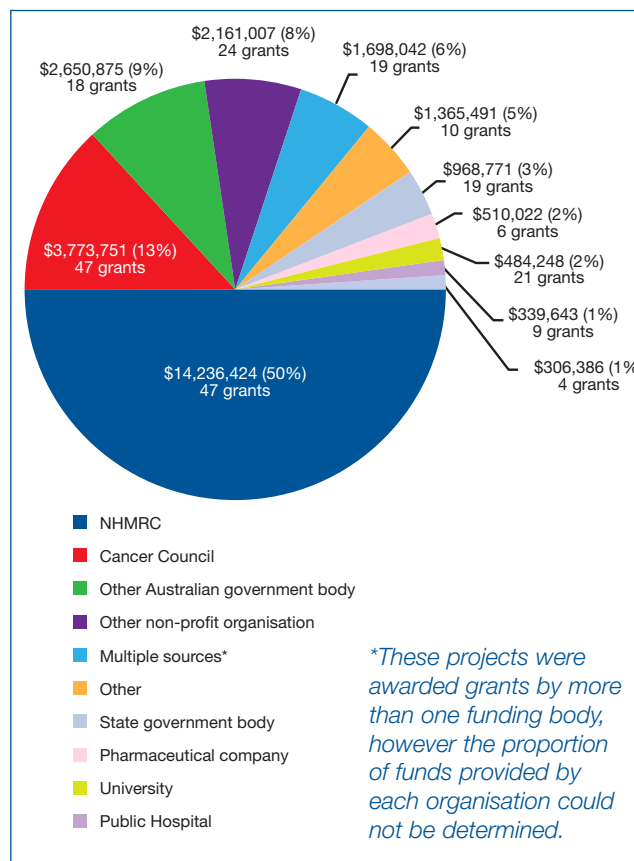
\*No adjustment for inflation in these figures has been made.

# REPORTS

(59%) to funding, predominantly through grants from the NHMRC, Australian Research Council and Cancer Australia.

Cancer Councils (largely Cancer Council WA) and other non-profit organisations made the second largest contribution (24%). All other individual sources each contributed less than 5% of research dollars to competitive funding. The State Government contributed less than \$1 million, or 3% of identified competitive funding.

**Figure 1: Sources of competitive cancer research funding for 2008-2010.**

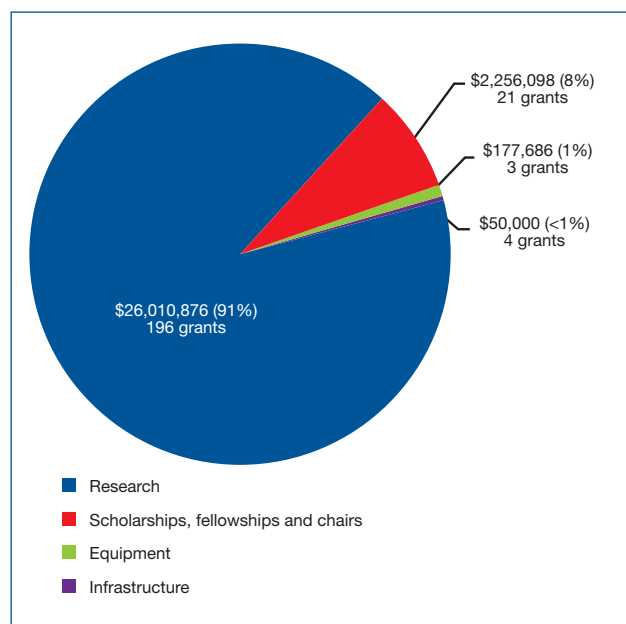


## Use of funding

Cancer research grants were categorised according to how the funds were used. Figure 2 shows the proportion of total funds which were allocated to general research, infrastructure, equipment and scholarships, fellowships or chairs. The majority of funding was specifically for research projects, followed by people support (eg. scholarships and fellowships).

Little information was received regarding Medical and Health Research Infrastructure Fund grants, which are awarded by the WA Government to applicants who meet a prescribed minimum threshold of research funding (ie. >\$400,000) from international and/or national peer-reviewed sources for the past three years. Given the unique circumstances under which Medical and Health Research Infrastructure Fund grants are awarded, and the lack of reliable data received, Medical and Health Research Infrastructure Fund grants were excluded from data analysis. The Department of Health WA Research Development Unit reported that the amount of Medical

**Figure 2: Use of competitive cancer research funding**

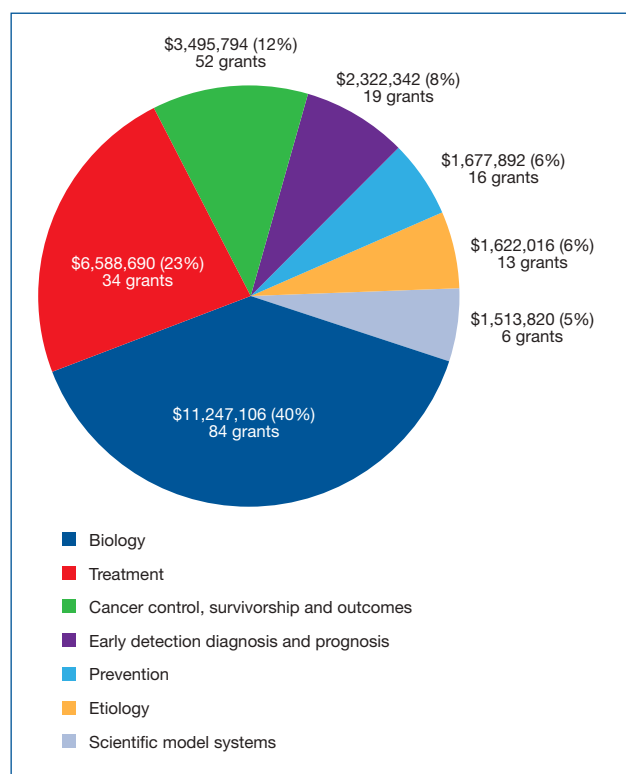


and Health Research Infrastructure Fund funding awarded during 2008-2010 was \$306,000, which represents approximately 2.7% of identified funding.

## Broad research areas for funded projects

Funded projects were classified into Common Scientific Outline categories, reflecting the primary focus of the research. The distribution of funding across the seven major Common Scientific Outline categories is illustrated in figure 3. The largest proportion of competitive funding

**Figure 3: Broad research areas (Common Scientific Outline codes) of competitively funded cancer research projects.**





was allocated to biology research, followed by treatment and research related to cancer control, survivorship and outcomes. Scientific model systems received the least amount of funding during 2008-2010.

## Disease sites studied

One hundred grants (40%) were awarded to projects that were not site-specific, or of a basic science nature. For projects that focused on one or more disease sites, the majority of funding went to mesothelioma (20%), leukaemia (19%), prostate (15%), breast (14%) and brain (12%) cancers (see figure 4). Research related to cancers of the testes, cervix, bladder, endometrium and oral cavity and lip received minimal funding.

To examine whether the pattern of site-specific cancer research funding across different tumour sites is consistent with burden of disease, potential years of life lost was compared against the amount of funding for the 17 most

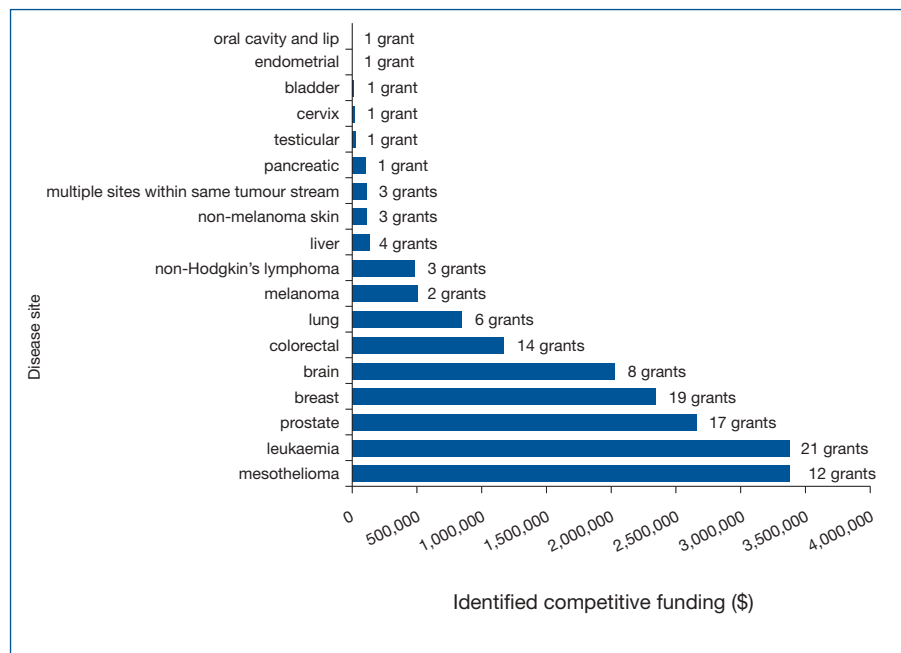
burdensome cancers in Australia (see figure 5).<sup>9</sup> While prostate cancer is the most commonly diagnosed cancer in Australia,<sup>10</sup> the amount of funding awarded to prostate cancer research in WA was relatively disproportionate to the potential years of life lost due to this disease. Mesothelioma and leukaemia also received a relatively large proportion of research funding compared to their burden of disease. Melanoma, myeloma and cancers of the lung, colorectum, pancreas, liver, oesophagus, stomach, ovary, kidney and bladder are among the top contributors of potential years of life lost due to cancer, but received relatively low or no identified cancer research funding during the audit time frame.

## Discussion

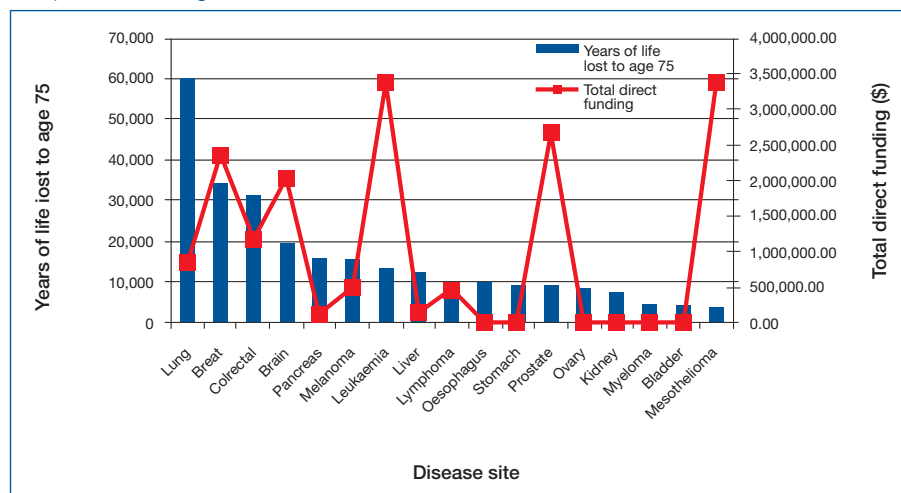
The main aim of the audit was to obtain an overview of cancer research funding in WA for the period 2008-2010.

The total number of organisations that provide cancer research funding is not known, so it is difficult to quantify what percentage of total cancer research funding was captured in this audit. Funding information most likely to be missing is that from smaller organisations whose research funding details are not publicly available. As a result, funding from major organisations with easily accessible funding information and the types of research they fund may be over-represented. However, given the method in which individuals were identified and followed up, it is likely that those who did not reply were not actively involved in cancer research during 2008-2010 and that most individuals involved in cancer research provided input to the audit.

**Figure 4:** Disease sites studied by competitively funded cancer research projects.



**Figure 5:** Potential years of life lost for cancer specific sites compared to the amount of competitive funding received.



Other types of data that may be under-represented in the audit are those related to funding for equipment, infrastructure or scholarships, fellowships or chairs. For these grant types, a discrepancy was noticed between data collected through the top-down and bottom-up approaches, whereby individuals were less likely to report such funding. Any future audits should make clear to participants which forms of cancer-related funding are relevant to the audit.

Cancer research in WA was funded by a variety of sources, with the Commonwealth Government (ie. NHMRC, Australian Research Council

and Cancer Australia) making the largest contribution. WA Government funding for competitive cancer research was relatively low (3%). In contrast, the NSW Government contributed 19% of total cancer research funding in NSW for 2004-2006. This relatively high level of state funding in NSW may be related to the fact that NSW (along with many other jurisdictions across Australia and the rest of the world) has identified research as a priority to improve cancer outcomes, and has mandated action to support and coordinate research endeavours in its Cancer Action Plan. The proportion of WA funding from international sources was also relatively low (5%) when compared to Victoria (25%)<sup>6</sup> and to Australia as a whole (13%).<sup>5</sup> Victoria and NSW also attract much larger amounts of Commonwealth funding in the form of NHMRC grants than WA.<sup>1,6</sup> These variations may be due, in part, to differences in audit methodology. However, the higher rate of international funding may also relate to the relative strength of those states' cancer research.

The broad areas of research and tumour sites studied in WA generally follow a similar pattern to that in other states and at a national level.<sup>1,5,6</sup> As is the case in Victoria and NSW, biology attracted a greater proportion of cancer research funding than any other broad research area, and most cancer research addressed multiple tumour sites or were basic science projects.<sup>1,6</sup> The audit also identified some cancer types which, relative to their burden of disease, may be underfunded. Given the potential for one or two very large grants in a specific area to skew the results, it is important that regular audits are conducted to obtain an accurate, up-to-date overview of cancer research funding.

Research is a key enabler of evidence-based medicine and optimal care for people with cancer. As such, research is increasingly identified around the world as an

important component of cancer management planning and an aspect of care warranting support by providers of health services. To increase the success of WA cancer researchers at a national and international level, support and capacity-building is needed at a local level. Inclusion of identified research priorities with targeted support in a state cancer control plan will ensure the development of research capacity in areas that will benefit this state. This audit has provided an overview of the broad research areas and tumour sites currently studied in WA and may, therefore, be useful in identifying priority areas for the plan.

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## AUSTRALIAN BEHAVIOURAL RESEARCH IN CANCER

### Behavioural Research and Evaluation (BREU) and Tobacco Control Research and Evaluation (TCRE) South Australia

#### National Primary Schools SunSmart Survey

Cancer Council SA will soon commence a national survey of primary schools across Australia. Funded by Cancer Council Australia, the primary aim of the survey will be to determine common sun protection policies and practices in primary schools across Australia and to examine the variation in these by factors such as SunSmart status, and over time. This will be the fourth round of the survey having previously been conducted in 1998, 2002 and 2005.

#### Tackling Smoking Education Program

The Tackling Smoking Evaluation program is currently evaluating the pilot phase of the Give up smokes for good social marketing campaign, which has been designed to reduce smoking prevalence among Aboriginal people in South Australia. The pilot phase of the campaign focused on the harms associated with tobacco use, and encouraged

Aboriginal people to quit smoking and minimise the harm to others. The Social Research Centre will hold focus groups with Aboriginal people (18-39 years) to collect qualitative data regarding the reach and effectiveness of the campaign in the pilot areas: Port Lincoln, metro-north Adelaide and Port Augusta. Tobacco Control Research and Evaluation (TCRE) program will also administer 200 surveys within two of the pilot locations (Metro-northern Adelaide and Port Lincoln) to assess recall of the campaign and tobacco use.

#### Quit onQ evaluation

In 2010, QUIT SA launched a mobile phone text message based smoking cessation service called Quit onQ, which was developed by Cancer Council Victoria. The TCRE program, in collaboration with Cancer Council Victoria, are conducting an evaluation to assess the effectiveness of Quit onQ (only) and Quit onQ in combination with the Quitline proactive callback program, in comparison with the Quitline proactive callback program (only), Quit packs (only), and no intervention. The study will compare quit rates and changes in smoking behaviour across the types of support offered to smokers

to determine effectiveness of the services at six weeks, six months and 12 months after their initial contact with the Quitline. Baseline data and six week follow up data have been collected, six month follow-up is currently in progress.

## **Centre for Behavioural Research in Cancer (CBRC), Victoria**

### ***Monitoring changes in ultraviolet radiation levels in Australia: Implications for skin cancer control***

It is estimated that nearly 450,000 Australians get skin cancer every year. Ultraviolet radiation (UV) from the sun has been identified as the cause of over 95% of skin cancers in Australia. Accordingly, the focus of skin cancer prevention programs over the past 30 years has been to reduce exposure to UV. Increases in UV have the potential to undermine the successes of these campaigns. Surface UV is dependent on the amount of ozone in the stratosphere. While signs of impact of international restrictions on the production of ozone-depleting substances have been observed, improvements have not yet returned ozone to pre-1970s levels. We collaborated with the Bureau of Meteorology to calculate clear sky UV over a 50-year period (1959-2009) for Australia, using two long-term ozone data sets derived from surface and satellite measurements, a radiation code and atmospheric meteorological fields.

The results showed increases in surface UV throughout Australia since the 1980s, with higher seasonal and annual averages occurring in more southerly latitudes than was previously the case. Increases were most pronounced during winter in the northern parts of Australia, when temperatures are more pleasant and people spend more time outdoors. In the south, increases in summer are more concerning, because this is when temperatures are warmer and sun exposure increases. Before the ozone layer recovers fully, it is expected that higher levels of UV will continue in most Australian regions, with an associated higher risk of skin cancer. This paper is in press in the *International Journal of Biometeorology*.

### ***A web-based intervention to reduce distress and improve quality of life among younger women with breast cancer: A randomised control trial***

Throughout 2010 and 2011, CBRC has been working on a randomised control trial testing the effectiveness of a web-based intervention addressing the information and supportive care needs of young women with breast cancer. The project led by Associate Professor Vicki White, has been funded by a grant from beyondblue: the national depression initiative, Cancer Australia and the National Breast Cancer Foundation. Based on input from consumers, the web-based intervention is designed around points of care and emotional responses to cancer. It provides information, existing resources and the contact details for organisations or services that can assist in each issue/area of need. The aim is to recruit 290 women aged under 50 and diagnosed with early stage breast cancer, with participants completing a baseline and two follow-up surveys over a six month period.

To date, 183 women have been recruited into the study with 97 assigned to the intervention group. Seventy-two per cent of women in the intervention group have accessed

the website, with the most frequently viewed information being: managing long-term effects from treatment (55% of users); possible side effects of tamoxifen (49%); breast reconstruction information, fears of cancer returning and finding a new normal (45% each). Thus far, 109 women have completed their first follow-up survey with 154 completing the baseline survey. Recruitment will continue into early 2012.

## **Viertel Centre for Research in Cancer Control (VCRCC), Cancer Council Queensland**

### ***Beating the Blues After Cancer study***

The aim of the Beating the Blues After Cancer study is to assess the efficacy and cost-effectiveness of accessible and affordable psychological interventions for distressed cancer patients and carers. By comparing two different support options, the study will determine the best possible way to help people affected by cancer. The study began in September 2009 and recruitment was completed on 3 August 2010, with 690 participants recruited from two Helplines randomly allocated to one of two support options – five tele-based sessions with a psychologist or one tele-based session with a nurse counsellor.

To date, over 540 participants have completed their intervention sessions and the three, six, and 12 month follow-up assessments, comprising of a short telephone interview and self-report survey. The 12 month data collection phase is scheduled for completion by October 2011. Data cleaning of the follow-up assessment data is ongoing, with a view to be available for analysis early 2012.

### ***Living with Prostate Cancer Study***

The latest study in the Prostate Cancer Research Program is the Living with Prostate Cancer Study, which is trialing a new support program for men recently diagnosed with prostate cancer. Unmet supportive care needs are highly prevalent in men with prostate cancer, and the difficulties associated with diagnosis and treatment is amplified by lifestyle factors such as obesity and physical inactivity. The two-armed randomised control trial will evaluate the effectiveness of a multimodal supportive care intervention, 1 compared to usual care, in reducing unmet supportive care needs, promoting regular physical activity, and improving overall wellness in men recently diagnosed with prostate cancer. The supportive care intervention consists of self-management resources and information, both print and web-based, as well as tele-based group peer support.

Men will be assessed at baseline, and at three, six and 12 months after recruitment and intervention commencement, to measure unmet supportive care needs, physical activity levels, psychological distress and quality of life. An economic evaluation will also be conducted to assess the cost-effectiveness of the intervention. The study will produce recommendations about: the efficacy of self-management and group peer support in reducing unmet supportive care needs and promoting overall wellness for prostate cancer survivors; the cost-effectiveness of these strategies; and an evidence-based supportive care intervention for men with prostate cancer that can be rapidly translated into the community. Recruitment is expected to commence in mid-2011.

## CANCER COUNCIL AUSTRALIA

### World cancer research agency finds possible link between mobile phones and cancer

Australians should not be alarmed about findings released from an expert group classifying mobile phones as “possibly carcinogenic to humans”, according to Cancer Council Australia.

Cancer Council Scientific Advisor and international carcinogens expert, Professor Bernard Stewart, said the findings released in June by the International Agency for Research on Cancer (IARC), found a “possible link” between mobile phones and cancer, but not a proven one.

“These findings show limited evidence linking mobile phones to glioma and acoustic neuroma and inadequate evidence to draw conclusions for any other types of cancer,” Professor Stewart said. “However, it does sound a warning bell and highlights the need more research in this area.”

According to Australian Institute of Health and Welfare data, brain cancer incidence has remained steady over a 25 year period to 2007, between 6.3 and 7.3 cases per 100,000 Australians.

Chair of Cancer Council Australia’s Occupation and Environmental Cancer Committee, Terry Slevin, said while IARC’s classification was ‘possible’ rather than ‘proven’ risk, it would be prudent for mobile phone users, particularly heavy users, to take measures to minimise any potential risk.

“There are practical measures people can take such as using hands free devices and more texting as an option to voice calls,” he said. “We would also urge greater caution for children using mobile phones as their brain tissue is still developing.”

“However, these findings need to be put in context. While we need to continue researching the possible link between mobile phones and cancer, it is important to remind people there are many more established cancer risk factors that we can take action every day. Strong action on clear cancer risks like tobacco, alcohol, excessive UV exposure and obesity remain a priority.”

### Less than half take home bowel cancer test despite high awareness

New Cancer Council research released in June shows although more than 80% of people aged 50+ were aware of a simple, at-home screening test for bowel cancer, less than half of those aware of FOBT had actually done the test.

The research also found that most respondents (75%) could not recall their GP ever mentioning the faecal occult blood test (FOBT) to them.

FOBT is recommended for all Australians 50+ every two years. Under the government’s National Bowel Cancer Screening Program, the test is provided free for people turning 50, 55 and 65. It is also available for purchase from other sources, such as pharmacies.

Chair of Cancer Council Australia’s Bowel Cancer Screening Committee, Anita Tang, said it was encouraging to see greater awareness of FOBT, however public health authorities were concerned it had not translated into higher levels of testing. Of particular concern, was poor promotion by GPs.

“Nearly all (94%) respondents saw their GP at least once in the previous 12 months, yet less than a quarter said their doctor had mentioned doing an FOBT,” she said. “We know from previous research that nine in ten people say they would take up screening if recommended by their doctor.”

Ms Tang said the most common reason given for not using an FOBT was “previous bowel tests”, most commonly colonoscopy. This suggested a large number of people were being referred for colonoscopy - a full-day procedure that requires fasting and sedation - when the simple at-home test (FOBT) might be appropriate.

“There also appears to be confusion about the role of screening, with some people citing a lack of symptoms as the reason for not doing an FOBT, despite the fact the test is aimed at finding pre-cancerous lesions or bowel cancers which often develop without warning signs.”

### Sugar coated regulations fail to save children from fast food ads

Attempts to tackle Australia’s childhood obesity crisis have been dealt a blow with voluntary regulations failing to reduce the level of junk food advertising to children, while the number of fast foods ads overall have increased.

University of Sydney and Cancer Council research published in June in the *Medical Journal of Australia* has revealed that people who watch just three hours of television per day are exposed to more than 1640 fast food ads per year – a jump of more than 430 ads per year since industry regulations were introduced in August 2009.

One of the study’s authors and Cancer Council nutritionist, Kathy Chapman, said the voluntary code had failed in what was supposedly its key objective, to reduce the number of fast food advertisements screened specifically during peak children’s viewing hours.

Six major fast food companies established the Australian Quick Service Restaurant Industry Initiative for Responsible Advertising and Marketing to Children (QSRI) in August 2009 to appease community concern on fast food advertising to children.

But according to Ms Chapman, the “sugar coated” code should be scrapped and replaced with “clear and meaningful regulations” that protect children at times they are watching television and reduce their exposure to the wrong types of food.

“One in four Australian children are overweight or obese and this important study confirms what we have known for a long time; junk food companies have failed to clean up their act under voluntary self-regulations,” she said.



“Parents are up against an unchecked multimillion dollar junk food industry and it’s not surprising that more than eight out of ten\* believe children should be protected from this deceptive marketing.”

## **Micronutrient supplements offer little benefit to cancer survivors**

Use of micronutrient supplements by cancer survivors provides little benefit, with survivors more likely to reduce the risk of recurrence and secondary cancers by maintaining a healthy weight, improved diet and physical activity, according to a review published in the July issue of *Cancer Forum*.

The researchers, from the University of Newcastle and Cancer Council, said cancer survivors were an important target for nutrition intervention as they were at increased risk of many chronic illnesses, such as cardiovascular disease, diabetes, cancer recurrence and secondary cancers.

Co-author, Kathy Chapman, a nutritionist with Cancer Council, said there was evidence of widespread use of supplements by cancer patients and survivors, with a study in the US reporting that up to 81% used vitamin or mineral supplementation. Most water-soluble vitamins were thought to be harmless at pharmacological doses, but there were concerns about safety, as some were known to be toxic at pharmacological doses.

In contrast, evidence that maintaining a healthy weight, improving diet and undertaking regular physical activity as ways to reduce risk, was increasing. “An international review by the World Cancer Research Fund concluded cancer survivors should follow the same diet, healthy weight and physical activity principles for cancer prevention as the general population,” she said.

## **Landmark day in public health, as Reps passes tobacco plain packaging bill**

Plain packaging took a giant leap forward in August when federal MPs passed legislation to introduce plain packaging for the sale of tobacco products sold in Australia from next year.

In a world first, tobacco products will be sold in unappealing olive brown packets from July 1 2012.

The previous day all federal MPs were sent a letter from 260 professors of health and medicine seeking unanimous support for legislation to mandate plain packaging of tobacco products sold in Australia.

Cancer Council Australia CEO, Professor Ian Olver, said Australia’s position as a world leader in tobacco control was significantly strengthened by the passage of the plain packaging bills in the House of Representatives.

“The evidence on how much young people in particular can be lured to smoking by the look and feel of the packaging is compelling, so this is a landmark day in restricting the way tobacco products can be promoted,” said Professor Olver.

“Health Minister Nicola Roxon showed great courage and conviction for taking on the tobacco companies and championing plain packaging.”

National Heart Foundation CEO, Dr Lyn Roberts, said young Australians turned off smoking by the sight of a drab brown pack with a more prominent graphic warning would greatly reduce their risk of premature cardiovascular disease.

“Other countries keen to reduce the population health harms of tobacco will be encouraged by Australia’s leadership on plain packaging,” Dr Roberts said.

## **Cancer still most feared illness**

Two thirds of all Australians fear cancer more than any other disease, according to research\* released in August.

Despite a 30% improvement in the survival rate of many common cancers in the past two decades, cancer is still feared significantly more than heart disease, dementia and stroke.

Both men and women – young and old – fear the disease. Those who know someone with cancer are almost twice as likely (66%) as others (36%) to be worried about cancer.

According to Cancer Council Australia, who commissioned the survey, the high prevalence of cancer in the community is a likely contributor to this concern. Eighty-four per cent of Australians know someone who has had cancer in the last 25 years.

This year alone, more than 110,000 Australians are expected to be diagnosed with the disease.

Although cancer affects many of us, Australia is a world leader in cancer survival with survival rates approximately 20% higher than the global average.

Cancer Council Australia CEO, Professor Ian Olver, said this gave Australians real cause for hope. “The survival rate for many common cancers has increased by 30 per cent in the past two decades,” he said. “Although one in two Australians will be diagnosed with cancer by age 85, more than 60% of cancer patients will survive more than five years after diagnosis.”

Conducted for Cancer Council Australia by Galaxy Research on the Galaxy Omnibus (20-23 May), interviewed 602 respondents aged 18 and above across Australia, representative of the population against ABS data.

## **Daffodil Day turns 25**

Daffodil Day celebrated its 25th anniversary in August by turning the country yellow.

Popular landmarks all over Australia turned yellow in celebration of Daffodil Day, one of Cancer Council’s most important fundraising events.

The Sydney Harbour Bridge’s city-facing southern pylon was bathed in a yellow glow with the event’s logo in the two days leading up to Daffodil Day.

Regions across NSW painted the town yellow joining in the celebrations turning The Cape Byron Lighthouse, the Newcastle Town Hall clock face and the Breakwater Lighthouse in Wollongong, yellow.

Victorian landmarks also turned yellow for the cause. With Federation Square projecting a yellow daffodil and the

# REPORTS

Daffodil Day logo for the two days leading up to event, AAIMI Park lit up in yellow from on the 22-28th August and the Crown Casino lobby turned yellow too.

More than 10,000 volunteers staffed over 1200 Daffodil Day sites nationally including train stations, street stalls and shopping centres. Schools and workplaces also joined in the festivities with many encouraging students and employees to wear yellow.

Daffodil Day is the largest fundraising event of its kind in the southern hemisphere and in 25 years has raised over \$100 million for vital cancer research, prevention and support services.



## CANCER AUSTRALIA

### **Cancer Australia strategic plan 2011-2014 released**

Cancer Australia recently released its new Strategic Plan (2011–2014) to articulate the direction and priorities for the agency over the next three years.

The plan was developed in consultation with a wide range of stakeholder groups and individuals, including consumers, health professionals, researchers, data experts, health service decision makers, Cancer Australia and NBOCC staff, NBOCC Board members and Cancer Australia Advisory Council members.

Stakeholders across all sectors expressed strong support for Cancer Australia's leadership mandate in national cancer control and a clear view about the strategic and distinct areas of contribution of Cancer Australia over the next three years.

People affected by cancer are at the centre of Cancer Australia's efforts. The agency will continue to engage with all relevant government, non-government and consumer stakeholders to harness efforts and resources, maximising the potential for the Strategic Plan to deliver its vision of reduced impact and improved wellbeing for people affected by cancer across Australia.

Copies of the Cancer Australia Strategic Plan 2011-2014 are available at the Cancer Australia website.

### **Breast and ovarian cancer resources**

Breast cancer and ovarian cancer will remain a priority for the new Cancer Australia as it delivers the Government's broader cancer programs and research priorities. Comprehensive evidence-based information about breast and ovarian cancer will continue to be available.

For more information please visit the Cancer Australia website, which is being upgraded. Cancer Australia's quarterly e-newsletter will continue to update subscribers on the agency's work. To subscribe please click visit the Cancer Australia website.

### **Release of the National Framework for Consumer Involvement in Cancer Control**

Cancer Australia in partnership with Cancer Voices Australia, have developed the National Framework for Consumer Involvement in Cancer Control, to enhance meaningful consumer involvement at all levels of cancer control in order to improve outcomes and experiences for people affected by cancer.

The National Framework for Consumer Involvement in Cancer Control is due to be released in 2011.

### **GP online learning on cancer screening**

Cancer Australia has developed an interactive online learning module, in collaboration with Royal Australian College of General Practitioners and Cancer Council Australia, designed to support the central role that GPs play in discussing and managing cancer screening. Visit [www.gplearning.com.au](http://www.gplearning.com.au) for more information.

### **Not just a woman's disease: information about breast cancer in men**

Although breast cancer is uncommon in men, accounting for less than one per cent of all breast cancers, it is important for men who find a change in their breasts not to let embarrassment or uncertainty prevent them following this up with their doctor as soon as possible. Finding breast cancer early means there are more treatment options and the chances of survival are improved.

To order the new resource, visit the Cancer Australia website.

### **Cheeky Check-up "Felt Yourself" Facebook avatar**

Cancer Australia has taken a fun, fresh approach to promoting breast awareness to younger women through social media, supported by funding from Estee Lauder Companies. A new interactive game has been launched on the Cheeky Check-up Facebook page, to encourage peer-to-peer engagement, discussion and promotion of breast awareness messages.

## CANCER VOICES AUSTRALIA

The role of the consumer is now firmly on the Government Agenda and we welcome both levels of government as they engage the 'people affected by cancer'.

To this effect Cancer Voices Australia (CVA) through its member base, now has its Board represented on 45 national and 24 state cancer committees – a considerable achievement.

### **CVA & Darcy v Myriad Genetics Inc.**

CVA is challenging the BRAC-1 gene patenting by Myriad, which follows on from the successful challenge in the US regarding this matter. Myriad, however challenged the decision and its appeal was successful.

CVA is still proceeding with the matter in Australia and it is scheduled for hearing in February 2012.

### **PBS deferrals**

In March 2011 in response to a decision by the Minister to defer the listing of a number of PBAC recommended drugs, CVA wrote to the Minister detailing our position on this subject.

CVA along with the Consumers' Health Forum and over 60 of CHF's members' met with the Minister in April 2011.

As a result of these meetings the minister has addressed the matter.

### **Radiation Oncology Services**

Working closely with the Department of Health and Ageing and the Tri-partite Committee, CVA has been a member of the committee that has overseen the launch of the National Dosimetry Centre and the Radiation Oncology Practice Standards – now out for public submission.

As a result of his work in this arena, John Stubbs, CVA's Executive Officer was presented with a Recognition Award for commitment to radiation oncology services in Australia.

### **Cancer Australia**

Following the successful amalgamation of Cancer Australia and the National Breast and Ovarian Cancer Centre, CVA has partnered with Cancer Australia to develop a National framework for Consumer Involvement Control..

Cancer Voices Australia continues to forge alliances with national and state groups and use 'the consumer voice' to promote common issues.

## CLINICAL GUIDELINES NETWORK

Cancer Council Australia's Clinical Guidelines Network is progressing well during its transition to publishing online clinical guidelines with its newly developed Cancer Guidelines Portal (wiki-based platform).

*Clinical Practice Guidelines for the Treatment and Management of Endometrial Cancer* were the first to test the public commenting function on the portal, uploaded to the site in July for comment.

### **Clinical practice guidelines for surveillance colonoscopy in adenoma follow-up, following curative resection of colorectal cancer, and for cancer surveillance in inflammatory bowel disease**

Final draft guidelines were submitted to the National Health and Medical Research Council in August for review and approval at the council's meeting in October and are expected to be available on the guidelines portal in 2012.

A derivative flowchart, based on the Clinical Practice Guidelines, will also be developed for colonoscopists and general practitioners.

### **Clinical practice guidelines for the prevention, treatment and management of lung cancer**

Revision of the treatment section (chapters 5 – Non-small cell lung cancer and 6 – Small cell lung cancer) is underway. Non-small cell lung cancer will be uploaded to

the guidelines portal by end of the year for public comment and will be followed by Small cell lung cancer in 2012.

Topic authors for non-small cell lung cancer have assessed the literature and performed critical appraisals on the wiki platform using the online critical appraisal form. Relevant organisations, experts and interested parties will be consulted during the public comment phase.

Prevention and screening will be the next area of focus for revision.

### **Clinical practice guidelines for the treatment and management of endometrial cancer**

The draft guidelines, which focus on management and treatment of apparent early stage low risk and high risk endometrial cancer, were released for public comment on the guidelines portal in early July.

The multidisciplinary working party met in September to review public submissions. A final version of the guidelines is expected to be available on the guidelines portal by the end of the year.

### **Clinical practice guidelines for the management of sarcoma**

Cancer Council Australia has established a working party with assistance from the Australasian Sarcoma Study Group to develop sarcoma management guidelines. Associate Professor Susan Neuhaus is chairing the working party, which had its initial meeting in July.

Key clinical questions have been developed by the working party members and a search strategy developed for literature searches.

## **Clinical practice guidelines for the management of Barrett's oesophagus and oesophageal adenocarcinoma**

Cancer Council Australia is planning development of guidelines for the detection, assessment and

management of Barrett's oesophagus and oesophageal adenocarcinoma, in partnership with Cancer Council NSW.

The multidisciplinary Working Party, chaired by Professor David Whiteman will hold its initial meeting in November.

For more information on guidelines activity contact Clinical Guidelines Network Manager, Christine Vuletich, on 02 8063 4100 or [christine.vuletich@cancer.org.au](mailto:christine.vuletich@cancer.org.au)

## **CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA (COSA)**

COSA's Annual Scientific Meeting (ASM), the premier gathering of cancer health professionals in our region, is being held from 15 to 17 November at the Perth Convention and Exhibition Centre

The meeting supports clinicians and researchers working in cancer from medical and radiation oncology, surgery, nursing, pharmacy and allied health.

This year's scientific program focuses on urological and prostate cancers, as well as the role of primary care in cancer. In 2011, COSA is partnering with the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP), which will help ensure the program includes state of the art presentations on prostate and other urogenital cancers.

For advanced trainees, COSA will host a weekend workshop 'Everything you need to know about colorectal cancer', 12-13 November 2011, at the St John of God Hospital in Subiaco.

If you haven't registered for the ASM or the Trainees weekend, we encourage you to do so via the conference website [www.cosa2011.org](http://www.cosa2011.org)

We are pleased to announce the 2012 ASM will be held in Brisbane in collaboration with the International Psycho-Oncology Society and their Australian partners, Cancer Council Queensland, the Psycho-Oncology Co-operative Research Group and the Australian Psychosocial Oncology Society. Further information will be available shortly.

Our activities over recent months have reflected the broad range of influence consistent with COSA's strategic directions. In addition to the ASM, COSA achieves an enormous amount with our limited resources, a snapshot of which is provided below.

- COSA has secured funding from Cancer Australia to develop a strategy for greater consumer engagement in clinical cancer research. We will work with our already established Cancer Trials Consumer Network, the Cancer Cooperative Trials Groups and other stakeholders to develop and implement this important project.

- In May 2011, COSA hosted its fifth workshop for health professionals working with Adolescents and Young Adults (AYA) with cancer, attended by over 100 people. Key recommendations included establishing 'AYA champions'; ongoing desire to meet the emotional and psychosocial needs of the AYA population; and the need for appropriate support for patient transition between paediatric and adult services. A full report is available on request.
- Our three guidelines for AYA cancer are at differing stages of development or completion:
  - o Fertility Preservation is complete and currently with the Department of Health and Ageing for review
  - o Psychosocial Issues – feedback from the public consultation is being incorporated in the final version
  - o Early Detection ('Lumps and Bumps') is under development.
- COSA's work in cancer care coordination continues to progress, with a conference planned for 6-7 March 2012 in Melbourne. An international speaker and some sponsorship has been secured. For more information please visit [www.cosacc2012.org](http://www.cosacc2012.org)
- Through our Developing Nations Interest Group, COSA has established a pilot fellowship program for mid-career oncologists and other cancer specialists from South East Asia to spend time in Australian centres. We welcomed our first COSA fellow in late August – a radiation physicist from Vietnam, who has a busy schedule observing at Liverpool, Royal Prince Alfred and Royal North Shore Hospitals. We are grateful to the College of Radiologists for their financial support for this fellow.

Arrangements are being finalised for a second fellow – a medical oncologist from Bangkok Thailand, whose visit to Royal Adelaide Hospital in October and November is also taking shape.

- COSA's *Head and Neck Nutrition Guidelines*, and *Guidelines for Neuroendocrine Tumours (NETs)* are



finalised and available on our wiki platform accessible via the COSA website [www.cosa.org.au](http://www.cosa.org.au)

- COSA has made multiple submissions to government on behalf of our members in response to important issues which affect our membership:
  - o to the Senate Inquiry regarding PBS deferrals
  - o to the World Health Organisation Civil Society Interactive Hearing on non-communicable diseases
  - o to the Department of Innovation, Industry, Science and Research regarding the 2011 Strategic Roadmap for Australian Research Infrastructure Roadmap

- o comment on the 2011 Strategic Roadmap for Australian Research Infrastructure Exposure Draft
- o regarding the Royal Australian and New Zealand College of *Radiologists Guidelines for Written Radiology Reports*
- o to the Medical Services Advisory Committee regarding genetic testing for hereditary mutations of the von Hippel-Lindau gene.

Please visit [www.cosa.org.au](http://www.cosa.org.au) for more information about COSA and the benefits of membership.

## MEDICAL ONCOLOGY GROUP OF AUSTRALIA

Applications open in November for MOGA's 5th Australia & Asia Pacific Clinical Research Development (ACORD) Workshop.

Held from 9 to 15 September 2012, MOGA will present the workshop with its collaborating partners, the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), American Association for Cancer Research, Cancer Council of Australia and Clinical Oncological Society of Australia.

ACORD is open to advanced trainees, junior clinicians and younger-mid career consultants working across all oncology specialities and related allied health professions, with an interest in developing their expertise in clinical trials design and research.

The program offers oncology professionals a unique one week residential training program and is the Asia-Pacific region's version of the highly regarded Flims and Vail Programs run respectively by European Society for Medical Oncology and American Society of Clinical Oncology.

Applicants are required to submit an outline of a research concept or protocol for a clinical trial that they wish to develop during and after the workshop. Sixty successful applicants from the Asia Pacific region will join an internationally renowned faculty of cancer specialists from around the globe.

Applications for the 2012 program open on 7 November and can be submitted online. For details visit [www.acordworkshop.org.au](http://www.acordworkshop.org.au) or call MOGA on 02 9256 9651.

### New chairman

The new Chairman of the MOGA, Associate Professor Gary Richardson, took up his position in early August after Associate Professor Michael Michael stepped down.

Professor Richardson stated that MOGA was at an important stage in its history with an ever-strengthening voice in advocating and lobbying on key oncology drug and treatment issues to benefit both patients and clinicians nationally, in addition to managing a range of important educational and professional programs.

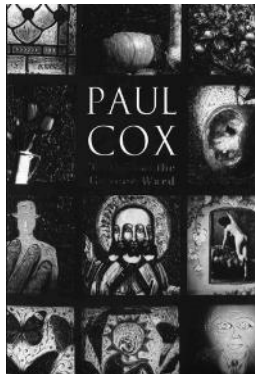
### Annual Scientific Meeting

MOGA held its 2011 Annual Scientific Meeting in Adelaide in August. The meeting examined advances in cancer care cost and value and considered the economic challenges associated with cancer care, along with sessions on the latest developments in lung cancer, colorectal cancer and neuroendocrine tumours.

The meeting was followed by the Best of ASCO Australia program, providing attendees with another forum in which to examine emerging international developments in oncology, in the Australian context.

## Tales from the Cancer Ward

Paul Cox  
Transit Lounge Publishing  
(2011)  
ISBN: 9780980846232  
208 pages  
RRP: \$29.95



This book by filmmaker Paul Cox is about his personal cancer odyssey. The author embarks on relating his inner soul to the daily intrusive encounters and the upheaving impact of dealing with liver cancer, whilst waiting for a liver transplant. Cox was diagnosed with liver cancer in February 2009. Nine months later he received a liver transplant.

From the book title *Tales from the Cancer Ward*, and the introduction, one may believe that Cox's own experience is mirrored by the experiences of Solzhenitsyn. A story set in a cancer ward, which deals with the themes of moral responsibility, mortality and hope. Solzhenitsyn's focus depicted cancer as an analogy of the Stalin era, an era of human degradation and oppression. Cox, on the other hand, draws very few parallels.

Cox's book traverses through the wilderness of his personal cancer journey. It is not an analogy between cancer and totalitarian regime. It is self-reflective. Rather than explore the reality of cancer, Cox takes the reader through various mazes. He develops a divergent view of life exploring his past, his career, money, politics and family.

When the author describes the emotional and psychological impact of being diagnosed with cancer, those impacts are described through bizarre dreams. In those dreams he grapples with the constraints and frustrations by the interminable wait for a suitable liver transplant donor. In his day to day living, he resents waiting for the phone call that a suitable donor has been found. This shackles him. He cannot plan ahead or travel as "...your life is in an endless holding pattern..."

The brief description of the author's experience from the impact and side effects of chemotherapy is a path well-trod by many others. It is heartfelt. Only those who have had chemotherapy can appreciate his descriptions when he states "...the chemotherapy snake was in my arteries..." and [chemotherapy] "...this poisonous attack on my organic being...", "...chemo cloud..." and feeling ill from the effects of chemotherapy. However, these poignant moments of vulnerability and mortality are often lost to the reader by the potpourri of distractions.

The author paints a clear picture of the frustrations which accompany a public patient in an Australian public health care system. Cox describes the nuisances of the ongoing repetition of being subjected to the myriad medical procedures and tests. The description of the parade of doctors he sees during outpatient visits defines the collective views and experiences of many.

His disappointment at missing out on a liver transplant is fuelled with a kaleidoscope of emotion. It is not until the last chapters the author finally reaches the end point of his goal, a liver transplant with a successful outcome.

There are many accounts of dreams throughout the book. The dreams appear to be a cathartic release. The bizarre nature of the dreams appears to be medically drug induced and hallucinogenic in nature. The dreams take the reader into a distorted and complex chasm that plunges you into an abyss of confusion at times. The dreams explain Cox's own fear of never being a liver transplant recipient and dying when he is desperate to live. Thus, the dreams distract from his message that he did survive cancer.

Despite the fact that the author submerged his emotions of cancer through the expression of dreams, he has endeavoured to share his cancer odyssey with anyone suffering from the same malaise in the hope that they too can triumph over cancer.

The book is a mixture of cathartic self-promotion and to some degree, reflections of human vulnerability when under siege as described in the dreams. It is not a self-help book for pending liver transplant recipients or any person facing similar circumstances. It is one person's personal cancer odyssey seen through his eyes. To recommend as a resource book falls flat as it is not an easy book to read.

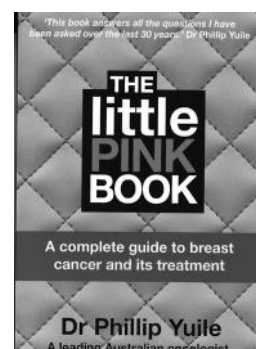
*Lesley McQuire, New South Wales.*

*Lesley is a cancer survivor who, for many years has been affiliated with cancer organisations such as Cancer Australia and Cancer Voices Australia, both as an advisor to government and as an advocate for cancer survivors. Lesley recently retired after many years working in the health sector.*

## The Little Pink Book: A complete guide to breast cancer and its treatment

Phillip Yuile  
Finch Publishing (2011)  
ISBN: 978-1-9214-6224-5  
296 pages  
RRP: \$29.95

There are many books available in the public domain on the topic of breast cancer. While the majority of these have been authored by women who have themselves experienced breast cancer, there are some helpful books written by health professionals that attempt to demystify the confusing landscape of cancer diagnosis, treatment options and ongoing care. *The Little Pink Book* is one of these.



There are several strengths of this book. The first lies in the

fact that it has been written by an oncologist in response to the myriad of questions asked by women (and some men) diagnosed with breast cancer and their families. It is therefore widely applicable to an Australian audience.

Secondly, it is a comprehensive guide (based on the best available evidence) that covers a wide variety of topics such as breast cancer's genetic predisposition, the advantages and disadvantages of support groups, complementary therapies, breast cancer in men and advanced breast cancer.

Thirdly, many of the chapters contain the voices of women who have experienced breast cancer and these threads add to the richness of the main text.

Fourthly, the complex language of cancer has been clearly explained. For example, a person can be very confused when results are explained in terms of 'absolute reduction in recurrence rates' and 'relative reduction in risk' (p134), yet Dr Yuile explains these simply and succinctly in the text.

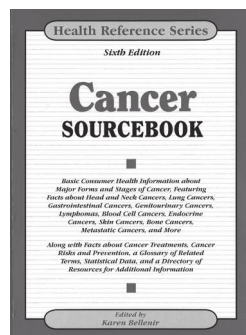
Finally, at the end of each chapter there is a summary of the key points, made which adds to the smooth progression from one chapter to the next.

*The Little Pink Book* is a valuable addition to the lay breast cancer literature. It would also be a useful resource for all health care professionals involved in the breast cancer journey.

*Katrina Breden, Palliative and Supportive Services, Flinders University, Adelaide.*

## Cancer Sourcebook

Edited by Karen Bellenir  
Health Reference Series Sixth Edition  
Omnigraphics (2011)  
ISBN: 978-0-7808-1145-4  
1105 pages  
RRP: US\$95.00



This sourcebook is the sixth edition in the Editor's Health Reference Series. The book provides the reader with a comprehensive and a contemporary view of the spectrum of cancer, its prevention, diagnosis and treatment, including end of life care. It provides the reader with statistical information and lifestyle issues that may increase risk factors for the development of cancer.

Although the book has a strong focus on cancer-related health care and services in an American context, it is a valuable resource for Australian consumers and health care professionals working in the area of cancer, especially in terms of access to online resources.

The text covers a range of treatment modalities and includes a chapter on complementary and alternative medicine. It should be noted that because of the US focus, information on certain treatments or services included in the book may not necessarily be available in Australia.

I found the book easy to follow, as the author has been very clear in her preface as to how to most effectively use this

resource. The book is divided into chapters related to each specific cancer. In the beginning of each chapter there is a general introduction about the cancer under discussion and then particular information related to detection, treatment modalities, pathology and at times some simple schematic drawings related to the cancer type.

The author discusses the process and benefits of obtaining a second opinion, and includes information about advance directives and living wills. A comprehensive glossary of cancer-related terminology provides an easy to understand reference for consumers and carers. The book contains excerpts and evidence from reputable organisations including the American Society of Clinical Oncology, Cancer Research UK and the American Institute for Cancer Research.

The author however, does not include any specific advice on survivorship or supportive care in any depth, except in the chapters on cancer recurrence and palliative care, although it is noted that the primary focus of the book is on cancer treatment and symptom management. One unique aspect of this book is the chapter on 'cancer fraud' and unproven therapies which hold false promises.

Overall, I would recommend this book to Australian consumers as a resource for basic information concerning the various types of cancer and treatment management, with the caveat that it has a significant American focus.

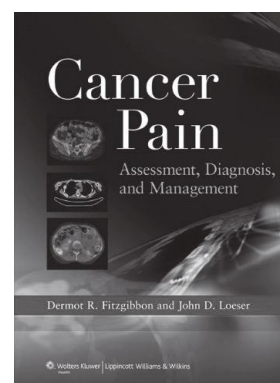
*Helena Green, King Edward Memorial Hospital, Subiaco, Western Australia.*

## Cancer Pain Assessment, Diagnosis and Management

Dermot R. Fitzgibbon and John D. Loeser  
Lippincott Williams and Wilkins (2010)  
ISBN-13:9781608310890  
378 pages  
RRP: US\$149.00

This excellent reference book was written by Associate Professor Dermot Fitzgibbon and Professor Emeritus John Loeser, both very experienced practitioners in the field of cancer pain and based in the University of Washington, Seattle. Its timely printing coincided with the last year of the 'Decade of Pain Control and Research', as designated by the U.S. Congress.

I found it refreshing to read this text as it looks at pain in a very holistic manner, from generalised epidemiology



through to the various tumour groups and pathophysiology, into the complex causes and manifestations of pain in the cancer patient group. This book looks into the psychological manifestations of pain and the diagnosis of cancer. It also covers the many painful side-effects of routine cancer treatments. Topics also include complimentary and alternative medicine



and an overview of nanotechnology which may lead to significant advances in the delivery of controlled release implantable analgesia.

Individual aspects of each topic are easily identifiable and are clearly labelled. Tables are used extensively to summarise important points throughout the discussion. The graphics contribute to the text in a meaningful way and the tables, particularly those directly related to the many different types of analgesia, are clear and easy to interpret. Each chapter concludes with an extensive reference list. It has been written for the American market and as such all statistical data is American.

I believe that this text would be beneficial for doctors and advanced practice nurses who are working and studying in the cancer and palliative care fields. It provides in-depth discussion into the wide variety of causes of pain and treatment modalities, although at times the discussion is very complex, drilling down to the molecular structure level, and may leave the average clinician feeling overwhelmed. It may benefit those of us who are requiring in-depth knowledge and evidence for research and/or teaching.

Included in the appendices are some valuable assessment tools and examples other patient information/consent forms.

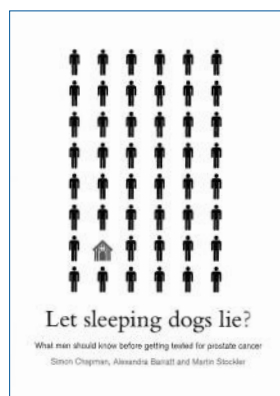
*Colleen Carter, Department of Palliative Care, Campbelltown and Camden Hospitals, New South Wales.*

## Let sleeping dogs lie? What men should know before getting tested for prostate cancer.

Simon Chapman, Alexandra Barratt and Martin Stockler  
Sydney University Press (2010)  
ISBN: 978-1-920899-68-4  
134 pages  
RRP: AU\$25.00

In the run up to the popular multi-cause fundraising activities of Movember, it is timely to draw attention to one of the causes covered under this umbrella – prostate cancer. When asked to review this book, I wondered exactly who it was written for. The authors take 14 pages to explain why they have written the book, but they don't clearly identify the intended audience.

And that is disappointing. This small book is written for men, but which groups of men? Smart and educated men in my circle have been diagnosed with prostate cancer or have been worried by high PSA tests. Yet, when discussing the book with them, they suggested it might be best suited as an adjunct text for students of the health professions. These men all invariably asked for the simplified fact sheet or executive summary – they would not necessarily have read the academic discussion



contained within. A shame – a missed opportunity to get a very pertinent and compelling message to the intended audience. How did this happen when the book was primarily penned by a life member and previous chairman of the Australian Consumer's Association. Was the book 'road tested' by consumers (perhaps a few non-health 'blokes' at least) for uptake and usability?

If a critical point for men worried about prostate cancer is when they are seeing a general practitioner, then the GP at the point of examination needs to ensure they address that man's unique history and factors that would warrant the path of PSA testing. I also wonder why the authors didn't collaborate with peak bodies or professional groups to ensure GPs are exposed to this significant case against routine screening.

I had a problem with the use of the proverb in the title: Let sleeping dogs lie? (To not try to change a situation because you might upset the status quo). Does trying to be provocative and controversial in such a controversial space help?

It is a very compelling read though, because of the controversies – every health professional should consider its key message as a principle (what does the evidence tell us?) in their practice and in their influence personally. The case is built strongly through the chapters: What is prostate cancer and how common is it? What is the risk of dying from prostate cancer? What is the risk of being diagnosed? What increases or decreases the risk of prostate cancer? How is it diagnosed? What are the treatments for early stage? To screen or not to screen? And, some further questions and answers.

The most telling message came for me on page 61 when the authors quoted Doctor R Albin (who discovered PSA in 1970) who wrote forcefully, in 2010, describing the test's popularity as "... a hugely expensive public health disaster .... the test is hardly more effective than a coin toss ... it can't detect prostate cancer and ... it can't distinguish between the two types of prostate cancer – the one that will kill you and the one that won't..."

The authors make the point, as did Professor Ian Olver, writing recently in *The Punch* (6 September 2011) that the debate has been messy and personal, much like a dirty schoolyard brawl. "Raising awareness is a catchcry for cancer events. Prostate cancer awareness is complicated like no other cancer by the mixed messages on early detection." The authors highlight some of the misinformation that has been 'peddled' of late in public media ... often in conjunction with specific fundraising initiatives. We all need to be mindful of these mixed messages – the public may have become wary and distrustful of 'competing' health professionals and organisations.

It is a useful and timely book. Download the PDF file free at: [hdl.handle.net/2123/6835](http://hdl.handle.net/2123/6835)

The general messages men receive about prostate cancer are confusing and aimed at either routine screening or individual choice (depending on the 'authority' giving the recommendation), despite the tenet of this book, that routine screening with PSA is not effective and that the key message of prostate cancer is that each man should consider his unique risks and hence the need for screening.

*Gabrielle Prest, New South Wales.*



# CALENDAR OF MEETINGS



## AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
<b>November</b>			
8-11	Australasian Leukaemia and Lymphoma Group Biannual Scientific Meeting	Brisbane, Queensland	Australasian Leukaemia and Lymphoma Group Website: <a href="http://www.allg.org.au">www.allg.org.au</a> Email: <a href="mailto:dilupa.uduwela@petermac.org">dilupa.uduwela@petermac.org</a> Phone: +61 3 9656 2764
15-17	Clinical Oncological Society of Australia 38 <sup>th</sup> Annual Scientific Meeting	Perth, Western Australia	Clinical Oncological Society of Australia (COSA) Website: <a href="http://www.cosa.org.au">www.cosa.org.au</a> Email: <a href="mailto:cosa@cancer.org.au">cosa@cancer.org.au</a> Phone: +61 2 8063 4100
<b>2012</b>			
<b>February</b>			
22-25	ANZGOG Annual Scientific Meeting	Gold Coast, Queensland	YRD (Aust) Pty Ltd Website: <a href="http://www.anzgog.org.au">www.anzgog.org.au</a> Email: <a href="mailto:anzgog@yrd.com.au">anzgog@yrd.com.au</a> Phone: +61 7 3368 2422
<b>March</b>			
6-7	Clinical Oncological Society of Australia Cancer Care Coordinators Conference	Melbourne, Victoria	Clinical Oncological Society of Australia (COSA) Website: <a href="http://www.cosa.org.au">www.cosa.org.au</a> Email: <a href="mailto:cosa@cancer.org.au">cosa@cancer.org.au</a> Phone: +61 2 8063 4100
<b>May</b>			
1-4	Trans-Tasman Radiation Oncology group 24th Annual Scientific Meeting	Darwin, Northern Territory	Trans-Tasman Radiation Oncology group (TROG) Website: <a href="http://www.trog.com.au">www.trog.com.au</a> Email: <a href="mailto:trog@trog.com.au">trog@trog.com.au</a> Phone: +61 2 4014 3911
24-26	9th Australasian Lymphology Association Conference	Cairns, Queensland	Australasian Lymphology Association Website: <a href="http://alaconference.com.au">http://alaconference.com.au</a> Email: <a href="mailto:ala@thinkbusinessevents.com.au">ala@thinkbusinessevents.com.au</a> Phone: +61 3 9417 1350
<b>July</b>			
6-7	Cancer Nurses Society of Australia 15th Winter Congress 2012	Hobart, Tasmania	Cancer Nurses Society of Australia (CNSA) Website: <a href="http://www.cnsa.org.au">www.cnsa.org.au</a> Email: <a href="mailto:info@cnsa.org.au">info@cnsa.org.au</a> Phone: (02) 8063 4100
<b>September</b>			
9-15	Australia & Asia Pacific Clinical Oncology Research Development (ACORD) Workshop 2012	Sunshine Coast, Queensland	Australia & Asia Pacific Clinical Oncology Research Development (ACORD) Website: <a href="http://www.acordworkshop.org.au">www.acordworkshop.org.au</a> Email: <a href="mailto:moga@moga.org.au">moga@moga.org.au</a> Phone: +61 2 8247 6210
<b>October</b>			
23-26	Sydney International Breast Cancer Congress 2012	Sydney, New South Wales	Sydney International Breast Cancer Congress 2012 Managers Website: <a href="http://www.sydneybreastcancer2012.com">www.sydneybreastcancer2012.com</a> Email: <a href="mailto:sydneybreastcancer2012@arinex.com.au">sydneybreastcancer2012@arinex.com.au</a> Phone: + 61 2 9265 0700
<b>November</b>			
13-15	Clinical Oncological Society of Australia 39th Annual Scientific Meeting	Brisbane, Queensland	Clinical Oncological Society of Australia (COSA) Website: <a href="http://www.cosa.org.au">www.cosa.org.au</a> Email: <a href="mailto:cosa@cancer.org.au">cosa@cancer.org.au</a> Phone: +61 2 80634100

# CALENDAR OF MEETINGS

## INTERNATIONAL

Date	Name of Meeting	Place	Secretariat
<b>November</b>			
1-6	Society for Immunotherapy of Cancer 26th Annual Meeting & Associated Programs'	Maryland, United States of America	Society for Immunotherapy of Cancer Website: <a href="http://www.sitcancer.org">www.sitcancer.org</a> Email: <a href="mailto:ncouto@sitcancer.org">ncouto@sitcancer.org</a> Phone: +414 271 2456
3 - 4	American Institute for Cancer Research Annual Research Conference 2011 on Food, Nutrition, Physical Activity & Cancer	Washington DC, United States of America	American Institute for Cancer Research (AICR) Website: <a href="http://www.aicr.org">www.aicr.org</a> Email: <a href="mailto:research@aicr.org">research@aicr.org</a> Phone: (800) 843-8114
3 - 5	ABC1 Advanced Breast Cancer – First Consensus Conference	Lisbon, Portugal	European School of Oncology (ESO) Website: <a href="http://www.abc-lisbon.org">www.abc-lisbon.org</a> Email: <a href="mailto:abc@eso.net">abc@eso.net</a> Phone: +39 02 85464 526
3 - 5	11th Meeting of the International Society of Geriatric Oncology	Paris, France	International Society of Geriatric Oncology Website: <a href="http://www.siog.org">www.siog.org</a> Email: <a href="mailto:siog@genolier.net">siog@genolier.net</a> Phone: +41 22 366 9106
5 – 7	The 16th World Conference of Cryosurgery	Paris, France	International Society of Geriatric Oncology Website: <a href="http://www.siog.org">www.siog.org</a> Email: <a href="mailto:siog@genolier.net">siog@genolier.net</a> Phone: +41 22 366 9106
6 - 9	National Cancer Research Institute Cancer Conference	Liverpool, England	National Cancer Research Institute (NCRI) Website: <a href="http://www.ncri.org.uk">www.ncri.org.uk</a> Email: <a href="mailto:ncriconference@ncri.org.uk">ncriconference@ncri.org.uk</a> Phone: + 02034638134
10 -11	21st Asia Pacific Cancer Conference 2011	Kuala Lumpur, Malaysia	21st Asia Pacific Cancer Conference (APCC) Website: <a href="http://www.apcc2011.com">www.apcc2011.com</a> Email: <a href="mailto:apcc2011@aosconventions">apcc2011@aosconventions</a> Phone: +303 4252 9100
16 - 17	IX Madrid Breast Cancer Conference	Madrid, Spain	DR. Hernán Cortés-Funes Website: <a href="http://www.madridbreastcancer2011.com">www.madridbreastcancer2011.com</a> Email: <a href="mailto:b.navarro@bnyco.com">b.navarro@bnyco.com</a> Phone: + 34 91 571 93 90
18	2011 World Cancer Leaders' Summit	Dublin, Ireland	Irish Cancer Society Email: <a href="mailto:reception@irishcancer.ie">reception@irishcancer.ie</a> Phone: + 353 1 2310 500
27-2/12	97th Radiological Society of North America Scientific Assembly and Annual Meeting	Chicago, Illinois, United States of America	Radiological Society of North America (RSNA) Website: <a href="http://www.rsna.org/rsnsa">www.rsna.org/rsnsa</a> Email: <a href="mailto:reginfo@rsna.org">reginfo@rsna.org</a> Phone: +1 630 571 7879
29 - 30	International Conference on Ovarian Cancer Screening 2011	London, England	Royal College of Physicians Website: <a href="http://www2.kenes.com/ocs2011/Pages/Home.aspx">www2.kenes.com/ocs2011/Pages/Home.aspx</a> Email: <a href="mailto:kenesuk@kenes.com">kenesuk@kenes.com</a> Phone: + 02073838030
30 – 3/12	AORTIC 2011 International Cancer Conference	Cairo, Egypt	AORTIC Website: <a href="http://www.aortic-africa.org">www.aortic-africa.org</a> Email: <a href="mailto:aortic@telkomsa.net">aortic@telkomsa.net</a> Phone: +27 21 689-5359 December
<b>December</b>			
8-12	34th Annual San Antonio Breast Cancer Symposium	San Antonio, Texas, United States of America	CTRC Research Foundation Website: <a href="http://www.sabcs.org">www.sabcs.org</a> Email: <a href="mailto:rmarkow@crec.net">rmarkow@crec.net</a> Phone: +1 210 450 5912

# CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
<b>2012</b>			
<b>January</b>			
12 - 13	Breast and Gynaecological cancer conference	Cairo, Egypt	European Society for Medical Oncology (ESMO) Website: www.bgicc.eg.net Email: bgicc2010@gmail.com Phone: +02 0101300236
31 - 3/2	23rd International Congress on Anti-Cancer Treatment	Paris, France	International Congress on Anti-Cancer Treatment (ICTACT) Website: www.icact.fr Email: valerie.caillon@im-events.com Phone: +00 33(0)1 4743 5000
<b>February</b>			
2 - 5	Up Close and Personalized, International Congress on Personalized Medicine	Florence, Italy	UPCP Website: www.upcp.org Email: ilanab@paragon-conventions.com Phone: + 41 22 5330 948
16 - 19	5th SAARC Congress of Radiology	Nepal	Nepal Radiologists' Association (NRA) Website: www.scr-2012nepal.org Email: scr_2012nepal@yahoo.com Phone: + 0097725534082
22 - 25	30th German Cancer Congress	Berlin, Germany	German Cancer Congress Website: http://dkk2012.de Email: bastian.nowotnick@kukm.de Phone: +49 (0)3643 2468-0
23 - 25	Palliative Medicine and Supportive Oncology 2012 The 15th International Symposium	Florida, United States of America	Cleveland Clinic Website: www.clevelandclinicmeded.com Email: cmeregistration@ccf.org Phone: +216.448.0777
<b>March</b>			
8 - 10	10th International Symposium on Targeted Anticancer Therapies	Amsterdam, Holland	NDDO Education Foundation Website: www.tatcongress.org Email: tat@mccm.nl Phone: +31 (0)88 0898100
9 - 10	ESMO conference on Sarcoma and GIST	Milan, Italy	European Society for Medical Oncology Website: /www.esmo.org Email: registration@esmo.org Phone: +41 (0)91 973 19 26
16 - 18	Women's Health 2012: The 20th Annual Congress	Washington DC, United States of America	National Cancer Institute Website: http://www.bioconferences.com/CONFERENCES/WomensHealth/ Email: womenshealth2012@liebertpub.com Phone: + 914 740 2100
20-24	8th European Breast Cancer Conference	Brussels, Belgium	European Cancer Organisation Website: www.ecco.org.eu Email: nicola.pellegrino@ecco-org.eu Phone: +32 02 775 02 07
20-24	15th World Conference on Tobacco or Health	Singapore	World Conference on Tobacco or Health Website: www.wctoh2012.org Email: info@wctoh2012.org Phone: +65 6496 5554
22-24	1st St Gallen International Gastro-Intestinal Cancer Conference	St Gallen, Switzerland	St.Gallen Oncology Conferences SONK Website: http://www.oncoconferences.ch/ Email: info@oncoconferences.ch Phone: +41 71 243 0032

# CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
<b>2012</b>			
<b>April</b>			
15 - 18	28th IABCR/Breakthrough Breast Cancer Conference	Manchester, United Kingdom	Manchester Cancer Research Centre Website: <a href="http://www.mcr.man.ac.uk">www.mcr.man.ac.uk</a> Email: <a href="mailto:iabcr-breakthrough@mcr.man.ac.uk">iabcr-breakthrough@mcr.man.ac.uk</a> Phone: + 0161 446 3156
18 - 21	3RD European lung cancer conference	Geneva, Switzerland	European Society for Medical Oncology Website: <a href="http://www.esmo.org">www.esmo.org</a> Email: <a href="mailto:lungcancer2012@esmo.org">lungcancer2012@esmo.org</a> Phone: +41 (0)91 973 19 24
<b>May</b>			
3 - 5	4th IMPAKT Breast Cancer Conference	Brussels, Belgium	European Society for Medical Oncology (ESMO) Website: <a href="http://www.esmo.org/events/breast-2012-impakt.html">http://www.esmo.org/events/breast-2012-impakt.html</a> Email: <a href="mailto:esmo@esmo.org">esmo@esmo.org</a> Phone: +41 91 973 19 00
9 - 13	ESTRO 31 International Oncology Forum	Barcelona, Spain	European Society for Therapeutic Radiology and Oncology (ESTRO) Website: <a href="http://www.estro.org">www.estro.org</a> Email: <a href="mailto:events@estro.org">events@estro.org</a> Phone: +32 2 775 93 40
<b>June</b>			
1 - 5	ASCO Annual Conference	Chicago, United States of America	American Society of Clinical Oncology (ASCO) Website: <a href="http://www.asco.org.au">www.asco.org.au</a> Email: <a href="mailto:membermail@asco.org">membermail@asco.org</a> Phone: (571) 483-1300
7 - 8	5th Familial Cancer Conference	Madrid, Spain	European School of Oncology (ESO) Website: <a href="http://www.eso.net">www.eso.net</a> Email: <a href="mailto:dmengato@eso.net">dmengato@eso.net</a> Phone: +39 02 8546451
28 - 30	MASCC/ISOO International Symposium "Supportive Care makes excellent cancer care possible"	New York City, United States of America	Multinational Association of Supportive Care in Cancer (MASCC) Website: <a href="http://www.mascc.org">www.mascc.org</a> Email: <a href="mailto:aschultz@mascc.org">aschultz@mascc.org</a> Phone: +45 4820 7022
<b>July</b>			
13	2012 Best of ASCO	Chicago, United States of America	American Society of Clinical Oncology (ASCO) Website: <a href="http://www.asco.org.au">www.asco.org.au</a> Email: <a href="mailto:membermail@asco.org">membermail@asco.org</a> Phone: (571) 483-1300
22-24	1st St Gallan International Gastro-Intestinal Cancer Conference	St Gallan, Switzerland	St.Gallen Oncology Conferences SONK Website: <a href="http://www.oncoconferences.ch/">http://www.oncoconferences.ch/</a> Email: <a href="mailto:info@oncoconferences.ch">info@oncoconferences.ch</a> Phone: +41 71 243 0032
<b>August</b>			
27 - 30	UICC World Cancer Congress	Montreal, Canada	Union for International Cancer Control (UICC) Website: <a href="http://www.worldcancercongress.org">www.worldcancercongress.org</a> Email: <a href="mailto:congress@uicc.org">congress@uicc.org</a> Phone: +41 22 809 1811



# CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
<b>2012</b>			
<b>September</b>			
13 - 15	2012 Breast Cancer Symposium	San Francisco, United States of America	American Society of Clinical Oncology (ASCO) Website: <a href="http://www.asco.org.au">www.asco.org.au</a> Email: <a href="mailto:membermail@asco.org">membermail@asco.org</a> Phone: + 57 1 483 1300
28 – 2/11	37th ESMO conference	Vienna, Austria	European Society for Medical Oncology Website: <a href="http://www.esmo.org">www.esmo.org</a> Email: <a href="mailto:registration@esmo.org">registration@esmo.org</a> Phone: +41 91 973 19 26
<b>October</b>			
	2nd International Conference on Cancer and the Heart	Texas, United States of America	MD Anderson Cancer Center Website: <a href="http://www.mdanderson.org">www.mdanderson.org</a> Email: <a href="mailto:register@mdanderson.org">register@mdanderson.org</a> Phone: + 713 792 2223
<b>November</b>			
24 - 30	4th ESO-SIOP Europe Masterclass in Paediatric Oncology	Rome, Italy	European School of Oncology (ESO) Website: <a href="http://www.eso.net">www.eso.net</a> Email: <a href="mailto:dknupfer@eso.net">dknupfer@eso.net</a> Phone: +41 91 811 8450
<b>2012</b>			
<b>January</b>			
24 - 26	2013 Gastrointestinal Cancers Symposium	San Francisco, United States of America	American Society of Clinical Oncology (ASCO) Website: <a href="http://www.asco.org.au">www.asco.org.au</a> Email: <a href="mailto:membermail@asco.org">membermail@asco.org</a> Phone: + 571 483 1300
<b>February</b>			
14 - 16	2013 Genitourinary Cancers Symposium	Florida, United States of America	American Society of Clinical Oncology (ASCO) Website: <a href="http://www.asco.org.au">www.asco.org.au</a> Email: <a href="mailto:membermail@asco.org">membermail@asco.org</a> Phone: + 571 483 1300
<b>March</b>			
12 - 16	13th International Conference of Primary Therapy of Early Breast Cancer	St Gallen, Switzerland	St Gallen Oncology Website: <a href="http://www.oncoconferences.ch">www.oncoconferences.ch</a> Email: <a href="mailto:info@oncoconferences.ch">info@oncoconferences.ch</a> Phone: +41 71 243 0032
<b>May</b>			
31 – 4/6	2013 ASCO Annual Meeting	Chicago, United States of America	American Society of Clinical Oncology (ASCO) Website: <a href="http://www.asco.org.au">www.asco.org.au</a> Email: <a href="mailto:membermail@asco.org">membermail@asco.org</a> Phone: (571) 483-1300

## CANCER COUNCIL AUSTRALIA

Cancer Council Australia is the nation's peak cancer control organisation.

Its members are the leading state and territory Cancer Councils, working together to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.



### **MEMBERS**

Cancer Council ACT  
Cancer Council New South Wales  
Cancer Council Northern Territory  
Cancer Council Queensland  
Cancer Council South Australia  
Cancer Council Tasmania  
Cancer Council Victoria  
Cancer Council Western Australia

### **AFFILIATED ORGANISATIONS**

Clinical Oncological Society of Australia

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Hon H Cowan

*Vice President*  
Mr S Foster

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Ms R Martinello  
Mr P Perrin  
Mr S Roberts  
Ms J Brown  
Mr J Harper

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## CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA

The Clinical Oncological Society of Australia (COSA) is a multidisciplinary society for health professionals working in cancer research or the treatment, rehabilitation or palliation of cancer patients.

It conducts an annual scientific meeting, seminars and educational activities related to current cancer issues. COSA is affiliated with Cancer Council Australia.



**Clinical  
Oncological  
Society of  
Australia**

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Associate Professor M Krishnasamy  
Dr H Dhillon  
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Professor J Zalcborg OAM

### **MEMBERSHIP**

Further information about COSA and membership applications are available from:

[www.cosa.org.au](http://www.cosa.org.au) or [cosa@cancer.org.au](mailto:cosa@cancer.org.au)

Membership fees for 2011

Medical Members: \$160

Non Medical Members: \$100 (includes GST)

### **PROFESSIONAL GROUPS**

Breast  
Cancer Nurses Society of Australia  
Cancer Pharmacists  
Cancer Biology  
Clinical Research Professionals  
Epidemiology  
Familial Cancer  
Gastrointestinal  
Gynaecology  
Lung  
Medical Oncology  
Melanoma and Skin  
Neuro-oncology  
Nutrition  
Palliative Care  
Paediatric Oncology  
Psycho-oncology  
Radiation Oncology  
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Social Work  
Surgical Oncology  
Urologic Oncology

## Information for contributors

*Cancer Forum* provides an avenue for communication between all those involved in the fight against cancer and especially seeks to promote contact across disciplinary barriers.

To this end articles need to be comprehensible to as wide a section of the readership as possible. Authors should provide sufficient introductory material to place their articles in context for those outside their field of specialisation.

### Format

*Cancer Forum* welcomes original articles about medical, scientific, political, social, educational and administrative aspects of cancer control. All manuscripts should be submitted by email to [info@cancerforum.org.au](mailto:info@cancerforum.org.au) as MS Word documents.

Length: 2000-2500 words.

Font: Arial - 20pt for title, 12pt for headings and 10pt for text.

Following the title, include your full name, organisation and email address.

Include an introductory heading and sub-headings that describe the content.

Number pages in the footer.

### Abstract

All manuscripts must include an abstract of approximately 200 words, providing a summary of the key findings or statements.

### Illustrations

Photographs and line drawings can be submitted via email or on disk, preferably in tiff or jpeg format, or as transparencies or high quality prints.

If images are not owned by the author, written permission to reproduce the images should be provided with the submission.

### Referencing

Reference numbers within the text should be superscripted and placed after punctuation.

The list of references at the end of the paper should be numbered consecutively in the order in which they are first mentioned and be consistent with the National Library of Medicine's International Committee of Medical Journal Editors' *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*.

eg. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med*. 2002 Jul 25;347(4):284-7.

A full guide is available at [www.nlm.nih.gov/bsd/uniform\\_requirements.html](http://www.nlm.nih.gov/bsd/uniform_requirements.html)

**The Editorial Board will make the final decision on publication of articles and may request clarifications or additional information.**

### Manuscripts should be emailed to:

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