

# CANCER FORUM



**July 2013**

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FORUM: Lung Cancer

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Reports

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Australian behavioural research in cancer

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# CANCER FORUM



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# CANCER FORUM

## Contents

### ■ ■ ■ Cancer Forum July 2013 – Lung cancer

Guest editors: Nick Pavlakis and Benjamin Solomon

<i>Lung cancer beyond 2013: many different diseases</i> Nick Pavlakis and Benjamin Solomon	143
<i>Screening for lung cancer</i> Henry M Marshall and Kwun M Fong	146
<i>Surgery for non-small cell lung cancer</i> Marosh Vrtik and Naveed Z Alam	150
<i>Radiotherapy in lung cancer</i> Shalini K Vinod and David L Ball	153
<i>Molecular pathology in lung cancer</i> Wendy A Cooper and Sandra A O'Toole	158
<i>EGFR targeted therapy and resistance</i> Csilla Hasovits and Nick Pavlakis	165
<i>Other novel molecular targets in non-small cell lung cancer: it's not all about EGFR</i> Ross Cruikshank and Brett Hughes	170
<i>Small cell lung cancer update</i> Danielle Ferraro and Michael Millward	174
<i>Malignant pleural mesothelioma</i> Florian Honeyball, Michael Boyer, Nico van Zandwijk, and Steven C Kao	178

### ■ ■ ■ Reports

<i>Australian behavioural research in cancer</i>	183
<i>Cancer Council Australia</i>	185
<i>Clinical Oncological Society of Australia</i>	187
<i>Faculty of Radiation Oncology, RANZCR</i>	187
<i>Medical Oncology Group of Australia</i>	188

■ ■ ■ <b>Book reviews</b>	189
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■ ■ ■ <b>Calendar of meetings</b>	190
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## ABBREVIATIONS

### Common abbreviations in this issue of *Cancer Forum*

ALK – anaplastic lymphoma kinase

COPD – chronic obstruction pulmonary disease

CT – computed tomography

CXR – plain chest radiography

DNA - deoxyribonucleic acid

EGFR – epidermal growth factor receptor

FGFR – fibroblast growth factor receptor

FISH – fluorescence in situ hybridisation

IHC – immunohistochemistry

MPM - malignant pleural mesothelioma

NSCLC – non-small cell lung cancer

PBS – Pharmaceutical Benefits Scheme

PCI – prophylactic cranial irradiation

PET– positron emission tomography

SABR – stereotactic ablative radiotherapy

SCC – squamous cell carcinoma

SCLC – small cell lung cancer

TGA – Therapeutic Goods Administration

TKI – tyrosine kinase inhibitor

VATS – video assisted thoracic surgery



## Lung Cancer

# LUNG CANCER BEYOND 2013: MANY DIFFERENT DISEASES

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Lung cancer continues to be the leading contributor to cancer-related mortality worldwide.<sup>1</sup> In Australia, lung cancer is the fourth most commonly diagnosed cancer, but the leading cause of cancer death, with non-small cell lung cancer (NSCLC) making up the vast majority of cases.<sup>2</sup> Despite public health policies and tobacco control legislation, smoking continues to be the main risk factor in Australia and worldwide.<sup>2</sup> While the incidence rate for lung cancer in men has been decreasing, there has been an increase in the incidence rate in women, paralleling smoking trends.<sup>2</sup> In Australia, the absolute number of lung cancer cases will continue to increase as the population ages.<sup>3</sup> Lung cancer in never smokers is also a significant health problem, accounting for greater than 12 per cent of lung cancer deaths.<sup>4</sup> Unfortunately, the large proportion of patients with lung cancer present late with advanced/metastatic disease, resulting in the high observed mortality rate that has improved only slightly over the last two decades (from 1982-1987 to 2000-2007 five-year relative survival increased from 8% to 11% for males and 10% to 15% for females).<sup>2</sup> Malignant pleural mesothelioma, the asbestos related malignancy of the pleura, also continues to be a problem in Australia with its high per capita incidence.<sup>5</sup> Despite the nationwide ban on importing and using all forms of asbestos from 31 December 2003, mesothelioma incidence continues to rise, with 612 new cases reported in Australia in 2011.<sup>6</sup>

This edition of *Cancer Forum* coincides with the 15th World Conference of Lung Cancer and is focused on lung cancer and mesothelioma management. It highlights current practice and recent developments in lung cancer screening, drug therapy, surgery, radiotherapy and ongoing developments in the molecular pathology of NSCLC.

### Non-small cell lung cancer

The last five years has seen a paradigm shift in the treatment of metastatic NSCLC, led by improvements in the understanding of the molecular biology of this disease. Historically, all patients with NSCLC were treated empirically with chemotherapy. Recent practice changing advances include the recognition of greater efficacy with certain chemotherapy regimens according to histologic sub-type. Different sub-types benefit from

maintenance therapies in non-progressing patients after first-line chemotherapy and the identification of molecular subgroups of adenocarcinoma that benefit from specific targeted therapies. These advances have seen the practical application of histologic sub-classification of NSCLC into two groups, squamous cell carcinoma and adenocarcinoma, where further molecular phenotyping to identify underlying 'driving' mutations has led to the use of specific targeted therapy, leading to more substantial clinical benefit than historically observed with empirical chemotherapy. These advances have recognised that lung cancer cannot be considered one disease and that where possible, effort should be made to tailor drug therapy in order to maximise therapeutic benefit for individual patients. The collective evidence for the management of lung cancer was recently reviewed by Cancer Council Australia to produce its new *Clinical Practice Guidelines for the management of lung cancer* ([http://wiki.cancer.org.au/australia/Guidelines:Lung\\_cancer](http://wiki.cancer.org.au/australia/Guidelines:Lung_cancer)). A novel approach used in the preparation of these guidelines was the use of a wiki platform, making it much easier to update the guidelines as new high-level evidence emerges for future change of practice.

While the majority of lung cancer patients present with largely incurable locally advanced or metastatic disease, those patients fortunate enough to have early disease at diagnosis can receive potentially curative treatment. Marshall and Fong review the development of lung cancer screening to date, extending from the historical failures of chest radiography screening through to the more promising approach of low dose computed screening as evaluated in the landmark National Lung Cancer Screening Trial.<sup>7</sup> The potential benefits in terms of detection of early stage disease, the potential for harm through false positives and adverse effects, and the cost-effectiveness of screening are reviewed together with the challenges of implementing screening programs.

Vrtik and Alam provide an overview of the role of surgery in the various stages of NSCLC.<sup>8</sup> The mediastinum remains an important area to accurately stage pre-operatively. Approaches to accurately stage the mediastinum are reviewed, including mediastinoscopy and endobronchial ultrasound guided trans-bronchial needle aspiration, with

the increasing availability and accuracy of endobronchial ultrasound greatly reducing the need for mediastinoscopy. In operable patients, surgery remains the treatment of choice for patients with Stage I, II and IIIA (T3N0, 1, T4 N0, 1) disease,<sup>9</sup> alone or as part of a multimodality treatment regimen. Complete surgical resection can be achieved by either lobectomy or pneumonectomy, whereas in high-risk surgical patients (those with significant medical co-morbidities or poor pre-existing lung function), lesser surgery can be performed. The greatest recent advance in surgery for lung cancer – video-assisted thoracoscopic surgery (VATS) – is reviewed, revealing how VATS lobectomy is increasingly considered the procedure of choice for patients with early stage lung cancer.

The important role of radiation therapy in the multidisciplinary management of lung cancer is discussed by Vinod and Ball.<sup>10</sup> Its importance as a potentially curative treatment modality in patients with inoperable early stage or locally advanced NSCLC, or in limited stage small cell lung cancer, and in palliating symptoms in patients with advanced disease, is reviewed. Recent technological advances that assist patient selection, improve identification of the tumour, individualise radiotherapy treatment according to patient specific motion and reduce normal tissue toxicities are highlighted, including the use of stereotactic ablative radiotherapy. While many of these changes have already been incorporated into clinical practice, Vinod and Ball also describe clinical trials evaluating these approaches.

Cooper and O'Toole discuss the recent advances in the molecular pathology of lung cancer, highlighting the key actionable somatic changes seen in lung cancer, with particular emphasis on EGFR mutations and ALK gene rearrangements in adenocarcinoma, as well as identifying promising new targets in squamous cell carcinoma of the lung.<sup>11</sup> Swaying the interest in this key ongoing area of research has been the identification that tumours harbouring driver mutations are 'addicted' to the effects of these molecular changes in an oncogene, making them key targets for inhibition, with large clinical benefits observed with targeted drugs. The first major discovery leading to practice change was in the identification of activating mutations in the gene for the epidermal growth factor receptor (EGFR or HER1). These activating mutations in the EGFR gene are found in approximately 10-15% of NSCLC patients, while in Asian populations, the frequency is higher (30-40%), especially in young women who have never smoked<sup>10</sup>. Adenocarcinomas harbouring activating EGFR mutations were shown in 2004 to be very sensitive to targeted EGFR-tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib.<sup>12</sup>

Cooper and O'Toole also review the available molecular genetic techniques used to identify EGFR (and other mutations) in lung cancer, highlighting their strengths and weakness, demonstrating how today, both tissue based biopsies and cytology specimens are adequate for mutation analysis. KRAS mutations are also discussed as a poor prognostic marker, occurring in nearly 40% of adenocarcinomas and predicting for insensitivity to EGFR-TKIs. More recently identified key molecular changes in adenocarcinomas include ALK gene rearrangements, occurring in up to four per cent

of cases. The molecular features of these are discussed, including the techniques used to identify them, such as fluorescence in situ hybridisation and the potential value of immunohistochemistry to identify ALK over-expression in lung adenocarcinomas. Other rare, but potentially targetable mutations in lung adenocarcinomas, include MET gene amplifications, BRAF mutations and ROS1 gene rearrangements. Promising new targetable oncogenes in squamous cell carcinoma are also highlighted.

The clinical results of the use of EGFR targeted therapies in patients with metastatic NSCLC with EGFR mutations and those with wild-type EGFR are discussed by Hasovits and Pavlakis.<sup>13</sup> The first clinical trials with EGFR-TKIs such as gefitinib and erlotinib, were designed to follow the traditional paradigm of empirical chemotherapy of 'one size fits all'. Disappointingly, the trials investigating the addition of erlotinib or gefitinib in unselected patients receiving standard chemotherapy failed to show a benefit, while trials investigating monotherapy with the EGFR-TKIs showed only modest response rates, with only erlotinib statistically proven to prolong survival compared with placebo in the 2nd/3rd line setting.<sup>14</sup> In a pivotal Asian study of selected patients (never smokers) with adenocarcinoma, substantial clinical benefit was observed using gefitinib in patients with sensitising EGFR mutations, resulting in significantly prolonged progression free survival and much higher response rates compared with chemotherapy.<sup>15</sup> Six studies have now confirmed similar benefits in response rates and progression free survival with first-generation EGFR-TKIs (gefitinib or erlotinib) in patients with sensitising EGFR mutations, compared with chemotherapy. This has resulted in a practice shift in patients with known sensitising EGFR mutations. Newer EGFR-TKIs have also been developed, with afatinib also showing superiority to first line chemotherapy in patients with EGFR mutations.

Despite the marked improvements in progression free survival with EGFR-TKIs in the first line setting compared with chemotherapy (increases in median progression free survival by 1.7-8.5 months),<sup>13</sup> tumour progression eventually develops due to drug resistance. The different clinical scenarios at progression, the proposed mechanisms for resistance and related treatments are discussed.

Cruikshank and Hughes review recent advances in identifying molecular targets beyond the EGFR.<sup>16</sup> Rapid progress in this area is exemplified by the identification of ALK gene rearrangements in a subset of NSCLC in 2007 and the subsequent phase I, II, and III clinical trials with the ALK inhibitor crizotinib, leading to approval by the US Food and Drug Administration in 2010 and subsequently by regulatory authorities in over 50 countries worldwide. ALK gene rearrangements now represent the second validated actionable genetic alteration in lung cancer after EGFR mutations. Progress in this area continues with characterisation of mechanisms of resistance to crizotinib and with clinical trials of novel, more potent ALK inhibitors, such as LDK378 and CH5424802. Numerous other targets have been identified in both adenocarcinoma (eg. ROS1, MET and B-Raf) and in squamous cell carcinoma (eg. FGFR1, PI3Kinase and DDR2) which are currently being evaluated in clinical trials.

## Small cell lung cancer

Small cell lung cancer accounts for about 11% of lung cancers in Australia. In contrast to the dramatic progress in non-small cell lung cancer, there have been few advances in small cell lung cancer over the last two decades. Ferraro and Millward provide a concise overview regarding the current state of the art with respect to staging and management of small cell lung cancer, including recent advances such as the use of prophylactic cranial irradiation in patients with advanced disease.<sup>17</sup> They detail attempts to target molecular abnormalities identified in small cell lung cancer, which to date have been largely unsuccessful, indicating the need for further basic and translational research into this aggressive and highly lethal variant of lung cancer. RT is sometimes useful for advanced localised disease, while for unresectable local and in transit recurrences confined to a limb, regional chemotherapy with vascular isolation (isolated limb perfusion or isolated limb infusion) is the current standard of care.<sup>17</sup>

Regional lymph node recurrence is best managed by surgical lymphadenectomy. Adjuvant post-operative radiotherapy has been shown in a recent Australian multicentre trial to significantly reduce the risk of regional recurrence in patients with surgically resected high risk stage III melanoma.<sup>18</sup>

## Mesothelioma

Honeyball, Boyer and colleagues review the current treatment strategies for malignant pleural mesothelioma, with discussion of novel systemic therapies.<sup>18</sup> Unfortunately, the pleural origin of this tumour and its insidious onset leading to presentation with advanced disease, means that traditional paradigms of curative tumour resection and additional therapies are restricted to highly selected patients in specialist centres, with uncertainty over benefit due to lack of randomised evidence. Thus the mainstay of treatment is supportive, including palliative surgery for recurrent effusions, radiotherapy and palliative care with chemotherapy, with platinum and pemetrexed used in fit patients to prolong survival and improve quality of life since 2003. Despite efforts over the last decade, targeted therapy for patients with MPM has proven to be elusive. Trials of maintenance therapy with thalidomide and second line therapy with vorinostat, a histone deacetylase inhibitor, have also been unsuccessful. New directions carrying hope for positive outcomes are discussed, such as the mammalian target of rapamycin (mTOR) inhibitors, and focal adhesion kinase (FAK) inhibitors.

## Conclusion

As in most other cancers, the greatest therapeutic progress in advanced or metastatic lung cancer has come from the greater understanding of the molecular pathogenesis of the disease and the identification of targeted therapies, resulting in much greater clinical benefit than historical empirical chemotherapy. In NSCLC, cure is achievable through early detection and surgery (or radiotherapy), with or without additional therapy. For the majority of patients with relapse or metastatic disease, the way forward is by identifying their cancer's molecular signature, hoping to find one predictive for greater benefit

from targeted therapies. And yet, drug resistance to such targeted therapies, as it was for chemotherapy, will result in treatment failure, requiring ongoing work to unravel the biology of this disease. In mesothelioma and small cell lung cancer, the search continues for the elusive molecular signatures that may leapfrog outcomes achieved using our current standard chemotherapy approaches. In all the diseases discussed here, it is clear that overall progress will depend on a co-operative, multi-disciplinary effort.

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## SCREENING FOR LUNG CANCER

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### Abstract

Lung cancer is a major global health issue and will remain so for decades to come. Lung cancer screening has the potential to reduce mortality from this disease and represents one of the most exciting developments in recent years. Screening appears to have taken hold in the US, yet has received a more cautious reception in other countries, probably due to a lack of accurate cost-effectiveness data and implementation capacity uncertainties. Refinement of screening using risk prediction to select the highest risk candidates is the next challenge and, coupled with an integrated smoking cessation program, could substantially improve cost-effectiveness. Future research will determine if biomarkers in biological samples will offer a low cost and minimally invasive method of screening and early detection. In this paper we review the development of lung cancer screening to date, the current state of the art and future directions for research.

Lung cancer causes more deaths worldwide than any other cancer, estimated at 1.4 million in 2008.<sup>1</sup> The insidious nature of the disease means that it is often of advanced stage at diagnosis.<sup>2</sup> The burden of current smoking and comorbidity can worsen prognosis.<sup>3,4</sup> Nihilism surrounding the disease may lead to delays in seeking or offering treatment.<sup>5</sup> All these factors contribute to the high mortality rate of lung cancer and minimal improvement in poor five-year survival over the last quarter century (8% to 11% for males and 10% to 15% for females).<sup>2</sup>

Although lung cancer rates are declining overall in Australia, thanks to concerted anti-smoking education and legislation efforts,<sup>6</sup> lung cancer remains a major health concern. Lung cancer incidence rates lag 20–25 years behind previous smoking trends for men and approximately 25–40 years for women.<sup>7</sup> In Australia, as in most industrialised nations, cigarette consumption by women peaked 20 or so years behind that for men.<sup>7</sup> Thus declines in lung cancer rates in men have been somewhat offset by increases in women, reflecting different stages of Lopez's 'epidemic' model for the sexes.<sup>8</sup> As Australia's demographic shifts to an older population, the absolute number of new cancer cases is predicted to increase.<sup>9</sup> An estimated two million Australians aged 55–74 are current or former smokers, representing a sizable proportion of the population who remain at-risk.<sup>10</sup> Even after quitting, absolute lung cancer risk remains elevated, which explains why the majority of cancer is detected in former and not current smokers.<sup>11,12</sup>

For many low and middle-income countries where anti-tobacco legislation and education are less rigorous, the high and/or rising prevalence of smoking is a more recent phenomenon, which means the lung cancer epidemic is yet to peak in these regions.<sup>1</sup>

Against this background, lung cancer screening using computed tomography (CT) scans represents a major opportunity to improve outcomes for this potentially curable disease. This paper reviews the history of lung cancer screening, the current state of the art and future directions.

### Screening with plain chest radiography

Because lung cancer is known to have an asymptomatic, preclinical phase, it was long held that screening, actively searching for early disease in healthy people 'at risk', may be effective. From the 1960s onwards, major efforts into screening using plain chest radiography (CXR) were instigated in Europe and the US. Although CXR screening detected more cancers, it had no effect in reducing mortality.<sup>13</sup> This apparent paradox is explained by the concept of overdiagnosis, where disease never destined to become clinically-apparent (e.g. a very indolent slow-growing tumour in a person who will die from cardiac disease), is detected by screening, treated and thus apparently 'cured'.

Overdiagnosis bias is a major concern in screening programs, as it exposes people who would never have developed clinically apparent disease to the risks of unnecessary treatment. It is the subject of much on-going debate in breast and prostate cancer screening.<sup>14–17</sup> Although the CXR studies had methodological limitations,<sup>13,18</sup> the lack of clear benefit meant CXR screening never became clinical practice. However, there was sufficient doubt that the large, well designed randomised Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial was set up in the US in 1993.<sup>18</sup> The results of the lung cancer part were published in 2011;<sup>19</sup> 77,445 participants aged 55–74 years old were randomised to annual CXR screening and 77,456 to usual care (no screening). After 13 years of follow-up, cumulative lung cancer incidence rates were similar (20.1 v 19.2 per 10,000 person years), as were stage and histology. CXR screening made no difference to risk of death from lung cancer, (RR, 0.99; 95% CI, 0.87–1.22), leaving no doubt that CXR screening is ineffective.

However, before the definitive result from the PLCO trial had been reported, interest turned to CT as a potential screening tool, the hypothesis being that CXR was too insensitive to detect truly early disease (eg. tumours <1–2cm diameter) but that CT, with its excellent spatial



resolution, could very easily detect small lesions. To reduce the burden of medical radiation to patients, low-dose protocols were developed, reducing the dose to ~1.5mSv per scan, considerably lower than ~7mSv from conventionally-dosed studies. Thus began the exploration of low-dose CT (LDCT) as a screening tool.

### Screening with Low Dose Computed Tomography (LDCT)

The first LDCT screening studies were from Japan and the US and were observational in design.<sup>20-22</sup> They established that LDCT screening was acceptable to the general population, feasible for large numbers of screenees and approximately three times as sensitive as CXR in detecting small tumours. Upwards of 84% of tumours were stage 1 compared to only 16% 'localised' stage in routine clinical practice,<sup>23</sup> thus most patients could be treated surgically. These exciting results led to calls for implementation of screening in the US, however as they were observational studies lacking control groups, no estimate of the effect on lung cancer mortality could be made. Survival was reported as a surrogate endpoint, but this is open to potential bias such as lead time and length bias. Lead time bias gives an apparent increase in survival (the time from diagnosis until death), simply because the date of diagnosis is brought forward, without requiring any effect on the natural history of the disease itself. Length bias describes the preference for screening to detect slower-growing tumours. Early in the piece, it was noted that adenocarcinoma was the predominant

histological subtype detected, but that rapidly growing tumours, such as small cell and squamous carcinoma had the potential to grow quickly during the interscan period. These aggressive tumours are thus more likely to be missed on screening and for the patient to present with symptoms or at an advanced stage. More indolent tumours, by definition, have a better prognosis than aggressive tumours, which therefore makes screening appear to be very effective.

To address these methodological limitations, randomised control trials were initiated. The two largest are the National Lung Screening Trial (NLST) in the US,<sup>24</sup> and the NELSON study in Holland/Belgium.<sup>25</sup> Both studies are adequately powered to be able to detect a mortality benefit. Several smaller European randomised control trials plan to combine their data in meta analysis.<sup>26</sup> To date, only the NLST has reached its primary endpoint. Their landmark paper in 2011 reported,<sup>24</sup> for the first time, a 20% reduction in lung cancer mortality in the LDCT-screened arm compared to the control (CXR-screened) arm. In response to this result, several US bodies now endorse screening and screening is now reimbursed by several health insurance companies.<sup>27-30</sup> Certain other countries have followed suit (table 1) yet others, including Australia, remain more cautious. The UK is conducting its own randomised control trial and the British Thoracic Society issued a statement to say that screening in the UK cannot be currently advocated.<sup>31</sup> So why is there such caution?

Guideline	Primary target population	Secondary target population	Screening interval and duration
National Comprehensive Cancer Network <sup>27</sup>	<ul style="list-style-type: none"> <li>Age 55-74 years</li> <li>30 pack-year smoking history</li> <li>Smoking cessation within the past 15 years</li> </ul>	<ul style="list-style-type: none"> <li>Age ≥50 years</li> <li>20 pack-year history</li> <li>One additional lung cancer risk factor (other than second hand smoke)</li> </ul>	Annual screening Until age 74 years
American Association for Thoracic Surgery <sup>29</sup>	<ul style="list-style-type: none"> <li>Age 55-79 years</li> <li>30 pack-year smoking history</li> </ul>	<ul style="list-style-type: none"> <li>Treated lung cancer, recurrence-free after four years' surveillance</li> <li>Age 50 to 79 years; 20 pack-year smoking history; 5 year cumulative lung cancer risk of ≥ 5%</li> </ul>	Annual screening Until age 79 years
American College of Chest Physicians and the American Society of Clinical Oncology <sup>28</sup>	<ul style="list-style-type: none"> <li>Age 55-74 years</li> <li>30 pack-year smoking history</li> <li>Smoking cessation within the past 15 years</li> </ul>	none	Annual screening Until age 74 years
American Cancer Society <sup>30</sup>			
French Intergroup for Thoracic Oncology and The French-Speaking Oncology Group <sup>32</sup>			

## Screening cost-effectiveness

Although the NLST has answered the fundamental question of whether screening can reduce mortality, several other important questions remain. Because screening is more than simply subjecting people to CT scans, lesion follow-up and downstream evaluation can significantly impact screening effectiveness. In addition, detailed costs of screening are still to be reported. The NLST has yet to publish its cost-effectiveness data, but preliminary reports suggest it will achieve the currently accepted standard of less than \$50,000 per incremental cost effectiveness ratio.<sup>33</sup> Modelled estimates of LDCT screening costs have varied enormously from highly cost-effective through to highly ineffective, making coherent synthesis of their results next to impossible.<sup>34</sup> An Australian study found screening was likely to be expensive and only cost-effective if very high-risk individuals were targeted and screening was either highly effective or very cheap.<sup>35</sup> However, this study took the assumption that screening would be undertaken by case-finding (i.e. screening offered opportunistically to individuals when they sought medical care) rather than centrally-organised mass screening. The healthcare model in the US is substantially different to that in Australia, thus extrapolation of NLST costs to this country requires caution. This issue may be assisted by our Australian study of lung cancer screening, the Queensland Lung Cancer Screening Study.<sup>36</sup> This pilot observational study is modelled on the NLST and should provide data on the cost of an NLST-style screening program locally.

## Screening harms

Other factors that will impact on any screening program's effectiveness and cost-effectiveness include the false-positive and adverse event rates. False-positive scans are a common problem. In the NLST, approximately 25% of scans were found to have nodules, yet >95% of these were proven to be benign (stability or resolution on serial CT follow-up). There is currently no way of conclusively diagnosing lung cancer from CT images; shape, margin and density all have low positive predictive value. Size is the best marker, the risk increasing with larger sized nodules. After follow-up scans have been obtained, growth is also an important clue. Nonetheless, benign lesions can have very similar appearances and thus biopsy is required to establish the diagnosis. Invasive procedures for benign disease are clearly unwanted. They have the potential to cause direct harm and increase the downstream costs of screening. Both the NLST and NELSON studies used protocols requiring biopsy whenever possible, and if the nodule was too small to biopsy (approximately less than 8mm diameter), required serial monitoring for evidence of growth. A recent systematic review of screening benefits and harms found the literature difficult to interrogate in terms of screening harms due to differing reporting methods in many studies,<sup>28</sup> however rates of non-surgical invasive procedures for ultimately benign diagnoses (eg. needle biopsy and bronchoscopy) were 1.2% in both the NLST and NELSON studies.<sup>24, 25</sup> Rates of surgical procedures (eg. thoracoscopy, mediastinoscopy or thoracotomy) for benign lesions were 0.7 and 0.6% respectively. In the NLST, the rate of complications after any invasive procedure was 33 per 10,000 screenees in the LDCT arm, mostly accounted for by post-surgical complications; the rate following bronchoscopy or needle biopsy was only 1.5 per 10,000 screenees.<sup>28</sup>

## Overall perspectives

Other questions that need to be addressed for successful implementation of a screening program include how best to recruit high risk individuals. NLST and NELSON found their participants were slightly above average for education and other markers of socioeconomic status. Lower socioeconomic status groups are important to target, as they have higher cancer rates and generally worse outcomes,<sup>37</sup> yet generally are less likely to avail themselves of screening.<sup>38-40</sup> The remoteness of many Australian communities may compound the problems of access and health care equity.<sup>41</sup>

Despite the potential benefit of screening, it is imperative that we acknowledge that the most important strategy to reduce future lung cancer risk is to help smokers quit. Smoking cessation remains one of the most cost-effective health interventions,<sup>42</sup> and therefore should form an important component of any future screening program. Indeed, the combination of an integrated smoking cessation program within a screening program could improve overall cost-effectiveness.<sup>43</sup>

An area of current interest is the use of predictive risk modelling in the context of screening. The appeal is that such models may better define the 'high risk' population and may also help decide the optimal screening interval. The NLST used a simple eligibility strategy based on age and smoking history. Although undoubtedly these are the two most important risk factors, many others are well-known to contribute to risk, for example family history of lung cancer, occupational and environmental exposures and chronic obstructive pulmonary disease diagnosis. Of the published models, the best validated and most comprehensive was developed by Tammemagi et al using the PLCO dataset and subsequently refined using the NLST dataset.<sup>44, 45</sup> In a retrospective comparison to the existing NLST eligibility criteria, they found using the risk model improved screening sensitivity (83% v 71%,  $P < 0.001$ ) and positive predictive value (4.0% v 3.4%,  $P = 0.01$ ), without loss of specificity (both 63%). Using the risk model, rather than simply age and smoking criteria, to select participants would have missed approximately 40% fewer lung cancers.

Another potential use for risk stratification is in deciding the screening interval. NLST used annual screening and this is advocated by current guidelines. The NELSON study incorporated a two year interval in its study between the second and third scan and an Italian study is randomising participants to annual or biennial screening.<sup>46</sup> Another Italian study found the presence of radiological emphysema on baseline CT scan improved risk stratification and hypothesised that this could be used to help determine the subsequent screening interval.<sup>47</sup>

Theoretically, better selection of high risk screenees and tailoring scan interval to risk will lead to a lower number of false positive scans and a higher yield of lung cancer. In turn, this will lead to a more efficient and cost-effective process. Two current American guidelines recommend the use of risk estimation for potential screenees who fall outside of the NLST eligibility criteria, but who have other known risk factors (table 1).<sup>27, 29</sup> However, it must be stated that currently no risk model has been prospectively tested in a screening context, although the UK Lung Screen is undertaking this task.<sup>48</sup>

The limitations of CT scans have been well documented;

exposure to radiation, poor positive predictive value for cancer diagnosis, time taken to read by radiologists and expensive capital costs. Other novel methods for early detection and screening are the subject of vigorous research, but are outside the scope of this article. These include, for example, detection of biomarkers in exhaled breath (eg. volatile organic compounds and exhaled breath condensate) and blood biomarkers. Many screening studies have collected samples for biomarker analysis and are expected to report their findings in the next few years.

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# SURGERY FOR NON-SMALL CELL LUNG CANCER

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## Abstract

Lung cancer remains the leading cause of cancer related deaths in Australia and worldwide. Despite recent advances in screening, diagnosis and treatment, long-term overall survival of lung cancer remains poor. Surgery, either alone or as part of a multimodality treatment regimen, plays an important role in the management of patients with non-small cell lung cancer. Complete surgical resection of early stage disease can be achieved by either lobectomy or pneumonectomy. Probably the greatest recent change in surgery for lung cancer is video assisted thoracic surgery. Controversy remains around the treatment of non-small cell lung cancer with mediastinal lymph node involvement (Stage IIIA – T1-3 N2). The potential role of surgery in the palliation of lung cancer patients is also addressed.

Lung cancer is the leading cause of cancer death in Australia<sup>1</sup> and worldwide.<sup>2</sup> The two main classes of lung cancer, with the classification based on biological behaviour, therapy and prognosis, are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is responsible for approximately 85% of all lung cancer cases.<sup>3</sup> Despite the recent advances in screening, diagnosis and treatment, the overall five year survival of lung cancer patients is 15.9%,<sup>4</sup> with late diagnosis being the major factor responsible for the poor overall prognosis.<sup>5</sup> Surgery, either alone or as part of a multimodality therapy, plays an important role in the treatment of lung cancer patients. The focus of this article is to review the current role of surgery in the management of NSCLC.

## Pre-operative mediastinal staging

Accurate staging of lung cancer is essential for both prognostic and therapeutic reasons. When extra thoracic disease spread has been ruled out, mediastinal lymph node status must be assessed prior to intervention. Due to its high diagnostic accuracy, positron emission tomography, combined with computed tomography (PET-CT), has become the investigation of choice for staging NSCLC.<sup>6</sup> PET-positive mediastinal uptake should generally be confirmed by invasive means, thereby ensuring that patients are not denied a curative option in the setting of a falsely positive PET-CT scan.<sup>7</sup> This is of particular importance in large central tumours, where atelectasis distal to the mass can result in enlarged and reactive mediastinal nodes which may be positive on PET-CT. It should also be noted that negative PET-CTs do not exclude the presence of micro-metastatic disease and can also be particularly less helpful in tumours with low metabolic activity.<sup>8,9</sup>

Mediastinal lymph node status can be assessed by either mediastinoscopy or endobronchial ultrasound guided trans-bronchial needle aspiration (EBUS-TBNA).

The choice of modality will often be dictated by local considerations in terms of available expertise and resources. Mediastinoscopy is the gold standard for evaluating mediastinal lymph nodes. It allows assessment of the following lymph node stations: high mediastinal station (station 1); right and left superior para-tracheal (station 2); right and left inferior para-tracheal (station 4); and subcarinal (station 7). The sensitivity of mediastinoscopy is reported between 72-89% (on average 81%), specificity is 100% and negative predictive value of 91%<sup>10</sup>. Recently, the use of video-mediastinoscopy has been introduced, improving visualisation of the surgical field and the accuracy of staging.<sup>11,12</sup>

In addition to those stations accessible by mediastinoscopy, EBUS-TBNA also allows sampling of hilar (station 10) and intrapulmonary nodes, with sensitivity of 88% and specificity of 100%.<sup>13</sup> As a result, it has greatly reduced the need for cervical mediastinoscopy. It is likely that mediastinoscopy will be increasingly used to confirm negative results of EBUS-TBNA, particularly when clinical/radiological suspicion persists, further increasing the sensitivity of this combined approach to 94%<sup>14</sup>. Similarly, the need for re-do mediastinoscopy after induction therapy can be avoided if pre-treatment assessment is carried out by EBUS-TBNA, thereby reserving mediastinoscopy for post-treatment restaging. Occasionally, endoscopic ultrasound fine needle aspiration may need to be used to assess stations 5, 7, 8 and 9, which are not accessible by the above two techniques.

Video assisted thoracic surgery (VATS) is used to definitively evaluate the hemithorax and mediastinum at the time of surgery. Ipsilateral pleural effusions (negative on cytology) should be proven to be reactive and pleural seeding excluded prior to embarking on definitive resection. In addition to lymph node stations 2, 4 and 7, VATS provides relatively easy access to lymph node stations 5, 6, 8 and 9, which are not readily accessible by the above discussed techniques.

## **Surgery for earlier stage lung cancer (stage I, II, IIIA – T3N0, 1, T4N0, 1)**

The decision to perform surgery with curative intent is based on the stage of the disease, as defined by the 7th edition of tumour, node, and metastasis classification (TNM),<sup>15</sup> tumour resectability and the patient's operability/fitness for surgery. The goal of surgery is complete resection of intra-thoracic disease. Currently, inoperable patients, surgery is the treatment of choice for patients with stage I, II and stage IIIA (T3N0, 1, T4 N0, 1) disease.

Complete surgical resection of early stage disease can be achieved by either lobectomy or pneumonectomy. Lobectomy is performed whenever technically possible in order to minimise perioperative morbidity and mortality (30 day mortality from the Society for Thoracic Surgeons for lobectomy is 2% v 5.6% for pneumonectomy).<sup>16,17</sup> Sleeve lobectomy with bronchoplastic techniques should be considered to decrease the requirement of pneumonectomy, if complete resections with clear margins can be obtained. T3-4 tumours (chest wall, pericardial, diaphragmatic and mediastinal invasion) require en block resection of invaded structures, with clear resection margins (R0) to ensure long term survival. Intra-operative mediastinal staging should be performed, but the extent of staging required remains controversial. Practice ranges from no formal assessment, to haphazard sampling, to systematic sampling, to nodal dissection. At a minimum, systematic lymph node sampling should be performed to accurately stage the disease.<sup>18,19</sup> Lymph node status is essential for predicting prognosis, as well as determining the need for adjuvant therapy. To date, a survival advantage of complete mediastinal lymph node dissection has been demonstrated by only one prospective randomised trial.<sup>20</sup>

In high risk surgical candidates, as judged by significant medical comorbidities or poor pre-existing lung function, sub-lobar resection with segmentectomy (preferred),<sup>21,22</sup> or wedge resection, can be performed. A segmentectomy is an anatomic resection similar to a lobectomy, with ligation of individual bronchovascular structures. This is in contradistinction to wedge resections, which involve transection of lung parenchyma only, generally with the use of staplers.

Sub-lobar resections have been associated with increased loco-regional disease recurrence rates and reduced long-term survival.<sup>23, 24</sup> There is growing evidence to support limited resections in some small tumours (<2 cm T1a),<sup>21</sup> i.e. adenocarcinoma in situ or minimally invasive adenocarcinomas,<sup>25</sup> or in elderly patients with small tumours.<sup>26</sup> Competing risks must be considered prior to embarking on surgical resection in this high risk subset.

Another offshoot of the use of CT based screening is the increased incidence of early small cancers. This trend began in Japan, where CT screening has been in place for decades. Intuitively, it seems that for small peripheral cancers, sublobar resections may be adequate, but to date lobectomy remains the standard of care. There are randomised control trials in progress comparing sublobar resections to lobectomy for small (<2cm) peripheral adenocarcinomas. The results are pending.

Another common scenario that presents itself with the increasing use of screening, as well as CT based surveillance of patients that have had previous resections, is that of patients presenting with second primary lung cancers years after an NSCLC resection. Often in these situations, a sublobar resection is performed for the compromised patient, who already has diminished pulmonary reserve. Similarly, it may be a valid choice in patients with other competing risks, for example, recently resected primaries from other sites (eg. head and neck).

Probably the greatest recent change in surgery for lung cancer is VATS. VATS lobectomies were first performed more than 20 years ago,<sup>27</sup> but are only now achieving more widespread acceptance and uptake. VATS lobectomy attempts to minimise the morbidity associated with a standard thoracotomy, a functionally debilitating incision. Two randomised trials performed in early stage non-small cell lung cancer patients have shown VATS lobectomy to be safer,<sup>27</sup> and have similar five year survival rates,<sup>28</sup> when compared with lobectomy performed through thoracotomy. Large case series have since been published, establishing VATS lobectomy as a safe procedure associated with low morbidity.<sup>29-32</sup>

Studies have also suggested that VATS lobectomy has been associated with reduced postoperative pain and earlier ambulation, as well as reduced pulmonary morbidity, making it possible to offer anatomical resection to the elderly, patients with poor lung function and with poor performance status.<sup>33-36</sup> Most importantly, VATS lobectomy has been shown to be oncologically sound, with no increase in loco-regional recurrence rate, as well as reduced systemic recurrence rate and improved five year survival rate when compared with open lobectomy.<sup>37</sup> Considering the available evidence (and the fact that large multicentre, randomised control trials are unlikely to ever be performed), VATS lobectomy should be considered as the procedure of choice for patients with early stage lung cancer.

## **Surgery for loco-regionally advanced lung cancer (stage IIIA – T1-3 N2)**

Controversy remains around the treatment of NSCLC with mediastinal lymph node involvement (stage IIIA – T1-3 N2). Two large randomised control trials that compared surgery combined with neoadjuvant therapy and definitive chemo radiotherapy, did not demonstrate overall survival benefit with surgical resections.<sup>38, 39</sup> However, subgroup analysis has demonstrated better survival rates for patients who underwent lobectomy and patients down staged to N0, 1 disease following induction chemotherapy.<sup>38,39</sup> Outcomes in the pneumonectomy group were compromised by an extremely high operative mortality of 26%.<sup>39</sup> Large single institution case series have since shown that pneumonectomy can be performed safely after induction therapy.<sup>40,41</sup> Considering the above data, surgery can be considered as part of a multimodality treatment regimen for patients with N2 disease, particularly those who are judged completely resectable, have responded to/been down staged by induction therapy and have single station non bulky nodal disease.

## Surgery for metastatic disease (stage IV)

The role of surgery for stage IV NSCLC is primarily focused on the improvement of patient quality of life. Malignant pleural effusions can be managed with VATS pleurodesis or, in cases where lung is trapped with cancerous peel and pleurodesis is unlikely to be successful, with a permanent subcutaneously tunnelled pleural drain insertion, which allows repeated fluid drainage. Similarly, airway intervention with laser, mechanical debridement and stenting play an important role in the management of malignant tracheo-bronchial stenosis and haemoptysis. In highly selected cases, where complete resection of intra thoracic and metastatic disease is possible, surgery can be considered in patients with solitary metastatic disease of the brain and adrenal glands, as part of a multimodality treatment regimen.<sup>42, 43</sup>

### Overview

In addition to its role in diagnosis and staging, surgery remains at the forefront among therapeutic modalities in the treatment of NSCLC. Despite progress in non-invasive staging with PET-CT, histological sampling of mediastinal lymph nodes via EBUS or mediastinoscopy remains critically important in the assessment of many patients. The choice of which modality to use will often depend on the local availability of resources and expertise. Complete resection remains the best chance for cure for patients with disease not involving the mediastinum, i.e. stage I, II and non N2 IIIA (i.e. T3N0 or N1 and T4N0 or N1). The established benefits of adjuvant chemotherapy suggest that adequate intraoperative mediastinal lymph node staging is required. At a minimum, systematic sampling of lymph node stations should be performed. VATS lobectomy has emerged as an acceptable treatment for early stage lung cancer. Studies have shown decreased pain, faster return to function and decreased morbidity with at least equal oncological results. It is important that the same operation is performed on the inside (ie. lymph node dissection) as would have been performed via a thoracotomy. An area of increasing interest is that of sublobar resection (either segmentectomy or wedge) for very small peripheral adenocarcinomas. Studies are ongoing, but lobectomy remains the standard of care. In loco-regionally advanced disease, surgery can be used as part of a multi-disciplinary approach with good results. Patients who do best are those who have had their mediastinum pathologically downstaged, or sterilised by neoadjuvant therapies prior to resection. In advance disease, surgery can play an important role in the palliation of breathlessness resulting from either pleural effusions or airway compromise. As is often the case in lung cancer, patients tend to benefit most when a multi-disciplinary approach is used.

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## RADIO THERAPY IN LUNG CANCER

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### Abstract

Radiotherapy is an important modality in the treatment of lung cancer. In Australia, up to 76% of patients have an indication for radiotherapy at diagnosis. This includes curative radiotherapy for patients with inoperable stage I and II non-small cell lung cancer, and in combination with chemotherapy, for patients with stage III non-small cell lung cancer and limited stage small cell lung cancer. There are challenges in delivering curative radiotherapy to this group of patients, many of whom have smoking-related comorbidities. However, newer technologies allow selection of appropriate patients for treatment, improve identification of the tumour, individualise radiotherapy treatment according to patient specific motion and reduce normal tissue toxicities. Image guided radiotherapy is increasingly becoming the standard of care, whereby the tumour position is confirmed on cone-beam CT performed on the linear accelerator prior to treatment. Intensity modulated radiotherapy is improving dose conformity and avoidance of normal tissue structures. Stereotactic ablative radiotherapy is currently being evaluated as a treatment option for patients with inoperable stage I non-small cell lung cancer. Radiotherapy is also an important palliative treatment for lung cancer, with well-established indications for palliation of thoracic symptoms such as airway obstruction, chest pain, cough and haemoptysis. Bone and brain metastases are common in lung cancer and radiotherapy remains the prime modality for alleviating symptoms from these. Multidisciplinary discussion of lung cancer patients is essential to ensure that appropriate patients receive the evidence-based benefits of radiotherapy.

Radiotherapy is an important modality in the treatment of lung cancer. According to evidence-based guidelines, 76% of patients diagnosed with lung cancer in Australia have an indication for radiotherapy.<sup>1</sup> Thoracic radiotherapy is a potentially curative treatment option for stage I-III non-small cell lung cancer (NSCLC) and limited stage small cell lung cancer (SCLC). It is also important in

palliating symptoms for those unfit for curative treatment or those who present with metastatic disease. Despite this, it remains underutilised for lung cancer patients in Australia.<sup>2,3</sup> This review will discuss important advances in radiotherapy for lung cancer in order to update referring clinicians.

## Patient selection

Patient selection for radiotherapy is ideally discussed at a multidisciplinary meeting where all specialists who treat lung cancer are present. Discussion at such a forum has been shown to increase the utilisation of both radiotherapy and chemotherapy.<sup>4</sup> There are many factors to consider when discussing the option of curative radiotherapy in patients. Generally, patients suitable for curative radiotherapy will have good performance status (ECOG 0-1), and locoregional disease extent (stage I-III). Despite the frequency of underlying chronic obstructive pulmonary disease in lung cancer patients, there are no cut-offs in terms of pulmonary function which determine suitability for curative radiotherapy.<sup>5</sup> Similarly, there is no upper limit to tumour size beyond which curative radiotherapy is not possible. In an observational study of 509 patients treated with curative radiotherapy, tumour volume was not an independent predictor of survival beyond 18 months.<sup>6</sup> In many cases, the ability to deliver a curative dose of radiotherapy may not be known until a radiotherapy plan is generated and evaluated according to dose volume metrics known to be predictive of lung toxicity. Hence assessment by a radiation oncologist is essential to ensure that patients do not miss out on potentially curative radiotherapy.

## Radiotherapy treatment

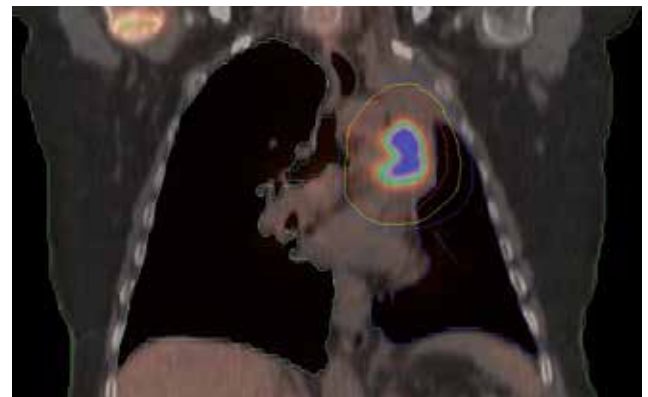
Once a recommendation for radiotherapy is made, there are several factors to consider in optimising the radiotherapy plan and treatment delivery. Accurate radiotherapy treatment of lung cancer is reliant on 18F-deoxyglucose position emission tomography (FDG-PET) scans both for patient selection for curative treatment and for tumour delineation. A contemporaneous PET scan, performed within the past month, is essential to ensure that the cancer has not progressed beyond a curable stage.<sup>7-9</sup> The registration of FDG-PET scans to the CT simulation scans for radiotherapy planning also improves delineation of lung cancer by reducing uncertainties, especially when there is adjacent atelectasis or consolidation (figure 1).<sup>10,11</sup>

Accounting for tumour motion with respiration is crucial to ensure that the whole tumour is encompassed by the radiotherapy fields. Commonly, this motion is measured at simulation on a 4D CT scan, where image acquisition is linked to phase of respiratory motion (figure 2). This allows individual tailoring of radiotherapy margins to a patient's specific tumour motion and minimises the risk of a geographic miss, where the tumour moves outside the radiotherapy field during treatment. A retrospective analysis of outcomes of 496 lung cancer patients treated with conventional 3D simulation and conformal radiotherapy, or 4D simulation and intensity modulated radiotherapy (IMRT), showed improved survival and reduced lung toxicity with the latter approach, although it is difficult to assess the impact of 4D CT alone.<sup>12</sup> Newer linear accelerators come with either kilovoltage or megavoltage CT scanning capability, allowing the possibility of image guided radiotherapy (IGRT), where the position of the tumour is verified at the time of treatment.

While the imaging options discussed above aim to ensure that the tumour is encompassed during all

phases of respiration, other technologies aim to treat the tumour at a specific phase in the respiratory cycle to minimise radiation of surrounding lung and hence toxicity. Respiratory motion can be reduced with abdominal compression devices or breathhold techniques.<sup>13</sup> However, patients with lung cancer who have underlying respiratory comorbidity are not always able to tolerate these. Respiratory gating is an alternative, whereby the radiotherapy beam is only turned on, in response to detection of an internal or external fiducial marker.<sup>13</sup>

**Figure 1:** Coronal CT with registered PET scan of patient with left upper lobe collapse from a centrally located FDG avid tumour. Tumour is encircled by lines of equal radiotherapy dose.



**Figure 2a:** Diagnostic coronal CT scan of a right lower lobe tumour.



Dose conformity to the tumour can be improved through IMRT. With this technique, a greater number of non-uniform radiotherapy beams are used to converge on the tumour. While this can limit dose to adjacent critical structures such as the spinal cord, it can sometimes also result in a greater volume of tissue receiving a lower dose, potentially increasing some toxicities. As stated above, a combination of IMRT and 4D CT planning has shown improved survival and reduced lung toxicity compared to conventional techniques.<sup>12</sup> This technique may increase patient suitability for curative radiotherapy by overcoming problems associated with tumour location adjacent to critical normal tissues.



**Figure 2b:** 4D CT scan of the same patient. The position of the tumour is imaged at all phases of the respiratory cycle, requiring a large increase in the volume to be targeted to avoid a 'geographic miss'.



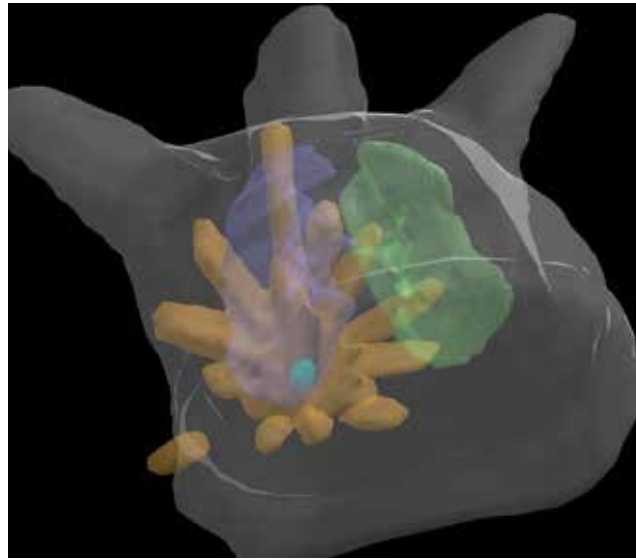
### Stage I NSCLC

Although surgery is the preferred treatment for stage I and II NSCLC, many patients are not fit for an operation because of smoking-related comorbidities. These patients can be considered for treatment with curative radiotherapy. As with other forms of high dose radiotherapy, treatment is given as a number of fractions over a period of four to six weeks, since this minimises risk of damage to normal tissues. Recently, technical innovations have allowed treatment to be given more precisely with multiple or moving beams, minimising dose to normal tissues and so reducing the need for fractionation. The method of giving precise treatment, in one to five very large doses, is known as stereotactic ablative radiotherapy (SABR) (figure 3). In a phase 2 North American trial of SABR in stage I NSCLC, the estimated control rate at the primary site was 97% at three years.<sup>14</sup> However, the treatment appears to be safe only for peripheral smaller tumours, as fatalities have been reported with centrally located or larger cancers.<sup>15</sup> An Australasian randomised trial (TROG 09.02 'CHISEL') is currently evaluating SABR against conventional radiotherapy.<sup>16</sup>

### Stage III NSCLC

For patients who have had complete resection of NSCLC, and who are found to have involvement of mediastinal lymph nodes, the effect of postoperative radiotherapy on survival is uncertain, and it cannot be recommended outside the trial setting.<sup>17</sup> For more advanced disease, which is unresectable for technical reasons or because of mediastinal lymph node involvement, fractionated radiotherapy in combination with concomitant chemotherapy is the standard of care.<sup>18</sup> The addition of surgery in this setting does not increase survival.<sup>19</sup> One exception where surgery does appear important for local control is the superior sulcus or 'pancoast' tumour, located in the apex of the lung.<sup>20</sup> The optimal chemotherapy regimen is not clearly settled, but one small randomised study suggested that cisplatin/etoposide is superior to carboplatin/paclitaxel.<sup>21</sup>

**Figure 3:** Multibeam (yellow) SABR treatment plan for a right lower lobe tumour (light blue). Right lung is violet and left lung green.



The addition of chemotherapy before or after concomitant chemoradiotherapy increases treatment toxicity but not survival.<sup>22,23</sup> There does not appear to be any advantage in increasing total radiotherapy dose from 60 to 74 Gy.<sup>24</sup> With five year survivals in excess of 20% being reported with chemoradiation,<sup>19</sup> and 18% at 10 years,<sup>25</sup> 'cure' is now a realistic goal for a significant minority of patients with inoperable NSCLC. For patients with T3-4 N0-1 superior sulcus NSCLC treated on a prospective phase II trial with a combination of radiotherapy, chemotherapy and surgical resection, survival was 44% at five years.<sup>20</sup>

It is now recognised that many cancers repopulate at an accelerated rate during treatment, and that this can be countered by shortening overall treatment time. A method for achieving this is continuous hyperfractionated accelerated radiotherapy (CHART), consisting of three treatments a day, seven days per week, so that treatment is completed in 12 days instead of 42. In a randomised trial in NSCLC, CHART improved local control and survival compared with conventional fractionation.<sup>26</sup> This benefit of shortening overall treatment time has since been confirmed by meta-analysis.<sup>27</sup> Accelerated radiotherapy has never been compared head-to-head with chemoradiation, but the challenges of delivering treatment three times per day, seven days per week, has limited the widespread adoption of CHART in comparison with chemoradiation. Both the addition of concomitant chemotherapy and accelerated fractionation increase oesophagitis, but there is less evidence of an effect on other toxicities.

Prophylactic cranial irradiation (PCI) is now well established in the treatment of SCLC. Brain metastasis is also common in NSCLC. In one prematurely terminated randomised trial, the actuarial risk at one year was 18% in patients with stage III disease.<sup>28</sup> This was reduced to 7.7% by PCI ( $P=0.004$ ), but there was no associated survival advantage, so it cannot be recommended for NSCLC outside the trial setting.

## Small cell lung cancer

The combination of chemotherapy and thoracic radiotherapy for locoregional (limited) SCLC is well established.<sup>29</sup> As with NSCLC, a shorter radiotherapy treatment time appears to be more effective, but the evidence is not as strong.<sup>27</sup> For practical reasons, chemotherapy is often started before combined chemoradiation, and one review demonstrated that the shorter the time between the start of chemotherapy and the end of thoracic radiotherapy, the better the survival.<sup>30</sup> This suggests that the phenomenon of accelerated repopulation may also occur in response to chemotherapy. The optimal radiotherapy dose is not clearly established, and is under investigation in two separate collaborative group trials.<sup>31</sup> Prophylactic cranial irradiation is a standard of care for patients who have achieved a complete response to initial treatment;<sup>32</sup> 25 Gy in 10 fractions appears to be as effective as higher doses.<sup>33</sup> Prophylactic cranial irradiation also produces a survival benefit in patients with extensive SCLC, provided they have had a response to chemotherapy.<sup>34</sup>

## Palliative radiotherapy

Symptom palliation is a common indication for radiotherapy, both for intrathoracic disease (haemoptysis, cough, dyspnoea and superior vena caval obstruction) and for metastatic sites such as bone and brain. The palliative benefit of thoracic radiotherapy is the same regardless of the radiotherapy fractionation scheme used, however longer fractionation schemes result in increased toxicity, especially oesophagitis.<sup>35</sup> Patients with NSCLC who have good performance status and thoracic dominant disease may get a survival advantage, as well as longer duration of symptom relief if higher doses (30-36Gy) are used.<sup>36</sup> The fractionation of palliative thoracic radiotherapy should be tailored to the performance status of the patient and disease burden.

Patients with brain metastases are usually treated with external beam radiotherapy for palliation. There is no advantage in prolonging radiotherapy beyond a week. In patients with 1-3 brain metastases and stable extra-thoracic disease, the addition of a stereotactic boost reduces steroid use and improves patient performance status at six months.<sup>37</sup> In those with a single metastasis, there is a modest improvement in survival with stereotactic boost. Following surgical resection of brain metastases, whole brain radiotherapy reduces intracranial progression and neurological deaths, but does not improve survival.<sup>38</sup> Many patients with brain metastases have poor performance status and corticosteroids alone may be just as effective as radiotherapy in terms of quality adjusted survival.<sup>39</sup> For bone metastases, single doses are as effective in relieving pain compared with fractionated courses, although there is more likelihood of causing a pain 'flare' with a single dose of 8Gy if there is an associated neuropathic component.<sup>40</sup>

## Treatment toxicity

With conventional radiotherapy, oesophagitis during treatment and radiation pneumonitis following treatment are the toxicities of concern. Whilst oesophagitis is usually only seen during radiotherapy and resolves shortly after

completion, it can have a considerable impact on a patient's quality of life and lead to poor nutrition. Factors predictive of oesophagitis include mean radiation dose to the oesophagus, twice daily treatment, chemotherapy and neutropaenia.<sup>41</sup> Early dietitian and/or feeding intervention should be considered under these circumstances.

Radiation pneumonitis occurs post-treatment to up to six months later. Factors predictive of this include increasing age, radiation dose to the lung and the volume of lung irradiated. The use of combined dose-volume metrics (such as the volume of lung receiving 5 Gy (V5) or 20 Gy (V20), or the mean lung dose) to evaluate plan safety is now standard practice.<sup>42</sup> Although the meta-analysis comparing sequential with concomitant chemoradiation did not demonstrate an increased risk of pneumonitis with concomitant chemotherapy,<sup>18</sup> the type of chemotherapy, in particular the taxanes, may be important in increasing risk.<sup>43</sup> Palma et al performed a meta-analysis and found that patients older than 65 years who were treated with concurrent carboplatin and paclitaxel had up a 57% incidence of grade 2 or higher pneumonitis (requiring medical intervention), regardless of lung radiation dose.<sup>43</sup> The choice of chemotherapy should be carefully considered in older patients, many of whom have pre-existing renal or auditory comorbidities, precluding the standard cisplatin and etoposide combination chemotherapy.

The toxicity profile of radiotherapy in lung cancer is changing with implementation of newer techniques. Chest wall pain and rib fractures are potential toxicities following SABR, although this risk can be minimised using risk-adapted fractionation according to the location of the tumour.<sup>44</sup> Toxicity from SABR is more common in central tumours with grade 3-4 toxicities occurring in up to 9% of patients.<sup>45</sup>

## Conclusion

Radiotherapy is an important modality for the treatment of lung cancer. Technological advances have improved patient selection for treatment, identification of tumour and treatment accuracy, while reducing treatment toxicities. Future opportunities for 'personalising radiotherapy' include the identification of genetic determinants of radiation response, and countering causes of radioresistance in the tumour environment such as hypoxia. A number of trials currently underway will guide future radiotherapy. These include the Trans-Tasman Radiation Oncology Group (TROG) trials, CHISEL (randomising patients with inoperable stage I-IIA NSCLC to conventional radiotherapy or SABR), PLUNG (randomising patients with stage III NSCLC unsuitable for curative radiotherapy to palliative radiotherapy alone, or with chemotherapy). In addition to the international trials mentioned above, ongoing randomised trials are also investigating the role of postoperative radiotherapy in completely resected NSCLC using modern techniques (LungART), and the combination of chemoradiation with cetuximab, a monoclonal antibody against the epidermal growth factor receptor, which may be implicated in repopulation (RTOG 0617).

For now, it is important that multidisciplinary discussion of patients takes place to ensure that appropriate lung cancer patients receive the existing, evidence-based benefits of radiotherapy.

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## MOLECULAR PATHOLOGY IN LUNG CANCER

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### Abstract

Increasing understanding of genomic changes in cancer is transforming the diagnosis and treatment of a subset of lung cancers. A significant proportion of lung adenocarcinomas harbour biologically relevant or targetable somatic genetic changes such as mutations, amplifications or translocations in a range of genes, including KRAS, EGFR, ALK, ROS1, MET and BRAF. This review highlights the key actionable somatic changes seen in lung cancer, with particular emphasis on epidermal growth factor receptor mutations and ALK gene rearrangements in adenocarcinoma, as well as identifying promising new targets in squamous cell carcinoma of the lung. Accurate and sensitive molecular testing is essential to ensure patients with this poor prognosis disease receive the correct therapy, but mutation testing in lung cancer poses particular challenges. As the majority of patients with lung cancer present with advanced disease that is unsuitable for resection, many biopsies submitted for molecular testing are small biopsies such as core biopsies and fine needle aspirate biopsies, often with only a very small amount of diagnostic material available for mutation analysis. This paper highlights the need for good communication between clinicians, radiologists and pathologists to ensure optimal samples for molecular testing and the benefits of testing for multiple genes in one assay.

While optimal treatment of lung cancer in the past depended largely on histological classification and tumour stage, advancements in understanding of the molecular pathology of lung cancer has revolutionised treatment strategies and drug development. A variety of oncogenic driver mutations have been identified in just over 50% of lung adenocarcinomas and are almost always exclusive of each other.<sup>1-3</sup> Tumours harbouring driver mutations are 'addicted' to the effects of the molecular aberration in an oncogene, which singularly drives tumour transformation by exclusively regulating critical downstream signalling pathways, making them key targets for molecular inhibition. Adenocarcinomas harbouring activating EGFR (epidermal growth factor receptor) mutations are sensitive to targeted EGFR-TKIs (tyrosine kinase inhibitors) such as gefitinib and erlotinib, while adenocarcinomas with anaplastic lymphoma kinase (ALK) or ROS1 gene rearrangements are sensitive to TKIs such as crizotinib.<sup>6</sup> These predictive molecular abnormalities have had a dramatic impact on pathologic assessment of non-small cell lung cancer (NSCLC) and established somatic gene mutation testing, as a routine part of lung cancer work-up for most patients with advanced stage disease. With the development of newer targeted agents and a greater understanding of the crucial role of molecular predictive markers, we can expect molecular pathology to play an increasing role in the diagnosis and management of lung cancer. Advances in the molecular understanding of lung cancer types other than adenocarcinomas, such as through the Cancer Genome Atlas Project comprehensive genomic characterisation of squamous cell carcinoma, has revealed potential molecular targets that may also impact other tumour types.<sup>7</sup>

### EGFR mutations in NSCLC

Epidermal growth factor receptor (also known as human EGFR or HER1) belongs to a family of tyrosine kinase receptors including EGFR, HER1, HER2/neu, HER3 and HER4, and consists of an extracellular ligand-binding domain, a membrane domain and an intracellular tyrosine kinase domain.<sup>8</sup> Upon ligand binding (by EGFR or TGF- $\alpha$ ), the receptor undergoes homo- or hetero-dimerisation and autophosphorylation of intracellular tyrosine residues within the activation loops of the catalytic tyrosine kinase domain. This leads to activation of a series of downstream cell signalling pathways involved in cell proliferation, survival, angiogenesis and metastasis, including the Ras-MAPK, PI3K-Akt and Jak-STAT pathways.

Activating mutations of the EGFR gene in lung cancer lead to markedly increased affinity for ATP and increased tyrosine kinase activity with disrupted auto-inhibition.<sup>11</sup> The TKIs gefitinib and erlotinib preferentially bind the ATP-binding pocket of mutant EGFR proteins displacing ATP, thereby inhibiting phosphorylation and activation of downstream signalling pathways.<sup>11-13</sup> A systematic review and meta-analysis of EGFR mutations as potential predictive markers for EGFR-TKI sensitivity, including 3101 patients with 1020 mutations from 59 eligible studies, demonstrated mutations were effective predictive biomarkers of patient response to TKI treatment.<sup>14</sup> A study combining patient data from predominantly western patients treated with EGFR-TKIs in five trials, found a response rate of 67% in patients harbouring sensitising EGFR mutations, with slightly better responses in patients with exon 19 deletions (compared to L858R mutations).<sup>15</sup> Determination of EGFR mutation status has therefore become standard practice when patients are being considered for EGFR-TKI treatment.

In Australia, and other western countries, activating mutations in the EGFR gene are found in approximately 10-15% of NSCLC patients, while in Asian populations the frequency is higher (30-40%). EGFR mutations are more common in patients who are younger, female gender and never-smokers.<sup>18-23</sup> While EGFR mutations are negatively correlated with increasing smoking history, they can occur at a lower frequency in patients who are current or ex-smokers. The reported better prognosis of patients with EGFR mutations may relate to their association with other favourable prognostic factors such as younger age and non-smoking status, as EGFR was not a significant prognostic factor in two large multivariate analyses. While there are distinct clinical features associated with EGFR mutations, a study combining patient data from several clinical trials found clinical features were inferior to EGFR mutation status at predicting response to treatment.<sup>15</sup>

Pathologically, EGFR mutations occur almost exclusively in adenocarcinomas, or lung cancer with an adenocarcinoma component including adenosquamous carcinomas, or more rarely, pleomorphic sarcomatoid carcinomas,<sup>30</sup> or combined small cell carcinoma with adenocarcinoma.<sup>31</sup> They have also been reported very rarely in EBV-associated lymphoepithelioma-like carcinomas.<sup>23</sup> Using microdissection techniques, EGFR mutations are generally found in both the squamous and glandular components of resected adenosquamous carcinoma. Small biopsies of metastatic adenosquamous carcinomas may show pure squamous cell carcinoma. A report of two such cases in never smokers demonstrated EGFR mutations in the squamous cell carcinoma component, as well as in the glandular component identified in other specimens.<sup>33</sup> It is therefore important that a biopsy diagnosis of squamous cell carcinoma in a never smoker should raise suspicion of an incompletely sampled adenosquamous carcinoma that could potentially harbour an EGFR mutation. Many large studies have found no EGFR mutations in squamous cell carcinomas, although others have reported them in a low proportion of squamous cell carcinomas, mostly in studies including small biopsy samples with little attention to histological diagnostic criteria. However, two cases of the sensitising EGFR mutation Leu861Gln were found in 178 squamous cell carcinomas (1.1%) that underwent comprehensive genome analysis as part of the Cancer Genome Atlas project, in which rigorous pathological assessment was undertaken.<sup>7</sup>

### Different EGFR mutations in NSCLC

Activating EGFR mutations occur in the kinase domain encoded by exons 18 to 21. The commonest EGFR mutations known to be sensitive to EGFR-TKIs occur in the ATP-binding loops of the kinase domain, namely exon 19 in frame deletions, exon 21 point mutations (L858R and L861Q) and the exon 18 point mutation G719X. Together, these alterations account for approximately 85-95% of EGFR mutations in NSCLC. In a comprehensive review of 2880 patients with 569 EGFR mutations, in frame deletions in exon 19, of which there are over 20 variants, accounted for almost 50% of all EGFR mutations.<sup>34</sup> The second commonest mutation is a single amino acid substitution of a leucine with arginine, resulting from a T to G substitution

in codon 858 in exon 21. These L858R mutations make up about 40% of EGFR mutations.<sup>34</sup>

EGFR mutations associated with primary resistance to EGFR-TKIs occur in approximately 5-10% of untreated adenocarcinomas. They mostly consist of insertions or duplications in exon 20, or the T790M mutation in exon 20 that can occur de novo, but is more commonly associated with acquired TKI resistance.<sup>36</sup> The T790M mutation restores the affinity of the EGFR receptor for ATP rather than TKIs,<sup>37</sup> thus conferring resistance to first generation TKIs. These primary resistance mutations can occur in isolation or in combination with more common sensitising EGFR mutations. In addition, genetic alterations in other genes that may coexist with activating EGFR mutations, such as PIK3CA mutations,<sup>1</sup> or rarely, primary MET amplification,<sup>38</sup> may circumvent sensitivity to TKIs by activating downstream signalling pathways.<sup>36</sup>

Acquired resistance occurs after an initial response to EGFR-TKI treatment and in 50% or more of cases is associated with development of a secondary EGFR mutation, usually T790M in exon 20,<sup>39-41</sup> (or selective expansion of previously undetected resistant clones). The T790M point mutation results in a single amino acid substitution of methionine for threonine in the ATP-binding pocket, which interferes with binding of EGFR-TKIs, in preference for ATP binding.<sup>37</sup> Second generation EGFR-TKIs with different binding sites to EGFR show potential to overcome this resistance mechanism.<sup>42</sup> The second commonest cause of acquired resistance results from MET oncogene amplification, which occurs in about 10-20% of cases and enables activation of the AKT pathway through ERBB3. More rarely, patients may relapse with small cell carcinoma. Strategies aimed at simultaneously inhibiting EGFR mutations associated with sensitivity and known resistance mechanisms are required to overcome the problem of acquired resistance.

In view of the range of possible activating mutations and the potential for coexistent sensitising and resistance EGFR mutations, it is important comprehensively assess the EGFR kinase domain including exons 18 to 21.

### EGFR mutation detection techniques

A variety of molecular genetic techniques may be used to identify EGFR (and other mutations) in lung cancer and they all have different strengths and limitations. Tissue based biopsies and cytology specimens are both adequate for mutations analysis.<sup>46</sup> A study of EGFR testing accuracy across 15 different centres in France found sample quality was more important than the type of molecular genetic techniques utilised.<sup>47</sup> Direct sequencing is limited by low sensitivity, requiring the mutation to be present in 20% of tumour cells in the sample and is also labour intensive. Sensitivity can be improved by enriching for tumour cells with dissection techniques.<sup>48</sup> Screening techniques such as high resolution melting analysis and denaturing high-performance liquid chromatography can improve analytic sensitivity. Targeted methods such as ARMS<sup>TM</sup> (Amplification Refractory Mutation System), PCR-Invader<sup>®</sup>, peptide nucleic acid-locked nucleic acid PCR clamp and Cycleave<sup>TM</sup>, generally have higher sensitivity and are more rapid than direct DNA sequencing, but only identify

specific targeted mutations and are unable to detect rarer or novel mutations. Multiplex platforms that enable concurrent testing of multiple genetic abnormalities, such as Sequenom MassArray and SNaPshot, enable a more comprehensive genotype to be efficiently established with relatively small amounts of DNA, and are likely to be more clinically beneficial as greater numbers of targeted agents become available.

EGFR mutation is often associated with EGFR gene amplification, particularly amplification of the mutant allele,<sup>53</sup> however several studies have shown EGFR gene copy number is inferior to EGFR mutation at predicting response to EGFR-TKIs. While EGFR mutation specific immunohistochemistry is relatively fast and cheap and can be undertaken in routine histopathology laboratories, it only detects two specific mutations (L858R in exon 21 and the E746-A750 exon 19 deletion) and is inferior to DNA molecular analysis at identifying mutations.

### KRAS mutations in NSCLC

KRAS mutations occur in about 38% of lung adenocarcinomas in an Australian population,<sup>1</sup> similar to that observed in other studies of western populations.<sup>58</sup> By contrast, KRAS mutations are less frequent in Asian populations with a frequency of 10-15%. KRAS mutations in NSCLC mostly occur at codons 12 and less often at 13 and 61.<sup>19</sup> KRAS mutations occur in adenocarcinomas, particularly poorly differentiated tumours, and are associated with mucinous and solid predominant tumour types.<sup>16</sup> They are more common in males and are strongly related to a history of smoking, with 30-43% of smokers harbouring KRAS mutations compared to 0-7% of non-smokers.<sup>62</sup>

A meta-analysis of KRAS mutations in NSCLC found these patients have a worse prognosis than patients with KRAS wild type tumours.<sup>63</sup> As expected of driver mutations, EGFR and KRAS mutations are almost always mutually exclusive in NSCLC, although rare cases of patients harbouring both activating EGFR mutations and KRAS mutations have been reported.<sup>58</sup> Not surprisingly, KRAS mutations predict insensitivity to EGFR-TKI treatment.

### ALK rearrangements in NSCLC

ALK is a receptor tyrosine kinase that belongs to the insulin receptor family and undergoes constitutive activation in a small subset of NSCLC through chromosomal rearrangement.<sup>65</sup> ALK is located on chromosome 2p and undergoes inversion leading to formation of an oncogenic fusion gene, most commonly EML4-ALK (echinoderm microtubule-associated protein-like 4), encoding a constitutively activated tyrosine kinase that stimulates cell proliferation, survival and migration pathways.<sup>66-68</sup> These oncogene addicted tumours are highly sensitive to inhibition, with a clinical trial of crizotinib demonstrating a response rate of 57%.<sup>6</sup> While ALK rearrangements have been reported to occur in 0.4-13.5% of NSCLC, in most unselected studies they are found in about 4% of cases.<sup>65</sup> More recent data suggests the incidence is closer to 1% of lung adenocarcinomas in Australian populations.

Clinical features associated with ALK rearrangements include younger patient age and non-smoking status,<sup>69-73</sup> similar to the typical EGFR clinical picture, although racial and gender associations are less apparent for ALK. Pathologically, ALK rearrangements are found almost always in adenocarcinomas,<sup>73</sup> particularly with solid, acinar, cribriform with extracellular mucin, or signet ring cell morphology.

As expected for a driver mutation, ALK rearrangements are almost always mutually exclusive with EGFR and KRAS mutations. ALK rearrangements have also rarely been reported to occur in combination with EGFR mutation, including a patient who was resistant to erlotinib treatment.<sup>79</sup> More recently, there has been a case report of a combined small cell carcinoma and adenocarcinoma harbouring EML4-ALK fusion in the small cell component, and EGFR exon 19 deletion in the adenocarcinoma component.<sup>80</sup>

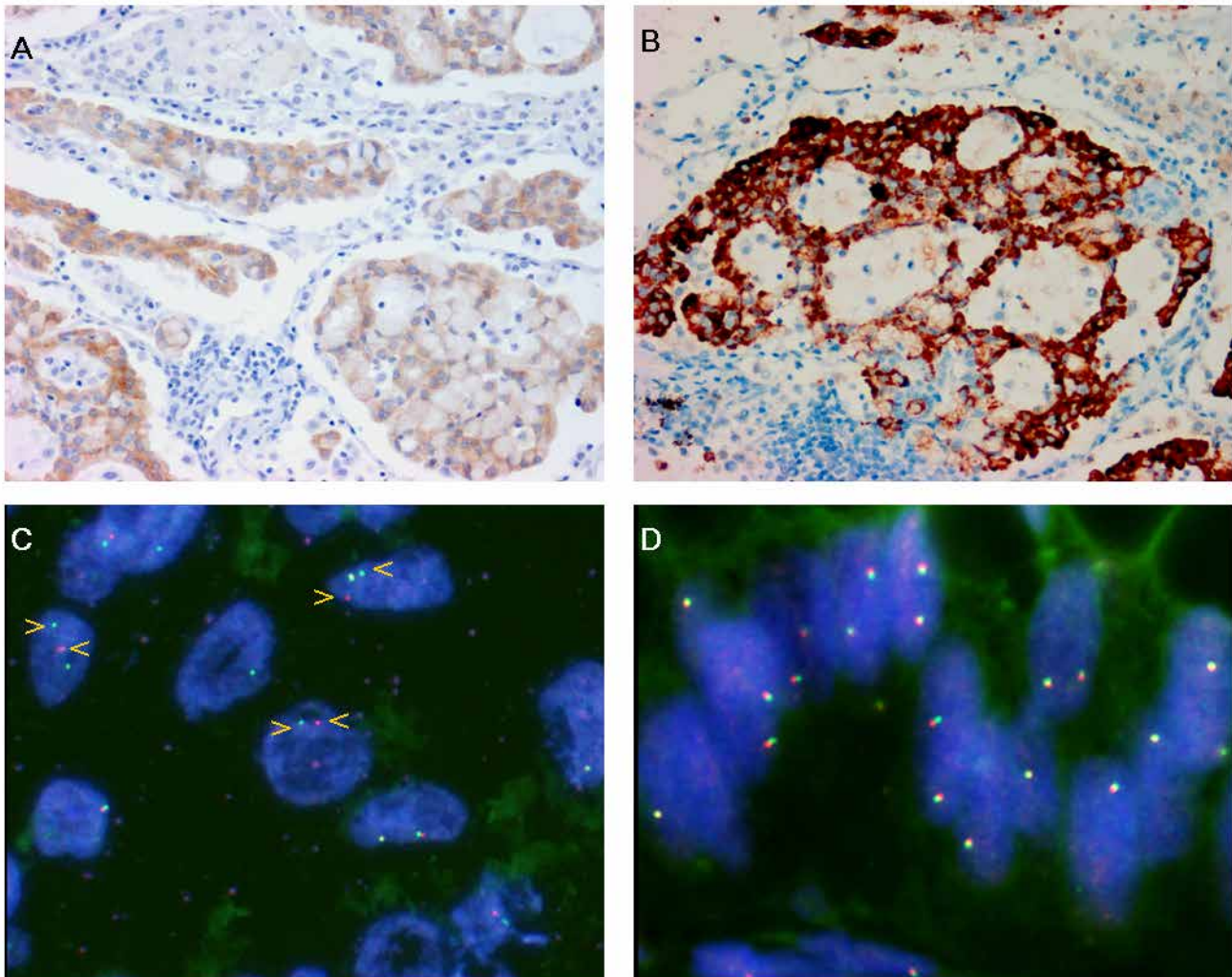
As with EGFR-TKIs, patients treated with crizotinib develop acquired resistance, the mechanism of which includes secondary ALK gene mutations, and activation of signalling pathways that bypass the inhibited pathway, including activation of EGFR signalling.<sup>82</sup>

Fluorescence in situ hybridisation (FISH), using a break-apart probe that targets the breakpoint of the ALK gene, is the standard method for identifying ALK rearrangements in clinical samples and has been validated in clinical trials.<sup>6</sup> In the US, ALK FISH is currently the only Food and Drug Administration approved technique for detecting ALK rearranged NSCLC, however this method is relatively labour intensive and costly, and can be technically challenging to interpret due to the inversion resulting in a subtle split in the FISH signal. There is increasing evidence that immunohistochemistry has very high sensitivity for detecting rearranged ALK using both the 5A4 clone and the newly available D5F3 clone, and could be used to screen for cases that could then be confirmed with FISH (figure 1). This is of particular importance in populations with low prevalence of the genetic abnormality, where it may not be cost-effective to undertake FISH in all cases. In addition, some crizotinib sensitive tumours may only demonstrate ALK alteration by immunohistochemistry and not FISH. While reverse-transcriptase PCR is highly accurate and can also be used to detect ALK rearrangements,<sup>88</sup> this technique is not practical in a routine clinical diagnostic setting, as there are 13 different breakpoints in EML4 from exon2 to 20, as well as some rarer non-EML4 fusion partners. All require different primers to target the fusion variants, some of which generate large amplicons not ideal for identification from paraffin embedded tissue in which the RNA is often quite degraded.

### Other potentially targetable mutations

Other rare, but potentially targetable mutations in lung adenocarcinomas, include BRAF mutations which have been reported to occur in about 3% of lung adenocarcinomas,<sup>89</sup> and in limited data to date are likely to be sensitive to the selective kinase inhibitors vemurafenib and dabrafenib.<sup>90</sup> Primary MET gene amplifications occur in approximately 4% of NSCLC,<sup>38</sup> and can potentially be

**Figure 1:** Immunohistochemistry can be used to identify ALK overexpression in lung adenocarcinomas, with ALK rearrangement using the 5A4 clone (A) and the D5F3 clone (B). ALK rearrangement can be confirmed with FISH using a breakapart probe demonstrating (C) rearranged signals (arrowheads show split red and green signals). By contrast, non-rearranged ALK shows a normal pattern of fused red and green signals (D).



targeted by MET inhibitors such as crizotinib. ROS1 gene rearrangements were discovered at the same time as ALK-rearranged NSCLC.<sup>66</sup> ROS1 encodes a transmembrane tyrosine kinase receptor and is located on chromosome 6.<sup>91</sup> It has high homology with the intracellular kinase domain and ATP binding site of ALK.<sup>92</sup> Activation of ROS1 leads to signalling through downstream oncogenic pathways, including PI3K/Akt, MTOR and RAS-MAPK/ERK pathways.<sup>93</sup> ROS1 rearrangements have been found to occur in up to 4% of lung adenocarcinomas,<sup>94-98</sup> and are mutually exclusive with other driver mutations. Patients harbouring ROS1 rearrangements have overlapping clinical features with ALK rearranged tumours. There is in vitro evidence of sensitivity to crizotinib in a NSCLC cell line harbouring ROS1 rearrangement, although it is unclear if the growth inhibition related to inhibition of ROS1 or MET amplification, which is also present in the HCC78 cell line.<sup>100</sup> One young non-smoker patient with a ROS1 rearrangement, showed near complete response to crizotinib treatment as part of a clinical trial.<sup>94</sup>

### Squamous cell carcinoma

While current targeted molecular therapies in lung cancer have almost exclusively been in adenocarcinomas, increasing knowledge and interest in the molecular genetics of other lung cancer types, particularly squamous cell carcinoma,<sup>101</sup> will hopefully have a clinical impact in the future. Recently the Cancer Genome Atlas Research Network, as part of the Cancer Genome Atlas project, published the first comprehensive assessment of genomic alterations in squamous cell carcinomas after profiling 178 tumours.<sup>7</sup> They found TP53 mutations in almost all cases and potential therapeutic targets in the majority (64%) of squamous cell carcinomas (64%). Promising new targetable oncogenes in squamous cell carcinoma include fibroblast growth factor receptor amplifications, PIK3CA mutations and DDR2 mutations.<sup>102</sup>

## Approach to molecular genetic testing in NSCLC

With an increasing range of molecular targeted treatments for selected NSCLC patients, there is increasing need for testing of multiple genes. An algorithmic approach exploiting the mutually exclusive nature of most of the genetic alterations can be used for efficiencies of time and cost (figure 2). The optimal algorithm in each centre will largely depend on local resources and expertise, as well as the nature of the samples. Adequate sample quality and tumour DNA quantity is essential to ensure accurate testing, as low quality samples can compromise results and impact patient care. As the majority of patients with lung cancer are inoperable at diagnosis, many of the biopsies submitted for mutation testing are extremely limited, posing significant challenges, including the risk of false negative and positive results. Clinicians, radiologists and pathologists need to have a co-ordinated multidisciplinary approach, with good lines of communication to ensure optimal specimens are submitted for testing, as inappropriate specimens may lead to unnecessary delays and repeat testing. Given the generally limited amount of biopsy material in NSCLC, multi-gene testing is cost and time effective to rapidly identify patients with targetable changes, while helping to exclude the need for unnecessary FISH or other molecular testing, for example in patients harbouring KRAS mutations. In our experience, assessment of EGFR, KRAS and other major driver mutations in parallel with immunohistochemistry for ALK with confirmatory FISH if required, is cost and time effective and makes the best use of limited tissue samples.

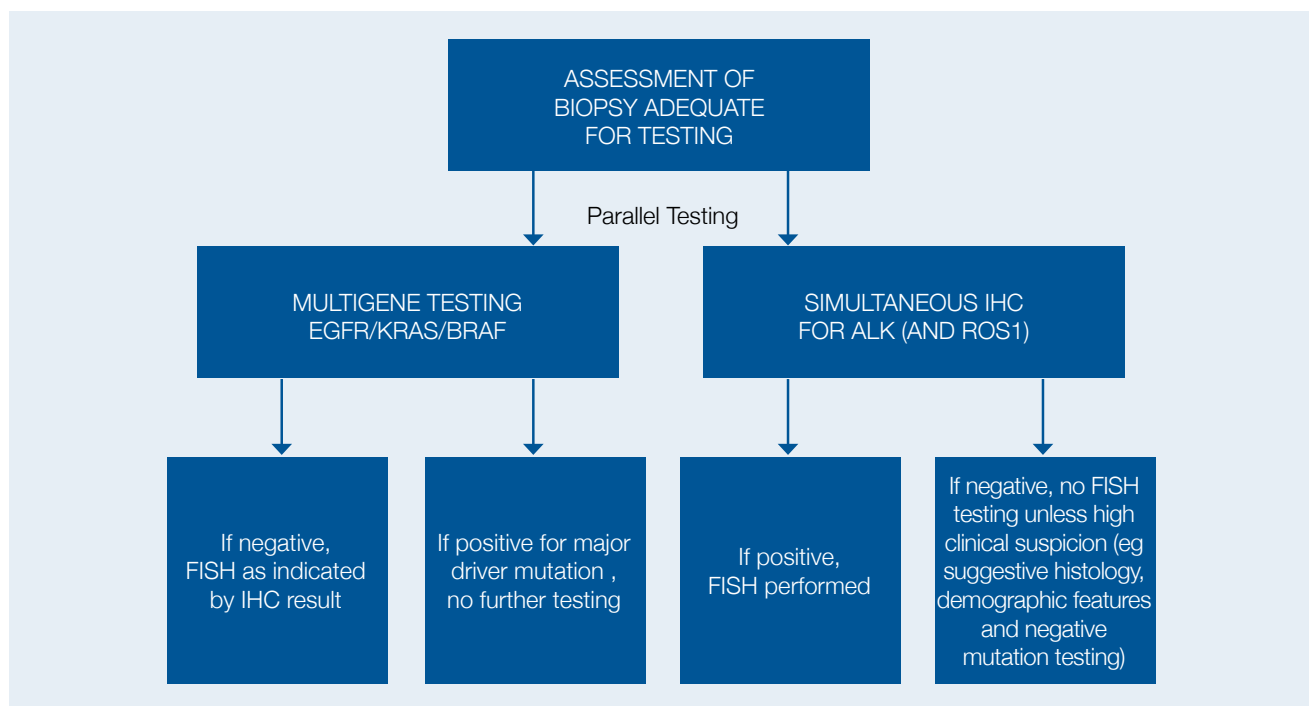
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**Figure 2:** Flow chart showing an algorithm for molecular genetic testing in lung adenocarcinomas.





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# EGFR-TARGETED THERAPY AND RESISTANCE

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## Abstract

The management of non-small cell lung cancer is undergoing a paradigm shift from empirically-selected treatment to personalised therapy, based on the clinical characteristics of patients and the histological and molecular features of their tumours. This has been driven by the identification of oncogenic 'drivers' responsible for cancer cell growth and survival, and the development of specific therapy targeting these. The pivotal discovery was the identification of mutations in the epidermal growth factor receptor and recognition of their exquisite sensitivity to epidermal growth factor receptor tyrosine kinase inhibitors. Defining this molecular cohort and instituting targeted therapy has led to significantly improved clinical outcomes over empirical chemotherapy. However, the development of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors therapy appears universal, and strategies to delay or overcome the emergence of this resistance remain to be defined.

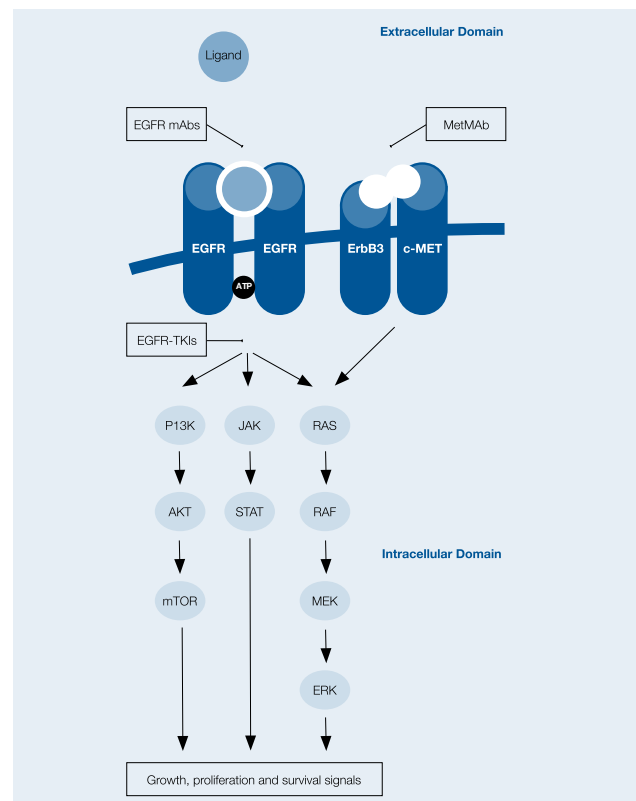
The identification that certain subtypes of non-small cell lung cancer (NSCLC) respond better than others to specific therapy has led the search to identify as many subtypes that exist in order to tailor therapy to these subtypes for maximum clinical benefit. Since the mapping of the human genome, modern molecular technology has enabled a detailed characterisation of the molecular characteristics of NSCLC, and in adenocarcinoma, new mutated genes have been recently identified beyond EGFR (epidermal growth factor receptor) that may be suitable drug targets.<sup>1</sup> These alterations are often responsible for the initiation and maintenance of cancer growth and are referred to as 'driver mutations'. This review outlines the identification of EGFR as a therapeutic target, describing its current role in treatment selection, the clinical outcomes of anti-EGFR targeted therapy and the identification of resistance to such therapies and future directions to overcome this.

## EGFR

EGFR (otherwise known as ErbB1/Her1) is a receptor tyrosine kinase that belongs to a family of four membrane-bound receptors. EGFR has been shown to be over-expressed in more than 60% of NSCLC cases, and is associated with a poor prognosis.<sup>2,3</sup> Activation of the EGFR by ligand binding results in its homo or hetero-dimerisation and intracellular tyrosine kinase activity. The downstream signalling regulated by EGFR is complex and multidimensional, involving the Ras-Raf-MEK, PI3K-Akt-mTOR, PKC and STAT pathways, and plays a critical role in cell-cycle progression and proliferation.<sup>4</sup> An outline of the EGFR signalling pathway is shown in figure 1. A number of mechanisms are responsible for the aberrant activation of the EGFR pathway in cancer cells, including enhanced ligand production, increased EGFR expression and mutations in the EGFR gene.

Specific mutations in the tyrosine kinase domain of EGFR were first reported in 2004.<sup>5-7</sup> They occur over exons 18 – 21, which encode the ATP-binding pocket of the kinase domain of EGFR and result in ligand-independent

**Figure 1:** The EGFR pathway and potential strategies to target this pathway. Ligand binding to EGFR induces conformational changes that result in the homo or hetero-dimerisation of the receptor and its subsequent autophosphorylation and downstream signalling.



constitutive activation of the receptor. These mutations have been shown to confer sensitivity to EGFR-tyrosine kinase inhibitors (TKIs) through their preferential binding of TKI over ATP. The two most prevalent activating mutations, accounting for approximately 85% of mutations observed, are deletions within exon 19 and point mutations in exon 21.<sup>8</sup> The frequency of EGFR

mutations observed depends upon the population studied, ranging from 5 – 20% in a caucasian population and up to 60% in selected asian patient populations. The clinical phenotype of a female, asian non-smoker with a tumour of adenocarcinoma histology predicts the highest likelihood of harbouring an EGFR mutation.<sup>9</sup>

There are two classes of EGFR inhibitors – TKIs that compete with ATP for binding to the intracellular kinase domain of EGFR and monoclonal antibodies (mAbs) that bind to the extracellular domain and block ligand binding. These two classes are discussed below.

## EGFR-TKIs in mutation positive patients

The initial evidence for the role of EGFR-TKIs in lung cancer treatment came from studies evaluating the first-generation agents, gefitinib and erlotinib. In the early studies of gefitinib undertaken in unselected patients before the rate of EGFR mutations were appreciated, response rates of < 20% were observed.<sup>10</sup> However, a subgroup of patients had dramatic and occasionally durable responses to these agents.<sup>11</sup> The underlying molecular basis for these unprecedented responses were activating mutations in EGFR.<sup>5-7</sup> With increasing understanding of the role of EGFR mutations in predicting EGFR-TKI sensitivity, studies have since

upfront EGFR-TKI. Furthermore, clinical selection for first-line EGFR-TKIs may miss a proportion of patients without defined clinical features who harbour an EGFR mutation that may benefit from such treatment given upfront.

Despite the impressive progression free survival results, none of the aforementioned studies, nor the subsequent meta-analyses, have demonstrated an overall survival benefit for TKIs compared to chemotherapy in EGFR mutation positive patients.<sup>18-20</sup> This is most likely due to the confounding effect of cross-over after study treatment. Hence, it has been inferred that survival is not compromised in EGFR mutation positive patients who receive upfront chemotherapy, as long as they receive an EGFR-TKI at some point along their treatment pathway. However, given the risk of attrition rate between first and second-line therapy, the risk of this strategy is that an individual patient may miss out on potentially effective treatment, which would be considered unacceptable in light of the impressive impact of EGFR-TKIs on clinical outcomes in mutation positive patients.<sup>21</sup> Henceforth, in clinical practice EGFR-TKIs are usually commenced as soon as sensitising mutations have been identified.

Second generation EGFR-TKIs have been developed that differ from the first-generation agents in forming

**Table 1:** Randomised studies comparing first-line first-generation EGFR-TKIs to chemotherapy in clinically or molecularly enriched cohorts for EGFR mutations. HR: hazard ratio.

Trial	Patient Selection	EGFR-TKI	Reference Arm	PFS (months)	HR	p Value
IPASS12	Clinical	Gefitinib	Carboplatin/ Paclitaxel	9.8 v 6.4	0.48	<0.001
First-SIGNAL13	Clinical	Gefitinib	Carboplatin/ Gemcitabine	8.4 v 6.7	0.61	0.084
NEJ00214	Molecular	Gefitinib	Carboplatin/ Paclitaxel	10.8 v 5.4	0.3	<0.001
WJTOG340515	Molecular	Gefitinib	Cisplatin/ Docetaxel	9.2 v 6.3	0.489	<0.0001
OPTIMAL16	Molecular	Erlotinib	Carboplatin/ Gemcitabine	13.1 v 4.6	0.16	<0.0001
EURTAC17	Molecular	Erlotinib	Platinum doublet	9.7 v 5.2	0.37	<0.0001

focused on evaluating EGFR-TKIs in the first-line setting in patients with EGFR mutations. Six studies have confirmed the benefit on response rate and progression-free survival of first-generation EGFR-TKIs used in EGFR mutation positive patients over chemotherapy (table 1). Two of these studies selected patients by clinical parameters, while the remainder mandated molecular confirmation of EGFR mutations prior to study entry. Their results highlight the importance of identifying EGFR mutations prior to initiating first-line EGFR-TKIs, as worse outcomes were observed for EGFR wild-type patients receiving EGFR-TKIs compared to chemotherapy (in IPASS study,<sup>12</sup> progression free survival hazard ratio (HR) 2.85, p<0.001). Hence, selecting patients for first-line therapy on the basis of clinical characteristics can be harmful, as it can result in worse outcomes for EGFR wild-type patients who receive

irreversible bonds with their target and binding to additional ErbB family members. It is hoped that these features can delay the emergence of resistance and improve upon the outcomes achieved with the first-generation EGFR-TKIs. Afatinib is one such agent that has been shown to improve progression free survival compared to platinum-pemetrexed chemotherapy in the first-line setting in EGFR mutation positive patients (11.1 v 6.9 months, HR 0.59, p 0.0004).<sup>22</sup> The progression free survival HR with afatinib appears similar to those seen with the first-generation agents, although it was compared with pemetrexed based chemotherapy, known to be superior in adenocarcinomas.<sup>23</sup> However, relatively high rates of class side-effects, such as skin rash and diarrhoea, were observed. Approval of afatinib in the first-line setting is currently under evaluation.

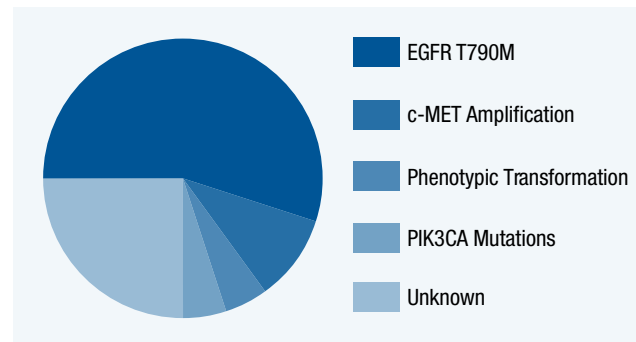
## EGFR-TKI resistance

Resistance to EGFR-TKIs can be divided into primary and secondary forms according to the timing in relation to targeted therapy. Primary resistance refers to de novo insensitivity of a tumour to EGFR-TKI treatment. Both EGFR mutations and activation of alternate oncogenes or pathways have been identified as possible causes. Insertion mutations in exon 20 represent less than 5% of mutations in the EGFR gene and preclude the binding of first generation EGFR-TKIs to the tyrosine kinase domain, conferring resistance.<sup>24</sup> Mutually exclusive mutations in KRAS, or the presence of the EML4-ALK fusion gene, also predict for primary resistance. Other less clearly validated markers include loss of PTEN, BRAF mutations and increased protein levels of IGF1R, MAPK, ABCG2 and BCL-2.<sup>25</sup>

While tumours harbouring activating EGFR mutations are typically exquisitely sensitive to EGFR-TKIs, tumour progression is generally observed after a median of 10-14 months, reflecting the development of acquired resistance.<sup>12</sup> A set of guidelines has been developed to standardise the clinical definition of acquired resistance and include: previous treatment with single agent EGFR-TKI and confirmed EGFR activating mutation and/or objective clinical benefit from EGFR-TKI treatment; systemic progression of disease while on continuous anti-EGFR treatment; and no intervening systemic treatment between cessation of EGFR-TKI and initiation of new therapy.<sup>26</sup> Acquired resistance is associated with the development of secondary mutations in EGFR or EGFR-independent activation of growth and survival pathways, as outlined in figure 2. The most common mechanism, observed in approximately 50% of cases of acquired resistance, is the development of a second EGFR gatekeeper mutation, T790M.<sup>27</sup> This mutation interrupts the binding of first-generation EGFR-TKIs and restores the receptor's affinity for its natural substrate ATP. The second major mechanism of acquired resistance, accounting for about 10% of cases, is amplification of the MET oncogene.<sup>28</sup> MET is a transmembrane receptor tyrosine kinase and its coupling to ErbB3 results in sustained activation of the PI3K/AKT signalling pathway, bypassing the inhibited EGFR. Phenotypic transformation has also been observed in the development of acquired resistance, including transformation to small cell lung cancer (SCLC) and epithelial to mesenchymal transition.<sup>29</sup> At least 30% of cases of EGFR-TKI resistance remain undefined mechanistically.

Traditionally, following the development of acquired resistance, determined according to standard response criteria, standard practice is to switch to conventional cytotoxic chemotherapy. However, a number of observations are challenging this empirical strategy. Firstly is the observation of clinically heterogeneous patterns of disease progression on EGFR-TKI therapy, including a single focus of progression, minimal multifocal progression and rapid multifocal or bulky progression. The observation of indolent cases of progression has led to some clinicians delaying the commencement of alternate systemic therapy through the continued use of first generation EGFR-TKI, local control measures involving surgery or radiotherapy or observation alone. A retrospective review of 42 patients with disease progression on erlotinib treatment found that 45% of the cohort had alternate systemic therapy delayed by more than three months through a combination of the aforementioned measures.<sup>30</sup> Secondly, there is emerging evidence that tumours can retain a degree of EGFR-TKI

Figure 2: Mechanisms of acquired EGFR resistance.



responsiveness even after the development of resistance. This is based on the observation of accelerated disease progression on EGFR-TKI withdrawal in a subset of patients with acquired resistance, a phenomenon referred to as 'disease flare'.<sup>31</sup> To account for this observation, it is hypothesised that resistant tumours contain a mixed population of TKI resistant and latent TKI sensitive cells, which rapidly repopulate on withdrawal of the selection pressure exerted by TKI therapy.<sup>32</sup> This has prompted investigation into a strategy of continued EGFR-TKI with concurrent systemic chemotherapy. While combinations of EGFR-TKI therapy and chemotherapy were not shown to be more efficacious than chemotherapy alone in a number of phase III studies in unselected patients, this approach is being re-visited in a selected cohort of EGFR mutation positive patients with acquired resistance to TKI therapy and utilising an intercalated approach in the administration of the two therapies.<sup>33-36</sup> Results of Phase III studies evaluating the question of continuing EGFR-TKI at progression and adding chemotherapy compared with chemotherapy alone are eagerly awaited.<sup>37</sup>

Further strategies designed to overcome the development of acquired resistance have focused on targeting the underlying mechanisms. This is particularly the case for the T790M mutation, which is the most common cause of acquired resistance and has emerging clinical data that suggests, paradoxically, a relatively favourable prognosis and more indolent course.<sup>38</sup> While preclinical studies suggest the second-generation irreversible EGFR-TKIs are active against cells harbouring the T790M mutation, clinical trials of these agents after progression on a first generation EGFR-TKI have shown limited activity.<sup>39,40</sup> The Lux Lung 1 trial of afatinib versus placebo in patients having previously received benefit from a first generation TKI (defined as disease control for  $\geq 6$  months) failed to demonstrate a survival advantage, although progression free survival was improved (3.3 v 1.1 months (HR 0.38, 95% CI 0.31-0.48;  $p < 0.0001$ )) and a small number of responses (7% RR) were observed with afatinib.<sup>40</sup> An alternate approach is to attempt vertical inhibition of the intracellular and extracellular domains of EGFR through the combination of an EGFR-TKI and mAb. While results for the combination of erlotinib and cetuximab were disappointing, more promising outcomes have been observed with the combination of cetuximab with afatinib in a phase IB/II trial.<sup>41,42</sup>

Increased signalling through MET has been identified as a mechanism of acquired resistance, and the efficacy of MET inhibition with the use of small molecular inhibitors and mAbs is being explored in this setting. A phase III study of the oral MET inhibitor tivantinib (ARQ197) in combination with erlotinib, compared to erlotinib alone, in previously treated

advanced NSCLC patients was discontinued following an interim analysis that concluded the primary endpoint of OS would not be met.<sup>43</sup> Detailed results are awaited. In contrast, a phase III clinical trial of the combination of MetMab with erlotinib in advanced pre-treated NSCLC with MET over-expression has been initiated, following phase II results which showed a significant benefit for the combination in patients with MET overexpression and a detrimental effect for the combination compared to erlotinib alone in patients without overexpression.<sup>44-46</sup> Combinations of other classes of inhibitors, such as the mammalian target of rapamycin, heat shock protein-90 and SRC inhibitors, with EGFR-TKIs have been conducted, yielding disappointing results.<sup>32</sup> This highlights the importance of identifying predictive biomarkers and elucidating molecular mechanisms underlying resistance in order to develop rational, genotype-driven therapies to overcome acquired resistance.

In cases of phenotypic transformation, there is anecdotal evidence of the persistence of the original EGFR mutation and efficacy of standard SCLC chemotherapy in cases of acquired resistance mediated by conversion to SCLC.<sup>29,47</sup> In preclinical models, the emergence of epithelial to mesenchymal transition features is associated with a loss of dependence upon the EGFR signalling pathway, although sensitivity to EGFR-TKIs may be restored with histone deacetylase inhibitors, an approach undergoing further evaluation.<sup>48</sup>

### EGFR targeted therapy in wild-type patients

While the greatest clinical benefits of EGFR-TKIs are observed in mutation positive patients, they also have a place in the management of wild-type patients. A number of studies were initiated in a variety of settings in unselected patients prior to the discovery of EGFR mutations.

In patients with wild-type tumours or unknown EGFR mutation status, there is no role for the use of EGFR-TKIs in the first-line setting. The IPASS and First-SIGNAL studies clearly demonstrated inferior outcomes for EGFR wild-type patients who received first-line gefitinib compared to chemotherapy.<sup>12,13</sup> Four trials administering EGFR-TKIs concurrently with chemotherapy in unselected patients were also negative.<sup>33-36</sup> However, in patients with stable disease following platinum-based therapy, erlotinib is an option for switch maintenance therapy based on the results of the SATURN trial, which demonstrated a progression free survival and overall survival advantage to erlotinib over placebo in this setting. However, there have been conflicting results regarding the clinical efficacy of EGFR-TKIs compared to chemotherapy in the second-line setting, including the non-inferiority of gefitinib to docetaxel, a progression free survival advantage to docetaxel compared to erlotinib and an underpowered trial suggesting comparable efficacy between erlotinib and pemetrexed or docetaxel.<sup>49-51</sup>

In patients with refractory disease, the BR.21 trial showed erlotinib to confer an overall survival benefit (6.7 versus 4.7 months,  $p=0.001$ ) and delayed time to symptom worsening compared to placebo in the second and third-line settings.<sup>52</sup> A similar trial conducted using gefitinib (ISEL) did not find a significant overall survival improvement.<sup>53</sup> Hence, only erlotinib is approved by the US Food and Drug Administration, Australian Therapeutic Goods Administration and Pharmaceutical Benefit Scheme for use in unselected

patients as a second or subsequent line of therapy. Reasons proposed for the discrepancy in outcomes between gefitinib and erlotinib in this setting include a poorer prognostic group of patients evaluated in the ISEL study and the dosing of gefitinib, which is given at well below its maximum tolerated dose (250mg/day v 800mg/day).

A number of EGFR-directed mAbs have been evaluated in NSCLC, with results for cetuximab from the FLEX trial having gathered the most interest to date. A statistically, but not clinically significant overall survival advantage, was observed with the addition of cetuximab to cisplatin/vinorelbine in patients with EGFR-expressing tumours as determined by immunohistochemistry (11.3 v 10.1 months, HR 0.87,  $p=0.04$ ).<sup>54</sup> EGFR mutation status did not predict for clinical outcome.<sup>55</sup> Subsequent analysis of this study has found a semiquantitative assessment of EGFR protein expression based on a histo-score predicted treatment outcomes, however this remains to be validated prospectively.<sup>56</sup> At present, cetuximab is not reimbursed and is not recommended as part of clinical lung cancer care outside of a clinical trial setting.

In summary, EGFR targeted therapy can offer a modest clinical benefit in certain settings in patients with EGFR wild-type tumours, which reflects the importance of the EGFR pathway on the malignant phenotype. However, further research is needed to identify predictive biomarkers for response in this heterogeneous patient group.

The recognition of the importance of the EGFR pathway in the malignant phenotype and development of therapies targeting EGFR has revolutionised the management of NSCLC. This is particularly true for the subset of patients identified to harbour EGFR mutations, where improved outcomes have been achieved with the personalisation of therapy using EGFR-TKIs compared to empirically-selected chemotherapy. To improve upon the survival gains achieved with EGFR targeted therapies, further research is required into the mechanisms of resistance in order to develop genotype-driven treatment options.

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## OTHER NOVEL MOLECULAR TARGETS IN NON-SMALL CELL LUNG CANCER: IT'S NOT ALL ABOUT EGFR

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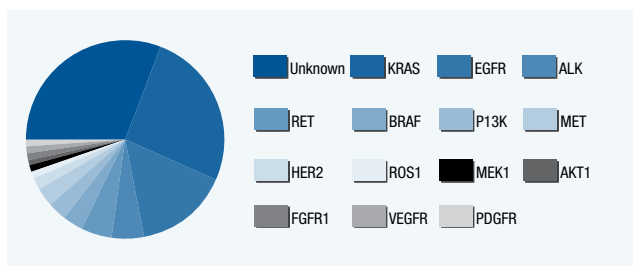
### Abstract

Identification and inhibition of molecular pathways that drive malignant cells have led to improved outcomes in the understanding and management of non-small cell lung cancer. This has been illustrated by the effective use of the EGFR-tyrosine kinase inhibitors erlotinib, gefitinib and afatinib, which have been major steps forward in targeted therapy for advanced and metastatic lung cancer in patients who harbour specific epithelial growth factor receptor mutations. This success continues to drive ongoing research in identifying other novel molecular pathways in malignant cells that may be exploited for targeted therapy. Some of the other current advances in identifying targetable genetic mutations and the development of therapies that may have a potential clinical impact on the management of both adenocarcinoma and squamous cell lung cancer are reviewed.

### Adenocarcinoma

Following on from the achievements of the EGFR inhibitors,<sup>1-3</sup> adenocarcinoma remains the most studied histology of non-small cell lung cancer (NSCLC) in the search for effective targeted therapies. These most recent breakthroughs have resulted in less emphasis being placed on the development of new, non-specific systemic chemotherapy agents but rather, more focus has been directed toward the identification of 'druggable' targets in the distinct molecular pathways that promote the oncogenic drive in malignant NSCLC cells. At this point in time, more than a dozen mutations have been identified which have shown potential for being targets of therapeutic agents (figure 1). Already, many new agents directed against specific molecular targets such as ALK (anaplastic lymphoma kinase), ROS1 and MET have been developed, which are showing encouraging results in the treatment of NSCLC and are currently the subject of ongoing clinical trials.

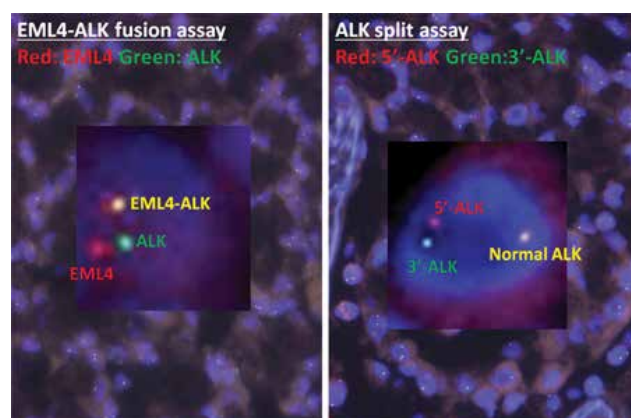
**Figure 1:**  
*Molecular subsets of driver mutations in lung adenocarcinoma*



### ALK translocation

Of all the novel molecular targets under investigation, the ALK-EML4 fusion gene has seen the most advances. This alteration, which is present in approximately 3-5% of patients with NSCLC adenocarcinomas,<sup>4</sup> involves a translocation of the ALK gene which results in a fusion rearrangement with the EML4 (echinoderm microtubule-

**Figure 2:** *FISH assays for EML4-ALK fusion gene in lung adenocarcinoma tissue.*



associated protein-like 4) gene (figure 2). The activated protein arising from this fusion promotes cancer cell growth and proliferation. The rearrangement is most often found in never or light smokers, younger age patients and adenocarcinomas with signet ring or acinar morphology. ALK gene rearrangements tend to occur independent of EGFR or KRAS mutations.<sup>5</sup>

The development of crizotinib, an oral selective inhibitor of ALK and MET tyrosine kinases, has seen a significant prolongation of progression free survival in those that harbour the gene rearrangement.<sup>6</sup> In the initial phase I trial (PROFILE 1001),<sup>7</sup> 119 ALK positive patients received crizotinib (250mg) twice daily, administered continuously on a 28 day cycle. Overall response rate was an impressive 61% (95% C.I. 52-70) in this heavily pre-treated population, with a median duration of response of 48 weeks.

Following on from this encouraging result, the phase II trial (PROFILE 1005) enrolled 136 patients who received crizotinib (250mg) twice daily in a continuous 21 day cycle.<sup>8</sup> The overall response rate, which was the primary endpoint of this ongoing trial, was reported to be 51.1% (95% C.I.



42.3-59.9), with a complete response reported in one patient and partial responses reported in 67 patients. The benefit of targeting ALK rearrangement positive NSCLC patients, who have received one prior platinum containing regimen, has now been confirmed in a phase III study.<sup>9</sup> In this study, crizotinib significantly increased progression free survival compared with single agent pemetrexed or docetaxel (median 7.7 months v 3.0 months) and also improved symptom related quality of life.

Currently a phase III trial<sup>10</sup> (PROFILE 1014) is underway, comparing chemotherapy (pemetrexed plus a platinum compound) with crizotinib in ALK positive patients with advanced NSCLC who have not received prior systemic therapy. If this trial confirms a significant progression free survival advantage, then this will establish crizotinib as the new standard of care for first line treatment of ALK rearranged NSCLC.

Second generation ALK inhibitors are now also in development and are hoped to be more potent and selective than crizotinib. In the future, these may be utilised as second line treatment to overcome acquired resistance, or may eventually supersede crizotinib as front-line therapy. One such agent, LDK378, reported an impressive objective response in 21 of 26 patients who had displayed resistance to crizotinib.<sup>11</sup>

### **KRAS mutation**

The RAS family of oncogenes encode for membrane-bound intracellular GTP-ases, which act as mediators in various downstream pathways including the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K). These signalling pathways control cellular proliferation and apoptosis. The KRAS protein is a member of the RAS family and is an early player in these signal transduction pathways. Activating KRAS mutations are observed in approximately 20 to 25% of lung adenocarcinoma and are generally associated with a history of smoking.<sup>12</sup> Identification of agents that specifically inhibit KRAS have proved difficult. Currently the focus of targeted therapy for patients with KRAS mutated lung cancer has been the downstream effectors of the activated RAS pathway. One such strategy is MEK inhibition. The MAPK pathway converges at the MEK1/MEK2 kinases, whose activation facilitates further downstream signalling leading to cellular proliferation.

In a recent phase II trial, 87 previously treated patients with KRAS mutant advanced NSCLC were randomly assigned to docetaxel with or without selumetinib, an oral MEK inhibitor.<sup>13</sup> The addition of selumetinib to docetaxel showed promising efficacy, with improved progression free survival (median 5.3 v 2.1 months, HR 0.58, 80% CI 0.42-0.79) and a trend toward increased overall survival (median 9.4 v 5.2 months, HR 0.80, 80% CI 0.56-1.14). Given that KRAS mutations in NSCLC have been associated with a poorer prognosis,<sup>14</sup> these findings warrant ongoing trials with such targeted therapies and further clinical investigation of these downstream pathways to identify other appropriate targets.

### **ROS1 translocation**

ROS1 is another receptor tyrosine kinase whose

translocation acts as a driver oncogene in 1 to 2% of NSCLC patients. Several ROS1 translocation fusions with other genes have been discovered in tumour types including gliomas, cholangiocarcinomas and NSCLC: CD74, SLC24A2 and FIG.<sup>15</sup> In NSCLC, these translocation are commonly associated with adenocarcinoma histology, younger patients and never smokers.<sup>16</sup>

Initial case reports found the ROS1 tyrosine kinase to be highly sensitive to crizotinib due to the high homology between the ROS1 and ALK kinase domains. Fourteen patients with the ROS1 mutation were treated in the original phase I trial with crizotinib. Eight patients (57%) showed an objective response to treatment.<sup>17</sup> Although the translocation is rare, current evidence supports the exploration of ROS1 as a target for existing and novel ALK inhibitors.<sup>16-17</sup> An open label trial (NCT00585195) using crizotinib in patients with ROS1 fusion NSCLC is in progress.

### **MET over expression**

MET is a tyrosine kinase receptor for hepatocyte growth factor. MET mediates activation of several downstream signalling pathways (PIK3/AKT, Ras-Rac/Rho, MAPK) which stimulate morphogenic, proliferative and anti-apoptotic activities. These pathways also promote cell detachment, motility and invasiveness.<sup>18</sup>

Of notable clinical significance is that MET amplification has been associated with resistance to EGFR inhibitors. One postulated resistance mechanism is the parallel activation of the MET signalling pathway, providing an alternative route for activation of downstream signals when EGFR is inhibited. MET over expression has been found in 5-22% of NSCLC patients with secondary resistance to EGFR-TKIs.<sup>19</sup> Accordingly, targeting the MET pathway has potential clinical significance.

Tivantinib (ARQ 197) is a selective tyrosine kinase inhibitor of MET. A phase II trial investigated erlotinib plus tivantinib in 173 previously treated (but EGFR-TKI naïve) patients.<sup>20</sup> The median progression free survival was 3.8 months for erlotinib plus tivantinib and 2.3 months for erlotinib alone. A subset analysis of patients with KRAS mutant tumours (n=10) showed a marked progression free survival benefit with the combination therapy (HR 0.18, 95% CI 0.05-0.70). Prior studies have shown that the presence of a KRAS mutation in NSCLC may confer a poorer prognosis. Based on these promising results, a phase III trial (MARQUEE) was undertaken involving patients with previously treated metastatic nonsquamous NSCLC, comparing erlotinib and tivantinib versus erlotinib and placebo.<sup>21</sup> The final results are yet to be presented, but the trial was closed after interim analysis indicated it would fail to meet its primary endpoint of overall survival improvement.

Another investigational agent targeting MET which is showing promising results is onartuzumab, an anti-MET monoclonal antibody. A randomised phase II trial was conducted involving pre-treated patients who were treated with onartuzumab and placebo, or onartuzumab and erlotinib.<sup>22</sup> In a subgroup analysis of patients with MET immunohistochemistry positive tumours, the progression free survival (HR 0.53; 95% CI 0.3-1.0) and overall

survival (HR 0.4; CI, 0.2-0.7) outcomes were better with the combination over erlotinib alone. Based on these results, a randomised phase III trial comparing erlotinib plus onartuzumab with erlotinib plus placebo in NSCLC patients with MET over expression is underway.<sup>23</sup>

### HER2 mutation

HER2 (ERBB2) is an EGFR family receptor tyrosine kinase. Mutations in exon 20 of HER2 have been detected in 1 to 4% of NSCLC tumours and, like ALK and ROS1, are seen more frequently in non-smokers.<sup>24</sup>

A phase II study involving afatinib, a potent irreversible ErbB family blocker, showed clinical activity in patients with metastatic lung adenocarcinomas bearing mutations in the kinase domain of HER2 gene.<sup>25</sup> Objective responses were observed in three patients, even after failure of other EGFR and/or HER2-targeted treatments such as gefitinib, trastuzumab and lapatinib. Larger trials are ongoing to further define its significance in NSCLC.

### BRAF mutation

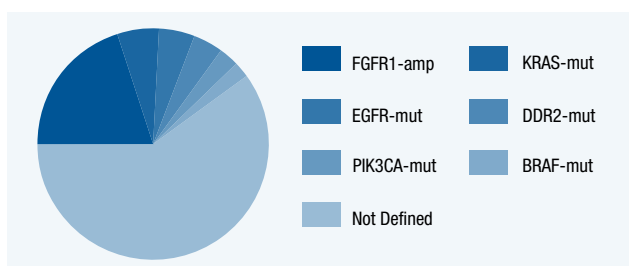
BRAF is a downstream signalling mediator of KRAS which activates the MAP kinase pathway. BRAF mutations have been observed in 1 to 3% of NSCLC and are associated with a history of smoking.<sup>26</sup> Activating BRAF mutations can occur at the V600 position of exon 15 (similar to that seen in melanoma)<sup>27-28</sup> or outside this codon. BRAF mutations have also been described as a resistance mechanism in EGFR mutation positive NSCLC.<sup>29</sup>

The BRAF inhibitor, dabrafenib, is being evaluated in a phase II study of patients with NSCLC containing the BRAF V600E mutation.<sup>30</sup>

## Squamous cell lung cancer

The advances in molecular targets and targeted therapies, while somewhat favouring adenocarcinoma to date, are not simply limited to this histological subtype of NSCLC. Recently, several molecular targets have also been identified in squamous cell NSCLC (figure 3) and currently, various therapeutic agents are being trialled with potential clinical impact.

**Figure 3: Molecular subsets of driver mutations in squamous cell lung cancer**



### FGFR1 amplification and mutation

Fibroblast growth factor receptor-1 (FGFR1) is a cell surface tyrosine kinase receptor. Its activation by fibroblast growth factor (FGF), leads to downstream signalling via PI3K/AKT, RAS/MAPK pathways that mediate cell growth,

survival, migration and angiogenesis. Approximately 20% of squamous cell cancers have oncogenic FGFR1 amplification.<sup>31</sup> This results in aberrant receptor activation and consequently, deregulated downstream signalling. Activating mutations of FGFR have also been identified in lung cancers.<sup>32</sup> With several mechanisms potentially involved in aberrant behaviour of malignant cells, it follows that targeted inhibition of FGFR offers a valuable modality for therapeutic intervention across multiple targets of genetic alterations.

Several FGFR inhibitors are in phase I or phase II trials; many of these are multi-targeted tyrosine kinase inhibitors. One of these is NVP-BGJ398, a potent pan-FGFR kinase inhibitor, which is currently in clinical phase I trials.<sup>33</sup> Results of a NSCLC patient who had tumour regression in response to BGJ398 have been published.<sup>34</sup> Other small molecule FGFR inhibitors such as AZD4547,<sup>35</sup> and Brivanib,<sup>36</sup> are also undergoing phase I and II trials.

### DDR2 mutation

The discoidin domain receptor 2 (DDR2) gene encodes a cell surface receptor tyrosine kinase that is mutated to an active form in about 4% of squamous cell lung carcinomas.<sup>37</sup> DDR2 binds collagen and has been shown to promote cell migration, proliferation and survival.<sup>38</sup> Dasatinib inhibits proliferation and ectopic expression of mutated DDR2 cell lines. Clinical trials are underway to determine its effectiveness. A case has been reported of a patient treated with a combination of dasatinib and erlotinib who was shown to have a tumour response.<sup>37</sup>

### PI3 kinase pathway

Phosphatidyl 3-kinase (PI3K) is an intracellular kinase that activates intracellular signalling through downstream effectors including AKT and mTOR. The PI3K-AKT pathway plays a central role in the survival and proliferation of many cancers.<sup>39</sup> One gene identified to be primarily involved in this pathway is the PIK3CA gene, which encodes for the catalytic subunit of PI3K. Gain of function mutations and somatic mutations have been found in PIK3CA which promote activation of the PI3K signalling pathway.<sup>40,41</sup> PIK3CA mutations may also promote resistance to EGFR-tyrosine kinase inhibitors in EGFR-mutant NSCLC.<sup>42</sup> PIK3CA mutations have been reported in 6.5% of squamous cell lung cancers.<sup>43</sup> Multiple inhibitors are in development which target PI3K (BYL719),<sup>44</sup> PI3K/MTOR (PF-04691502),<sup>45</sup> and the downstream AKT kinase (MK-2206).<sup>46</sup>

### PTEN loss

PTEN is a tumour suppressor gene which encodes a lipid phosphatase that inhibits the PI3K/AKT pathway. Reduction or loss of PTEN expression leads to up regulation of PI3K-AKT signalling. Its alteration has been reported in up to 70% of NSCLC, both in adenocarcinoma and squamous histology.<sup>47</sup> Cancers with PTEN loss may be more sensitive to inhibitors of the PI3K pathway and trials are underway to assess this.<sup>48</sup>

## Conclusion

Recognising the heterogeneity of mutations in individual cancers has brought about a new paradigm in our approach to cancer care in the 21st century. The growing range of molecular targets suitable as drug targets and the development of therapeutic agents directed against them, represents the keys to success in the personalised medicine approach to the treatment of cancer. In recent times, lung cancer leads the way in making this paradigm shift a reality.

Targeted therapies are already in existence which can be utilised to effectively manage advanced disease in lieu of traditional systemic cytotoxic chemotherapy.<sup>1-3</sup> Agents that are equally or more effective than traditional chemotherapy, have the advantage of less toxicity than that associated with systemic therapy, which is one of the goals that drives their development. Ongoing research to improve the understanding of the molecular pathways that drive malignancy will continue to transform the treatment of lung cancer in this way. Continuing to identify those molecular alterations with a view to targeting their specific pathways, will ultimately bring to fruition the concept of 'personalised medicine' in treating the various sub-types of lung cancer, with improved outcomes for patients.

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## SMALL CELL LUNG CANCER UPDATE

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### Abstract

Small cell lung cancer remains a highly lethal form of cancer, with few advances made in treatment over the last two decades. The use of platinum-containing doublet chemotherapy, and concurrent chemotherapy and thoracic irradiation in limited stage disease, remains the standard of care. To date, a number of trials have been conducted to assess the impact of newer chemotherapy agents, either for single agent activity or combined with standard chemotherapy, but with limited success. Many of the recent benefits seen in other forms of cancer (including non-small cell lung cancer) arise from the identification and targeting of specific molecular abnormalities that promote cancer growth and spread. However, although a range of targeted therapies have also been trialled in small cell lung cancer, and despite promising in-vitro data, these have not as yet produced major breakthroughs in clinical management. Further elucidation of the molecular mechanisms in small cell lung cancer and therapies directed at these abnormalities holds the key to improving outcomes in this condition, but requires significant ongoing work.

Small cell lung cancer (SCLC) accounts for 10-20% of all lung cancer, and is characterised by a high growth fraction, rapid doubling time and early metastatic spread. Despite being highly sensitive to chemotherapy and radiotherapy, five year survival rates remain dismal for this disease, and have altered little over time. Concurrent chemotherapy and thoracic irradiation has been used for limited stage disease for many years, and platinum based doublet chemotherapy has been the standard of care for extensive stage disease for decades. Avenues of investigation for new treatment options have included alternate chemotherapy agents, both alone and in combination with standard chemotherapy regimens, and targeted treatments. These strategies, many still in their early days, have yet to provide the benefits hoped for in SCLC, but provide some optimism for improved outcomes in the future.

### Current treatment

#### Staging

The division of SCLC into limited and extensive stage disease has been the standard classification used since the 1960s.<sup>1</sup> More recently, TNM classification of SCLC has been proposed by the International Association for the Study of Lung Cancer and is used in the American Joint Committee on Cancer 7th edition of 2010.<sup>2</sup> In this new system, M1 (with any T and N stage) denotes extensive disease, with limited stage disease defined as any T and N stage with no identified metastases (excluding T3 - T4 disease with multiple lung nodules that cannot be encompassed in one radiotherapy field and is therefore considered extensive stage disease). The TNM staging system has been shown to have prognostic value, with a statistically significant inverse association between

increasing T stage and survival, and a similar relationship with increasing N stage.<sup>3</sup> This staging system may help to better stratify patients in clinical trials of limited stage disease, but as yet is unlikely to change clinical decision making.

The use of PET scans in the evaluation of SCLC is also improving the accuracy of staging and the planning of treatment. Due to the highly metabolic nature of SCLC, PET scans can provide valuable information that may downstage, or more commonly upstage, disease.<sup>4</sup> This can be useful in tailoring treatment, including radiotherapy planning in limited stage disease, or altering management plans for those found to have extensive stage disease.

### **Limited stage disease**

Surgery may be appropriate for the very small number of patients (2-5%) who present with stage 1 disease, with consideration of adjuvant chemotherapy post operatively. The role of surgery has historically been unclear beyond stage 1 disease, with a lack of robust prospective trial data. A randomised Medical Research Council trial in the 1970s suggested that there was no benefit to surgery compared to radiotherapy in limited stage disease, although few early stage patients (T1-T2) were included.<sup>5</sup> More recent retrospective case series have suggested that surgery may be beneficial in appropriately selected patients, particularly with the improved ability for accurate staging now possible. For example, a retrospective series of 1415 patients reviewed at the Johns Hopkins Medical Institutions suggested a benefit for surgery in conjunction with chemotherapy in selected patients with early stage SCLC.<sup>6</sup> Review of the SEER database appears to confirm this observation in those with local disease only,<sup>7</sup> but is limited by the lack of information about subsequent treatment. It may be that surgery has a role in combination with neoadjuvant or adjuvant chemotherapy, but this needs to be further elucidated in prospective randomised trials.

Concurrent chemotherapy and thoracic irradiation remains the standard of care for higher stage limited disease that is encompassable in a radiotherapy field. Doublet chemotherapy containing a platinum agent in combination with etoposide is routinely used, with concurrent thoracic irradiation which may be given in a hyperfractionated format. The response rate ranges from 70 to 90%, with median survival of 14 - 20 months. Prophylactic cranial irradiation is recommended in those with complete response to treatment, with evidence from a meta-analysis that this strategy both decreases the development of brain metastases and prolongs survival.<sup>8</sup>

Despite initial responsiveness to chemotherapy, almost all patients will relapse and die of their disease. Median survival in those treated with second line chemotherapy is in the order of four to five months. A proportion of patients also demonstrate resistant disease, or relapse early (within three months of treatment). These patients do particularly poorly with second line chemotherapy, with response rates usually less than 10%.

With no clear evidence for the superiority of any one regimen, options for therapy include retreatment with platinum based chemotherapy for those who relapse more

than three months from completion of prior treatment, where response rates to second line treatment are in the order of 25%. Other possible management strategies include the use of CAV (cyclophosphamide/doxorubicin/vincristine), or topotecan in oral or parenteral formulation. Topotecan has been shown to be better than best supportive care in terms of progression free and overall survival in a phase 3 study,<sup>9</sup> and a phase 3 trial found it had similar survival outcomes to CAV (although topotecan did demonstrate better outcomes for symptom relief).<sup>10</sup> Clinical trial enrolment, if available and appropriate, remains an important consideration for such patients.

### **Extensive stage disease**

Platinum-based doublet chemotherapy has been recommended as first line treatment for extensive stage SCLC for decades. Cisplatin or carboplatin in combination with etoposide, has become the mainstay of treatment based on two randomised control trials that suggested there was a survival benefit to this approach. Cisplatin and carboplatin appear to be similar in terms of efficacy, based on a metaanalysis of four randomised trials in extensive and limited stage disease, with carboplatin frequently used for ease of administration and differing toxicity profile.<sup>11</sup>

Response rates for chemotherapy are generally in the order of 50 - 80%, with up to 30% obtaining a complete response. For those who demonstrate a response to chemotherapy, PCI should be considered based on evidence from a phase 3 study, which showed the one-year survival rate was 27.1% (95% CI, 19.4–35.5) in the radiation group and 13.3% (95% CI, 8.1-19.9) in the control group.<sup>12</sup> Consolidation thoracic irradiation may be appropriate for selected patients who respond well to chemotherapy, with evidence for decreased chest recurrences and prolonged survival with its use in a trial of those with extensive stage disease who had an excellent response to initial chemotherapy.<sup>13</sup> The patients randomised to receive radiation therapy had an improved survival, with five year survival of 9.1% compared to 3.7% (p=0.041) in those who received further chemotherapy alone. This finding is now being tested in a randomised prospective trial by the Dutch Lung Cancer Study Group (the CREST trial).

Palliative radiation therapy is also often used for painful bony metastases, established brain metastases, and other symptomatic complications in patients who have relapsed after chemotherapy.

## **New directions in treatment**

### **Chemotherapy**

Given the chemosensitivity of SCLC, the addition of a third chemotherapy agent to the standard platinum and etoposide combination has been explored in a number of studies. Paclitaxel in this setting showed no benefit in survival (but an increase in toxicity) in two studies.<sup>14,15</sup>

Newer agents have also been investigated in trials comparing these to standard chemotherapy. Trials in the Japanese population have shown promising results with the use of cisplatin and irinotecan in combination. The phase 3 Japanese Clinical Oncology Group 9511 showed a significant overall survival benefit for cisplatin/

irinotecan when compared to cisplatin/etoposide (12.8 v 9.4 months,  $p=0.002$ ),<sup>16</sup> but these results were not able to be replicated in the non-Japanese population, with no difference found in two larger randomised phase 3 trials.<sup>17,18</sup> It is hypothesised that the differing outcomes between the Japanese study and the subsequent US studies, and the dissimilar rates of adverse events noted (particularly diarrhoea and neutropenia), may be due to genotypic variations in these groups.<sup>19</sup>

The combination of cisplatin and topotecan has been shown to be at least as good as cisplatin and etoposide, but with a differing adverse event profile, including haematological toxicities, when parenteral topotecan is used.<sup>20</sup> Topotecan has also been investigated as a maintenance agent following benefit from cisplatin and etoposide therapy, but did not show a benefit in this setting.<sup>21</sup>

Amrubicin is licensed in some countries, such as Japan, for use in combination with a platinum agent for the treatment of small cell lung cancer. Amrubicin is a synthetic anthracycline, with promising data, including showing a response rate of 88.6% (95% CI 75.4% - 96.4%), with a median survival of 13.6 months (95% CI 11.1 - 16.6 months) when used in combination with cisplatin in a phase 1 - 2 trial.<sup>22</sup> These findings prompted a phase 3 trial of amrubicin with cisplatin compared to irinotecan and cisplatin, which showed that the amrubicin containing doublet was not equal to irinotecan and cisplatin.<sup>23</sup> The combination of amrubicin and irinotecan in a phase 1 study proved to be intolerable due to the significant rate of haematological toxicity, particularly neutropaenia.<sup>24</sup>

Temozolomide has been shown to have some activity in a phase 2 study of SCLC, particularly in those with brain metastases. A single arm study by Pietanza et al showed a 20% objective tumour response rate (in a mixed population of patients with relapsed sensitive or refractory disease), with a 19% response rate in those receiving 3rd line treatment, a group for whom no standard therapy exists.<sup>25</sup> This study also found that a larger number of cases with methylated O6-methylguanine-DNA methyltransferase (MGMT) had responses to treatment compared to those with unmethylated MGMT, suggesting a subgroup of patients who may have greater benefit from temozolomide.

### Targeted therapies

Given the success in other cancer types, and with limited success with new chemotherapeutic agents, attention has also turned towards identifying the molecular abnormalities present in SCLC that may be targets for personalised therapy.

SCLC is known to be highly angiogenic, with significantly higher levels of VEGF found in those with SCLC than healthy controls,<sup>26</sup> although there is mixed evidence for its prognostic value.<sup>27,28</sup> This information has led to the trial of established antiangiogenic treatments that have proved beneficial in other cancer types. Single arm phase 2 trials conducted by the Eastern Co-operative Oncology Group,<sup>29</sup> and the CALGB,<sup>30</sup> have shown a modest improvement in progression free survival, consistent with the findings of the SALUTE randomised phase 2 trial, but no significant survival benefit and no strong signal

to warrant progression to a phase 3 trial.<sup>31</sup> Aflibercept, a VEGF trap, has been tested in a phase 2 South West Oncology Group study in combination with topotecan and showed an improved disease control rate, but no survival differences when compared to topotecan alone.<sup>32</sup> Thalidomide has also been studied, but has not been found to be beneficial in a number of trials, including a randomised trial of 724 patients with limited and extensive stage disease in combination with chemotherapy, where there was no benefit in either progression free survival or overall survival.<sup>33</sup>

Trials of tyrosine kinase inhibitors with antiangiogenic properties have also not proved to be successful to date, with particular note made of the high levels of toxicity with these agents when used with chemotherapy. Both sunitinib and sorafenib have been investigated in phase 2 studies, with single agent treatment not found to be beneficial.<sup>34,35</sup> A small phase 2 trial has shown some benefit for sunitinib when used as maintenance therapy following first line chemotherapy,<sup>36</sup> but these results have not yet been validated in a phase 3 study. Sorafenib in combination with chemotherapy and as maintenance, despite showing some anti-tumour activity, produced too many adverse effects to be considered suitable for ongoing studies.<sup>37</sup> A trial of vandetanib used in the maintenance setting following response to first line chemotherapy did not show any benefit over placebo,<sup>38</sup> and similarly cediranib failed to show benefit in relapsed or refractory SCLC.<sup>39</sup>

Matrix metalloproteinases have also been targeted for therapy in small cell lung cancer. These are proteolytic enzymes that can act on the extracellular matrix to affect the tumour microenvironment. They are upregulated in almost all human cancers, and can promote cancer progression by influencing cell growth, migration and invasion, angiogenesis and metastasis. The matrix metalloproteinases inhibitors tanomastat and marimastat have been evaluated for a prospective role as maintenance therapy in those who had responded to first line therapy based on this finding, but no significant improvement was found compared to placebo treatment in either trial.<sup>40,41</sup>

There has been some evidence that a very small proportion of SCLC may harbour an EGFR (epidermal growth factor receptor) mutation (up to 4% in the analysis of 122 specimens from a Japanese centre.<sup>42</sup> These were found predominantly in mixed histology tumours that demonstrated both adenocarcinoma and SCLC cells. A small phase 2 study using gefitinib in unselected patients with chemosensitive and chemorefractory disease failed to show activity, likely due to the low rate of EGFR mutations.<sup>43</sup>

With *in vitro* evidence for the role of functional c-kit receptors in some small cell lines and inhibitory effects of imatinib,<sup>44</sup> human trials have been undertaken but have failed to show benefit. A phase 2 trial of 19 patients, hampered by the finding that kit positivity in tumour samples was significantly lower than hypothesised (21 v 70%), showed no anti-tumour effect from imatinib.<sup>45</sup> Subsequent phase 2 studies of imatinib in patients

selected for the presence of tumour c-kit protein expression failed to demonstrate any clinical activity in spite of patient selection, suggesting that target expression may not provide the answer to developing new targeted agents in this condition.<sup>46,47</sup>

Bcl-2 has also been an attractive target for attention in this disease. It is overexpressed by many tumours (including many SCLCs),<sup>48,49</sup> and overexpression is linked to chemotherapy resistance through bcl-2's regulation of the intrinsic apoptotic pathway. In vitro models have shown an increased efficacy of cisplatin and etoposide chemotherapy when used with an antisense oligonucleotide directed to bcl-2 mRNA.<sup>50</sup> Based on these findings, oblimerson, an antisense oligonucleotide, has been studied in combination with carboplatin and etoposide in a phase 2 randomised trial, but failed to show a benefit in objective or complete response rates, and demonstrated no survival benefit.<sup>51</sup>

Mutations in p53, RB1 and PTEN that may increase the susceptibility of SCLC cells to DNA damage and allow for synthetic lethality upon exposure to a PARP (poly(ADP-ribose) polymerase) inhibitor, have also been shown in SCLC.<sup>52,53</sup> In vitro, SCLC lines show sensitivity to PARP inhibition that is similar to that of BRCA-1 and PTEN mutated breast cancer lines, and a synergistic effect with the addition of chemotherapy,<sup>54</sup> suggesting this may be a novel strategy for tumour targeting. Trials are currently underway of PARP inhibitors in combination with chemotherapy in SCLC to further investigate the effectiveness of this strategy.

## Conclusion

Despite ongoing work, the prognosis for patients with SCLC remains grim. Many agents have shown promising early results that did not translate into clinical benefits in subsequent trials, or proved to have significant adverse events that limited their utility. There is hope that ongoing research and further elucidation of the molecular abnormalities that drive SCLC may lead to new avenues of therapy for small cell lung cancer, a malignancy which is in desperate need of more effective and durable treatments.

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## MALIGNANT PLEURAL MESOTHELIOMA

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### Abstract

Malignant pleural mesothelioma is a relatively uncommon disease associated with asbestos exposure. Its incidence increased markedly following the widespread mining and use of asbestos in many industries. The legal aspects regarding compensation cases for those who have developed this disease has raised its profile in the media, but also compounds the stress of diagnosis for patients. It has an insidious onset and may clinically and pathologically mimic other benign or malignant processes, complicating diagnosis. Radical surgery may be used for a highly selected population of malignant pleural mesothelioma patients in the context of multimodality treatment in an experienced thoracic surgical centre, but there is no randomised evidence to support its benefit. In most cases surgery is used to treat symptoms or obtain tissue for diagnosis. Combination of a platinum agent and pemetrexed is now widely used and shown to prolong life. Other treatments including radiotherapy, analgesics and supportive interventions are an integral part of the treatment of this disease. Further research is being undertaken on promising novel therapies for use in this disease, which will be discussed in this review.



Malignant pleural mesothelioma (MPM) is a neoplasm originating from mesothelial cells, which form the membranes surrounding the lung cavities. It is currently a disease mainly of the industrialised world, closely linked to asbestos exposure.<sup>1</sup> Seldom diagnosed prior to the advent of widespread asbestos mining in the early to mid twentieth century, it has risen in incidence over the last five decades.<sup>2,3</sup> According to the most recent Australian Institute of Health and Welfare data, in 2009 there were 666 cases of malignant mesothelioma diagnosed in Australia.<sup>4</sup>

This review will provide a brief overview of the diagnosis, current treatment modalities and some novel systemic treatment strategies that have been explored in MPM.

## Asbestos and malignant mesothelioma

MPM is a disease with particular relevance to Australia. Asbestos was first mined in Australia in the 1880s near Jones Creek, a town in NSW.<sup>5</sup> It was not until the late 1940s when the insulating properties of asbestos rendered it a useful product in the building industry during the post war building boom, and subsequent demand for asbestos saw mining production rise exponentially in mines in NSW, Tasmania, South Australia and Western Australia.<sup>5</sup> There has also been widespread exposure within the building and transport industries in which asbestos was broadly utilised.<sup>6</sup>

Asbestos mining ended in Australia in 1983, and it is expected that malignant mesothelioma related to occupational exposure will plateau in the coming decade. In a Western Australian study, however, a significant increase was noted in the number of people being diagnosed with malignant mesothelioma whose only exposure to asbestos must have occurred in a non-occupational setting (most likely during home maintenance and renovation). Between 2005 and 2008, 8% of males and 5% of females diagnosed with malignant mesothelioma in this series reported non-occupational exposure as their only exposure to asbestos.<sup>6</sup> These observations ask for confirmation in a case-controlled epidemiological study.

## Diagnosis

Clinical features of MPM usually develop gradually and may consist of constitutional symptoms including weight loss, fatigue and night sweats, as well as local symptoms such as dyspnoea and chest pain.<sup>7</sup> Initial investigations should include chest X-ray and computed tomography.

The most frequent finding on initial investigations is that of a pleural effusion. As MPM has different histological patterns (three major subtypes: epithelioid, sarcomatoid or mixed/biphasic),<sup>8</sup> and may resemble benign mesothelial disease, malignant lung disease or sarcoma, formal diagnosis on a tissue biopsy by a pathologist experienced in the diagnosis of MPM is recommended.<sup>8</sup>

The pathological diagnosis of MPM requires the observation of invasion of the neoplastic mesothelial cells into surrounding tissue on histological sections,<sup>8</sup> and the diagnosis should be supported by appropriate immunohistochemical labelling (two positive mesothelial markers and two negative carcinoma markers).<sup>9</sup>

Cytology-only diagnosis of epithelioid MPM on aspirated effusion fluid remains controversial, although cytological diagnosis is achievable in many cases with supportive immunohistochemical investigation, particularly when the cytological findings can be correlated with imaging studies (evidence of nodularity of the pleural disorder and evidence of invasion).<sup>10</sup> However, due to the low sensitivity of cytology only diagnosis reported in the literature,<sup>9,11</sup> it is generally recommended that video-assisted thoracoscopic surgery be performed to obtain pleural biopsy tissue, as it also allows for drainage of pleural effusion and access for pleurodesis.<sup>12</sup>

From a prognostic perspective, epithelioid histological type provides the best outlook. Other favourable prognostic factors include an Eastern Cooperative Oncology Group performance score of 1 or less, absence of anaemia or thrombocytopaenia, and a normal lactate dehydrogenase.<sup>13,14</sup> Emerging inflammatory markers, such as neutrophil-to-lymphocyte ratio may also assist in the prognostication of MPM patients.<sup>15-17</sup>

## Current treatment strategies

Treatment of an MPM patient should be provided by a multidisciplinary team ensuring multidisciplinary care, although there is no direct high-level evidence suggesting the benefit of the multidisciplinary approach. It may involve a single or multiple modality therapy involving surgery, chemotherapy, radiotherapy, and best supportive care. Recently, the draft of the *Australian National Guidelines for Diagnosis and Management of Pleural Malignant Mesothelioma*, prepared under the auspices of the National Health and Medical Research Council, has been released, and currently is open for public consultation.

### Surgery

Surgery may be used to palliate symptoms of pleural effusion,<sup>18</sup> or bulky pleural disease. More radical surgery with the intent to prolong survival may be used in selected patients with limited disease confined to one hemithorax. The most extensive radical surgery is extrapleural pneumonectomy (EPP), which involves excision of the pleura, lung, lymph nodes, diaphragm and pericardium en bloc. Pleurectomy and decortication is arguably a less radical procedure, in which the parietal pleura is removed and the lung is examined for any macroscopic evidence of disease, which if found is subsequently resected.<sup>19</sup> As it is impossible to achieve a clear microscopic surgical margin, treatment strategies have been developed to consolidate further control from surgery. In the case of EPP, typically chemotherapy is given as induction treatment, followed by surgery and then hemithoracic adjuvant radiotherapy.<sup>20,21</sup>

The MARS trial published in 2011 examined the survival benefits of EPP in comparison to no EPP after chemotherapy, as a secondary outcome. Twelve centres in the UK randomised 50 patients into the two arms of the study. In the trial, patients in the EPP arm had lower overall survival than those who were randomised not to have EPP.<sup>22</sup> One of the main controversies of the trial was the high perioperative mortality rate of 18% in those undergoing EPP, which compares poorly to

other documented rates worldwide – in the Australian experience, the 30 day mortality rate post-EPP is 5.7%.<sup>23</sup> Further, perioperative chemotherapy regimens were not standardised and there was a significant proportion of patients who were not treated to the study protocol. On this basis, the results of this trial cannot be generalised to other experienced centres. However, in view of the lack of randomised evidence for definite benefit, multimodality approach incorporating EPP should be considered experimental and restricted to institutions with significant surgical experience with high volumes of cases.

### **Chemotherapy**

It is only since 2003 that MPM has been shown to be responsive to chemotherapy agents. Vogelzang et al demonstrated that when patients received pemetrexed and cisplatin compared to cisplatin as monotherapy, they received a survival benefit (median overall survival 12.1 months v 9.3 months) and longer time to progression (median 5.7 months v 3.9 months).<sup>24</sup> This combination chemotherapy was also found to improve patients' symptoms and health-related quality of life, compared to cisplatin alone.<sup>25</sup> Retrospective analysis published in 2008 demonstrated similar 12 month overall survival rates between the combinations of cisplatin and pemetrexed, and carboplatin and pemetrexed (63% and 64% respectively), suggesting carboplatin equivalence with cisplatin in this regimen.<sup>26</sup> Raltitrexed, another antimetabolite, in combination with cisplatin, demonstrated similar improvements in median overall survival when compared with cisplatin monotherapy (11.4 months v 8.8 months).<sup>27</sup> Therefore, the first line standard of care for MPM patients currently is a platinum doublet with an antimetabolite, either pemetrexed or raltitrexed.

The role of maintenance chemotherapy following combination chemotherapy with platinum and pemetrexed has not been prospectively evaluated. A small non-randomised study demonstrated that pemetrexed maintenance therapy is well tolerated and is feasible to administer.<sup>28</sup> There is an ongoing randomised phase II trial evaluating the role of maintenance pemetrexed in patients with stable disease after first-line chemotherapy (NCT01085630).

Once patients progress after first-line chemotherapy, there is currently no standard of care in this setting, as there are no agents with randomised evidence demonstrating a survival benefit. Agents tested in the second line setting include pemetrexed alone in pemetrexed-naïve patients, and vinorelbine.<sup>29,30</sup> However, in a recent retrospective review from Memorial Sloan-Kettering Cancer Centre, the response rate for vinorelbine in a cohort of MPM patients who progressed after platinum-based therapy was found to be 0%.<sup>31</sup> Retreatment with pemetrexed-based therapy could be considered in patients with durable responses from previous pemetrexed-based treatment.<sup>32</sup> Patients should be encouraged to participate in clinical trials in this setting.

### **Radiotherapy**

Radiotherapy has a role in palliating symptoms of pain associated with chest wall involvement or metastatic

nodules.<sup>33</sup> The evidence for the use of radiotherapy prophylactically on biopsy tracts to prevent seeding remains inconclusive, and the two systematic reviews showed no significant effect on overall survival by prophylactic radiotherapy and therefore it is not recommended.<sup>34,35</sup>

### **Supportive care**

Symptom management of MPM is complex. Pain and dyspnoea are the most common symptoms which are reported in greater than 90% of MPM patients. These symptoms interface with psychological symptoms such as depression and anxiety, which may be heightened in an environment where patients are commonly involved in legal proceedings related to their occupational exposures. Initial management of dyspnoea should include addressing the patient's environment. Using fans to blow air across the face, opening doors and windows to create a sense of space and using cool face washes can all reduce the sensation of dyspnoea. Additionally, low dose oral opioids have also been shown to reduce symptomatic breathlessness.<sup>36</sup> Domiciliary oxygen has historically been used in the palliative setting to alleviate dyspnoea, however there is little evidence for its use in the absence of hypoxaemia.<sup>37</sup> Underlying causes of dyspnoea should be considered and managed appropriately. Most often, this involves draining recurrent pleural effusions and performing pleurodesis.

Pain should be managed with simple analgesics such as paracetamol, with the addition of opioids, and anti-inflammatory medications for nociceptive pain. Neuropathic pain may coexist with nociceptive pain and requires the use of co-analgesics such as antiepileptics or tricyclic antidepressants. Patients with refractory pain should be referred to a palliative medicine specialist, and other modalities of analgesia including radiotherapy, nerve blocks or intrathecal injections should be considered.<sup>36</sup>

Legal and compensation issues affect the majority of people diagnosed with MPM. Patients should be provided with practical information of how to navigate through the often complicated local system.

### **Novel systemic therapy**

Despite the promise of personalised treatment in other solid tumours, the approach of 'precision medicine' is not yet a reality for MPM patients, despite international efforts over the last decade. Although targeting EGFR, VEGF and PDGFR pathways has been successful in some other solid tumours, agents targeting these pathways have failed to demonstrate benefit in MPM patients. Here, we will discuss some of the molecular pathways that have been tested in the last decade and selected, and promising potential pathways that could be targeted.

### **Signalling Pathway Inhibition**

Although EGFR is over-expressed in most MPM, the EGFR-tyrosine kinase inhibitors, gefitinib and erlotinib, have been found to be ineffective in the treatment of MPM in two phase II trials in the first line setting.<sup>38,39</sup> Furthermore, two phase II trials using imatinib mesylate, a potent inhibitor of PDGFR receptor signalling and C-Kit, have shown a lack of efficacy and poor tolerability.<sup>40, 41</sup>

### Anti-angiogenesis

Agents targeting the VEGF pathway that have been tested in MPM include anti-VEGF antibody (bevacizumab) and small molecule tyrosine kinase inhibitors. Bevacizumab in combination with cisplatin and gemcitabine in a randomised phase II trial, has been shown not to prolong survival in MPM patients.<sup>42</sup> As cisplatin with gemcitabine is no longer a standard first line regimen, a further randomised study examining cisplatin and pemetrexed, with placebo or bevacizumab, is currently ongoing (the French IFCT-GFPC-0701 MAPS trial; NCT00651456).

Tyrosine kinase inhibitors inhibiting the VEGF receptors tested in unselected MPM patients include sorafenib, sunitinib, cediranib and vatalanib.<sup>43-48</sup> These agents were all examined in single-arm phase II trial fashion and yielded a response rate from 0 to 12%, and progression free survival from 1.8 to 4.1 months. It is difficult to know if these agents have definitive activity, as no randomised trials have been done to date. Identification of predictive markers for these types of agents has been elusive, making selection of patients who are likely to benefit difficult.<sup>44</sup>

Lastly, thalidomide (an angiogenesis inhibitor and cytokine modulator) in combination with cisplatin and gemcitabine, or alone, has been tested in two phase II studies and suggested some hint of prolongation of stability of disease.<sup>49,50</sup> However, a subsequent randomised trial evaluating maintenance thalidomide in non-progressing patients after initial pemetrexed based chemotherapy, failed to show a benefit in delaying tumour progression.<sup>51</sup>

### Epigenetic modulations

The recent discovery of the relatively common (25%) inactivation of the BRCA 1- associated protein 1 (BAP1) is of interest, as BAP1 has a role in control of gene expression through histone modification.<sup>52</sup> Vorinostat is a histone deacetylase inhibitor that alters gene expression and protein activity. The VANTAGE 014 study randomised MPM patients who failed prior pemetrexed and platinum therapy to either vorinostat or placebo.<sup>53</sup> Disappointingly, vorinostat did not significantly extend the overall survival in the second line setting. However, a phase I/II trial examining first line vorinostat with cisplatin and pemetrexed is ongoing (NCT01353482).

### Mesothelin

Mesothelin is expressed abundantly in the epithelioid subtype of the MPM tumour cells, which makes this an appealing therapeutic target.<sup>54</sup> There are several mesothelin-targeted immunotherapeutic approaches currently being tested, including SS1P (NCT01445392) and amatuximab (NCT00738582). Amatuximab (MORAb-009) is a chimeric monoclonal antibody that binds mesothelin and elicits antibody-dependent cellular cytotoxicity. It is currently the only agent in phase II development. The single arm clinical trial of amatuximab in combination with cisplatin and pemetrexed is ongoing in epithelioid and biphasic MPM patients. Preliminary results, presented at the 2012 International Mesothelioma Interest Group (IMIG) conference, demonstrated a radiological response rate of 39% and a median overall survival of 14.8 months.<sup>55</sup> As it is a single arm trial excluding the sarcomatoid MPM, which

typically has a poor prognosis, the preliminary result of this study is difficult to interpret.

### Other promising targets

Other important new targets in MPM are being examined and MPM is molecularly characterised by the loss of tumour suppressor genes, rather than gain of function mutation. An example is the inactivation of neurofibromatosis type 2 (NF2) in MPM in 35 - 40% of patients, which will be discussed here. NF2 encodes for a protein known as Merlin, which acts as a tumour suppressor. Through functional studies, it has been established that NF2 regulates a number of signalling pathways, with an NF2 loss leading to activation of mammalian target of rapamycin complex 1 (mTORC1) and the focal adhesion kinase (FAK).<sup>56,57</sup> Clinical interest in these drugs targeting these pathways is now high due to the availability of mammalian target of rapamycin (mTOR) inhibitors and FAK inhibitors. A phase I trial of GDC0980 (PI3K/mTOR inhibitor) showed some encouraging anti-tumour activity (tumour regression and prolonged disease control) in a subgroup of six MPM patients, reported in the 2012 International Mesothelioma Interest Group conference.<sup>58</sup> The use of FAK inhibitors in MPM is currently being considered.

### Conclusion

Progress in the treatment of MPM has been slow and the systemic treatment of MPM remains unchanged since the approval of pemetrexed used in conjunction with cisplatin in 2003. Beyond the first line treatment, there is currently no standard of care. The promise of 'precision medicine' is yet to arrive in the clinic for the treatment of MPM patients. Significant work is required through multidisciplinary research input into this devastating disease, starting with surgeons collecting high quality annotated specimen, translational scientists uncovering important molecular pathways and development of novel pathway or protein targeted drugs, as well as committed clinicians designing and conducting practice-changing clinical trials.

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## AUSTRALIAN BEHAVIOURAL RESEARCH IN CANCER

### **Behavioural Research and Evaluation Unit (BREU), South Australia**

#### ***Evaluation of the Flinders Far North Smoke-free ambassadors social marketing campaign.***

Country Health SA is implementing a localised smoke-free ambassadors social marketing campaign, with the aim to reduce the prevalence of smoking among Aboriginal communities in Port Augusta, Whyalla, Flinders and Far North (rural and remote areas of South Australia). With previous experience in evaluating indigenous specific tobacco programs, Cancer Council SA has been contracted to evaluate the impact of this campaign. The model for evaluation builds on previous experience in evaluating the state-wide indigenous specific social marketing campaign, 'Give up smokes for good'. Pre and post-surveys will be conducted with Aboriginal community members in Port Augusta, Whyalla, Quorn, Coober Pedy, Oodnadatta and Marree. A local research assistant will be employed within each of the communities to implement surveys via face-to-face interview. Consultation was undertaken in March with community representatives in each of the locations in the lead-up to data collection. Pre-surveys have been collected in Port Augusta (n=103) and data collection will begin in May for the five remaining sites, with an intended sample of 30 people from each community. Post-surveys are planned for April 2013.

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

#### ***Can counter-advertising reduce parents' susceptibility to nutrition content claims and sports celebrity endorsements?***

Counter-advertisements challenging industry marketing messages have been effective in reducing smoking behaviour and alcohol consumption. However, they have received little consideration in relation to obesity prevention efforts targeting food marketing. This study aimed to assess the impact of nutrition counter-advertisements on parents' appraisals of energy-dense and nutrient-poor (EDNP) food products featuring front-of-pack (FOP) promotions. Parents of children aged 5-12 years (N=1269), who were main grocery buyers, participated in a 2 x 2 between-subjects web-based experiment. First, parents were randomly shown an advertisement (counter-advertisement challenging FOP promotion or control advertisement) and recorded their reactions to it. Next, parents were randomly assigned a pair of food packages from the same product category to view: a healthier control pack with no FOP promotion and an EDNP product with a FOP promotion (nutrition content claim or sports celebrity endorsement). From this pair, parents nominated which product they would prefer to buy and which they thought was healthier, then completed ratings of the EDNP product. Compared to parents who saw a control advertisement, parents who saw a counter-advertisement perceived EDNP products

featuring FOP promotions to be less healthy, expressed a lower likelihood of buying such products, and were more likely to read the nutrition information panel on EDNP products before making their choices. These results suggest counter-advertising may be effective for minimising the negative influence of unhealthy food marketing and facilitating healthier food choices among parents.

#### ***What price quitting? The price of cigarettes at which smokers say they would seriously consider trying to quit.***

Deciding on an appropriate level for taxes on tobacco products is an important issue in tobacco control. This study, led by Michelle Scollo, aimed to describe the critical price points for packs for smokers of each pack size, to calculate what this would equate to in terms of price per stick, and to ascertain whether price points varied by age, socio-economic status and heaviness of smoking. A dual frame telephone survey of 586 regular smokers of factory-made cigarettes was conducted in Victoria in November 2011, with respondents asked to indicate the brand, size and cost of their usual pack and to estimate what price their preferred pack would need to reach before they would seriously consider quitting. Three-quarters of regular smokers could envisage their usual brand reaching a price at which they would seriously consider quitting, with \$20 the median nominated price point for all key demographic groups. The median price point at which regular smokers would consider quitting was calculated to be 80 cents per stick, compared to the current median reported stick price of 60 cents. These results suggest that if taxes can be set high enough to ensure that the cost of the smokers' preferred pack exceeds critical price points, this would likely prompt more people to seriously attempt quitting than if the price increased to a level even slightly below the price points.

### **Newcastle Cancer Control Collaborative (New-3C) NSW**

#### ***Improving psychosocial outcomes for haematological cancer patients: A RCT.***

Communicating treatment options, preparing patients for cancer treatments and providing them with information about how to manage side-effects of treatment are likely to be key to helping haematological cancer patients and their families cope with a diagnosis of cancer. With funding from Cancer Institute NSW, we are undertaking a randomised control trial to examine whether access to a web-based information program and nurse-delivered telephone support is effective in reducing depression, anxiety and unmet information needs among haematological cancer patients and those supporting them. A sample of 340 adult patients newly diagnosed with acute leukaemias and high grade lymphomas and significant others, is being recruited from tertiary referral hospitals in NSW. Subjects randomly allocated to the experimental group are provided



with access to a web-based program designed to provide effective communication, decisional support and adjustment. The website provides tailored information on a range of topics, including information about diagnosis, treatment options, side-effects, self-management strategies, impact of cancer on daily life, available support and complementary and alternative therapies. The intervention also includes access to a telephone helpline staffed by an experienced cancer nurse. Patients and significant others allocated to the usual care group receive care normally provided by their care team. Participants complete surveys at approximately two, four, eight and 12 weeks post-recruitment, examining levels of anxiety, depression and unmet needs, and experiences obtaining and understanding treatment information. To date, 12 participants from four hospitals are enrolled in the study.

**"Smoking is a part of my life now". A systematic review of the self-reported barriers to smoking cessation within selected socioeconomically disadvantaged groups.**

The prevalence of smoking is disproportionately higher in socially disadvantaged populations. Effective interventions to reduce smoking within these groups require an understanding of the factors that prevent disadvantaged groups from stopping smoking. This study aimed to identify and synthesise the literature describing the barriers to smoking cessation within selected disadvantaged groups and classify these barriers within the Social Determinants of Health framework.

Medline, Embase, CINAHL and PsycINFO were searched for publications prior to 31 March 2011. Inclusion criteria were: qualitative or quantitative descriptions of the self-reported barriers to smoking cessation within six socially disadvantaged groups: Indigenous populations; people with a mental illness; people of low socioeconomic status; the homeless; prisoners; and at risk youth. Identified barriers were categorised using the Social Determinants of Health framework. Methodological quality was assessed using existing adapted tools. Forty two papers were included in this systematic review (16 indigenous, 8 mental illness, 11 low SES, 3 homeless, 2 prisoners). Barriers to smoking cessation included: addiction to nicotine, lack of social support, high acceptability of tobacco use within communities, stressful life situations, limited resources to quit, cultural norms and socioeconomic factors. Most barriers were common across all groups, but differed in the way in which they manifested in each group. The barriers identified by this review suggest multiple factors have compounding effects on the ability of individuals in

disadvantaged groups to stop smoking. Encouragingly, many of the barriers identified are modifiable, and can be addressed by both social and health intervention programs and policies.

**Centre for Behavioural Research in Cancer Control (CBRCC) Western Australia (Curtin University and Cancer Council WA)**

***The Workplace as a setting for obesity prevention: barriers, enablers, and the employee preferences.***

Office-based workplaces encourage sedentary behaviour, increasing employees' risk of overweight/obesity by limiting time available for physical activity and nutritious meals. As the basis for planning a program to reduce prevalence of overweight/obesity, this study aimed to identify barriers/enablers and intervention strategies relevant to health promotion in office-based workplaces.

The project consisted of three stages. Qualitative data collection consisted of four focus groups with office-based employees (n=37) and 10 telephone interviews with managers (n=10). Verbatim transcriptions of focus groups and interviews were analysed using a thematic analysis approach. Quantitative data collection consisted of an online survey with office-based employees (n=111). Data analysis included frequencies, chi square tests and multiple regression.

Qualitative data analysis informed development of the online survey. Major findings of quantitative data analysis included the following: identification of barriers/enablers as significant predictors of physical activity/nutrition behaviours in the workplace; ranking of the most and least preferred individual, environmental and policy intervention strategies; and age/gender differences in barriers/enablers and preference for strategies.

The major benefits of the project have been: the identification of barriers/enablers for adopting/maintaining positive physical activity/nutrition behaviours in the workplace; identification of potential intervention strategies to inform development of health promotion for office-based employees; and contribution to obesity prevention in the long-term. The findings should assist in development of comprehensive evidence-based health promotion programs that consider environmental and policy influences, as well as the individual.

For further information, contact: Professor Peter Howat, Centre for Behavioural Research in Cancer Control, Curtin University, Western Australia. P.howat@curtin.edu.au.

## CANCER COUNCIL AUSTRALIA

### **Ruling on gene patents highlights need to change law**

Cancer Council Australia believes the Federal Court ruling to uphold the validity of patents on cancer-causing gene mutations highlights the need to change the law to protect health consumers from commercial gene monopolies.

CEO, Professor Ian Olver, said the decision reflected a lack of progress in patent law, which was based on centuries-old principles but being applied to rapidly changing technology.

"Discovering and isolating genetic materials is not inventive, yet the current law gives licence to biotechnology companies to claim ownership of naturally occurring substances," Professor Olver said. "The law must be changed to protect the community from gene monopolies."

### **New Zealand's tobacco plain packaging laws will help reverse 1 billion global death toll**

The health benefits of plain packaging for tobacco will soon be enjoyed across the Tasman, following the New Zealand Government's announcement in February that it will be the second country after Australia to adopt the ground-breaking policy.

The policy should end the use of cigarette packaging as a form of tobacco advertising in New Zealand, just as laws introduced in Australia last December have done.

Chair of Cancer Council Australia's Tobacco Issues Committee, Kylie Lindorff, said the evidence on the effectiveness of glossy packaging to lure new smokers had been around for decades.

"The announcement in New Zealand is a very encouraging development, since a total of 1 billion people globally will have died from the direct effects of smoking by later this century since tobacco products became mass-marketed," Ms Lindorff said.

### **New consumer website for cancer patients**

Cancer Australia, in collaboration with the Clinical Oncological Society of Australia, has launched a new online consumer resource for cancer patients participating in cancer research and trials.

The Consumer Learning website contains short online learning modules and video presentations to guide consumers through the clinical trial and research process. It includes information on the consumer's role in clinical trials, how research is formulated and an overview of the Cancer Cooperative Trials Groups in Australia.

Cancer Australia also launched a Consumer Involvement Toolkit, designed to support CEOs, managers, health professionals, researchers and policy makers to effectively involve consumers in their organisation's work.

Find out more at [www.consumerlearning.canceraustralia.gov.au](http://www.consumerlearning.canceraustralia.gov.au) and [www.consumerinvolvement.canceraustralia.gov.au](http://www.consumerinvolvement.canceraustralia.gov.au)

### **Celebrate 20 years of Australia's Biggest Morning Tea**

2013 marks 20 years of Australia's Biggest Morning Tea ([biggestmorningtea.com.au](http://biggestmorningtea.com.au)). Now one of Australia's most popular fundraising events, it is enjoyed by over a million Australians each year.

This year Australia's Biggest Morning Tea raised more than \$12 million, providing essential funds for cancer research, prevention programs and support services like Cancer Council Helpline (13 11 20), for people affected by cancer.

Throughout the months of April and May, Australians were invited to gather together with friends, family and colleagues, put the kettle on and tuck into some delicious morning tea treats.

### **Governor-General presents Cancer Council award to South Australian 'icon of healthcare advocacy'**

Decades of personal devotion to improved cancer outcomes in Australia were recognised when the Governor-General, Her Excellency Ms Quentin Bryce AC CVO, presented Cancer Council Australia's prestigious Gold Medal to "icon of healthcare advocacy", Mrs Judith Roberts AO.

Mrs Roberts, a former President of Cancer Council Australia and Chair of Cancer Council SA, is the first ever recipient of the award outside the field of clinical medicine.

Cancer Council Australia President, Mr Hendy Cowan, said that for Mrs Roberts to be the first non-clinician to receive the award spoke volumes for her longstanding contribution.

"Reducing the impact of cancer in Australia requires efforts from a number of fields, and as an advocate and administrator, Judith has made a peerless long-term contribution to cancer control in Australia," Mr Cowan said.

Mrs Roberts was a driving force in the establishment of screening programs for breast and cervical cancer in Australia – programs which have gone on to prevent thousands of cancer deaths in Australia.

## **New position statement on alternative and complementary therapies**

Cancer Council Australia has published a position statement on complementary and alternative therapies. The statement considers the evidence, risks and benefits associated with these therapies, and makes considered recommendations for cancer patients and health practitioners.

Key recommendations include:

- Supporting the right of individuals to seek information about complementary and alternative therapies and respecting their decision to use them, provided they are not at risk of being harmed.
- Encouraging people with cancer who are considering using non-conventional therapies to make an informed choice. This includes asking questions about the efficacy, risk, contraindications and cost of the therapy, as well as the qualifications of the practitioner.
- Encouraging people with cancer to discuss with their healthcare provider any complementary or alternative therapies they are using or considering using, in order to minimise risk.
- Encouraging healthcare providers to routinely discuss the use of complementary and alternative therapies with all cancer patients and survivors, in an open and non-judgemental manner.

The statement also recommends that the Therapeutic Goods Administration takes a more active role in warning consumers about false claims made in relation to the benefits of complementary and alternative medicines and for more scientific studies to examine the safety and efficiency of promising and commonly used complementary and alternative therapies.

You can read the full statement at [http://wiki.cancer.org.au/prevention/Position\\_statement\\_-\\_Complementary\\_and\\_alternative\\_therapies](http://wiki.cancer.org.au/prevention/Position_statement_-_Complementary_and_alternative_therapies)

## **New study shows why bowel cancer screening must be an election priority**

A study published in the *Medical Journal of Australia* in April shows why expanding the National Bowel Cancer Screening Program should be an election priority for both Labor and the Coalition.

The study of 3481 South Australian bowel cancer patients was a compelling addition to the convincing evidence that screening for bowel cancer saves lives on a cost-effective basis.

The study showed that patients who participated in the screening program were twice as likely as those who did not screen to be diagnosed with bowel cancer at its earliest stage, when it is easiest to treat.

Cancer Council Australia CEO, Professor Ian Olver, who co-authored an editorial, said bowel cancer was the

second-highest cause of cancer death in Australia and mortality could be significantly reduced if more cases were detected early.

“It’s critical that whoever is in government after the election has a plan for further program expansion in the next term of office,” he said.

## **Study: 61,000 cancer deaths avoided in 20 years**

About 61,000 Australian lives have been saved by improvements in cancer prevention, screening and treatment over the past 20 years, according to Cancer Council research released in May.

The study compared recent cancer deaths with the late 1980s, showing the largest reductions in deaths across all types of cancer were for lung, bowel and breast cancers, and an overall reduction of about 30 per cent in cancer deaths.

Annual lung cancer deaths have fallen by 2154 compared with what we could have expected if late-1980s trends had continued. There were also 1797 less bowel cancer deaths and 773 less breast cancer deaths.

Associate Professor Freddy Sitas, lead researcher from Cancer Council NSW, said the report clearly highlighted that the combined advances in cancer prevention, research and treatment were working and saving lives.

“We expect about 8000 deaths to be avoided each year if current advances in cancer are maintained,” he said.

However, the research revealed that some cancers have seen little improvement over the last 20 years, prompting a call for more research and investment.

Cancer types with the smallest improvements over 20 years included cancer of the brain (148 fewer deaths), pancreatic (69 fewer deaths) and oesophagus (64 fewer deaths).

## **Cancer Council Australia welcomes \$16 million investment in bowel cancer screening**

Cancer Council Australia welcomed a budget commitment of \$16.1 million over four years to support the National Bowel Cancer Screening Program, and called on all eligible Australians to take the screening test.

The new funds will help ensure that the program keeps pace with increasing pathology and postage costs and enable better data collection and monitoring as it moves towards expansion.

However, Cancer Council said the program would only realise its potential to save lives if it was accessed by more eligible participants and took the opportunity to encourage Australians eligible for the screening program to take part, reminding them that it could save their life.

As the federal election neared, Cancer Council would be calling on all candidates to build on the commitment announced in May, and the \$50 million in last year’s budget, to support further expansion of the program in the next parliamentary term.



## CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA

### Access to chemotherapy drugs

In recent months the Clinical Oncological Society of Australia (COSA) has been active in the issue surrounding the supply of chemotherapy drugs.

On 1 December 2012, docetaxel was subject to a PBS price reduction of 76.2%. Many pharmacies that provide chemotherapy have relied on the docetaxel PBS margin to cross-subsidise the costs of providing cancer pharmacy services. In the short-term, while negotiations with the Government continue, these costs have been absorbed, but this is not viable in the longer term, particularly with another round of PBS price reductions (including paclitaxel) on 1 April 2013.

In early 2013, the Senate called an inquiry into the access of chemotherapy drugs such as docetaxel, following concerns about the viability of cancer pharmacy services, particularly in the private sector. COSA determined it was essential to make a submission to the inquiry outlining the wide ranging ramifications of the PBS price disclosure cuts. The COSA submission was well received and the data presented was of great interest to the committee.

Dan Mellor, Chair of the COSA Cancer Pharmacists Group, represented COSA as a witness at the inquiry hearing on 28 March in Sydney. The committee recommendations were published in May.

I would like to thank the submission working group, chaired by Dan Mellor, for producing a high quality document in a short amount of time: Christine Carrington, Rhonda DeSouza, Paul Grogan, Dorothy Keefe, Sue Kirsas, Jude Lees, Dan Mellor (Chair), Ian Olver, Christopher Steer and Ben Stevenson.

### Annual Scientific Meeting

The 2013 ASM program in Adelaide will once again feature high quality presentations from national and international experts. Dr Harvey Jay Cohen from Duke and Professor Patricia Ganz from UCLA are just two of the invited international speakers – a full list of

confirmed speakers and the draft program are available on the conference website [www.cosa2013.org](http://www.cosa2013.org). The conference theme 'Cancer Care Coming of Age' will cover geriatric oncology and gastro-intestinal cancers.

One of the ASM highlights is the Presidential Lecture on the final day. We are pleased to announce that Professor Ian Maddocks has accepted our invitation to deliver the lecture. Professor Maddocks is an eminent palliative care specialist, who is recognised internationally for his work in palliative care, tropical and preventative medicine. Now Emeritus Professor at Flinders University, he continues daily care for the terminally ill. He was awarded Senior Australian of the Year in 2013.

### Leadership in improving cancer research

COSA continues to work with the Cancer Cooperative Trials Groups to progress issues of common interest. Together, we convened a workshop in November 2012 – Long-term follow-up of clinical trial participants: Challenges and opportunities – to enable stakeholders to discuss the current limitations and opportunities to increase long-term follow-up of clinical trial participants.

Key issues identified from the workshop presentations and discussions were:

- need for long term outcome data
- potential of health record linkage
- embedding research in clinical practice
- supporting clinical research professionals.

The workshop also resulted in an extensive list of recommendations for COSA and the trials groups, individually and collectively. The challenge will be to prioritise what is achievable in the short and long-term and by whom. COSA will continue to show leadership in this area and work with the trials groups and other organisations, to advocate for and implement the workshop recommendations.

*Marie Malica, Executive Officer*

## FACULTY OF RADIATION ONCOLOGY, RANZCR

The Royal Australian and New Zealand College of Radiologists has secured funding from the Department of Health and Ageing, through the Better Access to Radiation Oncology Program, to promote radiation oncology as a career.

The 'A Career in Radiation Oncology Project' will promote the three specialties – radiation oncologists, radiation therapists and radiation oncology medical physicists. The project is being carried out in conjunction with the Australian Institute of Radiography and Australasian College of Physical Scientists and Engineers in Medicine.

The objectives include:

- Building awareness of radiation oncology and the professions that support it, with a focus on career opportunities.

- Increase the number of qualified people entering the professions by educating high school and university students about the careers that support radiation oncology.
- Influence career planning decision-making at an early age (high school), followed by reinforcement at university levels as students embark on career choices.

A number of resources have been developed for the project, including a brochure, video, website, presentation and other promotional material. These resources will be utilised at careers events, including careers expos in urban and regional areas, post graduate careers expos, student seminars and career advisor seminars.

This project is expected to raise the profile of radiotherapy as a treatment, as well as the promotion of a career in radiation oncology.

For further updates on the project, visit [www.acareerinradiationoncology.com.au](http://www.acareerinradiationoncology.com.au)

Watch the Career in Radiation Oncology video at <http://youtu.be/5E5ssMKEBHs>

or scan the QR code:



## Support international radiation oncology development

The Faculty is keen to support radiation oncology in lower middle income countries in the Asia-Pacific region. In past years, the Faculty has sponsored radiation

oncology professionals from Vietnam and Malaysia to visit radiotherapy departments in Sydney. The objective is to share information and experience, and to establish long-term relationships between radiotherapy departments in Australia and lower middle income countries to enable the transfer of expertise.

The Faculty has established a Special Interest Group to support the Asia-Pacific radiation oncology sector, in order to raise the standard of radiation oncology and to develop the discipline in countries with minimal healthcare facilities and infrastructure. A number of radiation oncologists have expressed their interest in participating in this important program.

Australasian College of Physical Scientists and Engineers in Medicine and Australian Institute of Radiography are also involved in this important initiative to advance the delivery of safe, accurate and effective radiotherapy treatments in lower middle income countries in Asia-Pacific region.

*Prof Gillian Duchesne, Dean, Faculty of Radiation Oncology*

## MEDICAL ONCOLOGY GROUP OF AUSTRALIA

In the first quarter of 2013, the Medical Oncology Group of Australia (MOGA) reviewed and developed numerous submissions on new oncology drugs being considered as part of the Australian regulatory process, with the aim of providing up-to-date clinical and best practice advice. These included MOGA submissions on the breast cancer drugs, everolimus, eribulin and vinorelbine.

Continuing our role in the lobbying and advocacy for oncology drugs and treatments, the association also made a submission to the senate inquiry on the supply of chemotherapy drugs such as docetaxel, and national oncology drug shortages have remained on the association's agenda. The ongoing issue of concern is that clinicians and professional groups only find out about oncology drug shortages in pharmaceutical industry correspondence, and believe a national drug shortage alert system should be put in place, including a formal notification system. MOGA has also advocated that shortages should be addressed locally or addressed at a government level on behalf of less well supported facilities, as larger hospitals with pharmacies can source alternate supplies. MOGA is currently developing a list of essential oncology drugs that should not be allowed to go into shortage of supply in Australia, for the Federal Government's use in future planning.

In March, the Australian Federal Court ruled on a case challenging a company's patent over human genetic material, the BRCA1 gene. The court dismissed the case, finding isolated human DNA or RNA could be considered, "a manner of manufacture", as required under patent law. The MOGA Ethics Sub-Committee, chaired by Professor Ian Olver, is developing a position statement and some general guidelines or guiding principles in this complex area. The association's guidelines for interaction with the pharmaceutical industry are also being reviewed and updated.

Recently, the American Society of Clinical Oncology (ASCO) announced plans to significantly expand its international programs and efforts to address the growing

global cancer burden and care disparities. MOGA values its long standing collaborative relationship with ASCO through its international branch. Notably, ASCO has been a strong supporter of the ACORD program, as a founding program partner and in providing two faculty members to join the workshop faculty every two years since 2004, as well as nominating a senior ASCO member to sit on the ACORD planning committee. Applications for ACORD 2014 will open in early November and candidates considering making an application to attend are advised to start work on their clinical trials protocols.

Best of ASCO, which MOGA has presented annually since 2009, is also part of ASCO's international programs and has become a valued opportunity for Australian oncology professionals to review and debate the research findings that are presented each June in Chicago. Best of ASCO Australia has recently been confirmed for Saturday, 3 August, at the Melbourne Convention Centre. Once again, the association is pleased to invite all oncology and allied health professionals to register for the Best of ASCO Australia 2013 program. Please register early to ensure your place via <http://www.mogaasm2013.com>

The MOGA Annual Scientific Meeting 2013 - Blood, Biomarkers and Beyond - at the Melbourne Convention Centre (1-2 August) - will focus on biomarkers and their role in the routine management of patients with cancer and how they guide drug development.

International guest speaker, Professor Allen Chan, from the Chinese University Hong Kong, is a biomarker expert and a key member of one of the most exciting research teams working in this area globally. Professor Mark Ratain, from the University of Chicago, will also share his unique experience in the closely aligned areas of the pharmacogenomics and the pharmacology of anticancer agents. The meeting will feature other highlight sessions ranging from 'A supervisor's masterclass' through to a debate on 'Who should pay for high cost drugs?'



## Frontiers of Radiation Therapy and Oncology (Eds: JL Meyer and W Hinkelbein) Volume 43 IMRT, IGRT, SBRT - Advances in the Treatment Planning and Delivery of Radiotherapy

2nd edition, revised and extended edition.

Editor: John L Meyer Karger (2011) 495 pages

Karger: Basel 2011

ISBN: 978-3805-596800

RRP: CHF 198.00

Intensity Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT) and Stereotactic Body Radiation Therapy (SBRT) have been buzz words in radiotherapy technology for more than a decade. The technologies as such, and their applications, have been evolving significantly over this time and it is interesting to have an attempt at taking stock. The present compilation of review articles does this nicely.

The format is well suited to the topic. More than 40 authors provide an update on technological developments and their clinical applications in 24 chapters over nearly 500 pages. Each chapter is more a review article in itself than a chapter of a book; one can start reading anywhere in the book and cross references are few. This makes the book a useful text for practitioners who seek an update on a particular aspect of their work, and the practical focus of many chapters supports this. The authors are mostly radiation oncologists and medical physicists from North America, who have first-hand experience in the technology they describe.

The book is structured into five sections. The introduction consists of two overview chapters on advances in radiotherapy planning and delivery. The reader will enjoy these chapters which cover similar territory but are complementary rather than repetitive. This also illustrates an important feature of the new technologies - it is not all black and white and IMRT, IGRT and SBRT can be realised in many different ways. The third introductory chapter is concerned with the adoption of new technology from a health economics point of view. While seen largely from a North American perspective, this chapter covers important aspects of health care in general and would be excellent reading for clinical trainees - not necessarily to agree with everything written in the chapter, but to be prepared for the discussions we have to have.

The three main sections of the book are dedicated to IMRT, IGRT and SBRT. The structure is clever, as it combines IMRT and IGRT for the first two sections, the first technology focused and the second clinical. This is appropriate, as the excellent dose distributions that IMRT can produce rely on IGRT to get them in the right spot

within the patient, and most of the modern technology described here integrates IMRT and IGRT.

The clinical section on IMRT and IGRT is the longest section in the book and structured along clinical applications. There are chapters on head and neck cancers, thoracic cancer, breast cancer, upper gastrointestinal cancer, lymphomas and prostate cancer. These chapters provide valuable information for clinicians and many chapters conclude with a section entitled 'Guidelines for clinical practice'. These are not necessarily guidelines as set out by professional organisations or cancer institutes, but bullet lists of important information which make it easy to quickly recap a chapter.

The section on stereotactic body radiotherapy has a distinct clinical flavour. Thoracic, gastrointestinal and genitourinary cancers each have a chapter dedicated to them. The book concludes with two chapters on proton beam radiotherapy. This feels a bit like an afterthought, as proton radiotherapy is not new. However, it has the potential to benefit significantly from the new developments of IMRT and IGRT, as covered for photons in the rest of the book.

The book comes with a subject index and a (very) brief list of frequently used abbreviations. Several authors also provide on-line supplementary material. While the book works well without the supplementary material, some of the animations help the reader to appreciate a particular aspect of the technology.

In summary, this book provides a good overview of the current state of radiotherapy technology. A lot of the material is also published elsewhere, however it is the compilation of authoritative summaries with plenty of references which makes this book valuable. It would be good reading for most radiotherapy professionals and can be considered essential for everyone involved in teaching modern radiotherapy.

*Tomas Kron, Peter MacCallum Cancer Centre, Victoria.*

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# CALENDAR OF MEETINGS

## AUSTRALIA AND NEW ZEALAND

### July

10-13	Australia and New Zealand Breast Cancer Trials Group (ANZBCTG) 35th Annual Scientific Meeting	Brisbane, Queensland	Australia and New Zealand Breast Cancer Trials Group (ANZBCTG) Website: <a href="http://www.anzbctg.org">www.anzbctg.org</a> Email: <a href="mailto:enquiries@anzbctg.org">enquiries@anzbctg.org</a> Phone: +61 2 4985 0136
14-16	Australian & New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group Annual Scientific Meeting	Gold Coast, Queensland	Australian & New Zealand Urogenital and Prostate (ANZUP) Website: <a href="http://www.anzup.org.au">www.anzup.org.au</a> Email: <a href="mailto:info@anzup.org.au">info@anzup.org.au</a> Phone: +61 2 9562 5033
15-18	Health Informatics Conference (HIC)	Adelaide, South Australia	The Health Informatics Society of Australia (HISA) Website: <a href="http://www.hisa.org.au">www.hisa.org.au</a> Email: <a href="mailto:hic2013@hisa.org.au">hic2013@hisa.org.au</a> Phone: +61 3 9326 3311
18-19	The Inaugural National Palliative Care Research Colloquium	Melbourne, Victoria	Centre for Palliative Care Website: <a href="http://www.centreforpallcare.org">www.centreforpallcare.org</a> Email: <a href="mailto:centreforpallcare@svhm.org.au">centreforpallcare@svhm.org.au</a> Phone: +61 3 9416 0000
25-27	Cancer Nurses Society of Australia (CNSA) 16th Winter Congress	Brisbane, Queensland	Cancer Nurses Society of Australia Website: <a href="http://www.cnsawintercongress.com.au">www.cnsawintercongress.com.au</a> Email: <a href="mailto:cnsa@chillifoxevents.com.au">cnsa@chillifoxevents.com.au</a> Phone: +61 2 8005 1867

### August

1-2	Medical Oncology Group of Australia (MOGA) Annual Scientific Meeting	Melbourne, Victoria	Medical Oncology Group of Australia (MOGA) Secretariat Website: <a href="http://www.mogaasm2013.com">www.mogaasm2013.com</a> Email: <a href="mailto:moga@moga.org.au">moga@moga.org.au</a> Phone: +61 2 9256 9651
6-10	14th Australasian Prostate Cancer Conference and 2013 Prostate Cancer World Conference	Melbourne, Victoria	Australian Prostate Cancer Research Website: <a href="http://www.prostatecancercongress.org.au">www.prostatecancercongress.org.au</a> Email: <a href="mailto:pcwc2013@icms.com.au">pcwc2013@icms.com.au</a> Phone: +61 1300 792 466
25-31	InSiGHT 2013 Conference	Cairns, Queensland	Meeting Makers Website: <a href="http://www.wired.ivvy.com/event/cairns">www.wired.ivvy.com/event/cairns</a> Email: <a href="mailto:info@meeting-makers.com">info@meeting-makers.com</a> Phone: +61 3 8344 1831
26-28	Familiar Aspects of Cancer 2013	Cairns, Queensland	Meeting Makers

### September

2	2013 Survivorship Conference	Glenelg, South Australia	Australasian Society for Breast Disease Website: <a href="http://www.asbd.org.au">www.asbd.org.au</a> Email: <a href="mailto:info@asbd.org.au">info@asbd.org.au</a> Phone: +61 7 3847 1946
3-6	2013 Survivorship Conference	Glenelg, South Australia	Australasian Society for Breast Disease Website: <a href="http://www.asbd.org.au">www.asbd.org.au</a> Email: <a href="mailto:info@asbd.org.au">info@asbd.org.au</a> Phone: +61 7 3847 1946

### October

8-10	Australasian Gastro-Intestinal Trials Group (AGITG) Annual Scientific Meeting	Melbourne, Victoria	Australasian Gastro-Intestinal Trials Group (AGITG) Website: <a href="http://www.agitg.org.au">www.agitg.org.au</a> Email: <a href="mailto:agitg@ctc.usyd.edu.au">agitg@ctc.usyd.edu.au</a> Phone: 1300 666 769
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# CALENDAR OF MEETINGS

17-20	The Royal Australian and New Zealand College of Radiologists (RANZCR) 64th Annual Scientific Meeting	Auckland, New Zealand	The Royal Australian and New Zealand College of Radiologists (RANZCR) Website: <a href="http://www.ranzcr2013.com">www.ranzcr2013.com</a> Email: <a href="mailto:ranzcr@outshine.co.nz">ranzcr@outshine.co.nz</a> Phone: +64 7 823 1910
23-25	Oceania Tobacco Control Conference 2013	Auckland, New Zealand	Convention Management New Zealand Ltd Website: <a href="http://www.smokefreeoceania.org.nz">www.smokefreeoceania.org.nz</a> Email: <a href="mailto:dean@cmnzl.co.nz">dean@cmnzl.co.nz</a> Phone: +64 4 479 4162
23-25	2013 Translational Cancer Research Conference	Newcastle, New South Wales	Hunter Medical Research Institute Website: <a href="http://www.translationalcancerresearchconference.info">www.translationalcancerresearchconference.info</a> Email: <a href="mailto:cancerresearchconference@pco.com.au">cancerresearchconference@pco.com.au</a> Phone: +61 2 4984 2554
25-26	Cooperative Trials Group for Neuro-Oncology (COGNO) 6th Annual Scientific Meeting	Sydney, New South Wales	Cooperative Trials Group for Neuro-Oncology (COGNO) Website: <a href="http://www.cogno.org.au">www.cogno.org.au</a> Email: <a href="mailto:cogno@ctc.usyd.edu.au">cogno@ctc.usyd.edu.au</a> Phone: +61 02 9562 5000
27-30	15th World Conference on Lung Cancer	Sydney, New South Wales	International Association for the Study of Lung Cancer Website: <a href="http://www.2013worldlungcancer.org">www.2013worldlungcancer.org</a> Email: <a href="mailto:wclc2013@icsevents.com">wclc2013@icsevents.com</a> Phone: +1 604 681 2153
<b>November</b>			
12-14	Clinical Oncological Society of Australia's (COSA's) 40th Annual Scientific Meeting	Adelaide, South 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
12-15	Australasian Leukaemia and Lymphoma Group (ALLG) Scientific Meeting	Sydney, New South Wales	Australasian Leukaemia and Lymphoma Group (ALLG) Website: <a href="http://www.allg.org.au">www.allg.org.au</a> Email: <a href="mailto:info@allg.org.au">info@allg.org.au</a> Phone: +61 3 9656 9011
21-24	Global Controversies and Advances in Skin Cancer Conference	Brisbane, Queensland	Cancer Council Queensland Website: <a href="http://www.gc-sc.org">www.gc-sc.org</a> Email: <a href="mailto:admin@ccm.com.au">admin@ccm.com.au</a> Phone: + 61 7 3368 2644
<b>2014</b>			
<b>April</b>			
3-5	10th Australian Lymphology Association Conference	Auckland, New Zealand	Australasian Lymphology Association Website: <a href="http://www.alaconference.com.au">www.alaconference.com.au</a> Email: <a href="mailto:info@lymphology.asn.au">info@lymphology.asn.au</a> Phone: +61 3 9895 4486
<b>November</b>			
8-11	15th Biennial Meeting of the International Gynaecological Cancer Society (IGCS)	Melbourne, Victoria	International Gynaecological Cancer Society (IGCS) Website: <a href="http://www.igcs.org">www.igcs.org</a> Email: <a href="mailto:adminoffice@igcs.org">adminoffice@igcs.org</a> Phone: +1 502 891 4575

# CALENDAR OF MEETINGS

## INTERNATIONAL

### July

10-12	Worldwide Innovative Networking (WIN) 2013 Symposium	Paris, France	Congress by design Website: <a href="http://www.winsymposium.org">www.winsymposium.org</a> Email: <a href="mailto:win@congressbydesign.com">win@congressbydesign.com</a> Phone: +31 880 898 101
19-22	12th International Conference on Malignant Lymphoma	Lugano, Switzerland	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: +1 571 483 1300
26-28	Multidisciplinary Cancer Management Course (MCMC)	La Paz, Bolivia	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: +1 571 483 1300

### August

9-10	Best of American Society of Clinical Oncology (ASCO) Chicago	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: +1 571 483 1300
16-17	Best of American Society of Clinical Oncology (ASCO) Los Angeles	Los Angeles, 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: +1 571 483 1300
23-24	Best of American Society of Clinical Oncology (ASCO) Boston	Boston, 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: +1 571 483 1300
29-31	11th Annual Meeting of Japanese Society of Medical Oncology (JSMO2013)	Sendai, Japan	Congress Corporation Website: <a href="http://www.congre.co.jp/jsmo2013/english/index.html">www.congre.co.jp/jsmo2013/english/index.html</a> Email: <a href="mailto:jsmo2013@congre.co.jp">jsmo2013@congre.co.jp</a> Phone: +81 22 723 3211

### September

7-9	2013 Breast Cancer Symposium	San Francisco, United States	American Society of Clinical Oncology (ASCO) Website: <a href="http://www.breastcasym.org">www.breastcasym.org</a> Email: <a href="mailto:membermail@asco.org">membermail@asco.org</a> Phone: +1 571 483 1300
10-13	2nd International Conference on UV and Skin Cancer Prevention	Berlin, Germany	Porstmann Kongresse GmbH (PCO) Website: <a href="http://www.uv-and-skin-cancer2013.org">www.uv-and-skin-cancer2013.org</a> Email: <a href="mailto:ESCF2013@porstmann-kongresse.de">ESCF2013@porstmann-kongresse.de</a> Phone: +49 302 844 9919
22-24	5th International Symposium – Primary Systemic Treatment in the Management of Operable Breast Cancer	Cremona, Italy	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: +1 571 483 1300
26-1 Oct	17th European Cancer Organisation (ECCO) - 38th European Society of Medical Oncology (ESMO) - 32nd European Society for Therapeutic Radiology and Oncology (ESTRO) European Cancer Congress	Amsterdam, The Netherlands	European Cancer Organisation (ECCO) Website: <a href="http://www.ecco-org.eu">www.ecco-org.eu</a> Email: <a href="mailto:info@ecco-org.eu">info@ecco-org.eu</a> Phone: +32 2 775 0201
27-28	Cancer Survivorship Conference	Houston, United States of America	MD Anderson Cancer Centre Website: <a href="http://www.mdanderson.org">www.mdanderson.org</a> Email: <a href="mailto:dschultz@mdanderson.org">dschultz@mdanderson.org</a> Phone: +1 713 745 9208

# CALENDAR OF MEETINGS

## October

4-5	Symposia on Cancer Research, Genomic Medicine	Houston, United States	MD Anderson Cancer Centre Website: <a href="http://www.mdanderson.org">www.mdanderson.org</a> Email: <a href="mailto:register@mdanderson.org">register@mdanderson.org</a> Phone: +1 713 792 2223
10-11	5th InterAmerican Oncology Conference: 'Current Status and Future of Anti-Cancer Targeted Therapies'	Buenos Aires, Argentina	InterAmerican Oncology Conferences Website: <a href="http://www.oncologyconferences.com.ar/index.html">www.oncologyconferences.com.ar/index.html</a> Email: <a href="mailto:secretariat@oncologyconferences.com.ar">secretariat@oncologyconferences.com.ar</a>
10-11	Management in Radiology (MIR) Annual Scientific Meeting	Nice, France	Management in Radiology (MIR) Website: <a href="http://www.mir-online.org/cms/website.php">www.mir-online.org/cms/website.php</a> Email: <a href="mailto:office@mir-online.org">office@mir-online.org</a> Phone: +43 153 340 64
11-12	European Society in Breast Imaging (EUSOBI) Annual Scientific Meeting	Rome, Italy	European Society in Breast Imaging (EUSOBI) Website: <a href="http://www.eusobi.org">www.eusobi.org</a> Email: <a href="mailto:office@eusobi.org">office@eusobi.org</a> Phone: +43 1 535 89 25
11-13	4th International Symposium on Breast Cancer Prevention: Genes, the Environment and Breast Cancer Risks	Beirut, Lebanon	International Breast Cancer and Nutrition (IBCN) group Website: <a href="http://www.purdue.edu/breastcancer">www.purdue.edu/breastcancer</a> Email: <a href="mailto:kswank@purdue.edu">kswank@purdue.edu</a> Phone: +1 765 494 4674
10-12	Global Breast Cancer Conference	Seoul, Korea	INTERCOM Convention Services Inc. Website: <a href="http://www.gbcc.kr">www.gbcc.kr</a> Email: <a href="mailto:gbcc@intercom.co.kr">gbcc@intercom.co.kr</a> Phone: +82 2 501 7065
12-15	9th International Symposium on Hodgkin Lymphoma	Cologne, Germany	German Hodgkin Study Group (GHSG) Website: <a href="http://www.hodgkinsymposium.org">www.hodgkinsymposium.org</a> Email: <a href="mailto:info@hodgkinsymposium.org">info@hodgkinsymposium.org</a> Phone: +49 0 221 478 5933
17-18	International Clinical Trials Workshop	Santiago, Chile	MD Anderson Cancer Centre Website: <a href="http://www.mdanderson.org">www.mdanderson.org</a> Email: <a href="mailto:register@mdanderson.org">register@mdanderson.org</a> Phone: +1 713 792 2223
20-22	The 10th International Conference of the Society for Integrative Oncology (SIO)	Vancouver, Canada	Society for Integrative Oncology (SIO) Website: <a href="http://www.integrativeonc.org">www.integrativeonc.org</a> Email: <a href="mailto:cpd.info@ubc.ca">cpd.info@ubc.ca</a> Phone: +1 347 676 1SIO
24-26	European Society Cardiac Radiology (ESCR) Annual Scientific Meeting	London, United Kingdom	European Society of Cardiac Radiology (ESCR) Website: <a href="http://www.escr.org/cms/website.php?id=/en/meetings/escr_2013.htm">www.escr.org/cms/website.php?id=/en/meetings/escr_2013.htm</a> Email: <a href="mailto:office@escr.org">office@escr.org</a> Phone: +43 1 535 50 93
24-26	2013 Annual Meeting of the International Society of Geriatric Oncology (SIOG)	Copenhagen, Denmark	International Society of Geriatric Oncology Website: <a href="http://www.siog.org">www.siog.org</a> Email: <a href="mailto:laurence.jocaille@siog.org">laurence.jocaille@siog.org</a> Phone: +41 22 366 9106
31-1 Nov	Advances in Cancer Survivorship Practice: A Conference for Health Care Professionals	Houston, United States of America	MD Anderson Cancer Centre Website: <a href="http://www.mdanderson.org">www.mdanderson.org</a> Email: <a href="mailto:register@mdanderson.org">register@mdanderson.org</a> Phone: +1 713 792 2223
31-2 Nov	22nd Asia Pacific Cancer Conference (APCC) 2013	Tianjin, China	Chinese Anti-Cancer Association Website: <a href="http://www.apcc2013.com">www.apcc2013.com</a> Phone: +86 22 23359958 Email: <a href="mailto:secretariat@apcc2013.com">secretariat@apcc2013.com</a>

# CALENDAR OF MEETINGS

## November

3-6	5th International Cancer Control Congress	Lima, Peru	International Conferences Service Ltd Website: <a href="http://www.iccc5.com">www.iccc5.com</a> Email: <a href="mailto:ccc2013@icsevents.com">ccc2013@icsevents.com</a> Phone: +1 604 681 2153
4-8	International Psycho-Oncology Society (IPOS) 15th World Congress of Psycho-Oncology	Rotterdam, The Netherlands	International Psycho-Oncology Society (IPOS) Website: <a href="http://www.ipos-society.org/ipos2013">www.ipos-society.org/ipos2013</a> Email: <a href="mailto:info@ipos-society.org">info@ipos-society.org</a> Phone: +1 434 293 5350
6-8	Chemotherapy Foundation Symposium XXXI	New York, United States of America	The Chemotherapy Foundation Website: <a href="http://www.chemotherapyfoundationsymposium.org">www.chemotherapyfoundationsymposium.org</a> Email: <a href="mailto:jaclyn.silverman@mssm.edu">jaclyn.silverman@mssm.edu</a> Phone: +1 212 866 2813
7-8	2013 American Institute for Cancer Research (AICR) Annual Research Conference on Food, Nutrition, Physical Activity and Cancer!	Bethesda, Maryland	American Institute for Cancer Research Website: <a href="http://www.aicr.org/cancer-research/conference">www.aicr.org/cancer-research/conference</a> Email: <a href="mailto:aicrweb@aicr.org">aicrweb@aicr.org</a> Phone: +1 800 843 8114
7-9	Advanced Breast Cancer Second International Consensus Conference (ABC2)	Lisbon, Portugal	European School of Oncology (ESO) Website: <a href="http://www.abc-lisbon.org">www.abc-lisbon.org</a> Email: <a href="mailto:eso@eso.net">eso@eso.net</a> Phone: +39 02 85464 51
21-24	African Organisation for Research and Training in Cancer (AORTIC)	Durban, South Africa	African Organisation for Research and Training in Cancer (AORTIC) Website: <a href="http://www.aortic-africa.org">www.aortic-africa.org</a> Email: <a href="mailto:info@aortic2013.org">info@aortic2013.org</a> Phone: +27 21 689 5359

## December

6-8	Asia-Pacific Gastroenterology Cancer Summit 2013	Singapore	MCI – Dubai Office Website: <a href="http://www.apgcs.org">www.apgcs.org</a> Email: <a href="mailto:apgcs@mci-group.com">apgcs@mci-group.com</a> Phone: +971 4 311 6300
10-14	36th Annual San Antonio Breast Cancer Symposium	San Antonio, United States of America	Cancer Therapy Website: <a href="http://www.sabcs.org/">www.sabcs.org/</a> Email: <a href="mailto:sabcs@uthscsa.edu">sabcs@uthscsa.edu</a> Phone: +1 210 450 1550

## 2014

### March

17-21	12th International Congress on Obesity	Kuala Lumpur, Malaysia	International Association for the Study of Obesity (IASO) Website: <a href="http://www.iaso.org/events/ico/ico-2014">www.iaso.org/events/ico/ico-2014</a> Email: <a href="mailto:enquiries@iaso.org">enquiries@iaso.org</a> Phone: +44 20 7685 2580
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### May

6-9	Royal Australasian College of Surgeons Annual Scientific Congress 2014	Marinda Bay Sands, Singapore	Royal Australasian College of Surgeons Website: <a href="http://www.surgeons.org">www.surgeons.org</a> Email: <a href="mailto:college.sec@surgeons.org">college.sec@surgeons.org</a> Phone: +61 3 9249 1200
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### June

12-14	European Society of Thoracic Imaging (ESTI) Annual Scientific Meeting	Amsterdam, The Netherlands	European Society of Thoracic Imaging (ESTI) Website: <a href="http://www.myesti.org">www.myesti.org</a> Email: <a href="mailto:office@myESTI.org">office@myESTI.org</a> Phone: +43 1 5322165
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## 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 Oncology Society of Australia

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Professor I Olver AM

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Ms J Brown  
Ms J Fenton AM

## CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA

The Clinical Oncology 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.

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### **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 2013  
Medical Members: \$170  
Non Medical Members: \$110 (includes GST)

### **COSA Groups**

Adolescent & Young Adult  
Biobanking  
Breast Cancer  
Cancer Biology  
Cancer Care Coordination  
Cancer Pharmacists  
Clinical Trials Research Professionals  
Complementary & Integrative Therapies  
Developing Nations  
Epidemiology  
Familial Cancer  
Gastrointestinal Cancer  
Geriatric Oncology  
Gynaecological Cancer  
Lung Cancer  
Melanoma & Skin Cancer  
Neuroendocrine Tumours  
Neuro-Oncology  
Nutrition  
Paediatric Oncology  
Palliative Care  
Psycho-Oncology  
Radiation Oncology  
Regional & Rural Oncology  
Social Work  
Surgical Oncology  
Survivorship  
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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Website: [www.cancer.org.au](http://www.cancer.org.au)