Expert Forum

4th New Zealand Lung Cancer Conference

Making Education Easy | March 2012

In this review:

About Expert Forums

Expert Forum publications are designed to encapsulate the essence of a local meeting of health professionals who have a keen interest in a condition or disease state. These meetings are typically a day in duration, and will include presentations of local research and discussion of guidelines and management strategies.

Even for local events it is not always possible for everyone with a similar therapeutic interest to attend. Expert Forum publications capture what was said and allows it to be made available to a wider audience through the Research Review membership or through physical distribution.

Welcome to this review of the 4th New Zealand Lung Cancer Conference, held in Auckland on 16th March 2012.

This review is a summary of the information presented at the conference about ongoing projects that aim to improve systems and treatment outcomes nationwide, as well as exciting research being conducted in New Zealand and internationally, leading to the development of new treatment options.

SYMPOSIUM 1: REDUCING MORTALITY THROUGH EARLIER DIAGNOSIS

Timely diagnosis and staging of lung cancer: raising the standard

Chairs: Chris Lewis, Greg Frazer

Where we have come from: the 2004 and 2008 audits

Dr Wendy Stevens, MB BS, PhD, Dip Grad, Senior Health Services Researcher at the Northern Cancer Network and University of Auckland, currently the Principal Investigator of a 3-year Lung Cancer Project funded by a HRC_DHBNZ grant (Keynote speaker)

Five-year relative survival outcomes for lung cancer are lower in New Zealand than in several other countries, which is thought to be due to variations in clinical management. The audits aimed to document the lung cancer clinical pathway in the Northern Region, to provide a baseline for any improvements and to enable comparison with international data and standards.

The first clinical audit investigated clinical care management of 565 patients diagnosed with primary lung cancer in 2004 in four NZ DHBs.[1] The second audit examined the pathway from presentation to health care services until diagnosis for 272 patients diagnosed with primary lung cancer in 2008 in three NZ DHBs.[2] Findings revealed little change over the intervening four years, only a higher proportion of patients discussed at an MDM (from 28% in 2004 to 56% in 2008).

The audits revealed late presentation to health care services. Duration of symptoms was poorly recorded in both primary and secondary care records; 75% of all cases initially presented to primary care. Of the 25% who presented directly to secondary care, approximately 60% had seen a GP within the preceding 6 months for another problem. Thus, opportunities may exist within primary care to detect lung cancer earlier. Risk assessment was poor within general practice; smoking status recorded current smokers only and spirometry was seldom performed. Focus groups revealed nihilistic views among GPs regarding lung cancer. Within primary care, GPs took specific action at the initial presentation for 50% of patients, whereas suspicion was delayed for the other 50%. The most important triggers for raising the GPs' suspicion were haemoptysis or an abnormal CXR. Only 65% of cases had a CXR prior to secondary care, which is low compared with international data.

A high proportion of patients present to secondary care acutely (44% vs 21% in the UK). Only 26% of cases were referred by a GP to a respiratory specialist (vs 45% in the UK), and 13% were already under secondary care. Management within secondary care was consistent with international data. The majority have incurable disease at diagnosis.

While the median time from presentation to primary care to diagnosis was 65 days, a quarter of cases took >4 months to be diagnosed.

Factors influencing times to diagnosis:

- Inpatient/outpatient status
- Non-diagnostic initial bronchoscopy. Most required another bronchoscopy or CTFNA, delaying median time to diagnosis by 1 month.
- Systems delays in 10% of cases (lost referrals, lack of follow-up)
- Patient-related delays were much more common in Māori and Pacific people.

Compared to international data, the 2004 audit revealed low curative and palliative treatment rates, a low surgical resection rate and a low surgical resection rate for stage I/II NSCLC, all of which might influence some of the poor survival outcomes.

Factors influencing management:

- Tumour stage, age, comorbidity
- Patient preference and ethnicity. Pacific people were likely to decline palliative treatment. Māori were less likely to receive curative treatment and more likely to receive palliative treatment – a reappraisal of patient records revealed appropriate management decisions.
- Median times to treatment (2004) were longer for those receiving potentially curative treatment compared to palliative treatment.

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Barriers to the early diagnosis of lung cancer: results from HRC study and recommendations

Dr Wendy Stevens

The three-year Lung Cancer Project (*Identification of Barriers to the Early Diagnosis of Lung Cancer and Description of Best Practice Solutions*) from June 2009 to June 2012 is funded by a combined HRC_DHBNZ grant and involves numerous stakeholders (two Cancer Networks, three DHBs, four GP organisations, several Māori organisations, New Zealand Guidelines Group (NZGG), and several departments of the University of Auckland.

The main aims of the project are to:

- Map the clinical pathway from initial presentation to health care services until diagnosis
- Identify local barriers to early diagnosis and optimal lung cancer care
- Identify solutions to these barriers
- Develop recommendations based on the findings of the project and to perform an economic evaluation of those recommendations.

The project comprised several research components:

- Literature Review – to identify barriers and solutions in national and international literature
- Clinical Audit
- National Stock-take of Successful / Innovative Services (primary & secondary care) to identify initiatives in NZ to improve care relevant to lung cancer patients
- Practice Survey – to identify primary care services and processes of care
- GP Survey & Focus Groups - barriers & solutions from GP perspective
- Patient Interviews & Focus Groups of Patients & Whānau/Family – to identify barriers and solutions from patient/family perspective
- Economic evaluation.

Reports are available online at: www.northerncancernetwork.org.nz/Research/LungCancerResearchProject/.

Barriers to the early diagnosis of lung cancer

The three main barriers identified in this project from the patients' and whānau/family perspective:

- A lack of awareness of lung cancer symptoms and the benefits of early treatment
- Fatalistic attitudes to lung cancer and mistrust of the health system.
- The diagnostic period was described as the worst part of the pathway due to wait times, poor support and lack of information.

Patient and whānau/family recommendations included public education campaigns, GP education about lung cancer and a care coordinator they could relate to who could explain the pathway and provide information and support (especially at pre-diagnosis).

GP recommendations included clear investigation and referral pathways consistent across DHBs, with improved access to CT scans and the report. Immediate CT scan booking by radiology upon suspicious CXR. Rapid access clinics. Improved communication from secondary care – electronic access to records and care coordinator. They were keen for upskilling sessions by local respiratory specialists, and they asked for public education campaigns.

Project recommendations:

1. Facilitate Presentation & Patient Journey
   - Improve health literacy, especially for Māori and Pacific peoples, by **improving public awareness of lung cancer and developing information resources**
   - Adequately educated, supported and culturally appropriate **primary and secondary cancer care coordinators** to coordinate the patient journey
   - **Promote a whānau ora approach** by integration of care, including the development of networks between health care, social and community services to enable holistic care for health and non-health needs of patients and their whānau/family
   - Promote ongoing involvement of patients and their whānau/family in health care by obtaining **feedback** regarding their experiences
2. Primary Care
   - **Upskilling of primary care providers** to increase awareness of lung cancer, its risk factors and the benefits of early treatment
   - **Smoking status should be routinely recorded** in primary care records to facilitate identification of those at risk of lung cancer, and promote smoking cessation
   - **Improve GP utilisation of CXRs**
   - **Appropriate systems and safety nets** for following-up patients with **un-resolving symptoms, abnormal results and DNAs**
   - An **e-referral system** with standardised referral information template
   - An **audit tool for the assessment of GP lung cancer referral**
3. Secondary Care
   - **Regionally consistent investigation and referral pathways** aligned with national guidelines and standards
   - **Improve access to timely outpatient CT scans for suspected lung cancer**
   - **Develop a systematic approach to action referrals for suspected lung cancer** to ensure the time from receipt of GP referral to FSA is ≤2 weeks
   - Cases with symptoms/signs of lung cancer should be **promptly transferred to the care of a physician with an interest in respiratory medicine or lung cancer**
   - Develop systems to identify and manage cases with an **incidental finding of lung cancer** on radiological imaging
   - SCLC or **early-stage NSCLC should be prioritised for rapid transit** as survival gains are greatest for these patients
   - All lung cancer patients should be presented at an **MDM**
   - Appropriate and timely **communication** between secondary and primary care providers and with the patient

Where are we now: Cancer Networks: Chris Lewis

These four presentations from the Lung Cancer Networks in New Zealand showcased some of their initiatives designed to improve the process and the care of lung cancer patients in New Zealand.

Northern – Dr Geeta Gala: Electronic TMDM system

An evaluation in 2009 by the Northern Cancer Network (NCN) of all cancer MDMs in the Northern Region identified several gaps within the two existing Thoracic MDMs:

- The paper word template in Concerto was unable to capture all data fields and was time consuming. An electronic lung MDM template has subsequently increased MDM participation from 28% in 2004 to >85% in 2011.
- A business requirements document identified that the TMDM template should interface with existing systems (PiMS, CMS, Eclaire) and encompass the period from the scheduling of the MDM to the reporting requirement.
- The Soprano Medical Template (Concerto) has been adopted as the best solution for now. This is improving the MDM workflow and process, is user-friendly and will eventually incorporate e-referrals to the tertiary services, saving specialists' time with triage and grading. The template will enable the MDM decision to be sent directly to the patient's GP.

Outcome: Over the last two years, the NCN has produced data fulfilling several MOH indicators for faster cancer treatment.

Midland – Mr Nick Odom: VATS resection

Video-assisted thoracoscopic surgery (VATS) lobectomy has been performed for 15–20 years, but has only become more widespread in the last three years. Lobectomy is the gold standard operation for lung cancer surgery, accounting for around 70% of lung cancer resections.

Advantages of a videoscopic lobectomy include less pain, better coughing with easier clearance of secretions, fewer complications with sputum retention, faster recovery, earlier discharge and improved cosmesis. Disadvantages include a longer operating time, higher theatre costs, technical hazards, concern about the efficacy of treatment (i.e. tumour clearance) and about accuracy of staging. Nonetheless, long-term studies show that outcomes are comparable to open thoracotomy. Contraindications include large tumours, proximity to hilar structures, mediastinal involvement, chest wall involvement, and node involvement. Reasons that necessitate intra-operative conversion include failure of one lung anaesthesia, dense plural adhesions, matted hilar structures, sudden bleeding and repair of bronchus or lung tissue.

From 1 September 2011 to 1 March 2012, Waikato Hospital has performed nine VATS lobectomies; eight for cancer and one for a benign tumour. Only one was converted to open. Most patients were discharged on day 3 or 4.

Central – Shirley McLean: Regional MDM development

Central Region priorities for lung cancer include regional MDM development and supporting the implementation of the national service standards. Areas of focus are as follows:

- *Technology*: the Southern Cancer Network and Central Cancer Network (CCN) have collaborated on a joint RFP for the provision of conferencing solutions to enable all DHBs across the CCN Region to be linked and have access to super-regional meetings across the country. Geni-i has been approved as the preferred provider.
- *Data*: CCN will implement an electronic MDM proforma (a Concerto-based programme) across all DHBs in the Central Region. The data gathered will assist with reporting on a variety of indicators.
- *Quality*: When the videoconferencing is put in place, CCN will support DHBs to update TOR and meeting protocols for MDMs. CCN will also support DHBs to audit MDMs against the MDM Framework and develop remedial plans as required.
- *Coordination and Administrative Support*: A pilot project is proposed re MDM coordinator roles (an NZRCN initiative subject to Health Workforce NZ innovations funding).
- *Clinician Resource*: CCN have support from the Regional Human Resource Managers group to consider MDM responsibilities in job sizing requirements and position descriptions when reviewing existing positions or developing business cases for additional positions.
- *Potential funding of MDMs*: CCN have explored the development of a standardised MOH purchase unit for MDMs to be included in relevant service specifications. As Oncology Services was not agreed as a priority for completion this year, further work on these specifications are not endorsed for resource input.
- *Management of Private Patients*: CCN has approached private medical insurers to help develop a strategy that examines patient referrals to public MDMs as part of a standard of care for private patients.
- *Medico-legal*: CCN approached the Health & Disabilities Commission, the MPS and MOH to elicit opinion on medico-legal aspects of MDM decision-making. It appears that MDMs are a medico-legally safe decision-making process. CCN has subsequently developed a generic MDM Patient Information Sheet for adoption/adaption by DHBs.

Priorities for 2012/13:

- Implementation of a conferencing solution to support the functioning of MDMs in the CCN region
- Implementation of CCDHB's electronic MDM proformas to enable data capture
- Implementation of the CCN MDM Meeting Framework
- Subject to Health Workforce NZ innovations funding a pilot project re MDM coordinator roles.

Southern – Dr Ben Brockway: Fast Track Clinic

Lung cancer outcomes have historically been lower than expected for Dunedin, with 3.5-year data indicating survival rates of ~11%. 2008 data highlighted problems with access and moving patients from primary care into secondary care for investigation, with ~50% of lung cancer patients presenting via ED and around half of those presented from their GP via ED. Bronchoscopy lists are performed as day cases in Dunedin Hospital. The fast track clinic has relieved pressure on the ED and improved patient service without increased costs, and existing procedures are simply performed at a different time.

Referrals are reviewed at the x-ray meeting on a Tuesday morning and those selected for fast track are asked to come in on Thursday for full investigation/examination, and CT scans are reviewed by consultant and registrar respiratory physicians and radiologists by lunchtime. Other necessary investigations (bronchoscopy, bedside ultrasound and pleural biopsy) are performed the same afternoon and the patient can go home. The MDM is the next day (but tissue histology takes longer and is discussed the following week).

Benefits for staff and patients alike include the small number of team members, the chance to meet and talk with the consultant, and a wonderful learning opportunity for the registrars and undergraduate medical students. The single visit means less travel and time off work for patients.

After the introduction of the fast track clinic in 2009, ED referrals fell to almost nil, first specialist appointments within 14 days were increased to 94%, MDM discussion rates increased to 91% and 20/28 patients initiated lung cancer treatment within 62 days. The clinic is increasingly adopting TBNA and bedside US and it has witnessed a rapid increase in PET referrals. Communication is key – some improvements are needed in the process of giving the patients feedback as to their lung cancer status. Feedback so far from patients and families has been positive.

Setting up the clinic was a straightforward process. The faster diagnosis allows for faster palliation and psychological adjustment to the diagnosis of terminal disease, as well as more time for the Oncology unit to arrange for treatment within the recommended 62-day period.

Are there other ways to improve lung cancer outcomes?

Chairs: Christine Elder, Ben Brockway

Is targeted screening for lung cancer the answer?

Associate Professor Rob Young, University of Auckland

Targeted screening is one strategy that could be used prediagnosis to improve overall outcome. The vast majority of patients at high risk for lung cancer are current or former cigarette smokers. Emphysema is an indicator of lung damage caused by smoking; increasing evidence suggests that this lung damage is closely associated with increased risk of lung cancer. Typically, there is a nine month delay for a CT scan, during which time lung cancer can develop. It would therefore be useful to be able to screen for those most likely to be diagnosed with lung cancer.

In one study involving ~3500 patients who underwent CT screening, ~50% had either spirometry-based COPD or emphysema at baseline.[1] Of the ~100 lung cancer patients identified by CT over the three-year study period, 85% had underlying lung damage at baseline.

A highly targeted epidemiology-based risk model for lung cancer screening yields a lung cancer susceptibility score utilising five factors:

1. Age >45 years (90% of lung cancer patients aged >50 years)
2. Smoking exposure (>15 pack years)
3. Spirometry-identified COPD
4. Family history
5. Biomarkers (genetic or other).

This targeted selection identifies the highest risk group and is cost-effective, whereas non-targeted CT screening has a low pick-up rate, is costly and results in more harm than benefit.

The recently released NLST trial revealed a 20% reduction in lung cancer mortality among current or former smokers screened with low-dose CT versus those screened with CXR.[2] Huge issues with this study include low detection rates indicative of poor cost effectiveness, over-diagnosis resulting in unnecessary detection of indolent cancers and poor sensitivity due to overly strict eligibility criteria.

An analysis of triggers in smoking cessation identified a one-year quit rate of 65% in smokers diagnosed with lung cancer, and ~50% if they experience a heart attack.[3] Another study proposed that increasing motivational tension favours quitting (harms outweigh the benefits).[4] Health concern for self and family was cited as a reason for attempting to quit by three-quarters of participants in one study.[5]

Genetic testing for lung cancer risk can be personally relevant.[6] Genetic feedback of susceptibility in a US-based trial showed that smokers who underwent genetic testing had higher quit rates at 6 and 12 months than those in a smoking cessation programme alone.[7] An Auckland-based smoking study included 46 participants that agreed to genetic testing.[8] All were current smokers. After 6 months, 78% had reduced cigarette consumption (one-third of whom quit completely).

In summary

Prof. Young considers screening useful yet underutilised. He suggests that it may be useful to combine CT and smoking cessation, which together appear to be cost effective.

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Making NZ smokefree – can it be done, and what can you do to help?

Professor Richard Edwards, University of Otago, Wellington

The Ministry of Health's five-year plan for tobacco control in New Zealand (2004–2009) is commendable, but it remains unclear as to how the Ministry intends to achieve its action plan and the rather vague goal of smoke-free lifestyles lacks a timeline. In contrast, an `endgame' vision aims to achieve close to zero smoking prevalence, within a time-limited strategy. New Zealand data report a very slow decrease in smoking prevalence by ethnicity between 1991 and 2007, and has been slowest among those most affected, Māori and Pacific peoples.[1] Disturbingly, smoking rates among young adult Māori and non-Māori (15–24 years) have not changed substantially between 1996 and 2006.[2]

Prof. Edwards argued there is a strong moral and ethical case for action: tobacco is a uniquely hazardous product; smoking starts mainly among young children and adults; and protecting children from known hazards is generally viewed as a moral imperative and is a societal responsibility. This tobacco-free vision of New Zealand by 2020 – `Daring to dream' – has met with wide support among policy-makers, media and public health practitioners. Similarly, the Smokefree Coalition's Vision envisages a Tupeka kore/Tobacco free Aotearoa/New Zealand by 2020. In 2010, the Māori Affairs Select Committee (MASC) announced its support for making New Zealand a smoke-free nation by 2025. In their Response to the MASC Report, the New Zealand Government announced its goal of a smoke-free nation by 2025. However, the Government also underlined that this is an `aspirational goal'.

While many activities for achieving tupeka kore have been proposed, overarching strategies are needed to achieve endgame goals within a reasonable timeframe. Examples include regulation of nicotine content, a `sinking lid' on tobacco imports, a progressive reduction in retail supply, and a rapidly escalating tax and duty on tobacco products. A sinking lid would require a 10% annual absolute reduction in importation of tobacco products from 2010 to 2020, accompanied by further suppression of demand by adjunct policies and strategies.[6] Strong support for the end of tobacco sales in New Zealand has been expressed by the general population[4] and also by smokers.[5]

Prof. Edwards asks that health professionals engage with and support the 2025 tobacco-free vision, support clinical initiatives and help to hold the Government to account to turn aspiration into reality.

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Panel discussion and conclusions: the way forward

There have been mixed messages from the Government as to how seriously it is adopting the tobacco-free vision, with New Zealand Ambassador Mike Moore recently hosting the Governors and Ambassadors World Trade Reception in Washington DC, which was partly sponsored by tobacco company Philip Morris. Health clinicians are urged to remind the Government that New Zealand has a clear vision and a time limit within which to do it.

Young Investigator Session

Chairs: Mark McKeage, David Perez

Non-small cell lung cancer treated with radiotherapy alone or combined with chemotherapy – outcomes from 2002–2010

Dr John Chin, Waikato Hospital

This study retrospectively assessed the demographics and outcomes of 122 NSCLC patients (median age 65 years) attending the Waikato Hospital Regional Cancer Centre between 2002 and 2010. Patients were treated with a radical intent, either with definitive radiation alone, or combined with chemotherapy (sequential or concurrent). The majority of patients were smokers or ex-smokers, and of Māori ethnicity. Most had stage IIIA or IIIB NSCLC. Those with earlier stage disease often received radiation alone, whereas chemotherapy (mostly concurrent regimens) was often used in stage III disease.

At last follow-up, 60% had died from lung cancer, some remained alive with or without disease and a small proportion had died from unrelated causes. Those treated with concurrent chemo-radiation tended to do better than those given sequential chemo-radiation, who in turn tended to do better than the radiation-only group. Survival by radiation dose was higher for those given ≥60 Gy versus doses of <60 Gy. Long-term survival was also higher for patients on the cisplatin-based Dillman Regimen than those given carboplatin and paclitaxel. Toxicity included neutropenia and neuropathy, and high rates of chemoradiation-related pneumonitis and esophagitis.

An audit of cisplatin and vinorelbine tolerability for patients receiving adjuvant treatment of non-small cell lung cancer

Dr Abbey Jebb, Auckland Hospital

Chemotherapy is now proven in the adjuvant setting to improve OS in lung cancer, with an absolute 5-year survival benefit of 4.1%[1] to 15%,[2] with the greatest benefit in patients with stage II and IIIA disease. Adjuvant chemotherapy is now considered the standard of care for lung cancer in many countries worldwide. PHARMAC approved funded access for vinorelbine on 1st December 2007 for adjuvant treatment of stage IB to IIIA NSCLC in use with cisplatin, in patients with ECOG grade 0–1. An estimated 100 patients are eligible annually for this treatment in NZ.[3,4]

This audit sought to determine tolerability in patients receiving adjuvant chemotherapy in the Auckland region and to determine level of toxicity with the protocol of delivery over more cycles. A total of 29 patients received cisplatin and vinorelbine as adjuvant therapy for NSCLC between December 2007 and December 2010. The total cumulative dose of cisplatin received was relatively high (349 mg/m^2) and the average number of cycles was high (4.58). A low early cessation rate resulted in 79% receiving all planned cycles of chemotherapy.

All patients experienced some degree of toxicity from treatment; 25 (86%) experienced severe toxicity (grade ≥3) or necessitating a change in treatment (dose reduction or earlier cessation). Severe toxicities were more likely to be haematological, particularly severe neutropenia, whereas patients with only minor toxicities were equally likely to experience haematological or non-haematological toxicity. A comparison of toxicity and safety data between large

international trials[1,2,5] and the audit data revealed that patients in the Auckland study received a higher average dose than patients in the ANITA trial (304 mg/m^2), a higher average number of cycles than in the JBR.10 study (median 3 cycles, at 100 mg per cycle), and a lower rate of early cessation. However, rates of grade 3–4 neutropenia were similar between audit data and the international trial data.

In conclusion

- Treatment is being given to an appropriate patient population
- Significantly fewer patients than expected are receiving adjuvant chemotherapy
- Rates of toxicity do not appear to be higher with more cycles of cisplatin
- A higher proportion of patients are completing planned treatment, achieving higher total cumulative dose
- Unacceptable delay in chemotherapy initiation, reasons for this are unclear
- A number of limitations exist (retrospective, variable patient reporting and documentation, small sample population)
- Further analysis required.

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EGFR testing in New Zealand – getting the process right for Māori patients and their whānau

Dr Helen Winter, Dr Claire Hardie, Regional Cancer Treatment Service, MidCentral DHB

Research Centre for Māori Health and Development, Massey University

A 3-part study (comprising a clinicians' survey,[1] consultation with Māori patients and whānau,[2] cost study of EGFR testing) is investigating the feasibility of EGFR testing in New Zealand. Lung cancer has a disproportionate impact on Māori, who have a higher case-fatality ratio than non-Māori, which suggests that there may be differences between Māori and non-Māori in the stage of disease at diagnosis and/or differences in the health care received. This research was conducted by the Research Centre for Māori Health & Development with four Māori patients with advanced lung cancer and two whānau. It aimed to actively engage patients in decision-making about potential new clinical developments. Some patients experienced significant delays in diagnostic work-up, but once within the treatment pathway, patients progressed relatively quickly. An over-riding outcome was the impact of communication upon Māori, in particular how they are told their diagnosis and treatment options. This significantly affects how they and their whānau view their disease and treatment options. Most were agreeable to *EGFR* testing if they considered it beneficial for them or their whānau, or future generations. There was also a general willingness to consider tissue banking or sending samples overseas, if samples were safeguarded culturally and in the practical sense.

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Audit of asymptomatic brain metastases in lung adenocarcinoma

Dr Gareth Rivalland, Auckland City Hospital

Epidemiological, treatment and survival data were presented from eight patients with metastatic lung adenocarcinoma and occult brain metastases. All had extracranial metastatic disease.

The cohort had a median OS of 15.7 months, but median survival from diagnosis of brain metastases was only 3.75 months. Survival ranged from 1.7 months to 3.1 months in those with uncontrolled intracranial disease, versus 4.4 to 19.5 months in patients with controlled intracranial disease.

WBRT improves survival from 1–2 months to 3–6 months, with response rates of around 25–50%. Resection followed by WBRT for solitary lesions increases OS,[1] while stereotactic radiosurgery + WBRT increases OS in solitary metastases and improves care for patients with 1–3 lesions.[2] EGFR-TKI therapy has proven beneficial in cerebral metastases; in an Italian study, EGFR-TKI therapy successfully shrank brain metastases, even without prior WBRT.[3] In an Asian study, first-line EGFR-TKIs without RT resulted in a response rate of ~70% and a median survival of 18.8 months.[4] *EGFR* mutational status defines this response; response rates and OS are negligible in patients without *EGFR* mutations receiving erlotinib compared to those with the mutations.[5] Preclinical studies show that mutant *EGFR* confers increased sensitivity to RT[6] and response rates are highest (84%) for patients who have the mutation and receive EGFR-TKIs during WBRT.[7]

The safety of erlotinib and WBRT has been demonstrated in Phase 1 and Phase 2 trials.[8,9] A case series of nine patients recently demonstrated the feasibility of re-treatment with EGFR-TKI; notably, one patient developed extracranial resistance mutation but retained intracranial sensitivity.[10]

Trials are required to determine whether secondary screening and early intervention affects survival.

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SYMPOSIUM 2: TARGETED THERAPIES IN NZ: ACHIEVING THE BEST ACCESS

Chairs: Richard Sullivan, David Gibbs

The case for personalised therapy for advanced non-small cell lung cancer

Professor Michael Boyer, former Director of the Sydney Cancer Centre, and the Chief Clinical Officer of the Chris O'Brien Lifehouse at RPA (Keynote speaker)

The overall goal of treatment of advanced NSCLC is palliation rather than cure, with the intention of prolonging survival, controlling or minimising symptoms, or improvement and maintenance of quality of life. An additional goal is to gain knowledge of treatment of earlier stage disease, which might then be applied in a curative setting. How to best achieve these aims? Chemotherapy, RT and best supportive care have been used over the last 20–30 years. Irrespective of which treatment, factors that help with decision-making mostly concern the patient (age, PS, co-morbidities, symptoms, etc.); few factors concern the disease (histology, stage, site, etc.) and almost none involve its biology.

Chemotherapy response rates from several large, first-line Phase 3 trials in NSCLC range from 17% to around 30% at best. Using this traditional route of treatment means that to obtain a 20% response rate, the remaining 80% of patients are exposed to some level of treatment toxicity. Advances in chemotherapy regimens for stage 4 lung cancer have offered only modest improvements in median survival. Quality of life outcomes are difficult to compare between chemotherapy trials, mostly because of differing methodologies. Nevertheless, compared to no treatment, QOL is usually maintained or marginally improved with chemotherapy. When different types of chemotherapy are compared, there is little difference in global QOL.

Although anti-cancer treatment is already individualised – patient, tumour and drug factors are considered – none of these factors predict for outcome. In contrast, "personalised" therapy is based on prediction of outcome and of how likely a particular treatment is to benefit a patient.

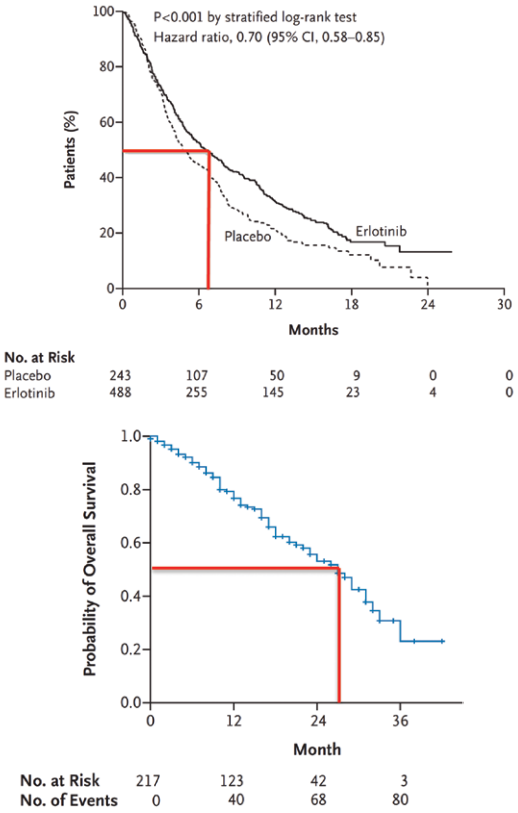
- Prognostic factors provide information about outcome in the absence of treatment e.g. T stage, N stage.
- Predictive factors provide information about the response to a particular treatment e.g. EGFR mutations and EGFR TKIs
- Some factors may be both predictive and prognostic e.g. *ERCC1* in early stage NSCLC is prognostic and also predicts for responsiveness to cisplatin.

One Phase 3 study in NSCLC demonstrated survival differences based on histological type.[1] Patients with stage 3B/4 NSCLC were randomised to cisplatin plus gemcitabine (control arm) or to cisplatin plus pemetrexed (experimental arm).[1] OS for cisplatin/pemetrexed was statistically superior to cisplatin/gemcitabine in patients with non-squamous histology, whereas in those with squamous histology, cisplatin/gemcitabine was superior.

Lung cancer involves a number of driver mutations.[2] The significance of most mutations is unknown, but a small group have been identified as "driver" mutations that are necessary for the initial development, progression and maintenance of a tumour. Tumours with these mutations are "oncogene addicted". Most known driver mutations in NSCLC code for signalling proteins. Identification of signalling pathways has led to the development of targeted therapies for NSCLC (e.g. RAS, EGFR, ALK, RAF).[3] The importance of these signalling pathways and their sequencing vary in different cancers.

The idea of treating specific mutations with specific drugs for lung cancer began with the publication of two papers in 2004, which recognised the existence of *EGFR* mutations.[4,5] Good evidence exists for treating patients selected on the basis of *EGFR* mutation. As shown in Figure 1, when erlotinib was given to unselected patients in the BR21 study, median OS was 6.7 months, compared with 27 months in a study that selected patients on the basis of *EGFR* mutation.[6,7]

Figure 1. Erlotinib: overall survival[6,7]



These nonrandomised data provide the first hint that treating a specific abnormality with a specific drug will provide substantial benefit. The most often quoted study in this field is IPASS (Iressa PAn ASia Study), which involved some phenotypic selection (i.e., patients were Asian, never or light ex-smokers, PS 0–2), but there was no attempt to select on a molecular basis.[8] Patients were randomised to TKI therapy with gefitinib or to standard chemotherapy with carboplatin and paclitaxel. Notably, testing for *EGFR* status revealed two distinct study populations: progression-free survival (PFS) was prolonged in the *EGFR* mutation-positive cohort given gefitinib, whereas EGFR mutation-negative patients did better on standard chemotherapy.

Survival curves are strikingly different in another study involving patients with advanced NSCLC who were selected on the basis of *EGFR* mutations; those who received first-line gefitinib had a significantly longer median PFS, compared with those given standard chemotherapy.[9] In Phase 3 studies of first-line TKIs, the difference in response rates between the chemotherapy and TKI cohorts is not great in the studies that clinically selected patients.[8,10] In contrast, response rates are ≥2-fold higher for molecularly-selected patients given a TKI versus chemotherapy.[7-9,11,12] Notably, the HR values for PFS are marginally significant for the clinically-selected studies and are dramatically lower (i.e. more effective) in the molecularly-selected studies (see Fig.2). Prof. Boyer predicts that OS will be significantly better for those molecularly-selected patients receiving a TKI first.

Figure 2. Phase 3 studies of first-line TKI: PFS[7-9,11,12]

Study	Selection	TKI	Median PFS Chemo (months)	Median PFS TKI (months)	HR
IPASS	Clinical	G	6	6	0.74
First Signal	Clinical	G	6	6	0.87
NEJ002	Molecular	G	5	11	0.32
Mitsudomi	Molecular	G	6	9	0.49
OPTIMAL	Molecular	E	5	14	0.16
EURTAC	Molecular	E	5	10	0.37

G = Gefitinib, E = Erlotinib

Analyses of changes in QOL in the IPASS study reveal greater improvements among patients with *EGFR* mutation-positive tumours treated with gefitinib versus those given chemotherapy, whereas the reverse was true for patients with *EGFR* mutation-negative tumours.[13] Clearly, it is important to know what the tumour characteristics of a tumour are, in order to treat patients with the right drug.

It can also be useful to determine Met protein levels of tumours. A recent Phase 2 study found no difference in outcomes in patients receiving erlotinib either alone or with MetMAB.[14] However, when analysed by Met protein levels, those who were Met diagnostic-positive had significant benefits with combination therapy in terms of PFS and OS compared to patients who received erlotinib alone. The reverse was found for Met diagnostic-negative patients.

Another example is the *ALK* gene. A subset of NSCLC patients may express a transforming fusion kinase that is a promising candidate for a therapeutic target as well as for a diagnostic molecular marker in NSCLC.[15] Crizotinib was assessed in 82 patients with *ALK*-positive disease.[16] Seventy-seven patients had tumour shrinkage and many had disease control for long periods of time, despite this being a heavily pre-treated cohort. At the time of data cut-off, the estimated probability of 6-month PFS was 72%, with no median for the study reached. Investigations into the use of crizotinib have progressed from treatment of very advanced disease to first-line metastatic treatment. The next step for all of these drugs would be to evaluate them in the appropriate patients in an adjuvant treatment setting.

Lung cancer treatment approaches: the future

The traditional, histological classification of lung cancer has been enriched with increasing knowledge about molecular subsets in NSCLC. The proportion of NSCLC with some type of identifiable mutation is now close to 50%. The challenge is how to turn this knowledge into meaningful treatments for patients. The BATTLE trial explored the feasibility of a biopsy-mandated, biomarker-based approach to treatment, in which chemorefractory NSCLC patients were adaptively randomised to targeted treatment based on relevant molecular biomarkers analysed in tumour specimens.[18] Prof. Boyer suspects that repeat biopsy testing will be the first barrier to be overcome – many patients will have been diagnosed on only a very few lymph node cells. Interestingly, the BATTLE trial enrolled 341 patients and obtained 324 biopsies.

The national cancer network (INCa) in France is systematically analysing molecular data to inform treatment programmes. By anticipating the marketing authorisation of the therapies targeting one of these molecular alterations, the programmes will be ready to perform the test as soon as the therapy is available. This organised national testing programme is what we probably need to be doing in Australia and New Zealand to catch up in this field, suggests Prof. Boyer.

Barriers to individualised therapy include:

- Mindset
  - Represents a new way of thinking about the disease and its treatment
  - Understanding of the importance of adequate samples and a preparedness to obtain them
- Drug Development Paradigm
  - Biomarkers needed much earlier in development
- Collaboration
  - Clinicians will not have all the answers to this
  - Closer working relationships needed with molecular pathologists / biologists
- Biology
  - Assumption that mutations are stable over time, and that tumour heterogeneity is not a problem
- Regulatory
  - Approval (reimbursement) of drugs may not be very useful without approval (reimbursement) of associated diagnostic tests
- Money
  - This can be expensive (but testing is becoming cheaper)
  - No clear proof (yet) that it is cost effective

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How EBUS sampling has altered lung cancer work-up

Dr Chris Lewis, Respiratory Physician, Auckland City Hospital

The traditional method of diagnosing lung cancer is by biopsy of the primary – by CT FNA or core, or by bronchoscopy with wash, brush or bronchial biopsy. CT radiographically stages the mediastinum, after which mediastinoscopy or surgical staging could be considered (or just accept the CT findings). Sensitivity and specificity of mediastinal staging modalities are as follows:[1]

	Sensitivity	Specificity
Chest CT	51%	86%
PET	74%	85%
"Blind" TBNA	78%	99%
Mediastinoscopy	78%	100%
EBUS – TBNA	90%	100%
EUS – TBNA	84%	99.5%

EBUS (endobronchial ultrasound) accesses a wider range of lymph nodes than those reached surgically. EUS (endoscopic ultrasound) can be used in the same way in the esophagus. Combined EBUS and EUS for mediastinal staging under the same sedation allows access to the majority of the mediastinum.

EBUS has good specificity and sensitivity. The modern trend is to perform EBUS first, for diagnosis and staging. If New Zealand patients with potentially operable disease could undergo a PET scan upfront, possibly instead of a CT or immediately after a CT, evidence of hot nodes on the PET scan would add weight to the strategy of approaching the node first. This potentially cuts several weeks off the patient's transition through the lung cancer pathway, without having to wait for other tests and diagnoses of samples. The downside is that the EBUS sample might be the only collection of malignant cells available for pathology; the much smaller samples and thus fewer tumour cells could potentially make diagnosis very difficult. EBUS has a similar diagnostic rate as another test followed by EBUS.[2] Thus, performing an EBUS first, even if negative, did not seem to particularly disadvantage patients, if they were selected correctly.

In a retrospective comparison of EBUS guide-sheath biopsy and CT FNA, the conclusions were that these methods yield:[3]

- Similar diagnostic efficacy
- Radial EBUS reduces pneumothorax risk in lesions not touching pleura
- GA was used for radial EBUS
- Need either very good command of lung anatomy, or navigation software
- Respiratory physician "control" of radial EBUS

Advantages of EBUS are:

- Safe, well tolerated, performed under conscious sedation
- Often offers diagnosis and staging of lung cancer in the same sitting
- A skilled cytopathologist on site may give you a provisional diagnosis at the procedure
- Organisation is controlled by the respiratory physician
- Can take days or weeks off work-up times

In summary

- Linear EBUS is a minimally invasive, daycase procedure which can both diagnose and stage lung cancer with accessible nodal metastases and thus shorten work up
- Radial EBUS may become an alternative to CT FNA for some peripheral lesions
- On-site pathological handling and interpretation of EBUS specimens is difficult and requires expertise, but can yield a provisional diagnosis the same day
- Cytology specimens obtained at EBUS contain far less malignant material than core biopsies or nodal resections

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Modern evaluation of lung cancer specimens

Dr Vladimir Osipov, Anatomic Pathology LabPlus, Auckland City Hospital

Lung tumours are probably a prime example of tumour heterogeneity. The pathology specimens may contain combinations of small-cell carcinoma and adenocarcinoma, with different patterns within adenocarcinomas as well. Different patterns are associated with different prognoses. The predominant pattern will be reported by the pathologist. A lung cancer structured reporting protocol has recently been agreed upon by New Zealand pathologists, which will result in uniform reporting by DML or LabPLUS of relevant information for specific cancers.

Dr Osipov predicts that increasingly, testing will be performed for mutually exclusive mutations in lung adenocarcinomas, for which targeted therapies exist. At present, Auckland City Hospital is able to conduct *ALK* testing in-house (by FISH or IHC), whereas *EGFR* is sent away for PCR testing. Auckland City Hospital expects to soon be introducing double staining, which will minimise the amount of tissue needed to determine the type of tumour before proceeding to molecular testing.

Mutation testing in NZ: role of the National Health Committee

Dr Mark O'Carroll, Respiratory Physician, Auckland City Hospital, member of the National Health Committee

Dr O'Carroll discussed the New Zealand drug and test approval system, and questioned whether the two should be linked.

Currently, New Zealand lacks a national list of funded tests. Diagnostic tests are developed at a local level and each DHB decides within its own right as to which tests will be funded and many are developed in-house. In contrast, the process for approving drugs is highly structured and regulated, subject to national coordination. To date, PHARMAC funding decisions have not evaluated co-dependent technology, where the efficacy or effectiveness of a drug is dependent upon a test. The NHC sees this evaluation as a way of entering the area of personalised medicine, which has enormous relevance for oncology and will increasingly confront the oncology world.

If New Zealand is to alter the way diagnostic tests are introduced, a number of different aspects need to be considered regarding their assessment and the potential impact upon funding decisions. Five key questions surround decision-making criteria as to *EGFR* testing that are of potential interest to the NHC:

1. Clinical safety and effectiveness of gene mutation testing for predicting response to treatment in terms of objective response rates
2. Diagnostic accuracy
3. Societal impacts on health and ethical considerations
4. Value for money: these new technologies are typically very expensive and careful thought is needed to ensure best use of those therapies for the best patients, to optimise and maximise value for money
5. Feasibility of adoption.

Many of the uncertainties surrounding the drugs and associated tests can only be resolved through considerations with all the relevant stakeholders. The NHC can play an important role by engaging with stakeholders and assisting with pragmatic decisions around the implementation and adoption of these tests. Ultimately, the NHC makes recommendations to the Health Minister within a feasibility framework and with consideration of fiscal spending.

Panel discussion: the way forward

Michael Boyer, Vladimir Osipov, Mark O'Carroll, Chris Van Vliet

Q: Does the NHC have any answers for the questions on cost-effectiveness of testing before offering treatment and of changes to the way treatment should be given compared with the current situation?

A: Some but not all. The situation in New Zealand differs from that in Australia, where the pharmaceutical industry can refer a test or technology to the Medical Services Advisory Committee and a Health and Technology agency for consideration of testing and associated costs.

Q: The Northern Region is examining a pathway to manage this issue and has been sending tissue samples to Australia with the intention of clarifying which groups of patients would be eligible if these tests were available and funding available for the associated treatments. What sort of programme does Australia have in place?

A: In the absence of a national programme, interested groups of clinicians have developed local programmes. For instance, Prof. Boyer and colleagues have adopted policy of testing all patients with metastatic adenocarcinoma, which has still to be achieved. In a research sense, they are testing many patients with early stage disease – not within routine care, but as part of individual research projects. Currently, in Australia, neither the drugs nor tests for *EGFR* are reimbursed in the first-line setting, which means they impact upon hospital budgets or, in the case of pharmaceuticals, may be supplied by the manufacturers through expanded-access programmes. A co-dependent technology assessment programme has been developed in Australia. It is expected that *EGFR* testing and erlotinib will be the first to go through that process, followed by *ALK* testing and crizotinib. This programme is not restricted to oncology drugs; a variety of other drugs and co-dependent diagnostics are lining up for consideration. However, while it sounds like a great concept, Prof. Boyer understands that it adds 6–12 months onto the assessment process compared with assessing the pharmaceutical itself.

Q: How does Prof. Boyer manage those patients with insufficient tissue?

A: If a patient is effectively asymptomatic, there is time to perform a repeat biopsy. If a patient is symptomatic and needs treatment relatively soon, Prof. Boyer would not wait for the results of the re-biopsy. At this stage, he does not believe sufficient data are available to show that the advantages of having first-line TKI versus chemotherapy are so vast compared with having second-line TKI treatment that he would wait 3 weeks for a patient who needs treatment.

Q: Should a TKI be offered to *any* patient without a nonmutating status who should undergo re-biopsy?

A: Prof. Boyer would not offer a first-line TKI without knowing the mutation status of the patient. If unknown, he would treat the patient as having negative status. However, data on second-line TKI treatment are different – the analysis on *EGFR* mutation status in the BR21 study shows basically no difference in outcome between first- and second-line TKIs. Based on this evidence, erlotinib will continue to be used as a second- or subsequent line treatment in patients with mutation status unknown.

Q: Would smarter, evidence-based trials help to answer questions around co-dependent technologies as to cost implications and benefits of particular treatment routes?

A: The time lag in performing the processes of these assessments always takes longer than is desirable. The challenge is that a relatively short turn-around is needed for a health technology assessment to be useful.

Q: Within a limited available budget, is there a population of patients with adenocarcinoma who could be specifically tested?

A: Prime candidates would include the ~30–40% of South-East Asians living in Auckland who have adenomas with *EGFR*-activating point mutations.

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