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Abbreviations used in this issue

AUC = area under the curve
BTBNA = bronchoscopic transparenchymal nodule access
EBUS = endobronchial ultrasound
ES-SCLC = extensive stage small-cell lung cancer
EUS-FNA = endoscopic ultrasound-guided fine needle aspiration
HR = hazard ratio
NSCLC = non-small cell lung cancer
OS = overall survival
PFS = progression-free survival

Welcome to another issue of Lung Cancer Research Review.

Highlights in this issue include studies investigating the benefits of exercise therapy post-surgery, the pros and cons of a range of diagnostic/staging techniques and tools, and the efficacy of several novel pharmacological agents in various types of lung cancer, including findings from the INSPIRE study.

We hope that you enjoy reading the selections in this issue of Lung Cancer Research Review and, as always, we look forward to receiving your comments and feedback.

Kind regards,
Dr Chris Lewis chrislewis@researchreview.co.nz
Dr George Laking georgelaking@researchreview.co.nz

High-intensity training following lung cancer surgery: a randomised controlled trial

Authors: Edvardsen E et al.

Summary: This was a single-blind, randomised controlled trial of high-intensity endurance and strength training (60 min three times a week for 20 weeks), starting 5-7 weeks after surgery, compared with standard postoperative care (control group). In the intention-to-treat analysis of 61 randomised patients, the exercise group had a greater increase in peak oxygen uptake (3.4 mL/kg/min between-group difference, p=0.002), which was the primary endpoint, carbon monoxide transfer factor (5.2% predicted, p=0.007), one-repetition maximum leg press (29.5kg, p<0.001), chair stand (2.1 times p<0.001), stair run (4.3 steps, p=0.002) and total muscle mass (1.36kg, p=0.012) compared with the control group.

Comment (CL): It has often struck me that an area which would benefit from some well conducted research studies is that of follow up after curative intent lung cancer treatment. In clinical practice, patients seem to suffer morbidity after lung cancer surgery despite a successful cancer clearance. The primary outcome of this study is as one might expect — that an exercise programme improves exercise performance — but the study provides a wealth of other useful information. Firstly, it demonstrates that it is feasible to conduct an exercise programme in this group just a few weeks after surgery, and that patients undergoing adjuvant chemotherapy can still be included — although a break was needed around the last cycle. The overall drop-out rate was much lower than the authors both allowed for and expected. Only a minority of patients had COPD, so benefits were not just confined to those who might ordinarily be referred for “pulmonary rehabilitation”. There were good improvements in muscle mass (which apparently has a relationship with all-cause mortality), and also in health-related quality of life. A “high” intensity of exercise was thought important, as a prior study had shown no benefit with “moderate”. This data will encourage me clinically to recommend physical rehabilitation for this group of patients. It would be really interesting if a larger, longer term study could be conducted with mortality included as an outcome. The QoL (SF-36) physical component summary score was 51.8±5.5 versus 43.3±11.3 (p=0.006) and the mental component summary score was 55.5±5.3 versus 46.6±14.0 (p=0.015) in the exercise versus control groups.

Reference: Thorax 2015;70(3):244–50

Abstract

Independent commentary by Dr Chris Lewis MD FRACP MRCP(UK)

Chris is a respiratory physician at the Auckland District Health Board. He has a particular interest in lung cancer. He is chair of the lung tumour stream of the Northern Cancer Network, a member of the national lung cancer working party of the Ministry of Health, and an invited member of the Australian Cancer Council lung cancer guideline group, developing the world’s first wiki-based cancer guidelines. At ADHB, Chris is chair of the lung cancer multidisciplinary meeting and set up New Zealand’s first endobronchial ultrasound (EBUS) service for minimally invasive diagnosis and staging of lung cancer. He also has an interest in interventional bronchoscopy for palliation of central airway tumours. He previously undertook subspecialist training at Papworth Hospital in the UK, where there is a leading regional lung cancer unit.

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Making Education Easy
Metastatic non-small cell lung cancer: a benchmark for quality end-of-life cancer care?

**Authors:** Philip J et al.

**Summary:** This retrospective cohort study investigated the quality of end-of-life care for patients with metastatic NSCLC from first hospitalisation for metastatic disease until death. Patients underwent limited aggressive treatment such as intensive care (5%) and chemotherapy (<1%) at the end of life; however, many patients died in acute hospitals (42%) and 61% had a length of stay >14 days in the last month of life. Although 62% were referred to palliative care services, this occurred late in the illness. The odds ratio (OR) of dying in an acute hospital bed versus death at home or in a hospice unit decreased with supportive care (OR 0.65; 95% CI 0.56-0.75).

**Comment (CL):** I found the findings of this study to be an interesting follow on from the 2010 NEJM early palliative care randomised trial (N Engl J Med 2010;363(8):733–42), which demonstrated a mortality benefit. The authors have taken an interesting approach in their discussion, suggesting (reasonably) that lung cancer could be used as a benchmark for the quality of palliative care services in general – given the short survival of lung cancer patients. Whilst this is a less rigorous, retrospective review of palliative care access, the numbers and timeframe are impressive and interesting and consistent messages emerge (see abstract). Whilst chemotherapy was rarely given close to death, only a third of patients did not flag for any indicator of “aggressive care” in the 30 days prior to death. Nearly half died in an acute hospital bed, and over half spent more than 14 of their last 30 days alive on an acute ward. As per the NEJM study, involvement of palliative and supportive care services substantially increased the likelihood of dying at home or in a hospice. Another interesting finding was that palliative care involvement was very common if a patient died during their first “metastasis admission”, but only 10% were referred during that admission if they survived to discharge. Whilst one study weakness was that only hospital-based palliative care services were able to be measured, there is a clear suggestion that patients may be referred to palliative care too late to be able to build up and trust community supports which would in turn reduce use of acute services. These are difficult and tough issues to address – where would cancer patients prefer to die, and what is best (and toughest of all, most cost-effective) at a health system level? The NEJM paper suggested that early palliative care involvement improved most patient-reported indicators such as mood and quality of life.


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Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomised controlled trial

**Authors:** Navani N et al.

**Summary:** In this open-label, multicentre, pragmatic, randomised controlled trial, patients who had undergone a CT scan and who had suspected stage I-IIIA lung cancer were recruited from six UK centres and randomly assigned to either EBUS-TBNA or conventional diagnosis and staging (CDS), for further investigation and staging. If a target node could not be accessed by EBUS-TBNA, then EUS-FNA was used as an alternative procedure. A total of 133 patients were randomly allocated to treatment: 66 to EBUS-TBNA and 67 to CDS (one later withdrew consent). Two patients from the EBUS-TBNA group underwent EUS-FNA. The median time to treatment decision (primary endpoint) was shorter with EBUS-TBNA (14 days; 95% CI 14-15) than with CDS (29 days; 23-35), which resulted in a hazard ratio of 1.98, (1.39-2.82, p<0.0001).

**Comment (CL):** This is one of those unfortunate studies that I suspect was an excellent idea when it was designed and commenced, but by the time the results were ready clinical practice has already moved on based on other data. However, this is apparently the only randomised controlled trial comparing upfront EBUS (or EUS)-guided TBNA directly with a strategy of conventional diagnosis then mediastinal staging. The design is interesting and would now be unlikely to be replicated in clinical practice. The diagnostic approach was only individualised in the conventional group (by an MDT), who were not allowed to have EBUS/EUS at any point. On the contrary, all the patients in the EBUS/EUS group underwent this as the first procedure, irrespective of the size of their lymph nodes on chest CT, and without a prior CT PET scan. In this group, a full systematic examination of all nodal stations was carried out; any node suspected to be metastatic on “size and location” was aspirated (median size was 12mm); and even if there were no enlarged nodes, the node thought most likely to be draining the primary lesion was aspirated. In this group, 45% of patients received diagnosis and staging in one procedure and the number and time of investigations prior to treatment decision was reduced. Whilst I think that, in clinical practice in 2015, investigation of suspected lung cancer should be individualised, this study does support strong consideration of well conducted, systematic endobronchial and/or endoscopic staging as the first test for combined diagnosis and staging. With MOH faster cancer treatment targets now part of our working lives, speedy work-up times will be even more important to achieve.


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First-line crizotinib versus chemotherapy in ALK-positive lung cancer

**Authors:** Solomon BJ et al.

**Summary:** This first-line phase III trial compared the efficacy of the ALK inhibitor crizotinib with that of standard chemotherapy as first-line treatment in 343 patients with advanced ALK-positive non-squamous NSCLC. Patients were randomised to receive oral crizotinib 250mg twice daily or IV chemotherapy (gemcitabine 1000 mg/m² plus either cisplatin 75 mg/m² or carboplatin target AUC 5-6 mg/mL/min) every 3 weeks for up to six cycles. Median PFS was significantly longer with crizotinib than with chemotherapy (10.9 vs 7.0 months; HR for progression or death with crizotinib 0.45; 95% CI 0.35-0.60; p<0.001).

**Comment (GL):** As highlighted in the NEJM 2009 paper in the NEJM established EGFR TKI as the first-line treatment for patients with sensitising EGFR mutations, but we did not know if the corresponding rule would hold true for crizotinib and ALK mutations. Now we more or less do – in this study by Solomon et al, crizotinib had a significant PFS advantage over platinum and paclitaxel. There was no OS benefit, although interpretation was confounded by a 70% post-chemotherapy crossover rate to the crizotinib arm. The NZ price (via CMPMedica) in July 2015 is $6669.25 per month. The median duration of treatment was 10.9 months, total cost just under $100,000. And if the TPPA drafters win through, that’s right where the cost will stay.


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What science can do.
**Endobronchial ultrasound-guided cryobiopsies in peripheral pulmonary lesions: a feasibility study**

Authors: Schuhmann M et al.

Summary: These German investigators evaluated the safety and feasibility of the cryoprobe in combination with EBUS for the diagnosis of peripheral lung lesions. Patients with peripheral lung lesions of up to 4cm were enrolled. After identifying the lung lesion by radial EBUS, forceps biopsies and cryobiopsies were performed in a randomised order. The peripheral lung lesion was reached in 31/39 randomised patients. The overall diagnostic yield was 60.5%; it was 74.2% in the lesions reached by EBUS. The diagnosis was made with forceps as well as cryobiopsy in 19 cases and with cryobiopsy alone in four cases. Cryobiopsies were significantly larger than forceps biopsies (11.17mm² vs 4.69mm²; p<0.001). There was one case of moderate bleeding.


Abstract

Bronchoscopic transparenchymal nodule access (BTPNA): first in human trial of a novel procedure for sampling solitary pulmonary nodules

Authors: Hert Hij et al.

Summary: These investigators, from the same German clinic, developed a novel procedure that allows sampling of solitary pulmonary nodules (SPNs) via a transparenchymal approach, and reported the results from this procedure as a first in human trial. The prospective single-arm interventional study recruited patients with a SPN detected on CT imaging, which was suspicious for lung cancer, who were suitable for surgical resection. Using the patient’s CT image, an optimal airway wall point of entry (POE), and an avascular path through lung tissue from the POE to the SPN was calculated. A tunnel tract was created from the POE to the nodule using a set of catheter-based tools under fused fluoroscopy guidance. The patients proceeded to surgical resection immediately after the biopsy and were followed-up for 6 months after the procedure. Twelve patients were recruited and a tunnel pathway was created in 10 patients. There were no adverse events during the procedures. Adequate biopsies were obtained from 10 patients (83%), which correlated with the histological findings from the surgical resection. Inspection of the resected lobes did not reveal any safety concerns and indicated appropriately tunnelled pathways to the nodule.


Abstract

**Comment (CL):** The field of lung cancer continues to evolve, particularly with regards to personalised, targeted therapies and immuno-oncology treatments. The phrase “tissue is the issue” is often heard at meetings, and a downside of the success of minimally invasive endoscopic lung cancer staging has been the small, cytology samples produced which may be inadequate for detailed testing. A common session at the same meetings is also the rather morosely titled “What will be the role of the respiratory physician in lung cancer in the future?”, and these two papers provide some hope: the role may be learning ever more clever new bronchoscopic techniques to acquire sizeable tissue samples for our oncologists, even in patients not suitable for CT biopsy (or perhaps where the respiratory physician prefers to do the diagnostic procedure him or herself). These two papers come from the world-leading Thoraxklinik in Heidelberg, Germany, where they have been fortunate enough to recently spend a month undertaking an interventional bronchoscopic attachment.

The first paper is a feasibility study of the technique of peripheral cryobiopsy. This involves the use of radial EBUS to navigate to peripheral lung lesions, but rather than taking a small forceps biopsy through a guidewash, using a cryotherapy probe to freeze the area of the lesion and thus remove a rather more substantial amount of tissue. This study demonstrated that cryobiopsy produced larger samples than forceps biopsies, and that these had a higher rate of being diagnostic. There is a risk of bleeding, although that was low in this study. Cryobiopsies are also too large to fit through the working channel of a bronchoscope, meaning that the whole scope and probe must be removed and the lesion then “re-found”. For these reasons, I think this procedure is likely to require general anaesthesia and a secure airway — although this is standard in Heidelberg and increasingly in Australia, it would be a departure from usual practice in New Zealand and add cost.

The second feasibility study examines accessing peripheral lung nodules which are unable to be reached via a bronchus. Thus, this paper examines an even more novel idea: creating a path through the lung parenchyma to reach the nodule and take forceps biopsies. The technique requires the use of some clever radiologic planning and mapping software in order to create a safe path avoiding blood vessels (so sadly the radiologist is not rendered entirely redundant). This proved possible in 10 of 12 cases, including one track as long as 9cm. The left upper lobe proved to be the most difficult site, as recalling our anatomy lessons, there are a number of large blood vessels around the bronchi there. The procedure times were not unduly long. The study was performed in lobes that were about to be surgically removed, and subsequent histological examination revealed a reassuring absence of complications. Having seen the speed and skill of the bronchoscopists in the Heidelberg unit, I am not sure that these techniques will be so easily learnt and performed by “ordinary” bronchoscopists! However, it will be interesting and exciting in coming years to see if, and how, these and other novel bronchoscopic techniques will be integrated into lung cancer practice.

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practitioner Educational Programme Stage 2 (GP2P) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please click here to download your CME MOPS Learning Reflection Form. One form per review read would be required.
Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Authors: Slotman BJ et al.

Summary: In this European, multicentre, randomised, phase III study, 247 patients with WHO performance score 0-2 and confirmed ES-SCLC who responded to chemotherapy received thoracic radiotherapy (30 Gy in ten fractions) and 248 no thoracic radiotherapy. OS at 1 year was not significantly different between groups: 33% (95% CI 27-39) for the thoracic radiotherapy group versus 28% (95% CI 22-34) for the control group (HR 0.84, 95% CI 0.69-1.01; p=0.066). However, in a secondary analysis, 2-year overall survival was 13% (95% CI 9-19) versus 3% (95% CI 2-8; p=0.004).

Comment (GL): This European group has been intensifying treatment for people with ES-SCLC, using approaches historically reserved for limited stage. Their earlier randomised trial found a 1:4 1-year survival gain with prophylactic cranial irradiation (PCI), although due to increased toxicity PCI has not been universally adopted. The authors do not reveal how many patients were screened. This is of interest, as eligibility depended on a radiation oncologist’s subjective assessment of treatability using acceptable radiation fields. The study was negative for its primary endpoint of 1-year OS, but positive on a secondary endpoint of 2-year OS, with a 10% absolute increase. In contrast to the experience with PCI, the trend to increased toxicity with extra treatment did not reach significance. The orthodox conclusion here is still “need another randomised trial”. Perhaps the authors regret not designing their study around the 2-year survival comparison. The benefit looks convincing, with the group most likely to benefit appearing to be those in whom diagnosis of extensivity was on the basis of intrathoracic disease only. From my observation, many radiation oncologists are happy to offer this. Research Review welcomes correspondence!

Reference: Lancet 2015;385(9962):36–42

Abstract

Pembrolizumab for the treatment of non-small-cell lung cancer

Authors: Garon EB et al.

Summary: The aim of this phase I study was to assess the efficacy and safety of programmed cell death 1 (PD-1) inhibition with pembrolizumab in patients with advanced NSCLC. Patients receiving pembrolizumab (either 2 or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks) were assigned to either a training group (n=162) or a validation group (n=313). PD-L1 expression in tumour samples was assessed with results reported as the percentage of neoplastic cells with staining for membranous PD-L1 (proportion score). The overall objective response rate was 19.4%, and the median duration of response was 12.5 months. PD-L1 expression in ≥50% of tumour cells was selected as the cut-off from the training group. The response rate was 45.2% among patients with a proportion score of ≥50% in the validation group. Among all the patients with a proportion score of ≥50%, median PFS was 6.3 months; median OS was not reached.

Comment (GL): And so to the hope of immune checkpoint inhibition. Here is a phase II trial of PD-1 inhibition with the PD-1 ligand 1 (PD-L1)-targeted monoclonal antibody pembrolizumab. This study is important for guiding current development of pembrolizumab towards the 20-25% of patients whose lesions show high (>50%) PD-L1 expression. And for guiding PHARMAC towards an inevitable meeting with an approximately $150,000 per annum price-tag for a drug of relevance to some highly prevalent cancers.


Abstract

Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014)

Authors: Krug LM et al.

Summary: This international, multicentre, phase III trial investigated whether vorinostat as second-line or third-line therapy improved survival in patients with measurable advanced malignant pleural mesothelioma and disease progression after one or two previous systemic regimens. Vorinostat or matching placebo was given twice daily on days 1, 2, 3, 8, 9, 10, 15, 16, and 17 of a 21-day cycle. For 661 patients randomised to receive vorinostat (n=329) versus placebo (n=332), median OS was 30.7 weeks (95% CI 26.7-36.1) versus 27.1 weeks (95% CI 23.1-31.9) (HR 0.98, 95% CI 0.83-1.17; p=0.86).

Comment (GL): Here is an abundantly negative trial of a histone deacetylase inhibitor, which made it to phase III in an accelerated trajectory bypassing phase II. The clinical need in this setting remains high – patients who have progressed after standard first-line treatment with pemetrexed. The best next idea the authors could come up with is that histone deacetylation might be relevant to the 20% subset of mesothelioma patients with BAP-1 mutant lesions. The authors felt that having a 1:1 randomisation put people off enrolling in their trial, which was five years in the making. They looked wistfully at the experience of a competing trial with tremelimumab, which had a 2:1 randomisation, the advantage of “hype regarding immune checkpoint inhibitors”, and enrolled in just 18 months. 2:1 randomisation for enhanced recruitment is an interesting proposition because one still requires a minimum number of events in both arms, meaning that a 2:1 trial has to be 50% larger, and 50% more expensive – but would offer a big pay-off if it got an agent to market 3.5 years faster. But if shrinking the market to a BAP-1 targeted 20%, they will probably be back to 5 years’ recruitment. Drug development is not easy.


Abstract

Necitumumab plus pemetrexed and cisplatin as first-line therapy in patients with stage IV non-squamous non-small-cell lung cancer (INSPIRE)

Authors: Paz-Ares L et al.

Summary: In this international, multicentre, open-label, phase III study, 633 patients with an ECOG performance status of 0-2 and adequate organ function were randomly assigned to treatment with either cisplatin 75 mg/m² and pemetrexed 500 mg/m² on day 1 of a 3-week cycle for a maximum of six cycles alone (n=318) or with necitumumab 800mg on days 1 and 8 (n=315). No significant difference in OS between treatment groups was observed. The median OS was 11.3 months (95% CI 9.5-13.4) in the necitumumab plus pemetrexed and cisplatin group versus 11.5 months (10.1-13.1) in the pemetrexed and cisplatin group (HR 1.01 [95% CI 0.84-1.21]; p=0.96).

Comment (GL): I wanted to put this study in this month’s issue, because combining EGFR targeting with platinum chemotherapy did not work with the small molecule TKI gefitinib and indeed was arguably the cause of a decade-long delay in the whole field – gefitinib’s clinical resurrection only happening after the publication of Mok’s paper revealing the predictive power of EGFR mutation. Then in 2003, Pirkner et al published the FLEX study which found a small OS benefit (1.2 months) for the Bristol-Myers Squibb monoclonal antibody cetuximab targeting the extracellular EGFR domain (TKI’s are intracellular), in combination with cisplatin and vinorelbine. Cetuximab is a chimeric (“xi-type”) antibody, with potential for immune recognition. This study funded by Eli Lilly evaluated necitumumab, a human (“mu-type”) antibody, in combination with pemetrexed and cisplatin. It was hoped that the combination would have a lower marrow toxicity. It generated a set of superimposed survival curves. Moreover there was no hint of benefit proportional to level of EGFR expression. My hunch is that the benefit, such as it was, of cetuximab, may have been related to immune recognition – an advantage available to the chimeric ahead of the humanised agent.


Abstract

Independent commentary by Dr George Laking MD PhD FRACP

George is a Medical Oncologist at Auckland DHB, specialising in treatment of respiratory malignancy. He is an Otago graduate who trained in Wellington and at the Christie Hospital in Manchester. George’s MD studies were in tumour perfusion using PET scanning, and his PhD is on the economics of diagnosis. Outside the DHB George is also active as a member of PTAC (Pharmac’s Pharmacology and Therapeutics Advisory Committee), and the Smokefree Coalition. George’s whakapapa ties are to Te Whakatōheia in the Eastern Bay of Plenty, and he is the current Chair of Te Ohu Rata o Aotearoa (Te ORA, the Māori Medical Practitioners’ Association).