Lung Cancer Research Review™

Making Education Easy

Issue 6 – 2015

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Abbreviations used in this issue

EGFR = epidermal growth factor receptor
NSCLC = non-small cell lung cancer
OS = overall survival
PFS = progression-free survival
SABR = stereotactic ablative radiotherapy

Welcome to the sixth issue of Lung Cancer Research Review.

Highlights in this issue include an apparent survival benefit in lung cancer patients who quit smoking, improved quit rates with the use of low-nicotine content cigarettes, and a survival benefit with bevacizumab in patients with non-squamous NSCLC (BEYOND) and with nivolumab in advanced squamous (CheckMate 017) and non-squamous (CheckMate 057) NSCLC but not with gefitinib in EGFR-mutation-positive NSCLC (IMPRESS). Other highlights include worse survival with wedge and segmental resections compared with lobectomy for clinical stage IA NSCLC and radiotherapy as an option for treating small primary tumours in stage I NSCLC and being potentially advantageous for patients with shorter life expectancies.

We hope that you enjoy this issue of Lung Cancer Research Review and look forward to receiving your comment and feedback.

Kind regards,

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Tobacco cessation may improve lung cancer patient survival

Authors: Dobson-Amato KA et al.

Summary: This study used descriptive statistics and Cox proportional hazards models to assess whether tobacco cessation was associated with lung cancer survival among lung cancer patients at a single centre. Patients were screened with a standardised tobacco assessment at presentation and those who had used tobacco within the past 30 days were automatically referred to a telephone-based cessation service. Demographic, clinical information, and self-reported tobacco use at last contact were obtained via electronic medical records and the cancer centre's tumour registry for all lung cancer patients referred to the service over a 2-year period. Eighty percent of patients (250/313 patients referred to the cessation service) were successfully contacted and participated in ≥1 telephone-based cessation call; 40.8% (102/250) of persons contacted reported having quit at the last contact. After controlling for age, pack year history, sex, performance status, time between diagnosis and last contact, tumour histology, and clinical stage, a statistically significant increase in survival was associated with quitting versus continued tobacco use at last contact (HR = 1.79; 95% CI: 1.14-2.82) with a median 9-month improvement in OS.

Comment (GL): Any day is a good day to stop smoking. I suspect most who quit on diagnosis of cancer are just happy to leave their little pack of white-suited traitors behind. In this paper, Amato and colleagues suggest there may be a detectable survival benefit. The key reference is the US Surgeon General's report from 2014, "The Health Consequences of Smoking—50 Years of Progress", Chapter 6: Cancer, pp 284–291 *Adverse Health Outcomes in Cancer Patients and Survivors*. In the case of lung cancer, one question is whether people live long enough to get a benefit from quitting, i.e., futility. Unsurprisingly, no-one is proposing a randomised trial. The authors rightly note the risk of *survival bias* within the longitudinal cohort study design. Because patients with lower risk cancers live longer, they have more time to quit – in other words, quitting behaviour might just be a marker of lower risk cancer. But the authors tested for this, and found no association between time and quit events. That would fit with the observation that most smokers with cancer who quit, do so at the time of diagnosis.

Reference: J Thorac Oncol. 2015;10(7):1014–9
Abstract

Independent commentary by Dr George Laking MD PhD FRACP

George is a Medical Oncologist at Auckland DHB, specialising in treatment of respiratory malignancy. Outside the DHB George is also active as a member of PTAC (Pharmac's Pharmacology and Therapeutics Advisory Committee), and the Smokefree Coalition. **FOR FULL BIO CLICK HERE.**

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.
FOR FULL BIO CLICK HERE.

BEYOND: A randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/ paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer.

Authors: Zhou C et al.

Summary: This was a phase III trial undertaken to confirm in a Chinese patient population the efficacy seen with first-line bevacizumab plus platinum doublet chemotherapy in global studies. Adults (n=276) with locally advanced, metastatic, or recurrent advanced non-squamous NSCLC were randomised to receive IV carboplatin (AUC, 6) and paclitaxel (175 mg/m^2) [CP] on day 1 of each 3-week cycle, for ≤6 cycles, plus IV placebo (PI+CP; n=138) or bevacizumab (B+CP; n=138) 15 mg/kg, on day 1 of each cycle, until progression, unacceptable toxicity, or death. PFS was significantly prolonged with B+CP versus PI+CP (median, 9.2 v 6.5 months, respectively; HR, 0.40; 95% CI, 0.29-0.54; p<0.001). OS was also significantly prolonged with B+CP versus PI+CP (median, 24.3 v 17.7 months, respectively; HR, 0.68; 95% CI, 0.50-0.93; p=0.0154). Safety was comparable with previous studies of B+CP in NSCLC.

Comment (GL): This is a small phase III study, but it is notable for its design and conclusions. Firstly, whereas most studies of infusional anti-cancer treatment in Western populations are open label, in this Chinese population, the investigators achieved double-blinding and placebo-control. Secondly, whereas the global reference study reported just a 2 month increment in OS (12.3 months with bevacizumab, 10.3 months without; Sandler et al.: N Engl J Med. 2006;355:2542-2550), Zhou et al. report 6.6 extra months (24.3 vs 17.7 months). How are these differences explained? Contributory factors would include the difference in populations (North American versus East Asian, 43% vs 19% ≥65 years age); a decade's separation in time (better prospects for EGFR-targeted treatments); and the play of chance. Bevacizumab remains a registered but not funded treatment in NZ for this indication. The price hurdle remains significant.

Reference: J Clin Oncol. 2015;33(19):2197–204
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial

Authors: Soria JC et al.

Summary: In this multicentre phase III trial, 265 adult patients with chemotherapy-naive, stage IIIB–IV EGFR-mutation-positive advanced NSCLC with previous disease control with first-line gefitinib and recent disease progression were randomised to receive gefitinib 250mg (n=133) or placebo (n=132) once daily. All patients also received the platinum-based doublet chemotherapy cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 on the first day of each cycle. After completion of a maximum of six chemotherapy cycles, patients continued their randomly assigned treatment until disease progression or another discontinuation criterion was met. In the gefitinib group, 98 (74%) patients had disease progression compared with 107 (81%) in the placebo group (HR 0.86, 95% CI 0.65–1.13; p=0.27; median PFS 5.4 months in both groups [95% CI 4.5–5.7 in the gefitinib group and 4.6–5.5 in the placebo group]). In the gefitinib group, 37/132 patients (28%) reported serious adverse events compared with 28/132 patients (21%) in the placebo group.

Comment (GL): Just because one part of a cancer escapes EGFR tyrosine kinase inhibition (TKI) does not mean the whole cancer does. Moreover, we know that for EGFR TKI-sensitive tumours, targeted treatment is superior to cytotoxics (Mok et al., N Engl J Med 2009; 361:947-957). That is part of the background to the hypothesis for this placebo-controlled randomised trial. The finding of no benefit is a valuable negative. How to relate this to data from other illnesses in which there has been support for continuing targeted treatments after progression? The authors point out the heterogeneity amongst patients about which more is still to be learnt (oligometastatic progression, slow progression, specific genetic mechanisms of resistance). Moreover, small molecule targeted treatments such as gefitinib lack the immunogenic dimension of monoclonal antibodies.

Reference: Lancet Oncol. 2015;16(8):990–8
Abstract

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Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Authors: Chang JY et al.

Summary: The aim of this meta-analysis was to assess OS for SABR versus surgery by pooling data from two independent, randomised, phase III trials of SABR in patients with operable stage I NSCLC (STARS and ROSEL) that closed early due to slow accrual. Data from a total of 58 patients randomly assigned to treatment (31 to SABR and 27 to lobectomy) was analysed. Median follow-up was 40.2 months (IQR 23.0–47.3) for the SABR group and 35.4 months (18.9–40.7) for the surgery group. Six patients in the surgery group died compared with one patient in the SABR group. Estimated OS at 3 years was 95% (95% CI 85–100) in the SABR group compared with 79% (64–97) in the surgery group (HR 0.14; 95% CI 0.017–1.190, log-rank p=0.037). Three (10%) patients in the SABR group had grade 3 treatment-related adverse events and no patients given SABR had grade 4 events or treatment-related death.

Reference: Lancet Oncol. 2015;16(6):630–7
Abstract

Comparative effectiveness of surgery and radiosurgery for stage I non-small cell lung cancer

Authors: Yu JB et al.

Summary: This study used the Surveillance, Epidemiology, and End Results-–Medicare linked (SEER) database to identify patients who were aged ≥67 years and underwent SBRT or surgery for stage I NSCLC from 2007 to 2009. A total of 367 SBRT patients and 711 surgery patients were identified and matched. Acute toxicity (0-1 month) was lower from SBRT versus surgery (7.9% vs 54.9%, p<0.001). At 24 months after treatment, there was no difference between treatment groups (69.7% vs 73.9%, p=0.31). The incidence rate ratio (IRR) for toxicity from SBRT versus surgery was 0.74 (95% CI, 0.64-0.87). Overall mortality was lower with SBRT versus surgery at 3 months (2.2% vs 6.1%, p=0.005) but by 24 months overall mortality was higher with SBRT (40.1% vs 22.3%, p<0.001). For patients with short life expectancies (<5 years), there was no difference in lung cancer mortality (IRR, 1.01; 95% CI, 0.40-2.56); however, patients with long life expectancies (≥5 years) had greater overall mortality (IRR, 1.49; 95% CI, 1.11-2.01) as well as a trend toward greater lung cancer mortality (IRR, 1.63; 95% CI, 0.95-2.79) with SBRT versus surgery.

Reference: Cancer. 2015;121(14):2341–9
Abstract

Comment (GL): Two skirmishes in the "SABR wars" – the first a meta-analysis of two randomised trials, the second a comparative-effectiveness study using the SEER database. It is established that SABR (aka SBRT) is an effective, well-tolerated treatment for small primary tumours. Neither SABR nor surgery can cure distant metastatic disease, the principal cause of death in this illness. What SABR also cannot do is clear nodal basins, potentially the source of residual cancer that could in its own right prove fatal. So a question for proponents of SABR is, when is it okay to not treat a nodal basin? The SEER data show that SABR patients with Stage I NSCLC (n=383) have been older than surgical patients (n=3852), with a greater burden of disability and co-morbidity. After propensity matching, the data suggest SABR may be advantageous for patients whose life expectancy is not >2 years. Initially SABR has lower acute complications and mortality. By the two year mark it shows higher mortality, mainly from non-cancer causes. By the five year mark SABR also has higher lung cancer specific mortality. The pooled RCT data are a much smaller population, n=58, reflecting the difficulty recruiting to these trials. This study reported 3-year OS of 95% for SABR and 79% for surgery, statistically significant at p=0.037, HR 0.14. Imagine the positive spin such figures would achieve were this a new drug! Despite this, the authors conclude scientific equipoise – the analysis cannot be taken at face value, in light of small sample size, short follow-up, and potential selection bias. SABR poses a classic problem for randomised trials. The question is much more about the matching of individual patients to treatments than about which of two treatments works best in a homogeneous population. So far the SEER data have proved the most enlightening.

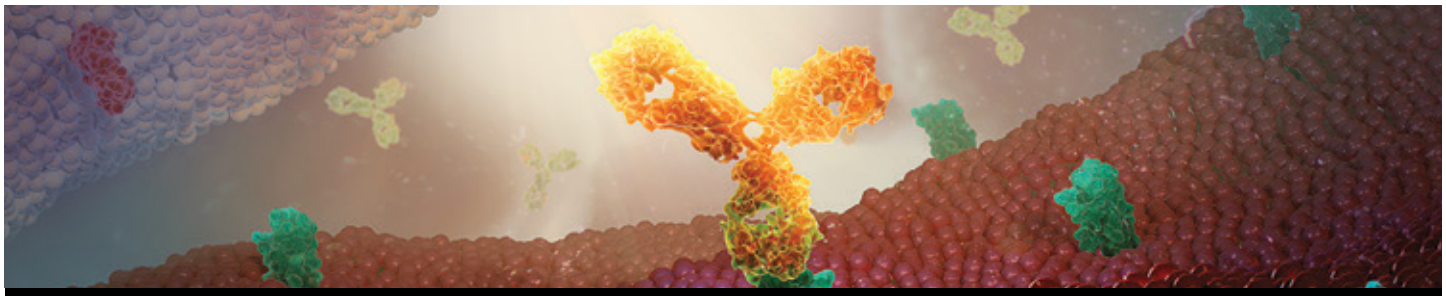
Randomized trial of reduced-nicotine standards for cigarettes

Authors: Donny EC et al.

Summary: In this randomised, double-blind, parallel-group clinical trial, adults (n=840) who were smoking ≥5 cigarettes per day, and had no current interest in quitting smoking, were randomly assigned to smoke for 6 weeks either their usual brand of cigarettes or one of six types of investigational cigarettes that had nicotine content ranging from 15.8mg per gram of tobacco (typical of commercial brands) to 0.4mg per gram. In the 780 participants who completed the study, the average number of cigarettes smoked per day was lower for participants randomised to cigarettes containing 2.4, 1.3, or 0.4mg of nicotine per gram of tobacco (16.5, 16.3, and 14.9 cigarettes, respectively) than for participants randomised to their usual brand or to cigarettes containing 15.8mg per gram (22.2 and 21.3 cigarettes, respectively; p<0.001). Participants assigned to cigarettes with 5.2mg per gram smoked an average of 20.8 cigarettes per day, which did not differ significantly from the average number among those who smoked control cigarettes. Adverse events were generally mild and similar across the groups.

Comment (CL): Amongst the many potential tactics to try to reduce smoking rates, I must admit I had not been aware of the idea described in this paper and accompanying editorial, which starts with the quote "People smoke for the nicotine but die from the tar", and explores the philosophical question of separating the two (and accepting nicotine dependence to a degree). It also points out that previous "light" cigarettes in the 1970-80s included design features that allowed smokers to increase the amount of nicotine inhaled per cigarette, such as having "ventilation holes" that could be occluded! The result of this study is very interesting, and possibly counter-intuitive – that reducing the nicotine content of cigarettes actually reduced the number smoked and improved quit rates, at least in the short term of this study – rather than smokers using more of them to try to get their "hit". Longer term studies are needed though, in particular to ensure that smokers do not compensate by using other forms of nicotine – especially in this era of "electronic cigarettes" – or worse "black market" tobacco. Perhaps the greatest appeal of low nicotine cigarettes would be their lesser ability to "hook" the young. Of course, a compulsory national strategy of such cigarettes would require legislation and the co-operation of the tobacco industry itself – with the current plain packaging fight hardly encouraging.

Reference: N Engl J Med. 2015;373(14):1340–9
Abstract



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Survival after sublobar resection versus lobectomy for clinical stage IA lung cancer: an analysis from the National Cancer Data Base

Authors: Khullar OV et al.

Summary: This retrospective cohort study utilized the National Cancer Data Base to assess possible oncologic equivalence of sublobar resection with lobectomy for early-stage NSCLC. A total of 13,606 patients undergoing lobectomy, segmentectomy, or wedge resection for pre-operative clinical T1A N0 NSCLC were identified. Both segmentectomy and wedge resection were associated with significantly worse OS versus lobectomy (HR: 1.70 and 1.45, respectively; both p<0.001), with no difference in 30-day mortality. Median OS for lobectomy, segmentectomy, and wedge resection were 100, 74, and 68 months, respectively (p<0.001). Sublobar resection was associated with increased likelihood of positive surgical margins, lower likelihood of having >3 lymph nodes examined, and significantly lower rates of nodal upstaging.

Comment (CL): Studies of this important question have proved very difficult, and are yet to yield conclusive results. This study shares the theoretical weaknesses of previous retrospective observational studies – it is hard to escape the fact that patients are usually selected for limited surgical resection rather than lobectomy for a reason, and that reason is usually impaired physiological pulmonary reserve, and/or comorbidities. For this reason, I wonder whether OS is actually the best measure – recurrence-free survival might have been more illuminating. However, this study describes a very large, heterogeneous and well-defined cohort, in addition to using "propensity matching" statistical methodology to try to adjust for the criticisms I have outlined. There is a suggestion that limited resection in "better" centres – ensuring adequate surgical margins and regional nodal clearance – may negate some of the survival differences. Also, there is no 30-day mortality advantage to more limited resection – so to my mind this is an argument that actually SABR may be the better treatment – avoiding surgical morbidity and mortality whilst accepting a (perhaps) inferior lung cancer specific survival. Such papers also provide interest in the small print – the statistically superior survival for patients with non-government insurance and on higher incomes being sobering.

Reference: J Thorac Oncol. 2015;10(11):1625–1633
Abstract

Evaluating cryoablation of metastatic lung tumors in patients—safety and efficacy: The ECLIPSE trial—interim analysis at 1 Year

Authors: de Baere T et al.

Summary: This Health Insurance Portability and Accountability Act (HIPAA)-compliant, multicentre, single-arm study included 40 patients with 60 lung metastases treated during 48 cryoablation sessions, with ≥12 months of follow-up currently available. It assessed the feasibility, safety, and local tumour control of cryoablation for treatment of pulmonary metastases. The most common primary cancers were colon (40%), kidney (23%), and sarcomas (8%). Mean size of metastases was 1.4±0.7cm (0.3-3.4), and metastases were bilateral in 20% of patients. Local tumour control rates were 56/58 (96.6%) and 49/52 (94.2%) at 6 and 12 months, respectively. Patient's quality of life was unchanged over the follow-up period. One-year OS rate was 97.5%. The rate of pneumothorax requiring chest tube insertion was 18.8%. There were three grade 3 procedural complications during the immediate follow-up period.

Comment (CL): Management of oligometastatic disease in the chest from non-lung cancer tumours is an interesting topic, and one suspects that discussion of it often bypasses Thoracic Multidisciplinary Meetings and thus those who read this review. Pulmonary metastatectomy is often advocated and performed particularly in colorectal cancer, and the main aim seems to be to improve disease-free survival, but as the eminent surgeon Tom Treasure of University College London in particular has opined in several articles, the actual evidence base for this practice is very weak. It is understandable, therefore, that less "invasive" (and perhaps cheaper) techniques are evolving to try to address this issue. This prospective evaluation of another percutaneous technique (following on from RFA, microwave, etc.) is interesting and clearly has merit, as it is being conducted in a rigorous fashion, although it is not entirely clear why an "early" report has been published rather than waiting for the study to actually be completed, and whether further patients are to be recruited. There is always a fundamental problem when performing a non-randomised study of a concept with a limited evidence base and where the existing "gold standard" is itself somewhat unproven; indeed, the authors agree in their concluding paragraph that larger RCTs will be required.

Reference: J Thorac Oncol. 2015;10: 1468–1474
Abstract

Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer

Authors: Brahmer J et al.

Summary: This randomised, open-label, phase III study evaluated the efficacy and safety of nivolumab versus docetaxel in patients with advanced, previously-treated squamous-cell NSCLC. A total of 272 patients were randomly assigned to receive nivolumab 3 mg/kg every 2 weeks or docetaxel 75 mg/m^2 every 3 weeks. The median OS was 9.2 months (95% CI, 7.3-13.3) with nivolumab versus 6.0 months (95% CI, 5.1-7.3) with docetaxel. The risk of death was 41% lower with nivolumab than with docetaxel (HR, 0.59; 95% CI, 0.44-0.79; p<0.001). At 1 year, the OS rate was 42% (95% CI, 34-50) with nivolumab versus 24% (95% CI, 17-31) with docetaxel. The response rate was 20% with nivolumab versus 9% with docetaxel (p=0.008). Expression of the PD-1 ligand was neither prognostic nor predictive of benefit. Treatment-related adverse events of grade 3/4 were reported in 7% of the patients in the nivolumab group versus 55% of patients in the docetaxel group.

Reference: N Engl J Med. 2015;373:123–135
Abstract

Nivolumab versus docetaxel in advanced nonsquamous non-Small-Cell Lung Cancer

Authors: Borghaei H et al.

Summary: This randomised, open-label, phase III study assigned chemotherapy-experienced patients with non-squamous NSCLC to receive nivolumab 3 mg/kg every 2 weeks or docetaxel 75 mg/m^2 every 3 weeks. Median OS was 12.2 months (95% CI, 9.7-15.0) among 292 patients in the nivolumab group versus 9.4 months (95% CI, 8.1 -10.7) among 290 patients in the docetaxel group (HR for death, 0.73; 96% CI, 0.59-0.89; p=0.002). The OS rate at 1 year was 51% (95% CI, 45-56) with nivolumab versus 39% (95% CI, 33-45) with docetaxel. With additional follow-up, the 18-month OS rate was 39% (95% CI, 34-45) with nivolumab versus 23% (95% CI, 19-28) with docetaxel. The response rate was 19% with nivolumab versus 12% with docetaxel (p=0.02). Nivolumab was associated with even greater efficacy than docetaxel across all end points in sub-groups defined according to pre-specified levels of tumour-membrane expression (≥1%, ≥5%, and ≥10%) of the PD-1 ligand. Treatment-related adverse events of grade 3/4 were reported in 10% of the patients in the nivolumab group versus 54% of those in the docetaxel group.

Reference: N Engl J Med. 2015;373(17):1627–39
Abstract

Comment (CL): As a respiratory physician, I am aware that immuno-oncology is an area that is exciting and rapidly advancing but with which I am yet to get to grips. Much of my exposure so far has been gained through the lay press, with excited articles outlining the latest wonder drugs as "game changers", particularly striking in the area of metastatic melanoma. Sad personal stories on the internet and *Sunday* programme have followed.

On the face of it, therefore, the results of these two randomised open-label studies initially seem a disappointment. Nivolumab, compared with the existing "standard" therapy of docetaxel post-progression after first-line chemotherapy in lung cancer, provides a clear but relatively small improvement in OS of around 3 months. This is a little larger than the magnitude of benefit in many previous chemotherapy comparison trials, but less than the improved survival now expected with targeted therapies (and, dare I return to a favourite hobby horse, similar to the benefit of early palliative care seen in a previous trial in the same journal). These studies seem to have avoided the issue of patients exiting and "crossing over" to the new drug on progression, which one suspects has blunted the survival benefit seen in some targeted therapy studies. Yet scratching below the surface there are many positives. Nivolumab was clearly better tolerated than docetaxel. Benefits may be better in current or ex-smokers and patients with squamous cell carcinomas, who have to date largely missed out on the targeted therapies – in fact, most patients shared in the improved survival, and those with mutations did less well. The PD-L1 expression appears predictive of response in non-squamous patients, although I understand that testing for this adequately is fraught with difficulty. Another point of interest is how response to these agents is harder to gauge than with previous therapies, as reactions somewhat analogous to "paradox" in successful TB treatment may initially occur.

These agents are (presumably) very expensive. It is clear, though, that a small number of patients get a large and durable benefit. For the NZ context, I hope that further studies looking at predictors of response occur, so that these drugs may be targeted towards those likely to derive such benefits.