Respiratory RESEARCH REVIEW™

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Issue 193 – 2022

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Abbreviations used in this issue

ctDNA = circulating tumour DNA
HR = hazard ratio
LDH = lactate dehydrogenase
NSCLC = non-small-cell lung cancer
OR = odds ratio
$PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤2.5µm

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Welcome to the first Respiratory Research Review of 2022 with the topic of lung cancer.

Lung cancer continues to be the leading cause of cancer death, making up 25% of all cancer deaths. More people die of lung cancer than of colon, breast and prostate cancer combined. About 6% of men and women will be diagnosed with lung cancer during their life time, with the average age of 70 years. A French group looking at 1329 patients aged less than 50 years who had undergone resection for primary lung cancer found that almost half reported cannabis combined with tobacco smoking. Many had significant emphysema and more surgical complication: their title, 'Cannabis use and lung cancer: time to stop overlooking the problem'.

Despite advancing therapies like immunotherapy, the 5-year survival for lung cancer is only about 18%, much lower than for breast cancer (90%), colorectal cancer (65%) and prostate cancer (99%). Patients with lung cancer, like all cancer patients, are overwhelmed with anxiety, depression and fear. Lung cancer patients have the additional burden of living with the stigma of it being self-induced. This stigma is a possible dark side of Smokefree campaigns. Two colleagues report in their editorial 'Lung cancer – why the stigma? And what can be done?' that half of all lung cancer patients report experiencing stigma from healthcare providers. Colleagues from New York developed an empathy communication skills training module particularly tailored for those providing cancer care.

Our colleagues from the Peter MacCallum Cancer Centre in Melbourne, together with the Massachusetts General Hospital in Boston, have published an authoritative Lung Cancer seminar in The Lancet. They reviewed the evidence for screening, the histological classification and the most common ontogenetic mutations. Alesha Thai and colleagues have generated a table of outcomes comparing the use of targeted and immune checkpoint inhibitors to treat lung cancer. The table comparing historical platinum-based approaches with targeted therapies, and immune therapy in metastatic NSCLC (non-small-cell lung cancer) shows encouraging impacts on survival rates. Actually, immunotherapy for NSCLC is becoming common enough that some Canadian colleagues, including a former medical student of mine, wrote a review, matching the immunotherapeutic approach to the patient characteristics, like patients with poor performance status, patients on steroids, patients with pre-existing autoimmune conditions, and rechallenging with immune checkpoint inhibitors after side effects.

Probably more relevant for hospital-based doctors is the European Respiratory Society's statement on thoracic ultrasound. It naturally covers its efficacy in the management of malignant pleural effusions. It is rather comprehensive and recalls its use in the assessment of the chest wall, pneumothorax, interstitial lung disease, lung consolidation and the diaphragm. The statement comments on training. Training in thoracic ultrasound does not quite compare, as yet, with the evidence published a systematic literature review on the 'Methodological quality of guideline for training or competency processes for basic point-of-care echocardiography in critical care'. Closer to our own field is the review: 'Avoid the trap – nonexpanding lung', which differentiated between lung entrapment and trapped lung, with diagnostic algorithms and suggestions for management/treatment.

Thank you for your continued interest in Research Review publications. If you wish to start the year off with a light discussion, you may wish to take the quiz prepared by our American colleagues to estimate the treatment effect of anticoagulation in atrial fibrillation, management of mild hypertension, benefit of osteoporosis prophylaxis and treatment of hypercholesterinaemia. The free five-item questionnaire and detailed answers are in the appendix, the performance of our American colleagues can also be found in this article on the 'Clinician conceptualization of the benefits of treatments for individual patients'.

With best wishes for a safe, successful and solid year 2022.

Kind regards,

Professor Lutz Beckert
lutzbeckert@researchreview.co.nz

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Independent commentary by Professor Lutz Beckert

Professor Lutz Beckert is the Associate Dean Medical Education with the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or with the view of future collaborations.

Development and validation of a deep learning algorithm detecting 10 common abnormalities on chest radiographs

Authors: Nam JG et al.

Summary: These researchers developed DLAD-10, a deep learning algorithm for detecting ten common abnormalities on chest x-ray, using data from 146,717 training radiographs obtained from 108,053 patients. External validation of DLAD-10 revealed area under the receiver operating characteristic curve values of 0.895–1.00 in a same-day CT-confirmed (normal:abnormal 53:147) dataset and 0.913–0.997 in an open-source (normal:abnormal 339:334) dataset when compared with three radiologists. Compared with radiologists (pooled), DLAD-10 correctly classified significantly more critical abnormalities (95.0% vs. 84.4% [p=0.01]). Simulated reading tests for patients presenting to an ED revealed that when aided by DLAD-10, pooled readers detected significantly more abnormalities, both critical (70.8% vs. 29.2% [p=0.006]) and urgent (82.7% vs. 78.2% [p=0.04]). DLAD-10 assistance also led to reductions in mean time-to-report for critical and urgent radiographs (640.5 vs. 3371.0 sec and 1840.3 vs. 2127.1 sec, respectively [p<0.01]) and mean interpretation time (20.5 vs. 23.5 sec [p<0.001]).

Comment: Deep learning is a branch of artificial intelligence that is particularly good at identifying patterns in and mapping chest abnormalities according to categories/diagnoses. These Korean researchers trained an algorithm on almost 150,000 radiographs to detect diagnoses like pneumothorax, mediastinal widening, pneumoperitoneum, nodule/mass, consolidation, pleural effusion, linear atelectasis, fibrosis, calcification and cardiomegaly. In a routine setting, the deep learning algorithm outperformed radiologists. However, in the emergency setting, the radiologists picked up more critical diagnoses. In their editorial, Lucio Calandriello and Simon Walsh give us the **bottom line: deep learning can provide decision support for radiologists and are almost ready for clinical practice.**

Reference: Eur Respir J 2021;57:2003061
Abstract

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Sex and survival after surgery for lung cancer

Authors: Sachs E et al.

Summary: Prognoses were compared between women versus men who had undergone pulmonary resection for lung cancer in this Swedish population-based observational cohort study (n=6356). Compared with men, women had a lower mortality risk following pulmonary resection (HR 0.73 [95% CI 0.67, 0.79]), with respective absolute 1-, 5- and 10-year survival differences of 3.0%, 10% and 12% and a restricted mean survival time difference at 10 years of 0.84 years; consistent findings were evident across several subgroups.

Comment: Currently, the incidence of lung cancer is falling twice as fast in men than in women, reflecting the delay in tobacco uptake and cessation by women (Lancet 2021;398:535–54). This retrospective study based on more than 6000 lung cancer patients in Sweden provides some good news for women. Women have a better survival rate after resection of a lung cancer, even when corrected for histological type, stage, comorbidities, lifestyle factors, socioeconomic status and age. Their survival benefit is 3% at 1 year and 12% at 10 years. **Bottom line: while lung cancer diagnoses are still increasing, resection of early-stage cancer is successful in women.**

Reference: Chest 2021;159:2029–39
Abstract

Hā Ora: secondary care barriers and enablers to early diagnosis of lung cancer for Māori communities

Authors: Kidd J et al.

Summary: Improved communication and understanding of cultural needs is needed within healthcare services involved in the secondary care of lung cancer in Māori communities. A kaupapa Māori approach was used to carry out nine community hui and nine primary healthcare provider hui in five rural localities in the Midland region of NZ. Barriers and enablers in specialist services and treatment related to access to care, engagement with specialists, communication with specialist services and cultural values and respect. Barriers and enablers in the whānau journey related to agency and the impact on whānau. Findings also highlighted the active efforts made by whānau to foster health literacy in future generations.

Comment: Previously, we cited some of Sue Crengle's work that lung cancer mortality for Māori is almost three times greater than for non-Māori (Respiratory Research Review issue 181). The Te Huataki Waiora School of Health research group provides insights from the midland region, with researchers using the kaupapa Māori research approach. They ran nine hui/focus groups of community members and primary care providers. The community groups included cancer patients and whānau. Themes identified included access to care, engagement with specialists, communication with specialists, cultural value and respect, and the whānau journey. **Bottom line: the urgency to understand cultural needs and to improve communication are key findings, as are Māori resilience and whānau advocacy.**

Reference: BMC Cancer 2021;21:121
Abstract

Chronic effects of high fine particulate matter exposure on lung cancer in China

Authors: Li J et al.

Summary: Response patterns of lung cancer associated with high exposure to $PM_{2.5}$ were reported for a cohort of 118,551 Chinese individuals followed from 1992 to 2015. This cohort experienced 844 incident lung cancers over 915,053 person-years of follow-up, causing 701 subsequent deaths. Nonlinear exposure-response curves were seen for lung cancer associated with $PM_{2.5}$ exposure, with steeper slopes occurring at higher concentrations. Compared with participants exposed to the lowest $PM_{2.5}$ quintile, the lung cancer risk was increased across the second to fifth quintiles (respective adjusted HRs 1.44 [95% CI 1.10, 1.88], 1.49 [1.12, 1.99], 2.08 [1.42, 3.04] and 2.45 [1.83, 3.29]), as was the likelihood of lung cancer-associated mortality (1.83 [1.33, 2.50], 1.80 [1.29, 2.53], 2.50 [1.62, 3.86] and 2.95 [2.09, 4.17]).

Comment: This time last year we witnessed the Australian bush fires. I recall the limited evidence of their adverse effects on cardiac disease, airways disease and lung cancer. This group of Chinese researchers used participants from cardiovascular epidemiology registries and correlated clinical outcomes with $PM_{2.5}$. $PM_{2.5}$ pollution data were obtained from US satellite images and ground-based monitors. More than 100,000 people were followed and 844 developed lung cancer. **Bottom line: air pollution with fine particles is a risk factor for developing lung cancer. Large gains can be made with a small improvement in air quality.**

Reference: Am J Respir Crit Care Med 2020;202:1551–9
Abstract

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Provision of smoking cessation resources in the context of in-person shared decision-making for lung cancer screening

Authors: Shen J et al.

Summary: This was a US-based retrospective study of 423 current smokers (70% male) participating in initial lung cancer screening shared decision-making. Of the study participants, documentation consistent with shared decision-making was evident for only 26%, only 39% had received ≥1 smoking cessation resource, and only 5% received both counselling referrals and medication. A multivariate analysis revealed a Charlson Comorbidity Index score of ≥2 was associated with a significantly lower likelihood that any smoking cessation resource had been provided (OR 0.53 [95% CI 0.31, 0.81]), as was ordering by a provider other than the participant's primary care provider or specialist (0.55 [0.32, 0.96]).

Comment: In 2021, articles on lung cancer screening were amongst the most downloaded articles (JAMA 2021;325:962–70) and we may engage in a focussed lung cancer screening trial in NZ in 2022. These US-based researchers remind us that any contact with the health service is an opportunity for smoking cessation. However, in their survey of 400 men participating in lung cancer screening in Seattle, only 17% were offered a prescription for tobacco addiction and only 5% received counselling and medication referral. Steven Zeliadt's title of his accompanying editorial gives us the **bottom line: smoking cessation resources can and should be integrated into lung cancer screening.**

Reference: Chest 2021;160:765–75
Abstract

Lung cancer probability and clinical outcomes of baseline and new subsolid nodules detected on low-dose CT screening

Authors: Kim YW et al.

Summary: These researchers reported on the characteristics of subsolid nodules detected on low-dose CT in 22,631 never-smoker and 27,501 ever-smoker South Korean adults. There were 5116 pure ground-glass opacity nodules and 1609 part-solid nodules detected in 4545 participants, with a higher overall subsolid nodule incidence in never- versus ever-smokers (10.7% vs. 7.7% [p<0.001]). Among the subsolid nodules with follow-up CT scans (n=4918), 30.0% of baseline subsolid nodules and 78.9% of new subsolid nodules resolved spontaneously. Among biopsied subsolid nodules (n=293), 77.5% were lung cancer (all adenocarcinomas except one). There was no significant difference between baseline and new cancerous subsolid nodules for pathological invasiveness or initial stage. New subsolid nodule detection at follow-up screening was significantly associated with lower likelihoods of lung cancer (OR 0.26 [95% CI 0.14, 0.49]) and overall growth (0.39 [0.26, 0.59]), and a greater likelihood of resolution (6.30 [5.09, 7.81]).

Comment: One of the unsettling events during nodule surveillance of patients is the occurrence of new nodules on the CT scan while monitoring old nodules. This Korean study follows more than 50,000 subjects who underwent CT screening to assess the incidence, characteristics and nodules occurring in never-smokers during lung cancer screening. Nodules occurred during the screening in 10% of never-smokers, almost 80% resolved and only 1.1% turned out to be ultimately malignant. **Bottom line: at least in an Asian population, new nodules have a low probability of lung cancer, and may need less aggressive follow-up.**

Reference: Thorax 2021;76:980–8
Abstract

Usefulness of circulating tumor DNA in identifying somatic mutations and tracking tumor evolution in patients with non-small cell lung cancer

Authors: Roosan MR et al.

Summary: The usefulness of analysing ctDNA versus solid tumour biopsies was explored in a retrospective evaluation of 370 adults with NSCLC. Among 473 ctDNA samples analysed, 1688 somatic mutations were detected, with 177 of the samples showing ≥1 actionable mutation for currently available US FDA-approved NSCLC therapies. There was co-occurrence of *MET* and *CDK6* amplifications with *BRAF* amplifications (false discovery rate, <0.01), and gene-level mutations were mutually exclusive in *KRAS* and *EGFR* (false discovery rate, 0.0009). An association between low cumulative percentage ctDNA levels and longer PFS was identified (HR 0.56 [95% CI 0.37, 0.85]). Patients with a *BRAF*, *PIK3CA* or *KRAS* mutation had significantly shorter OS (respective HRs for death, 2.35 [95% CI 1.24, 4.6], 2.77 [1.56, 4.9] and 2.32 [1.30, 4.1]). There was gene-level concordance of 93.8%, whereas a positive concordance rate of 41.6% was seen. ctDNA analyses revealed more targetable gene mutations than tissue biopsy samples. Repeated ctDNA samples revealed treatment response and tumour evolution over time.

Comment: NSCLC accounts for 85% of all lung cancer cases and is increasingly treated with targeted therapies (JCO Oncol Pract 2021;17:465–71). This American research group is challenging the gold-standard role of a tissue biopsy. Tissue biopsies are costly, painful and risky, and they are difficult to repeat. We have previously reviewed (Respiratory Research Review issue 120) the role of cell-free DNA (also known as 'liquid biopsy') in estimating the cancer burden in lung cancer. These researchers used ctDNA from 370 patients with lung cancer and compared the outcomes with results from tissue biopsies. **Bottom line: ctDNA may offer additional opportunities to identify targetable mutations beyond tissue biopsy samples.**

Reference: Chest 2021;160:1095–107
Abstract

Breast and lung effusion survival score models: improving survival prediction in patients with malignant pleural effusion and metastasis

Authors: Molina S et al.

Summary: The ability of a continuous risk-prediction model to predict survival of patients with malignant pleural effusions and known metastatic disease was explored in a retrospective cohort of patients who underwent thoracentesis at a single centre during 2014–2017. Discrete (LENT-D) and continuous (LENT-C) models were generated using LENT variables, for which predictors' performances were assessed. The model was developed using data from a cohort of 562 patients and validated in a cohort of 727 patients. Significant interactions were seen between cancer type and neutrophil-to-lymphocyte ratio (p<0.0001), pleural fluid LDH level (p=0.029) and bilateral effusion (p=0.002). Disease-specific models for lung, breast and haematological malignancies had respective C-statistic values of 0.72, 0.72 and 0.62, and the combined model's C-statistic value was 0.67. In contrast, both LENT-D and LENT-C underperformed (respective C-statistic values, 0.60 and 0.65).

Comment: In 2005, we reported on the LENT score to estimate the survival of patients with malignant pleural effusions (Respiratory Research Review issue 108). The simple LENT score utilises LDH level, ECOG (Eastern Cooperative Oncology Group) status, blood neutrophil-to-lymphocyte ratio and tumour type to predict survival. These Mexican and US authors used data from 500 patients to design, and data from 700 patients to validate BLESS (Breast and Lung Effusion Survival Score). As the accompanying editorial points out, this is the first tumour-specific survival score. **Bottom line: the BLESS score provides more accurate survival estimates for breast and lung cancer patients with malignant pleural effusions.**

Reference: Chest 2021;160:1075–94
Abstract

Role of thoracic ultrasonography in pleurodesis pathways for malignant pleural effusions (SIMPLE)

Authors: Psallidas I et al.

Summary: Adults with malignant pleural effusion requiring talc pleurodesis were randomised to thoracic ultrasonography-guided care (n=159) or standard care (n=154) in this open-label trial. Compared with standard care, thoracic ultrasonography-guided care was associated with a significantly shorter median length of hospital stay in the intent-to-treat population (2 vs. 3 days [p<0.0001]) and was noninferior for pleurodesis failure at 3 months in the per-protocol population (29.7% vs. 31.2%). The intervention group also had a shorter mean time to chest tube removal (2.4 vs. 3.1 days [p=0.0057]) and there was no significant between-group difference for all-cause mortality, symptom scores or quality of life scores, except for a lower EQ-5D visual analogue scale score at 3 months in the standard care group. Thoracic ultrasonography-guided care was cost effective when compared with standard care.

Comment: About 15% of patients with lung cancer develop a malignant pleural effusion, and about 80% require a therapeutic intervention. The success rate of pleurodesis is between 50% and 80%, and current guidelines suggest that a chest drain can be removed following talc slurry if it drains less then 500mL in 24 hours. These UK authors randomised about 300 patients to standard treatment or with thoracic ultrasound-guided care. Gary Lee wrote the most learned editorial, appreciating the effort of providing an evidence base for talc pleurodesis and pointing out shortcomings. **Bottom line: ultrasound-guided care reduced the hospital stay without reducing the success rate.**

Reference: Lancet Respir Med; Published online Oct 8, 2021
Abstract

Indigenous perspectives on breaking bad news: ethical considerations for healthcare providers

Authors: Cassim S et al.

Summary: The experiences of Māori patients with lung cancer and their whānau in receiving bad news were collected via 23 semistructured interviews and nine focus groups in four districts in the Midland region of NZ. Best practice included understanding the centrality of the healthcare provider-patient relationship and whānau ties in the healthcare journey, as well as providing patients with the full range of viable treatment options, including hope, clear advice and guidance. The study findings hold implications for providing culturally safe and humanistic cancer care when breaking bad news to Māori and indigenous patients.

Comment: Only 15% of patients with lung cancer are diagnosed early enough to consider curative treatment options. Breaking bad news is part of the daily practice of dealing with lung cancer patients. The Te Huataki Waiora School of Health group used Māori researchers and Māori tikanga to interview Māori patients and their whānau about ethical implications of receiving bad news. Māori patients and whānau appreciated options and clear advice given, hope maintained, analogies, simple language, and the role of whānau being appreciated. **Bottom line: breaking bad news can build on general guidelines; in addition, Māori patients/whānau appreciate anchoring delivery of bad news in a Māori health model.**

Reference: J Med Ethics 2021;47:e62
Abstract