Respiratory RESEARCH REVIEW™

Making Education Easy

Issue 181 – 2021

In this issue:

Abbreviations used in this issue
CML = chronic myeloid leukaemia
EGFR = epidermal growth factor receptor
GP = general practitioner
TKI = tyrosine kinase inhibitor

Welcome to the first issue of Respiratory Research Review for 2021 with the topic of lung cancer.

Lung cancer is the third most commonly diagnosed cancer in NZ. With almost 2500 new diagnoses of lung cancer each year, and more than 1600 lung cancer deaths, it is by far the most common cause of death from cancer in NZ. NZ has about 3500 GPs, so in their daily workload, a GP is probably going to look after one patient with lung cancer about once every 18 months. Hopefully, this review contributes to your preparedness to look after these patients.

Case finding for lung cancer is unrewarding as the 'typical' lung cancer symptoms like a persistent cough, cough with chest pain, recurrent chest infections and cough with haemoptysis are all so frequent that they hardly identify lung cancer (npj Prim Care Respir Med 2020). As 2020 has shown, in NZ we enjoy a more integrated system, a stronger public health service and commitment from the government to follow science. While systematic screening may improve lung cancer survival rates, the government policy of Smokefree Aotearoa 2025 is likely to have the biggest impact on the health of New Zealanders. It is estimated that about 80% of all smokers and 100% of smokers with comorbidities will have contact with the health system in 2021. Based on American data, only 10% of smokers are prescribed cessation medication and 4% are referred to quit services. And while we feel accountable for blood pressure or diabetes control, we don't feel the same sense of accountability for the smoke-free status of our patients. Depending on the GP, the quit rate of patients is between 4% and 87% (Chest 2020). We can make a difference in our individual practices.

The effect of the pandemic on the disruption of our cancer services in April/May/June 2020 still needs to be assessed. It is likely not as bad as in Britain, where it is feared that the delays in diagnosis through the COVID-19 pandemic are likely to result in an additional 3500 avoidable cancer deaths as outlined in a BMJ blog.

The Year of the Nurse has been extended from 2020 into 2021 by the WHO. Lancet Oncology has published a short series on oncology nursing, highlighting the crucial contribution and impact of oncology nursing. Written by nurses, they highlight the scope, skill set, ability, roles and responsibility of nurses along the cancer care continuum. The second article highlights nursing shortages, ideas for training, occupational hazards, as well as oncology nurse burnout. These articles are well written with case vignettes as panel discussions, which make great review points. Our regional journal is also running a series edited by Alistair Miller and Emily Stone: 'Essential update in lung cancer medicine'. The article on 'An examination of two dichotomies: women with lung cancer and living with lung cancer as a chronic disease' makes a good starting point.

Sue Crengle and colleagues have published on the 'Impact of low-dose CT screening for lung cancer on ethnic health inequities in New Zealand: a cost-effectiveness analysis', and suggest that it may become a particular tool to address the more than triple rate of lung cancer mortality in Māori compared with non-Māori. See also the article on 'The most commonly diagnosed and most common causes of cancer death for Māori New Zealanders'. In the international realm, the European Society of Radiology and European Respiratory Society have published a statement paper on lung cancer screening. They are overall cautiously positive and provide a good bridge to the first articles in this review. The authors highlight five key steps in shared decision making, which we repeat, as they are arguably relevant for all clinical management plans.

1. Acknowledge the importance of shared decision-making.
2. Discuss in a balanced way the potential harms, benefits and uncertainty.
3. Acknowledge the clinical situation and different options to every patient.
4. Elicit participants preferences and values.
5. Agree on a plan for the next step in the decision-making process.

Welcome to 2021 – and please continue sending questions or comments.

Kind regards,

Professor Lutz Beckert
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Each month we highlight a particularly excellent paper with our butterfly symbol.

Variation in patient smoking cessation rates among health-care providers

Authors: Almaaitah S et al.

Summary: Smoking quit rates were assessed for a retrospective, observational cohort of ~1 million smokers aged ≥18 years who had attended ≥3 ambulatory primary-care visits, with two visits ≥1 year apart, from 22 US healthcare organisations, between January 2012 and December 2018; 56% of the patients had their smoking status documented in 2017. The overall quit rate (≥1 year of abstinence) was 24%. Patient characteristics associated with quitting included older age, Hispanic ethnicity, being married, urban residence, commercial insurance, pregnancy and a diagnosis of pneumonia, myocardial infarction, ischaemic heart disease, cataract or asthma, while Medicaid insurance, low income, high body mass index, peripheral vascular disease, alcohol-related diagnosis and chronic obstructive pulmonary disease were negatively associated. Quit rates varied across health systems (14.3–34.5%), practice sites (5–66%) and healthcare providers (4–87%). Smoking deterrents were prescribed to 10.2% of smokers, and 3.9% were referred for counselling.

Comment: The first article in a lung cancer review ought to be on smoking cessation, as only 10–15% of all lung cancers occur in never-smokers (JAMA Oncol). In this American study on 1 million patients, only 60% had their smoking status documented; in NZ, we have reached this health target for 95% of our patients. However, not all smokers are routinely offered smoking cessation aids or offered referrals to quit services. As the editorial points out, smoking cessation advice is the most cost-effective treatment. **Bottom line: quit rates of patients vary between 4% and 87% depending on the GP.**

Reference: Chest 2020;158:2038–46
Abstract

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The most commonly diagnosed and most common causes of cancer death for Māori New Zealanders

Authors: Gurney JK et al.

Summary: This NZ research reported cancer incidence, mortality and survival data for the 2007–2016 period to clarify cancer burden among Māori, following the 1996–2006 landmark Unequal Impact II report. The absolute burden of cancer among Māori was the focus, but this burden was also compared with that experienced by non-Māori, and changes in relative disparities were also assessed. Lung cancer was the most commonly diagnosed cancer among Māori at 401 cases per year, and had the second highest age- and sex-standardised incidence rate at 42 per 100,000 after breast cancer (45 per 100,000). Relative to other cancers, the survival disparity for lung cancer between Māori and non-Maori was relatively low with a hazard ratio of 1.3 (95% CI 1.2, 1.4), but the mortality burden for lung cancer was much higher at 311 Māori deaths per year. While lung cancer incidence and mortality declined over the decade studied, the survival disparity between Māori versus non-Māori remained relatively unchanged.

Comment: The New Zealand Medical Journal took a strong position in its edition for September 4, 2020 in dedicating a whole issue on racism in the health sector in Aotearoa NZ. Most articles are open access and it is worthwhile looking at our national data. In this article, Jason Gurney and colleagues document the most common cancers and age- and sex-standardised mortality rates. Lung cancer death is 'off the charts' if one chooses a scale with a resolution to identify the impact of lymphoma or thyroid cancer for comparison. The authors' **bottom line: tobacco control, early detection of lung cancer via screening and provision of best practice should have an impact in the short-to-medium term.**

Reference: N Z Med J 2020;133(1521):77–96
Abstract

'I'm putting my trust in their hands': a qualitative study of patients' views on clinician initial communication about lung cancer screening

Authors: Golden SE et al.

Summary: These researchers undertook semistructured interviews for 51 patients from three institutions with established lung cancer screening programmes to assess the respondents' experiences with respect to communication and decision-making with clinicians. The respondents were able to recall only a few specific harms or benefits of screening, but consistently reported they were satisfied with the amount of information provided. It was reported by all respondents that clinicians had not explicitly asked them about their values and preferences, and around half the respondents reported some distress associated with anticipation of their results. Nearly all the respondents expressed satisfaction regarding their role in the decision-making process. The respondents generally reported high levels of trust in clinicians, despite many reporting that they did not experience all defined aspects of shared decision-making.

Comment: In the covering summary, we have highlighted five key steps in shared decision making when advising a patient whether to participate in lung cancer screening. This research from the USA interviewed 51 patients, who were enrolled in a lung cancer screening programme, to evaluate the quality of communication in this shared decision-making process. Patients were not dissatisfied; however, they also hardly recalled any information exchange and, in particular, did not recall any possible disadvantages of screening. The authors' **bottom line: patients may place greater importance on interpersonal aspects of communication rather than information exchange.**

Reference: Chest 2020;158:1260–7
Abstract

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Predictive values of lung cancer alarm symptoms in the general population

Authors: Haastrup PF et al.

Summary: Survey and registry data were used to calculate predictive values and likelihood ratios of symptoms indicative of lung cancer in a prospective cohort of 69,060 individuals aged ≥40 years randomly selected from the Danish population. How the predictive values were affected by smoking status and GP contact for alarm symptoms was also assessed. Fewer than half the patients with a lung cancer diagnosis had reported an alarm symptom during the 6 months prior to the diagnosis. The positive predictive values associated with alarm symptoms were generally very low, even among patients reporting GP contact for such symptoms; dyspnoea, hoarseness and loss of appetite had the highest predictive values alongside current heavy smoking. The negative predictive values were all around 100%.

Comment: A persistent cough, recurrent chest infections, chest pain with coughing and haemoptysis are symptoms of early lung cancer; however, they are also symptoms for more common, benign conditions. These Danish authors surveyed almost 40,000 individuals for lung cancer 'alarm symptoms' to estimate the predictive values of these symptoms. Not surprisingly, all of these respiratory symptoms were very common in a general population (e.g. 9% reported a chronic cough) and the positive predictive value was very low. **Bottom line: referral guidelines should not be overzealous for specific respiratory symptoms; a cluster of symptoms and signs may prove to be a stronger predictor of lung cancer.**

Reference: npj Prim Care Respir Med 2020;30:15
Abstract

Reduced lung-cancer mortality with volume CT screening in a randomized trial

Authors: de Koning HJ et al.

Summary: Male (n=13,195; primary analysis) and female (n=2594; subgroup analyses) former or current smokers aged 50–74 years were randomised to undergo low-dose CT screening for lung cancer at baseline, and years 1, 3 and 5.5 or no screening in this trial. The average CT screening rate among men was 90.0%, an average of 9.2% of screened participants required ≥1 additional CT scan due to an initially indeterminate result, and the referral rate on detection of suspicious nodules was 2.1%. After 10 years of follow-up, the respective lung cancer incidences in the screening and control groups were 5.58 and 4.91 per 1000 person-years and the respective lung-cancer mortality rates were 2.50 and 3.30 deaths per 1000 person-years. Compared with no screening, the screening group had reduced 10-year lung cancer-related mortality (rate ratio 0.76 [95% CI 0.61, 0.94]), with similar values at years 8 and 9. Among women, the rate ratio for 10-year lung cancer-related mortality was 0.67 (0.38, 1.14), with values of 0.41–0.52 in years 7–9.

Comment: The National Lung Cancer Screening Trial was published in 2011 and demonstrated a mortality reduction in the screened group with a very large number of false-positive lung nodules. The formal publication of this NELSON trial confirms the reduction in mortality to a similar degree but with significantly fewer incidental nodules. The results of this trial are summarised in a 2-minute 'Quick Take'. Overall, the researchers estimated that approximately 60 deaths from lung cancer were prevented by offering four CT scans to 8000 participants. **Bottom line: lung cancer screening reduced mortality – we now need to demonstrate cost effectiveness.**

Reference: N Engl J Med 2020;382:503–13
Abstract

Integrating genomic features for non-invasive early lung cancer detection

Authors: Chabon JJ et al.

Summary: These authors present improvements to cancer personalised profiling with the use of deep sequencing (CAPP-Seq)5, which analyses ctDNA (circulating tumour DNA), to better facilitate screening applications. They showed that while ctDNA levels are very low in early-stage lung cancers, most patients have increased levels prior to treatment and its presence is strongly prognostic. They also report that most somatic mutations in the cfDNA (cell-free DNA) of patients with lung cancer and of risk-matched controls reflect clonal haematopoiesis and are nonrecurrent. Compared with tumour-derived mutations, clonal haematopoiesis mutations occur on longer fragments of cfDNA and lack smoking-associated mutational signatures. These findings were combined with other molecular features to develop a machine-learning method (Lung-CLiP), which robustly discriminated early-stage lung cancer patients from risk-matched controls. Lung-CLiP was found to perform similarly to tumour-informed ctDNA detection, and enabled tuning of assay specificity in order to facilitate distinct clinical applications.

Comment: Clinical case finding of lung cancer is difficult, and lung cancer screening is probably cost effective; however, it is resource intense. The analysis of cfDNA or ctDNA is already used in assessing the genotype in the management of advanced lung cancer. In this article, a group of American authors report methods for the detection of early-stage lung cancer using a cfDNA-based machine-learning platform, named lung cancer likelihood in plasma (Lung-CLiP). As the editorial points out, **bottom line: minimally invasive liquid biopsy could become a screening tool for at-risk individuals for lung cancer. If validated, this could lead to a marked reduction in lung cancer mortality.**

Reference: Nature 2020;580:245–51
Abstract

Osimertinib in resected *EGFR*-mutated non-small-cell lung cancer

Authors: Wu Y-L et al., for the ADAURA Investigators

Summary: Patients with completely resected *EGFR* mutation-positive non-small-cell lung cancer were randomised to receive osimertinib 80mg (n=339) or placebo (n=343) once daily for 3 years in this phase 3 trial. Compared with placebo, the 24-month disease-free survival rate was greater for osimertinib recipients with stage II–IIIA disease (primary endpoint; 90% vs. 44%; hazard ratio for disease recurrence or death, 0.17 [99.06% CI 0.11, 0.26]) and for the overall study population (89% vs. 52%; 0.20 [99.12% CI 0.14, 0.30]), and a greater proportion of osimertinib recipients were alive without CNS disease at 24 months (98% vs. 85%). OS data were immature at the time of reporting; there had been nine deaths in the osimertinib arm and 20 in the placebo arm. No new safety signals were reported.

Comment: TKIs (tyrosine kinase inhibitors) have significantly improved the survival of patients with non-small-cell lung cancer and an *EGFR* mutation. We have previously reviewed the efficacy of the third-generation TKI, osimertinib, and local data on the licensed but not funded agent are available (JTO Clin Res Rep). In this study, the authors used osimertinib as adjuvant chemotherapy in patients with stage Ib–IIIa therapy, who had surgery with curative intent. The trial results are summarised in a 2-minute 'Quick Take'. **Bottom line: osimertinib conferred a significant survival benefit when used as adjuvant therapy in patients with resected lung cancer and an *EGFR* mutation.**

Reference: N Engl J Med 2020;383:1711–23
Abstract

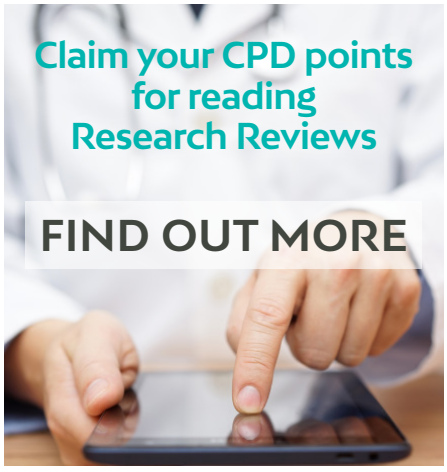
Pulmonary complications of Bcr-Abl tyrosine kinase inhibitors

Authors: Weatherald J et al.

Summary: TKIs targeting the Bcr-Abl oncoprotein, which have revolutionised CML (chronic myeloid leukaemia) treatment, have variable profiles of kinase inhibition and off-target effects, resulting in a broad range of potential toxicities. Dasatinib is the TKI most often implicated in pulmonary complications, but the other Bcr-Abl TKIs have also been implicated. The most frequent pulmonary complication of TKIs is pleural effusion, mostly associated with dasatinib or bosutinib use. In terms of the most serious pulmonary complication, pulmonary arterial hypertension rates the highest, and has been associated with dasatinib, bosutinib and ponatinib (but not imatinib); this complication is often reversible upon TKI discontinuation. Rare cases of interstitial lung disease have been associated with TKIs, mainly imatinib.

Comment: TKIs are making an impact in lung cancer treatment; however, this group of medications starting with imatinib has revolutionised the care of CML, so that patients with CML can now expect a normal life expectancy. Many will have been treated for several years with TKIs and up to a third may suffer respiratory side effects in the years following treatment, particularly after treatment with dasatinib. This article presents a well written review of the frequency, mechanism and treatment options. **Bottom line: TKIs can cause exudative pleural effusion, chylothorax, interstitial lung disease and pulmonary arterial hypertension.**

Reference: Eur Respir J 2020;56:2000279
Abstract



Association of palliative care use and setting with health-care utilization and quality of care at the end of life among patients with advanced lung cancer

Authors: Vranas KC et al.

Summary: The impact of palliative care on healthcare utilisation and quality of care was reported for a retrospective cohort of 23,142 US patients with stage IIIB–IV lung cancer between 2007 and 2013; 57% of the cohort received palliative care, and 36% of initial palliative care encounters were in the outpatient setting. Compared with patients who did not receive palliative care, those who received initial palliative care in the outpatient setting had lower rates of emergency department visits (adjusted incidence rate ratio 0.86 [95% CI 0.77, 0.96]) and hospitalisations in the last 30 days of life (0.64 [0.59, 0.70]), and ICU admissions in the last 30 days of life were reduced in those who received initial palliative care encounters in inpatient and outpatient settings (respective adjusted odds ratios 0.63 [0.53, 0.75] and 0.42 [0.35, 0.52]). Palliative care also significantly reduced the likelihood of healthcare utilisation due to chemotherapy-associated toxicity (adjusted odds ratio 0.88 [95% CI 0.82, 0.95]).

Comment: This study on more than 20,000 patients with advanced lung cancer demonstrates, on a rather large scale, what is becoming the standard of care in NZ. Just a little more than half of these patients with stage IIIb and IV lung cancer received specialist palliative care; however, this was often delivered as an inpatient assessment. The authors and editorial pose the challenge to integrate palliative care integral to lung cancer care. **Bottom line: early palliative care in an outpatient setting was associated with fewer emergency visits, hospital admissions, ICU admissions and improved quality of care.**

Reference: Chest 2020;158:2667–74
Abstract

An evaluation of the contents of advance care plans and their use in patients admitted to a public hospital

Authors: Speelberg HB et al.

Summary: These researchers reviewed the medical records of 149 hospitalised patients with an advance care plan to evaluate concordance with actual treatment received; minority ethnic groups were under-represented compared with census data. Goal-of-care choice was measurably impacted by increasing age, but not by comorbidity severity. Across 411 hospital admissions, the patient was classified as incompetent in 60. Adherence to the goal of care was evident for 59 of these cases, and adherence to treatment preferences was recorded for six of seven cases. Among 55 individuals who had died after writing their advance care plan, 63% died at their preferred place or with no preference stated.

Comment: Based on a review of 150 advance care plans, the authors found that nearly half of the people chose their goal of care to be symptom focussed only, without life-prolonging treatment. That correlated to the age and weakly to the comorbidities. Of the 411 admissions, in 60 incidences the patient was deemed to be noncompetent to participate in clinical decision-making. Reassuringly, the goal of care was adhered to in 59 cases, and no patient received unwanted CPR. **Bottom line: advance care plans are a useful tool to document patient choice and encourage self-determination, and they can guide care.**

Reference: N Z Med J 2020;133(1526):55–66
Abstract

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.

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