Welcome to the first Respiratory Research Review of 2019 on the topic of lung cancer. We hope you had the opportunity to have some time off. Patients recognise that healthcare professionals “need to ‘look after their own well-being so that they don’t become needy themselves’” [NZ Med J 2018;131(1468):25]. We have chosen ten articles covering the continuum of care from detection and diagnosis, to therapeutic approaches, management of effusions and end-of-life care. In 2019, we are thinking about two new features for Respiratory Research Review: i) a ‘butterfly of lung wings’ to signal my favourite article; and ii) one article in each review covering a generic topic, like the impact of school marks on medical school performance or the relationship between the length and the ‘boringness’ of a presentation? What do you think?

This first review starts positively with an article on the global public health victory for tobacco plain-packaging laws in Australia. By December 2012, Australia had fully implemented plain-packaging laws for all tobacco products. Cuba, Dominican Republic, Honduras and Indonesia challenged the Australian law under the dispute settlement procedures of the WTO (World Trade Organization). It found in 2016 that “tobacco plain-packaging laws were not more trade restrictive than necessary for the legitimate objective of protecting public health under the WTO agreement on Technical Barriers to trade”. This judgment together with the unsuccessful legal challenges in the High Courts of Australia and Hong Kong is a strong political signal for other states.

Prevention or early detection is the most cost-effective management for lung cancer, which is now the most common cause of cancer death in men and women. While new, promising and effective therapies are being added to our therapeutic armamentarium, the International Agency for Research on Cancer recently judged that “No country can afford to treat its way out of the cancer problem”. We pick up several articles on screening and the hurdles to overcome, very encouraging articles on case finding, and cough as a possible early symptom — ‘Got a cough? Get a check’ [Thorax]. Also, Christopher Slatore and Renda Wiener have combined forces and published a wonderful review: ‘Pulmonary nodules: a small problem for many, severe distress for some, and how to communicate about it’.

‘Lung cancer staging: a concise update’ [Eur Respir J] is exactly this — brief, clinically up-to-date and readable. ‘Endobronchial ultrasound-guided transbronchial needle aspiration: safe as it sounds’ [Respiratory Medicine] and ‘Unexpandable lung from pleural disease’ [Respiratory Medicine] are two clinically applicable reviews. Both, the ERS and the ATS have published evidence-based guidelines/statements on the management of malignant pleural effusions. About 3.5–5% of patients receiving cancer immune checkpoint immunotherapies will develop pulmonary toxicity; most will respond to steroid therapy. Two more excellent reviews are the Diagnosis and management of malignant pleural effusions and end-of-life care. In 2019, we are thinking about two new features for Respiratory Research Review: i) a ‘butterfly of lung wings’ to signal my favourite article; and ii) one article in each review covering a generic topic, like the impact of school marks on medical school performance or the relationship between the length and the ‘boringness’ of a presentation? What do you think?

The final word in the first review of 2019 goes to our patients. Three articles are in this section: i) ‘Breakthrough cancer pain management: a review of international and national guidelines’ [BMJ Support Palliat Care]; ii) ‘Why we need more poetry in palliative care’ [BMJ Support Palliat Care], a plea for the narrative, for poetry, and with great references for poems; and finally iii) a qualitative study published in NZ Med J, a patient view of compassion which elicits four themes: connection, a positive presence and warmth, respect and a caring attitude. In the end, the patients advise trainee health professionals [NZ Med J].

Best wishes for 2019; enjoy the selection, and please give some feedback on the new features.

Kind regards
Professor Lutz Beckert
lutzbeckert@researchreview.co.nz

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www.researchreview.co.nz
Symptoms at lung cancer diagnosis are associated with major differences in prognosis

Authors: Athey VL et al.

Summary: These researchers reported survival outcomes according to symptoms at presentation for 3800 cases of lung cancer among patients presenting to a UK multidisciplinary team during 1997–2011, for whom the overall median survival duration was 183 days. Twelve symptom groups were identified. Compared with cough alone, the risk of death was significantly greater for patients presenting with breathlessness (hazard ratio 1.86 [95% CI 1.54, 2.24]), systemic symptoms (1.91 [1.48, 2.45]), weight loss (2.46 [1.90, 3.18]), chest pain (1.96 [1.56, 2.45]), cough with breathlessness (1.59 [1.28, 1.98]), neurological symptoms (3.07 [2.45, 3.84]) and other combinations of symptoms (2.05 [1.75, 2.40]).

Comment: The first two articles are arguably the clinician’s voice during the debate on cost, efficacy and quality control of lung cancer screening. Clinicians from Doncaster, UK, reviewed the clinical presentation of almost 4000 patients with lung cancer and related their presenting symptoms to their survival. Chillingly, the overall survival was only 183 days. Patients presenting with a cough, with or without haemoptysis or signs of a respiratory tract infection, had better long-term survival compared with patients presenting with breathlessness, systemic symptoms, chest pain, weight loss or neurological symptoms. Bottom line: cough may serve as a prominent symptom in public health campaigns.

Reference: Thorax 2018;73:1177–81

Abstract

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Lung cancer stage-shift following a symptom awareness campaign

Authors: Kennedy MPT et al.

Summary: These authors reported on an early diagnosis campaign consisting of public and primary-care facing components for lung cancer started in 2011 in the UK. Compared with the 3 years before the campaign was launched, there was an 80.8% increase in community-ordered yearly chest x-ray rates during the subsequent 3 years (from 18,909 to 34,194) along with a significant shift towards earlier stage lung cancer detected (p<0.0001); the proportion diagnosed with stage VII increased (35.3% vs. 26.5%) and the number of diagnoses for higher stages decreased by 9.3% from 1254 to 1137.

Comment: ‘Got a cough? Get a check’ was the tagline for a cancer awareness campaign. It was part of a whole-systems approach that included support for GPs, community advertising with the line ‘if you have a cough, breathlessness or chest pain for over 3 weeks, you need a chest x-ray’, and funding for a chest x-ray self-referral service. This initiative led to an 80% increase in chest x-ray referrals and diagnosis of almost 6000 lung cancers, with about a 10% reduction in late-stage diagnoses and an 8% stage shift towards earlier stage lung cancer. Bottom line: a coordinated awareness campaign led to increased lung cancer diagnosis and increased early-stage cancer detection.


Abstract

For more information, please go to www.medsafe.govt.nz
Geographical variations in the use of cancer treatments are associated with survival of lung cancer patients

Authors: Møller H et al.

Summary: Associations between treatment variations according to geographic location in England and survival were explored by analysing the records of 176,225 patients with lung cancer. Improvements in survival were seen over the study period (2010–2014). Variations in active treatments were seen among geographical regions, with interquintile ranges of 9–17% for surgical resection, 4–13% for radical radiotherapy and 22–35% for chemotherapy. It was estimated that at 2 years, if all treated proportions of patients were the same as in the highest quintiles, 188 and 373 deaths would have been potentially avoidable per year for surgical resection and radical radiotherapy, respectively, and at 6 months, 318 deaths per year could have been avoided if chemotherapy use for all patients reflected that of the highest quintile. Adjustments for age, sex, socioeconomic status, performance status and comorbidities did not significantly alter these results.

Comment: Over 2018, several articles examined the lower lung cancer survival rate in the UK compared with the US. In this article, the authors linked geographical variation in treatment with treatment outcomes. From the data available, the survival rate was better for higher rates of surgical resection, radical radiotherapy and chemotherapy. The authors estimated that at 2 years, 188 deaths might have been avoided with surgery, and 373 with radical radiotherapy. At the 6-month point, chemotherapy might have postponed 318 deaths. Bottom line: treatment matters – and this article is an invitation to delve deeper into the causes of treatment variations.

Reference: Thorax 2018;73:530–7

Abstract

Low rates of eligibility for lung cancer screening in patients undergoing computed tomography angiography

Authors: Lyne C et al.

Summary: These authors reviewed the smoking histories of 229 patients undergoing CTCA (CT coronary angiography) at two tertiary hospitals. One quarter of the patients were current or former smokers aged 55–80 years, and of these, <50% were eligible for CTCA screening according to the PLCO 2012 risk model. It was concluded that for patients undergoing CTCA, full thoracic field imaging as routine screening is likely to cause net harm and is therefore not appropriate.

Comment: It could have been such a simple, elegant idea. CTCA frequently reveals pulmonary nodules. Why don’t we use the opportunity of CTCA to perform complete CT scans and so screen for lung cancer at the same time? Colleagues from Perth examined this logically. Patients who undergo CTCA frequently present with chest pain and a low risk of coronary artery disease. Examining it systematically, the authors found that only about 10% of patients who underwent a CTCA would have qualified for lung cancer screening. Bottom line: routine screening of patients undergoing CTCA is likely to result in net harm.


Abstract

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Assessment of plasma proteomics biomarker’s ability to distinguish benign from malignant lung nodules

Authors: Silvestri GA et al., for the PANOPTIC Trial Team

Summary: The prospective, observational PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) trial involved measurement of the relative abundance of two plasma proteins (LG3BP and C163A) in 685 patients with 8–30mm lung nodules to evaluate the accuracy of an integrated proteomic classifier for identifying benign nodules. In a subgroup of 178 patients with a cancer probability of ≤50% (as assessed by physicians), the lung cancer prevalence was 16%. For distinguishing benign nodules from malignant ones, the integrated proteomic classifier returned sensitivity and specificity values of 97% and 44%, respectively, and a negative predictive value of 98%. The classifier was significantly superior to PET, validated cancer prevalence was 16%. For distinguishing benign nodules from malignant ones, the integrated proteomic classifier returned sensitivity and specificity values of 97% and 44%, respectively, and a negative predictive value of 98%. The classifier was significantly superior to PET, validated lung nodule risk models and physician cancer probability estimates. It was determined that use of the integrated classifier would reduce procedures being performed on benign nodules by 40% while misclassifying 3% of malignant nodules.

Comment: As discussed previously (Respiratory Research Review, issues 132 and 144), the incidental finding of lung nodules is one of the major drivers of screening costs, and can also be anxiety provoking for patients (Chest). This PANOPTIC study is an important proof-of-concept study exploring if biomarkers can be used to risk stratify pulmonary nodules. Nawar Nasrallah and Catherine Sears expertly review this study in the accompanying editorial. The title of their editorial serves as our bottom line: ‘Biomarkers in pulmonary nodule diagnosis – is it time to put away the biopsy needle?’.

Reference: Chest 2018;154:491–500

Risk of suicide after cancer diagnosis in England

Authors: Henson KE et al.

Summary: The risk of suicide among English patients with a range of cancers was assessed, and associated risk factors identified, in this population-based study covering 4,722,099 individuals with cancer diagnosed over a 20-year period, of whom 3,509,392 were aged >60 years at diagnosis. There were 2491 deaths recorded as suicide, representing 0.08% of all deaths during follow-up, for a standardised mortality ratio of 1.20 (95% CI 1.16, 1.25) and an absolute excess risk of 0.19 per 10,000 person-years. Patients with mesothelioma had the greatest increase in suicide risk (4.51-fold increased risk; 4.20 extra deaths per 10,000 person-years), followed by pancreatic, oesophageal, lung and stomach cancer (3.89-, 2.65-, 2.57- and 2.20-fold increased risks, respectively). The risk of suicide among patients with cancer was greatest during the first 6 months following diagnosis (standardised mortality ratio 2.74 [95% CI 2.52, 2.98]).

Comment: This article and accompanying editorial made me reflect on aspects of cancer I don’t frequently come across in the hospital setting. The numbers are depressing: over 20 years almost 5 million people were diagnosed with cancer and 2500, which is about 1 in 1000, died of suicide during this period. Social isolation, psychological pain, hopelessness and a desire to escape were motivations for suicide. The risk of suicide is increased about 5-fold with a diagnosis of mesothelioma and almost 3-fold with a lung cancer diagnosis. Bottom line: the risk of suicide is the highest in the first 6 months after diagnosis and may suggest an unmet need for support.

Reference: JAMA Psychiatry 2019;76:51–60

Abstract

Complementary medicine, refusal of conventional cancer therapy, and survival among patients with curable cancers

Authors: Johnson SB et al.

Summary: This US-based retrospective, observational study explored the impact of adding complementary medicines to conventional cancer treatment on survival; from a cohort of nearly 2 million patients, 258 who used complementary medicines with conventional treatments were compared with 1032 matched controls who had been conventionally treated only. Compared with patients who received conventional treatments only, those who also reported complementary medicine use had higher refusal rates for surgical treatments (7.0% vs. 0.1% [p<0.001]), chemotherapy (34.1% vs. 3.2% [p<0.001]), radiation therapy (53.0% vs. 2.3% [p<0.001]) and hormone therapy (33.7% vs. 2.8% [p<0.001]), and they had a lower 5-year overall survival rate (82.2% vs. 86.6% [p<0.001]). Use of complementary medicines was associated with an increased risk of death in a multivariate model that did not include treatment delay and refusal (hazard ratio 2.08 [95% CI 1.50, 2.90]), but significance was lost when these two covariates were included (1.39 [0.83, 2.33]).

Comment: This is my favourite article in this selection because the authors combine clarity, compassion and clinical relevance. Between 48% to 88% of patients use complementary therapies like herbs, vitamins, minerals, traditional Chinese medicine, homeopathy and naturopathy. Complementary and alternative therapies are a multibillion-dollar industry, may improve QOL and can make patients feel more hopeful. These US authors found a cohort of almost 2 million cancer patients and examined the effect of complementary medicine. Bottom line: patients who use complementary therapies are more likely to refuse standard therapies and so had about 2-fold greater risk of death.

Reference: JAMA Oncol 2018;4:1375–81

Abstract

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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.
Higher lung cancer incidence in young women than young men in the United States

Authors: Jernal A et al.

Summary: This investigation into invasive lung cancer diagnoses among Americans aged 30–54 years between 1995 and 2014 revealed that over the past 20 years, the age-specific incidence of lung cancer has generally decreased among men and women in this age group across all races and ethnic groups, but the decline has been steeper for men. Among non-Hispanic whites born since 1965, the female-to-male incidence rate ratios have increased, and have surpassed 1.0 in those aged 30–49 years. There has been convergence of sex-specific incidence rates among non-Hispanic blacks, Hispanics and non-Hispanic Asian-Pacific Islanders, and there was crossover from a higher incidence among men to women only among Hispanics. While the prevalence of cigarette smoking has increased among women born since 1965, it generally has not exceeded the prevalence for men.

Comment: This article is published by the division of Cancer Epidemiology and Genetics of the National Cancer Institute. The good news is that parallel to the reduction in smoking, the incidence of lung cancer has fallen. However, it has fallen more rapidly in men than women. One of the puzzles in the data is that women have virtually never smoked more than men; however, now women carry a higher burden of nonsmoking occupational exposure. Bottom line: the historical pattern of higher incidence of lung cancer among men than women has reversed.

Abstract

Randomized controlled trial of urokinase versus placebo for nondraining malignant pleural effusion

Authors: Mishra EK et al.

Summary: These UK researchers assessed the effects of intrapleural urokinase on dyspnoea and pleurodesis success in patients with nondraining malignant effusion who were randomised to either three doses of intrapleural urokinase 100,000IU every 12 hours or placebo. Mean daily dyspnoea VAS scores over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]). Urokinase recipients has effusion size reductions over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]). Urokinase recipients had effusion size reductions over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]). Urokinase recipients had effusion size reductions over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]). Urokinase recipients had effusion size reductions over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]). Urokinase recipients had effusion size reductions over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]). Urokinase recipients had effusion size reductions over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]). Urokinase recipients had effusion size reductions over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]). Urokinase recipients had effusion size reductions over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]). Urokinase recipients had effusion size reductions over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]). Urokinase recipients had effusion size reductions over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]). Urokinase recipients had effusion size reductions over 28 days did not differ significantly between the groups (mean difference, 3.8mm [p=0.36]). Time to pleurodesis failure was measured over 12 months. Pleurodesis failure rates did not differ significantly between the urokinase and placebo groups (37% vs. 32% [p=0.65]).

Comment: It has been known for about 20 years or so that thrombolytic therapy for malignant pleural effusion is safe and leads to improved drainage and radiological improvement. These British authors present a large trial focussing particularly on outcomes which matter to patients, namely dyspnoea, pain and pleurodesis failure. After randomising 71 patients to urokinase 100,000 units daily for 3 days or placebo, they found some difference in the chest x-ray score, a reduced hospital stay and an improved survival rate associated with urokinase; however, bottom line: intrapleural urokinase did not reduce dyspnoea or improve pleurodesis compared with placebo and cannot be recommended in malignant pleural effusions.

Reference: Am J Respir Crit Care Med 2018;197:502–8
Abstract

Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2)

Authors: Muruganandan S et al.

Summary: Patients with symptomatic malignant pleural effusions were randomised to 60 days of daily (n=43) or symptom-guided (n=44) drainage with 6 months of follow-up in this open-label trial. No significant difference was detected between the daily and symptom-guided drainage groups for mean daily breathlessness VAS score (primary endpoint; ratio of geometric means, 1.32 [p=0.18]), and daily drainage was associated with greater proportions of participants who developed spontaneous pleurodesis over the 60-day intervention and 6-month follow-up periods (37.2% vs. 11.4% [p=0.0049] and 44.2% vs. 15.9% [p=0.004], respectively) and significantly improved patient-reported QOL measures (p=0.0174). There was no significant between-group difference for pain scores, hospital stay duration or mortality. The respective serious adverse event rates in the aggressive and symptom-guided drainage groups were 25.6% and 27.3%, and there were five and six cases of pleural infection in the respective groups.

Comment: Congratulations to Elaine Yap who represented NZ in this randomised controlled trial on the management of malignant pleural effusions. Patients with indwelling (tunnelled) pleural catheters reported no difference in breathlessness, pain, days spent in hospitals or mortality, whether their chest drain was aspirated daily or symptom-guided. However, patients undergoing daily drainage experienced more spontaneous pleurodesis and also improved QOL than the symptom-guided group. The accompanying editorial reflects on appropriate outcomes in pleural interventions and the role of the n=1 trials. Bottom line: daily aspirations may lead to earlier pleurodesis and associated increased QOL.

Abstract