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Respiratory Research Review™

Making Education Easy

Issue 144 – 2018

In this issue:

Abbreviations used in this issue

COPD = chronic obstructive pulmonary disease
CT/PET-CT = (positron emission tomography) computed tomography
FEV = forced expiratory volume
FVC = forced vital capacity
HR = hazard ratio
LMWH = low-molecular-weight heparin
NSCLC = non-small-cell lung cancer
OR = odds ratio
QOL = quality of life
TKI = tyrosine kinase inhibitor
VEGFR/EGFR = (vascular) epidermal growth factor receptor
VTE = venous thromboembolism

Welcome to issue 144 of Respiratory Research Review.

Sometimes I wonder if the world really is changing faster, or if the world is changing at a steady pace and it only seems faster as I am getting older. As we are starting a new year, I would be interested to hear some of the readers' opinions. We are starting 2018 with a selection of research published on lung cancer, and I am grateful for my colleagues who publish a more detailed review several times a year. This selection of nine articles in manageable chunks to review, provides an overview for people in busy clinical jobs and reflects articles that raised my interest.

Readers who wish to reflect on lung cancer, almost starting afresh, are encouraged to read either of the following excellent reviews. 'The shifting landscape for lung cancer: past, present, and future' published as part of the 100-year anniversary of the 'blue' Am J Respir Crit Care Med. The authors remind us that lung cancer was extremely rare; in an autopsy series at the University of Dresden (Germany) in 1878, lung cancer was found in only 1% of all cancer patients – today it accounts for about 27% of all cancers, causing 1.6 million deaths each year. The invention of the cigarette-making machine started an epidemic of cancer, which has only just started to subside in this century in Western countries. The authors give an authoritative review of ongoing and future aspects of prevention, diagnosis and treatment. The other review is written by colleagues in Grosshansdorf (Germany) and published in N Engl J Med on 'Precision diagnosis and treatment for advanced non-small-cell lung cancer'. This article is also extremely well written and easy to read. If one has – purely theoretically – somewhat got left behind in the changing paradigm of diagnosis and treatment, these 10 pages (including pictures) will bring one up to speed.

All of us will consult with patients who have an incidentally detected lung nodule discovered on CT scanning. This often causes anxiety in the patient and doctor, leading to a flurry of further CT scans. Now that the results of further screening trials like the NELSON and PamCan are available, the Fleischner Society has published a revised guideline on how to manage these incidentally discovered nodules with an explicit focus on reducing the number of unnecessary follow-up examinations. Some of the key changes are that nodules <6mm in size in a low-risk setting don't need any routine follow-up. This is actually another relatively easy 10-page read.

"Which organ systems are most likely affected by immune-related adverse events in the setting of immune checkpoint blockade?" This is one of the ten clinical questions the authors of the N Engl J Med review use to structure their review; the answer to this question is that the gastrointestinal tract, endocrine glands, skin and liver are most often affected. As pembrolizumab is becoming available to treat NSCLC (non-small-cell lung cancer) and immune checkpoint blockade therapy is starting to revolutionise cancer care, this is a rather timely review. Personally, I enjoyed the discussion on whether patients with immune-related adverse events, in particular vitiligo, have a better cancer response rate.

Finally, for my physician colleagues in respiratory medicine, just a reminder that we have 2 years to get organised to fulfil the very sensible criteria outlined in the 'Thoracic ultrasound recognition of competence: a position paper of the Thoracic Society of Australia and New Zealand'. It is a thoughtful document giving guidance and addressing the clinical reality in Australia and NZ – the key recommendations are: i) attendance of an approved ultrasound course; ii) maintaining a log book of at least 40 scans; iii) taking a formative assessment; and (finally) iv) passing a barrier assessment.

With best wishes again for 2018 – may we continue to work together to improve outcomes for our patients.

Kind regards

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Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening Trial

Authors: Brain K et al.

Summary: This analysis of data from 4055 participants aged 50–75 years from the UKLS (UK Lung Cancer Screening) Pilot Trial sought to determine the effect of low-dose CT screening on smoking cessation among smokers at high risk of developing lung cancer. The participants completed baseline questionnaires and were randomised to CT screening or no screening. According to self-reported smoking habit, 759 intervention participants and 787 controls were smokers at baseline. Smokers were asked whether they had quit smoking since joining UKLS at T1 (2 weeks after baseline scan results or control assignment) and T2 (up to 2 years after recruitment). At T1, smoking cessation rates were 8% among controls versus 14% among those in the intervention arm; the corresponding proportions at T2 were 21% and 24%, respectively. Participants who underwent screening were more likely than controls to quit smoking at T1 (adjusted OR 2.38 [95% CI 1.56, 3.64]) and T2 (1.60 [1.17, 2.18]). Intervention participants who needed additional clinical investigation were more likely to quit in the longer term compared with controls (adjusted OR 2.29 [95% CI 1.62, 3.22]) and those who received a negative result (2.43 [1.54, 3.84]).

Comment: Smoking is estimated to cause 86% of lung cancers. Health systems around the world are grappling with the cost effectiveness of lung cancer screening. The question has been raised whether patients see a negative result as a 'licence to smoke'. Based on data from the UK lung cancer screening pilot trial, the authors were able to explore this in 4055 participants. The good news is participation in the trial led to a 21% cessation rate in the control group and a 24% in the screened group. **Bottom line: participation in lung cancer screening is a powerful stimulus to cease smoking.**

Reference: Thorax 2017;72(10):912–8
Abstract

Exposure to low dose computed tomography for lung cancer screening and risk of cancer

Authors: Rampinelli C et al.

Summary: This was a secondary analysis of data from the COSMOS trial, in which high-risk asymptomatic current or former smokers (≥20 pack-years) aged ≥50 years with no history of cancer in the prior 5 years underwent low-dose CT lung cancer screening; a risk-benefit analysis was performed. There were 42,228 low-dose CT and 635 PET CT scans performed in 5203 participants over the trial's 10-year period. The median effective radiation doses accumulated by the tenth year of screening were 9.3 and 13.0 mSv for men and women, respectively. The respective lifetime attributable risks of lung cancer and major cancers after 10 years of CT screening were 1.4–5.5 and 2.6–8.1 per 10,000 screened individuals, with variations by age and gender – women aged 50–54 years had ~3- to 4-fold higher risks than men aged ≥65 years. The respective numbers of screening-induced lung and major cancer cases over the 10 years were 1.5 and 2.4, corresponding to an additional 0.05% risk of induced major cancers. There were 259 lung cancers diagnosed during the 10 years of screening; one radiation-induced major cancer would be expected for every 108 lung cancers detected by screening.

Comment: Tobacco smoking is the most common cause of lung cancer; other causes include inhalation of carcinogens through marijuana or hookah, exposure to radon, asbestos, diesel exhaust and ionising radiation. Exposing individuals to ionising radiation during lung cancer screening may increase the risk of lung cancer. These Italian authors used the data from the 40,000 participants in the COSMOS trial in Milan. Over 10 years the median cumulative radiation dose of screening was 9.3 mSV for men and 13.0 mSV for women on top of background radiation exposure of about 2.7 mSV per year. **Bottom line: for every 108 lung cancers detected through screening, one major cancer may be induced.**

Reference: BMJ 2017;356:j347
Abstract

Incidence and relative risk for developing cancer among patients with COPD

Authors: Ho C-H et al.

Summary: Data from Taiwan's National Health Insurance Research Database were queried to identify the incidence of malignant diseases among 13,289 patients diagnosed with COPD and 26,578 matched controls. Cancer diagnoses were identified for 973 patients with COPD and 728 controls over average follow-up durations of 3.9 and 5.0 years, respectively. Compared with controls, patients with COPD had a higher cancer diagnosis rate (7.3% vs. 2.7%; adjusted HR 2.8 [95% CI 2.6, 3.1]). The most common cancers diagnosed among patients with COPD were lung, liver, colorectal, breast, prostate and stomach cancers.

Comment: This prospective observational study is based on the National Health Insurance Research Database in Taiwan. The researchers define two groups, about 13,000 patients with COPD and about 26,000 well-matched control subjects. Over the next decade or so, 4.2% of the participants were diagnosed with any type of cancer, 7.3% of patients with COPD and 2.7% of the control group. The most common types of cancer included lung, liver, colorectal, breast, prostate and stomach cancers. A major weakness of this study is that the authors don't report smoking rates. **Bottom line: the risk of developing lung cancer in patients with COPD is about three times higher than in patients without COPD.**

Reference: BMJ Open 2017;7(3):e013195
Abstract

For more information, please go to www.medsafe.govt.nz

Predictors of long-term compensatory response of pulmonary function following major lung resection for non-small cell lung cancer

Authors: Takahashi Y et al.

Summary: Long-term pulmonary function after major lobar resection for NSCLC was investigated in 137 patients. Spirometry data obtained 10–14 months postsurgery were used to calculate the ratios of actual/predicted postoperative FEV_1 and actual/predicted postoperative FVC, and their relationships with clinicopathological factors and immunohistochemistry for pro-SPC (prosurfactant protein C), TTF-1 (thyroid transcription factor-1) and VEGFR2 were investigated. A strong correlation was seen between the two ratios (r=0.628 [p<0.001]). Greater compensatory response was defined as both ratios being >120%. Greater compensatory response was associated with both decreased smoking index (p<0.001) and greater resected subsegments (p=0.037). Case-matched comparisons revealed that never-smokers had significantly greater compensatory responses than smokers in the ratios of actual/predicted postoperative FEV_1 (119.9% vs. 107.5% [p=0.030]) and actual/predicted postoperative FVC (117.9% vs. 107.2% [p=0.046]). Normal lung parenchymal pro-SPC, TTF-1 and VEGFR2 expression was greater in patients with greater versus lesser compensatory responses (p<0.001 for both). There were also significant correlations between pro-SPC, TTF-1 and VEGFR2 expression and the degree of compensatory response, particularly among smokers (respective r values 0.631, 0.705 and 0.732 [p<0.001 for all]).

Comment: The principal driver in increasing survival in lung cancer is early detection. We use a formula to estimate the postoperative lung function remaining. This detailed study from Japan followed a cohort of 140 patients following lobar resection for about a year after surgery; roughly half had a diagnosis of COPD, the other half didn't. The initial estimate of postoperative lung function was reasonably accurate. Interestingly, patients with a high level of immunostaining of VEGFR2 in normal lung tissue had a better long-term recovery. **Bottom line: peak compensatory recovery occurred at about 9 months and was significantly better in never-smokers.**

Reference: Respirology 2017;22(2):364–71
Abstract

Tracking the evolution of non-small-cell lung cancer

Authors: Jamal-Hanjani M et al., for the TRACERx Consortium

Summary: This paper reported findings from the UK-based prospective TRACERx (Tracking Non–Small-Cell Lung Cancer Evolution through Therapy) study, which was ongoing at the time of reporting, on intratumour heterogeneity in 327 tumour regions for 100 early-stage NSCLC tumours samples that had undergone multiregion whole-exome sequencing. Widespread intratumour heterogeneity was seen for both somatic copy-number alterations and mutations. Although driver *EGFR*, *MET*, *BRAF* and *TP53* mutations were almost always clonal, >75% of the tumours contained heterogeneous driver alterations that occurred later in evolution, commonly in the *PIK3CA* and *NF1* genes and also those involved in chromatin modification and DNA damage response and repair. Genome doubling and ongoing dynamic chromosomal instability were both associated with intratumour heterogeneity, and resulted in parallel evolution of driver somatic copy-number alterations, including *CDK4*, *FOXA1* and *BCL11A* amplification. An association was identified between elevated copy-number heterogeneity and increased risk of recurrence or death (HR 4.9 [$p=4.4\times10^{-4}$]).

Comment: This is arguably my favourite paper in this selection of articles because the authors demonstrate that intratumour heterogeneity correlates directly with survival. This study has the potential to significantly alter our understanding of cancer, moving away from the paradigm of clonal homogeneity and understanding the impact of heterogeneous drivers to explore survival and target therapies to encapsulate the diversity. In this early report, the authors demonstrate that driver mutations start as clonal aberrations; however, heterogeneous driver alterations occurred in more than 75% of cancers. **Bottom line: the higher the intratumour heterogeneity, the higher the risk of recurrence or death.**

Reference: N Engl J Med 2017;376(22):2109–21
Abstract

Osimertinib in untreated *EGFR*-mutated advanced non-small-cell lung cancer

Authors: Soria J-C et al., for the FLAURA Investigators

Summary: Patients with untreated *EGFR* mutation-positive advanced NSCLC were randomised 1:1 to receive osimertinib 80mg once daily or a standard EGFR-TKI (tyrosine kinase inhibitor) agent (gefitinib 250mg once daily or erlotinib 150mg once daily) in this phase 3 trial. Compared with the standard EGFR-TKIs, osimertinib was associated with: i) a longer PFS duration (primary endpoint; 18.9 vs. 10.2 months), decreasing the risk of disease progression or death (HR 0.46 [95% CI 0.37, 0.57]); ii) a longer median response duration (17.2 vs. 8.5 months); iii) a similar objective response rate (80% vs. 76%; OR 1.27 [95% CI 0.85, 1.90]); iv) a greater 18-month survival rate (83% vs. 71%), with a lower risk of death (HR 0.63 [95% CI 0.45, 0.88]); and v) a lower grade ≥3 adverse event rate (34% vs. 45%).

Comment: After impressive initial treatment responses with EGFR-TKIs, many tumour cells acquire resistance to therapy. Diagnosing the acquired mutations often requires a second biopsy; however, it is treatable with the third-line TKI, osimertinib. These researchers are reporting on a study using osimertinib as the first-line therapy in patients with *EGFR*-mutated NSCLC. These are early results not reporting any survival benefit; however, osimertinib has good central nervous system penetration, has a favourable side effect profile, makes T790M diagnosis irrelevant and, **bottom line: improved PFS from 10 to 19 months.**

Reference: N Engl J Med 2018;378(2):113–25
Abstract

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Edoxaban for the treatment of cancer-associated venous thromboembolism

Authors: Raskob GE et al., for the Hokusai VTE Cancer Investigators

Summary: Patients with cancer who had experienced an acute symptomatic or incidental VTE were randomised to receive 6–12 months of LMWH for ≥5 days followed by oral edoxaban 60mg once daily (evaluable n=522) or subcutaneous dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily (evaluable n=524). The composite primary outcome (recurrent VTE or major bleeding during the 12 months after randomisation) was seen in 12.8% of the edoxaban group and 13.5% of the dalteparin group (HR 0.97 [95% CI 0.70, 1.36]; p=0.006 for noninferiority); when these outcomes were considered separately, edoxaban recipients had a lower recurrent VTE rate (7.9% vs. 11.3%) but a higher major bleeding rate (6.9% vs. 4.0%).

Comment: VTE is an important complication reducing survival and QOL. Some therapies like immune checkpoint blockade may increase the risk of VTE. LMWHs are superior to warfarin in reducing VTEs. Here, an international consortium of researchers compared LMWH with a direct oral factor-Xa inhibitor, edoxaban, for the treatment of VTE. The bleeding rate was slightly higher (36 vs. 21 patients), which the authors relate to the higher number of patients with stomach cancer in the edoxaban group. **Bottom line: edoxaban was not inferior to LMWH in reducing the rate of recurrent VTE in cancer patients.**

Reference: N Engl J Med; Published online Dec 12, 2017
Abstract

Randomized trial of pleural fluid drainage frequency in patients with malignant pleural effusions

Authors: Wahidi MM et al.

Summary: Patients with malignant pleural effusions were randomised to pleural fluid drainage every day (n=73) or every other day (standard; n=76) via a tunnelled pleural catheter in the ASAP trial. Compared with the standard drainage protocol, the more aggressive daily drainage was associated with a greater autopleurodesis rate following the placement of the indwelling pleural catheters (complete or partial response based on symptomatic and radiographic changes; primary outcome; 47% vs. 24% [p=0.003]) and a shorter median time to autopleurodesis (54 vs. 90 days), with no significant between-group difference for adverse event rate, QOL or patient satisfaction.

Comment: Richard Light is the senior author of this North American study utilising a tunnelled intrapleural catheter, not as a destination treatment, but as a tool to achieve pleurodesis. This so-called autopleurodesis has also become the focus of new catheter technology, like creating catheters coated with silver nitrate. The authors randomised about 150 patients with malignant pleural effusions to drainage every second day versus daily drainage. More patients had pleurodesis with daily drainage and required the catheter *in situ* for a shorter time period; adverse events, QOL and patient satisfaction were no different. **Bottom line: daily drainage of pleural fluid via a tunnel catheter leads to earlier freedom from the catheter.**

Reference: Am J Respir Crit Care Med 2017;195(8):1050–7
Abstract

Nonmalignant pleural effusions

Authors: Walker SP et al.

Summary: Data were reported for a prospective cohort of 356 unselected patients presenting to a pleural service who were diagnosed with nonmalignant pleural effusion. These patients had a mean age of 68 years and 69% were male. Cases with cardiac, renal and hepatic failure were associated with 1-year mortality rates of 50%, 46% and 25%, respectively. Bilateral effusions (HR 3.55 [95% CI 2.22, 5.68]) and transudative effusions (2.78 [1.81, 4.28]) were associated with a worse prognosis, with 1-year mortality rates of 57% and 43%, respectively.

Comment: Most patients have nonmalignant pleural effusions caused by an infection, inflammatory process, surgery or pulmonary embolism, or by systemic factors such as heart, liver or renal failure. The Bristol group reviewed 782 cases presenting to their pleural service and 356 were judged to be nonmalignant pleural effusions. The most common causes included infections (40%) and for about a quarter no cause could be identified. Patients with malignant effusion had a mortality rate of 70% at 12 months; however, the mortality in patients with nonmalignant pleural effusions was 50% in heart, 46% in renal and 25% in liver failure. **Bottom line: nonmalignant pleural effusions are not benign and carry significant mortality risk.**

Reference: Chest 2017;151(5):1099–105
Abstract

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Independent commentary by Professor Lutz Beckert.

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