Welcome to the first issue of Respiratory Research Review for 2017.

We are starting off the year with a review of articles related to lung cancer. Selecting ten articles to be representative of an illness that affects 1.8 million people worldwide and causes 1.6 million deaths each year, more than the next four most common cancers combined, is not easy, and I am pleased my colleagues create a dedicated Lung Cancer Research Review several times per year.

We are starting with an analysis of the four Nordic twin cohorts, which now has well above 100,000 twin individuals (Thorax). Any familial and genetic effects decrease with age, and not surprisingly the analysis confirms that smoking causes lung cancer. This confirmation may be necessary because it is still debated by the tobacco industry; an example can be seen in their study (pdf; 3.0MB) sponsored by ‘Freedom Organisation for the Right to Enjoy Smoking Tobacco’ (FOREST), which published ‘The pleasure of smoking’. It also helps us to stay focussed on smoking cessation, and each of us can possibly take some credit for achieving 22 million fewer smoking-attributable deaths in the last 7 years (Tobacco Control). David Levy and colleagues reflect on the success of the WHO-sponsored mPOWER tobacco-free initiative, which more than 140 countries have signed up to; mPOWER is the acronym for monitoring tobacco use, Protecting people from tobacco smoke, Offering help to quit smoking, Warning people about the danger of tobacco, Enforcing bans of tobacco advertising, promotion and sponsorship and Raising tobacco taxes. The more aspects that are embraced, the more powerful this initiative is.

In the year 2017 we will see an ongoing debate about the cost effectiveness of low-dose CT scanning for lung cancer screening as the results of the European studies are published (Thorax). North America and Canada are offering lung cancer screening for people aged 55–74 years who have at least a 30-pack-year history of smoking, and they are starting to report on outcomes (Chest). An important study from the UK reports on the psychological effects of lung cancer screening (Thorax). With up to 50% of people screened for lung cancer showing incidental lung nodules, the American Thoracic Society has developed a great one-page patient education leaflet, “What is a lung nodule?” (pdf; 320KB).

The really big news in lung cancer therapy will be immunotherapy, particularly with immune checkpoint inhibitors. Tony Mok and Herbert Loong are asking carefully if we are ready for immune checkpoint inhibitors in lung cancer (Lancet). A variety of articles point towards success as primary therapy (N Engl J Med) and for previously treated cancer (Lancet). The N Engl J Med has also run a review article on ‘Molecular and biochemical aspects of the PD-1 checkpoint pathway’, a report on fulminant myocarditis and a timely review of the ‘Cardiovascular toxic effects of targeted cancer therapies’. If you wish to reflect on one article in a journal club, an almost utopian article comes from Massachusetts. The group reports on combining tumour antigen-targeting antibodies, a recombinant IL-2 with extended half-life, an anti-PD-1 antibody and a T-cell vaccine to achieve eradication of large, established tumours in a mouse model.

The remaining articles in this issue of Respiratory Research Review focus on topics relevant to the patients we are seeing in our clinics: the joint adverse effect of airflow limitation in addition to emphysema on the CT scan (Eur Respir J), the reassuring absence of tumour spreading along indwelling chest drains (Respiratory), the possible tumour-enhancing properties of malignant pleural effusions (Respirology), and determining the duration of palliative care before death for patients with advanced disease (BMJ Open).

We are looking forward to feedback and comments, if your time allows.

Kind regards

Professor Lutz Beckert
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Lung cancer, genetic predisposition and smoking

Authors: Hjelmborg J et al., on behalf of the Nordic Twin Study of Cancer (NorTwinCan) collaboration

Summary: These authors analysed data from 43,512 monozygotic and 71,895 same-sex dizygotic twin individuals from the Nordic Twin Study of Cancer in an attempt to identify genetic and environmental causes of lung cancer, taking smoking status into account. There were 1508 cases of incident lung cancer recorded during a median of 28.5 years of follow-up. Nearly all of the 30 monozygotic and 28 dizygotic pairs concordant for lung cancer were current smokers at baseline and only one concordant pair was seen among never-smokers. The risk of lung cancer before a certain age conditional on lung cancer in the co-twin before that age (i.e. case-wise concordance) was significantly greater among ever-smokers than the cumulative incidence for both monozygotic and dizygotic pairs. This relative recurrence risk significantly decreased with age among monozygotic pairs but did not change among dizygotic pairs. The respective heritability values of lung cancer for current- and ever-smoker pairs were 0.37 and 0.37. Among smoking discordant pairs, the risk of lung cancer for an ever-smoker twin versus their never-smoker twin counterpart was significantly increased in both monozygotic and dizygotic pairs (respective HRs 5.4 [95% CI 2.1, 14.0] and 5.0 [3.2, 7.9]).

Comment: The genetic profile of lung cancer is becoming relevant in the treatment. In particular, the treatment of epidermal growth factor receptor mutations in adenocarcinoma of the lung enhances disease-free survival and reduces the risk of distant metastasis (Chest). It is reasonable to reflect on the influence of genetic predisposition to develop lung cancer. This group from Helsinki reviewed data on more than 40,000 monozygotic and 70,000 dizygotic twin individuals, reporting about 1500 lung cancers over 28 years. Bottom line: familial effects appear to decrease with age and the effect of smoking becomes dominant. Smoking causes lung cancer.

Reference: Thorax; Published online Nov 14, 2016

Abstract

Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval

Authors: Yousaf-Khan U et al.

Summary: The results of the fourth low-dose CT screening round for lung cancer after a 2.5-year interval, as assessed in the randomised Dutch-Belgian Lung Cancer Screening trial, were reported; there were 7915 individuals in the screening arm. There were 46 cancers detected by screening in the fourth round, and as assessed in the randomised Dutch-Belgian Lung Cancer Screening trial, were reported; there were 7915 individuals in the screening arm. There were 46 cancers detected by screening in the fourth round, and there were 28 interval cancers detected between the third and fourth screens. Compared with the second round of screening with a 1-year interval, the fourth round detected significantly higher proportions of stage I-II cancers (17.3% vs. 6.8%) and squamous-cell, bronchoalveolar and small-cell carcinomas (p=0.001). Compared with a 2-year interval, screening at 2.5-year intervals was associated with a higher nonsignificant stage distribution (stage IIIb/IV, 17.3% vs. 6.8%) and squamous-cell, bronchoalveolar and small-cell carcinomas. Most cancers discovered were in stage I-II and most cancers were adenocarcinoma; a total of 31 patients underwent resection of the tumour without any perioperative mortality. Bottom line: even outside a clinical trial, screening increased the detection of lung cancer at an early stage.

Comment: As eluded to before (Respiratory Research Review issues 96 and 107), the US and Europe are evaluating lung cancer screening with low-dose CT scans using different scanning intervals, scanning modalities and endpoints to identify early lung cancer. The European cohorts hope to demonstrate a 25% reduction in lung cancer mortality over 10 years and significantly lower false-positive rates for lung nodules. The effect of the 2.5-year screening interval was that the cancer was detected at a more advanced stage. The main implications of this report of the Dutch-Belgian NELSON trial are discussed in the accompanying editorial. Bottom line: lung cancer screening intervals should not be extended beyond 2 years.


Abstract

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Long-term psychosocial outcomes of low-dose CT screening

Authors: Brain K et al.

Summary: The long-term psychosocial impact of low-dose CT lung cancer screening was evaluated in participants from the UKLS (UK Lung Cancer Screening) randomised pilot trial, which compared such screening (n=2018) with usual care (n=2019). Participants who received positive screening results had significantly greater cancer distress scores at 2 weeks postscreening, but not at 2 years. Although anxiety and depression scores at 2 years were significantly higher in the control arm, the absolute differences were small and not clinically relevant. Compared with intervention participants, significantly fewer control participants were satisfied with their decision to participate in the trial at both 2 weeks and 2 years. Women, current smokers, participants aged ≤65 years, those with lung cancer experience and those recruited from the Liverpool area exhibited significantly greater cancer distress, irrespective of trial allocation (p<0.001).

Comment: Screening can increase anxiety and depression. This is particularly relevant in lung cancer screening, which is plagued by the detection of lung nodules in 10–50%. The authors added questionnaires at baseline and 2 years after screening to the intervention and control groups of the UKLS trial. Not surprisingly, the ‘worry score’ went up after receiving an unfavourable screening result; however, these results were not sustained over time. The accompanying editorial gives us the bottom line: anxiety related to positive test results does not breach clinically significant thresholds and appears to resolve on follow-up.


Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer

Authors: Reck M et al., for the KEYNOTE-024 Investigators

Summary: Patients with previously untreated advanced NSCLC (non-small-cell lung cancer) with PD-L1 expression on ≥50% of tumour cells and no sensitising mutation of the EGFR gene or translocation of the ALK gene were randomised to receive pembrolizumab 200mg every 3 weeks or platinum-based chemotherapy in this open-label phase 3 trial; the participants could crossover from the chemotherapy group to the pembrolizumab group if their disease progressed. Compared with chemotherapy, pembrolizumab was associated with significantly longer median progression-free survival duration (primary endpoint; 10.3 vs. 6.0 months), a significantly greater estimated 6-month overall survival rate (80.2% vs. 72.4%), a greater response rate (44.8% vs. 27.8%) and a longer median response duration (not reached vs. 6.3 months), with significantly reduced risks of disease progression or death (HR 0.50 [95% CI 0.37, 0.68]) and death (0.60 [0.41, 0.89]). Furthermore, there were fewer treatment-related any-grade and grade 3–5 treatment-related adverse events with pembrolizumab versus chemotherapy (73.4% vs. 90.0% and 26.6% vs. 53.3%, respectively).

Comment: This article, the first author a medical school classmate, is introducing a new concept by defining the expression of PD-L1 as a membranous expression of PD-L1 in at least 50% of tumour cells. Patients with adenocarcinoma without the EGFR or ALK mutation and who had not had previous systemic therapy were randomised to receive platinum-based chemotherapy or the humanised monoclonal antibody against PD-1, pembrolizumab. Pembrolizumab demonstrated an almost doubling of the survival time in the selected group. The accompanying editorial by Bruce Johnson gives us the bottom line: immunotherapy with checkpoint inhibitors will replace chemotherapy in at least a subset of lung cancers.


Joint effect of airflow limitation and emphysema on postoperative outcomes in early-stage nonsmall cell lung cancer

Authors: Shin S et al.

Summary: The combined effects of airflow limitation and emphysema severity on postoperative pulmonary complications and overall survival following complete resection for early-stage NSCLC were explored in a retrospective group of 413 men with pathological stage I or II disease. Multivariable analyses revealed that the risk of any postoperative pulmonary complication was increased in men with moderate-to-severe versus no airflow limitation (adjusted OR 2.23) and in men with versus without emphysema (1.77). Moreover, men with both airflow limitation and emphysema had a markedly increased risk of postoperative pulmonary complications (adjusted OR 8.90), and their risk of death was also increased.

Comment: The promise of screening to reduce the toll of lung cancer will only be fulfilled if patients undergo successful resection of early-stage lung cancer. A number of studies reflect on our performance of lung cancer surgery, including the increased mortality in the last few years (Eur Respir J) and how to optimise treatment for postoperative lung cancer recurrence (Eur Respir J). This study from South Korea reports that patients with emphysema, defined by CT criteria, in addition to moderate-to-severe airflow limitation have an increase of nine times more postoperative complications and poorer survival. Bottom line: emphysema detected on CT scanning is an independent risk factor of poor outcome.


Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board.

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www.turnopenpress.co.nz
Histopathology of removed indwelling pleural catheters from patients with malignant pleural diseases

Authors: Tobin CL et al.

Summary: The histological findings following removal of 41 indwelling pleural catheters from patients with underlying pleural malignancies were reported, the indwelling pleural catheters had been in situ for a median of 126 days. The underlying malignancy was mostly mesothelioma (n=18), followed by breast, tubo-ovarian and lung carcinomas. All removed indwelling pleural catheters had fully intact catheter tubing, and no evidence of direct tumour invasion or cancer cell growth was evident on the surfaces of any of the 29 indwelling pleural catheters that underwent histological examination. There was evidence of malignant cells within organising fibrinous tissues in the lumen of 11 catheters, and all 29 of the removed indwelling pleural catheters showed acute (n=10) and/or chronic tissue inflammation or invasion.

Comment: Indwelling, tunnelled catheters are frequently used to control malignant pleural effusions and allow patient-directed drainage as an outpatient. In this study from Perth, the authors reassure us that catheters do not promote cancer growth. Investigating a cohort of 49 patients with indwelling catheters, with catheter in situ times between 43 and 226 days, none showed evidence of tumour invasion or growth along the catheter surfaces. Given this reassuring performance, the authors of the accompanying editorial ask if they may evolve to deliver local therapy.

Bottom line: long-term, tunnelled chest catheters may evolve to deliver local therapy.


Outcomes of prognostic disclosure: associations with prognostic understanding, distress, and relationship with physician among patients with advanced cancer

Authors: Enzinger AC et al.

Summary: This observational research involved 590 patients with progressive metastatic solid malignancies after ≥1 line of palliative chemotherapy who were followed until death. The patients were grouped according to whether or not their oncologist had provided them with an estimate of prognosis at baseline. Willing patients (n=590) also estimated their own life expectancy, and all completed assessments on patient physician relationships, distress, advance directives and end-of-life care preferences. The patients’ median survival was 5.4 months. Although 71% of the patients indicated a desire to be informed of life expectancy, only 17.6% recalled a prognostic disclosure by their physician. Among patients who estimated their life expectancy, estimates were more realistic and less likely to differ from actual life expectancy among those who recalled prognostic disclosure versus those who did not; recall of prognostic disclosure was associated with a 17.2-month decrease in the patients’ estimates. Each 12-month increase in self-estimated life expectancy was associated with lower likelihoods of having a do-not-resuscitate order (adjusted OR 0.439 [95% CI 0.296, 0.630]) and preference for life-prolonging over comfort-oriented care (1.493 [1.091, 1.939]). No association was seen between prognostic disclosure and worse patient-physician relationship rating, sadness or anxiety.

Comment: It may be difficult for physicians to accurately estimate survival; it is not certain patients want this information and disclosing a grim prognosis may destroy hope. In a cohort of 590 patients, 419 (71%) reported that they wanted to be told their life expectancy; however, only 104 (17%) recall that this had been disclosed. The average survival in this cohort was 5.4 months; participants who had their life expectancy disclosed estimated their survival between 6 and 36 months, and participants who hadn’t had a prognostic disclosure estimated 12 months to 15 years. Bottom line: providing a prognostic disclosure didn’t increase patients’ distress or worsen the patient-physician relationship.

Reference: J Clin Oncol 2015;33(32):3809–16

Malignant pleural fluid from mesothelioma has potent biological activities

Authors: Cheah HM et al.

Summary: The potential effects of malignant pleural effusions in promoting growth, migration and chemoresistance of mesothelioma were explored using pleural fluid samples obtained from 56 patients with mesothelioma, 60 with metastatic pleural cancer and 35 with benign disease. Exposure to a 30% pleural fluid dilution from patients with mesothelioma versus controls resulted in a median 2.23-fold increase in proliferation in five mesothelioma cell lines (p<0.0001), and a median 2.13-fold increase in cell migration in six mesothelioma cell lines. Compared with saline controls, tumours infused with daily instillations of pleural fluid showed significantly faster median growth in a murine flank model of mesothelioma by day 13 (52.5 vs. 28.0 cm2; p=0.028). Adding 30% malignant pleural effusion to culture media resulted in significant protection for mesothelioma from cisplatin/pemetrexed-induced cell death in three cell lines compared with controls (p<0.001). Matched pleural fluid and cultured mesothelioma cells from the same patients did not exhibit significantly different growth effects compared with unmatched pairs.

Comment: This is a further study from our colleagues in Perth, this time exploring the effect of pleural fluid from mesothelioma directly onto cancer growth. We frequently drain these malignant pleural effusions because they cause shortness of breath and impair quality of life. In this important proof-of-concept study, the authors used cell cultures of mesothelioma cell lines infused into a murine model of mesothelioma to demonstrate potent biological effects on cancer growth. Bottom line: malignant pleural effusions may be less an ‘innocent bystander’ and may provide a medium that enhances tumour progression.


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Abstract

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What determines duration of palliative care before death for patients with advanced disease?

Authors: Bennett MJ et al.

Summary: The duration of palliative care prior to death and influencing factors were explored in a retrospective cohort of 4650 UK patients (median age 75 years) from community and hospital palliative care services; 3903 of the patients had cancer diagnoses. Significant predictors of palliative care duration prior to death were age, diagnosis and place of referral, with age independently associated regardless of diagnosis. Patients aged >75 years received 29 fewer days of palliative care than those aged <50 years, those with a noncancer diagnosis received 13 fewer days than those with cancer, and those referred to hospital palliative care received 24.5 fewer days than those referred to community palliative care services.

Comment: Palliative care services aim to relieve suffering and improve quality of life. Cumulative evidence suggests that 3–4 palliative care contacts in the 6 months before death is associated with better end-of-life care. The authors report the referral pattern of almost 5000 patients in a large dataset from Leeds, UK. The mean number of days receiving palliative care was 34 days for patients with cancer and 21 days for patients with noncancer conditions. Bottom line: the timing of referral to palliative care limits the patients’ quality of end-of-life care.

Reference: BMJ Open 2016;6:e012576

Abstract

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