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Dear APSR Colleagues

The last 12 months have seen significant advances for lung cancer. Some of these are early in the translational pipeline or are emerging technologies, but provide important targets in our fight against lung cancer.

These advances include a better understanding of the molecular basis of lung cancer, hope that low dose CT screening may reduce lung cancer mortality, improved staging techniques via EBUS, as well as novel therapies and end-of-life care.

The advances from diagnosis to treatment, both anti-cancer and palliative, provide improvements in outcomes for our patients and also encouragement for all of us to contribute more research to further benefit our lung cancer patients. There is much more to be done!

Your colleagues

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Baseline characteristics of participants in the randomized national lung screening trial

Authors: Aberle DR et al.


URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2994863/?tool=pubmed

Comment: This is an important paper because of the decision by the National Lung Screening Trial (NLST) DSM to stop the trial, based on a positive interim result (final results to be published), which indicated that low dose CT screening will reduce mortality from lung cancer.

The (NLST) is a randomized study conducted at 33 US sites, comparing lung cancer mortality among persons screened with low dose helical computerized tomography (LDCT) against persons screened with chest radiographs. The NLST enrolled 53,456 persons, with 26,733 randomly assigned to chest radiographic screening and 26,723 to LDCT screening. The characteristics of the participants were as follows: 31,533 (59%) were men, 39,234 (73%) were <65 years old, 25,779 (48%) were current smokers, and 16,839 (32%) had a college or higher degree. Median cigarette exposure was 48 pack-years.

We await the final results with great anticipation, since LDCT screening, if proven effective and cost-effective, is very likely to change the way we approach the early detection of lung cancer.

Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial

Authors: Annema JT et al.


URL: http://jama.ama-assn.org/content/304/20/2245.long

Comment: Curative intent surgery provides the best outcome for our lung cancer patients; accurate staging to correctly select patients is key to this benefit. Mediastinal nodal staging is recommended for patients with resectable non-small cell lung cancer (NSCLC).

These investigators from Ghent, Leiden, Leuven and Papworth randomized patients with resectable (suspected) NSCLC, in whom mediastinal staging was indicated based on computed or positron emission tomography. The arms were either surgical staging or endosonography (combined transesophageal and endobronchial ultrasound [EUS-FNA and EBUS-TBNA]), followed by surgical staging in case no nodal metastases were found at endosonography. Thoracotomy with lymph node dissection was performed when there was no evidence of mediastinal tumour spread. Patients (n = 241) were randomized, 118 to surgical staging and 123 to endosonography, of whom 65 also underwent surgical staging. Nodal metastases were found in 41 patients (35%; 95% confidence interval [CI] 27%-44%) by surgical staging compared with 56 patients (46%; 95% CI 37%-54%) by endosonography (P = 0.11), and in 62 patients (50%; 95% CI 42%-59%) by endosonography followed by surgical staging (P = 0.02). Thoracotomy was unnecessary in 21 patients (18%; 95% CI 12%-26%) in the mediastinoscopy group compared with 9 (7%; 95% CI 4%-13%) in the endosonography group (P = 0.02). The complication rate was similar in both groups.

Therefore, the investigators concluded that among patients with (suspected) NSCLC, a staging strategy combining endosonography and surgical staging resulted in greater sensitivity for mediastinal nodal metastases and fewer unnecessary thoracotomies, compared with surgical staging alone. These findings strengthen the data underpinning the need for clinicians dealing with lung cancer to adopt these recent endobronchial interventional procedures.
Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data

Authors: Arriagada R et al.
URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2853682/?tool=pubmed
Comment: These well regarded investigators undertook two comprehensive meta-analyses to update the information on the effects of adding adjuvant chemotherapy to surgery, or surgery plus radiotherapy, in operable non-small-cell lung cancer (NSCLC), using individual patient data.

The first meta-analysis of surgery plus chemotherapy compared with surgery alone was based on 34 trial comparisons and 8,447 patients (3,323 deaths). Adding chemotherapy after surgery improved survival (hazard ratio [HR] 0.86, 95% CI 0.81-0.92, \( P<0.0001 \)), with an absolute increase in survival of 4% (95% CI 3-6) at 5 years (from 60% to 64%).

The second meta-analysis of surgery plus radiotherapy and chemotherapy versus surgery plus radiotherapy was based on 13 trial comparisons and 2,660 patients (1,909 deaths). Again, adding chemotherapy to surgery plus radiotherapy was beneficial (HR 0.88, 95% CI 0.81-0.97, \( P=0.009 \)), representing an absolute improvement in survival of 4% (95% CI 1-8) at 5 years (from 29% to 33%).

Therefore, the conclusion was that the addition of adjuvant chemotherapy after surgery, for patients with operable NSCLC, improves survival, irrespective of whether chemotherapy was adjuvant to surgery alone or adjuvant to surgery plus radiotherapy. This study reminds us to consider the role of adjuvant therapy in patients with surgically resected lung cancer.

Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial

Authors: Croswell JM et al.
URL: http://www.annals.org/content/152/8/505.full
Comment: There is increasing interest in the use of low-dose computed tomography (CT) for screening of lung cancer, but as with most things in life, there is a balance, a yin and yang as it were, to the potential benefits of lung cancer screening.

Using Kaplan-Meier analysis, the investigators assessed the feasibility study for the National Lung Screening Trial (NLST), in which current or former smokers, aged 55 to 74 years, with a smoking history of 30 pack-years or more and no history of lung cancer (\( n = 3,190 \)) were randomised to low-dose CT or chest radiography, with baseline and one repeated annual screening, and follow up for one year after the final screening.

They found that an individual's cumulative probability of one or more false-positive low-dose CT examinations was 21% (95% CI 19% to 23%) after one screening and 33% (95% CI 31% to 35%) after two. The rates for chest radiography were 9% (95% CI 8% to 11%) and 15% (95% CI 13% to 16%), respectively. A total of 7% of participants with a false-positive low-dose CT examination and 4% with false-positive chest radiography underwent an invasive procedure as a consequence.

The conclusion was that the risks of false-positive results on lung cancer screening tests are substantial, after only two annual examinations, particularly for low-dose CT. These findings will need to be considered in the context of interim results indicating a mortality benefit in the NLST.
Lung cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

Authors: Hocking WG et al.
URL: http://jnci.oxfordjournals.org/content/102/10/722.long

Comment: The pace of medical research appears to be increasing given the recent release of interim results from the NLST low-dose CT screening study. In contrast, this study was started back in 1993, showing the need for committed and dedicated researchers, as well as funding for issues, which by necessity have a long time horizon. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was initiated specifically to determine whether screening would reduce mortality rates from PLCO cancers.

Participants \((n = 77,464)\), aged 55-74 years, were randomly assigned to the intervention arm of the PLCO Cancer Screening Trial between 1993 and 2001, and received a baseline chest radiograph (CXR), followed by three annual single-view CXRs at 10 US screening centres. A total of 564 lung cancers were diagnosed, of which 306 (54%) were screen-detected cancers. Of these, 87% were non-small cell lung cancers. Among the non-small cell lung cancers, 59.6% of screen-detected cancers and 33.3% of interval cancers were early stage (I-II).

The conclusions were that the PLCO Cancer Screening Trial demonstrated the ability to recruit, retain, and screen a large population over multiple years at multiple centres. A higher proportion of screen-detected lung cancers were early stage, but a conclusion as to whether CXR screening can reduce lung cancer mortality must await the final PLCO results, which are anticipated at the end of 2015.

Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer

Authors: Kwak EL et al.
URL: http://www.nejm.org/doi/full/10.1056/NEJMoa1006448#t=articleTop

Comment: For those of us fortunate enough to witness the changes for the better in our therapeutic armamentarium against lung cancer, this study demonstrates the benefits of high quality scientific research coupled with collaborative clinicians and the important contribution of the pharmaceutical industry.

Oncogenic fusion genes consisting of EML4 and anaplastic lymphoma kinase (ALK) are present in a subgroup of non-small-cell lung cancers, representing 2 to 7% of such tumours. These investigators explored the therapeutic efficacy of inhibiting ALK in such tumours, in an early-phase clinical trial of crizotinib (PF-02341066), an orally available small-molecule inhibitor of the ALK tyrosine kinase.

Compared to patients without ALK rearrangements, patients with rearrangements tended to be younger, had little or no exposure to tobacco smoke and had adenocarcinomas. At a mean treatment duration of 6.4 months, the overall response rate was 57% (47 of 82 patients, with 46 confirmed partial responses and one confirmed complete response); 27 patients (33%) had stable disease. A total of 63 of 82 patients (77%) were continuing to receive crizotinib at the time of data cutoff, and the estimated probability of 6-month progression-free survival was 72%, with no median for the study being reached. The drug caused grade 1 or 2 (mild) gastrointestinal side effects.
Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR

Authors: Maemondo M et al.


URL: http://www.nejm.org/doi/full/10.1056/NEJMoa0909530#t=articleTop

Comment: Data from around the world, and in particular from the Asian-Pacific region, has resulted in increasing recognition that non-small-cell lung cancer (NSCLC) with sensitive mutations of the epidermal growth factor receptor (EGFR) is highly responsive to EGFR tyrosine kinase inhibitors such as gefitinib and erlotinib.

In this RCT, 230 chemotherapy-naive patients with metastatic NSCLC and EGFR mutations were allocated to receive either gefitinib or carboplatin-paclitaxel. At the planned interim analysis of the first 200 patients, progression-free survival was significantly longer in the gefitinib group than in the standard chemotherapy group (hazard ratio [HR] for death or disease progression with gefitinib, 0.36; \( P < 0.001 \)), resulting in early termination of the study. The gefitinib group had a significantly longer median progression-free survival (10.8 months, compared with 5.4 months in the chemotherapy group; HR 0.30; 95% confidence interval 0.22 to 0.41; \( P < 0.001 \)), as well as a higher response rate (73.7% vs. 30.7%, \( P < 0.001 \)). The median overall survival was 30.5 months in the gefitinib group and 23.6 months in the chemotherapy group (\( P = 0.31 \)). The most common adverse events in the gefitinib group were rash (71.1%) and elevated aminotransferase levels (55.3%), and in the chemotherapy group, neutropenia (77.0%), anaemia (64.6%), loss of appetite (56.6%), and sensory neuropathy (54.9%). One patient receiving gefitinib died due to interstitial lung disease.

This study demonstrates that first-line gefitinib for patients with advanced NSCLC, who were selected on the basis of EGFR mutations, improved progression-free survival, with acceptable toxicity, as compared with standard chemotherapy. As EGFR mutations are much more frequent in the Asian-Pacific region than in Western countries, these findings have important practice implications for us.

Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer

Authors: Weiss J et al.


URL: http://stm.sciencemag.org/content/2/62/62ra93.full

Comment: This is another example of the significant advances that are likely to result from diligent, focussed and quality translational research. Unlike lung adenocarcinomas with epidermal growth factor receptor (EGFR) mutations or EML4-anaplastic lymphoma kinase (ALK) fusions, which respond to treatments that inhibit EGFR and ALK, respectively, therapeutically exploitable genetic alterations in squamous cell lung cancer are currently lacking.

These investigators identified frequent and focal fibroblast growth factor 1 (FGFR1) gene amplification in squamous cell lung cancers (\( n = 155 \)), but not in other lung cancer subtypes. Using cell-based screening with the FGFR inhibitor PD173074 in a large panel of lung cancer cell lines (\( n = 83 \)), they demonstrated that this compound inhibited growth and induced apoptosis specifically in those lung cancer cells with FGFR1 gene amplification.

We look forward to other studies confirming that FGFR1 gene amplification is common in squamous cell lung cancer, as well as clinical trials that will hopefully demonstrate that FGFR inhibitors may be a viable therapeutic option in lung squamous cell carcinomas.
Multiple independent loci at chromosome 15q25.1 affect smoking quantity: a meta-analysis and comparison with lung cancer and COPD

Authors: Saccone NL et al.
URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2916847/?tool=pubmed

Comment: Recently, genetic association findings for nicotine dependence, smoking behaviour, and smoking-related diseases converged to implicate the chromosome 15q25.1 region, which includes the CHRNA5-CHRNA3-CHRNB4 cholinergic nicotinic receptor subunit genes. These investigators performed a meta-analysis across 34 datasets derived from subjects of European ancestry, including 38,617 smokers who were assessed for the number of cigarettes smoked per day, 7,700 lung cancer cases and 5,914 lung cancer-free controls (all smokers), as well as 2,614 COPD cases and 3,568 COPD-free controls (all smokers).

The study demonstrated statistically independent associations of rs16969968 and rs588765 with smoking (mutually adjusted \(P\) values <10\(^{-35}\) and <10\(^{-8}\), respectively). rs578776 also demonstrated association with smoking, after adjustment for rs16969968 (\(P<10^{-8}\)).

Replication of lung cancer susceptibility loci at chromosomes 15q25, 5p15, and 6p21: a pooled analysis from the International Lung Cancer Consortium

Authors: Truong T et al.
URL: http://jnci.oxfordjournals.org/content/102/13/959.long

Comment: This consortium conducted a coordinated pooled genotyping study, investigating single nucleotide polymorphisms at chromosomes 15q25 (rs16969968, rs8034191), 5p15 (rs2736100, rs402710), and 6p21 (rs2256543, rs4324798) from 21 case-control studies that included 11,645 lung cancer patients and 14,954 control subjects, of whom 85% were white and 15% were Asian.

Associations between 15q25 and the risk of lung cancer were replicated in white ever-smokers (rs16969968: odds ratio [OR] 1.26, 95% confidence interval [CI] 1.21 to 1.32, \(P_{\text{trend}} = 2 \times 10^{-25}\)), and this association was stronger for those diagnosed at younger ages. For the chromosome 5p15 region, statistically significant associations were confirmed in whites, for both rs2736100 (OR 1.15, 95% CI 1.1 to 1.2, \(P_{\text{trend}} = 1 \times 10^{-10}\)) and rs402710 (OR 1.14, 95% CI 1.09 to 1.19, \(P_{\text{trend}} = 5 \times 10^{-8}\)). Similar associations were identified in Asians (rs2736100: OR 1.23, 95% CI 1.12 to 1.35, \(P_{\text{trend}} = 2 \times 10^{-5}\); rs402710: OR 1.15, 95% CI 1.04 to 1.27, \(P_{\text{trend}} = 0.007\)).

These two studies demonstrate the contribution of the Human Genome Project and modern molecular techniques to our understanding of clinical observations, i.e. there is a likely contribution of family history to an individual's risk for smoking and developing lung cancer. Once validated in prospective studies, such knowledge will enable us to more accurately risk-stratify individuals who are at risk.
Gene expression-based prognostic signatures in lung cancer: ready for clinical use?

Authors: Subramanian J, Simon R


URL: http://jnci.oxfordjournals.org/content/102/7/464.long

Comment: Another product of the Human Genome Project is our relative ease in proofing the expression of thousands of genes on a single microarray or gene chip. Microarrays have been extensively used to study gene expression in lung cancer cells. One of the aims of such studies is the development of gene expression-based prognostic signatures for lung cancer. Indeed some of these tests are being marketed and are now in use for certain cancers such as breast cancer.

The ultimate aim of such studies should be the development of well-validated clinically useful prognostic signatures that would improve therapeutic decision making beyond current standards of practice. This leading bioinformatics group has critically reviewed published studies and found little evidence that any of the reported gene expression signatures are ready for clinical application, and has identified problems in the design and analysis of many of the studies. The authors suggest a set of guidelines to aid the design, analysis, and evaluation of prognostic signature studies. These guidelines emphasize the importance of focused study plans to address specific, medically important questions, and the use of unbiased analysis methods to evaluate whether the resulting signatures provide evidence of medical utility beyond prognostic factors based on standard of care.

Those of us undertaking genomic research will need to remember the high quality and rigour displayed by “practice-changing” clinical trials, which convince clinicians of the need to change practice or policy; such quality is evident in most RCTs of therapy, particularly those required for registration studies.

Early palliative care for patients with metastatic non-small-cell lung cancer

Authors: Temel JS et al.


URL: http://www.nejm.org/doi/full/10.1056/NEJMoa1000678#=article&t=articleTop

Comment: Due to the poor outcomes of lung cancer, many of us work very closely with and practice palliative care medicine. This study provides the evidentiary base for remembering to do this early and for more of our patients. The investigators are to be congratulated on conducting high quality research in an area that researchers traditionally consider to be challenging.

This research team randomly assigned patients with newly diagnosed metastatic non-small-cell lung cancer to receive either early palliative care integrated with standard oncological care or standard oncological care alone, with assessment of quality of life and mood. Of the 151 patients who underwent randomization, 27 died by 12 weeks and 107 (86% of the remaining patients) completed the assessments. Patients assigned to early palliative care had a better quality of life than did patients assigned to standard care alone (mean scores on the FACT-L scale, in which scores range from 0 to 136, with higher scores indicating better quality of life: 98.0 vs. 91.5; \( P = 0.03 \)). In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16% vs. 38%, \( P = 0.01 \)). Despite the fact that fewer patients in the early palliative care group than in the standard care group received aggressive end-of-life care (33% vs. 54%, \( P = 0.05 \)), median survival was longer among patients receiving early palliative care (11.6 months vs. 8.9 months, \( P = 0.02 \)).

This study indicated that care at the end of life was less aggressive but survival was longer in patients who received early palliative care, compared with those who received standard care. These findings should help reaffirm the place of palliative care in our multidisciplinary lung cancer teams.
Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised controlled lung cancer screening trial

Authors: van der Aalst CM et al.


URL: http://thorax.bmj.com/content/65/7/600.long

Comment: With the results from the National Lung Screening Trial (NLST) just around the corner and the results from the Dutch–Belgian randomised controlled lung cancer screening (NELSON) trial expected some time later, it seems lung cancer screening may become a reality. Screening may also provide secondary benefits apart from lung cancer detection, in that smokers may be more receptive to cessation messages at the time of screening. With this in mind, the NELSON investigators report the effect of lung cancer screening on smoking abstinence in male smokers participating in the NELSON trial.

Participants aged 50 to 75, who were at high risk for lung cancer, were randomised to either lung cancer screening using low-dose CT or no screening. All smokers received written material on cessation. Smoking behaviour was evaluated by questionnaire in two random samples of male smokers in the screening arm (n = 641) and control arm (n = 643), before and 2 years after randomisation. The investigators found that 16.6% of the participants quit smoking; however, screening was associated with a lower rate of prolonged abstinence (14.5%) compared with no screening (19.1%) (odds ratio 1.40, 95% confidence interval 1.01 to 1.92; \( P <0.05 \)), although there was no significant difference when an intention-to-treat analysis was performed.

This study shows that trial participants were inclined to stop smoking more than average (i.e. 3-7% in the general adult population), and suggests that screening is indeed a ‘teachable moment’, at which smoking behaviour can be improved. However, the rate of smoking abstinence was significantly lower in those who underwent screening than in the control group, raising the concern that screening may create some relief among smokers based on false confidence.