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Complications associated with endobronchial ultrasound-guided transbronchial needle aspiration: a nationwide survey by the Japan Society for Respiratory Endoscopy.

Authors: Asano, F. et al.

Reference: Respir Res, 2013, 14: 50-58

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3655828/

Comment

Endobronchial ultrasound-guided needle aspiration (EBUS-TBNA) is thought to be a relatively safe method of obtaining cytological and histological diagnosis of paratracheal and peribronchial lesions and is an especially sensitive and specific means for mediastinal lymph node staging of lung cancer. It has largely replaced mediastinoscopy in this setting, owing to it's comparable diagnostic rate, minimal invasiveness and cost benefit. With increasing use of TBNA in staging and diagnosis of lung cancer around the world, occasional reports of significant complications have led some physicians to question whether the previously reported safety of EBUS-TBNA by skilled and experienced operators is a true reflection of its safety in everyday clinical practice.

This Japanese study, involved a nationwide, retrospective questionnaire survey of senior fellows, each representing 455 institutions that perform EBUS-TBNA. Information regarding their institution's experience with the procedure during an 18month period, January 2011 – June 2012, was requested. Two-hundred and ten (46.2%) of these facilities performed 7345 cases of EBUS-TBNA using a convex probe with the main indication being diagnosis of suspected lung cancer and staging of lung cancer and the main targets hilar and mediastinal lesions as well as a small number in the lung parenchyma. Complications due to procedures performed simultaneously with EBUS-TBNA were excluded.

Complications were reported for 1.23% of cases (n=90) in 32 facilities, a rate higher than reported in previous meta-analyses but may at least in part reflect the broader definition of complications, in particular haemorrhage, which was the commonest reported complication (50 cases with only 1 case of massive haemorrhage reported). Infectious complications occurred 14 cases. Rates of other complications such as respiratory failure, pneumothorax, cardiovascular complications and tumour rupture were low, and 1 case of cerebral infarction resulted in the only reported death in the study (mortality rate 0.01%). Of the cases with complications, most were performed by operators with less than 50 cases of EBUS-TBNA experience and 47.4% by operators who had not previously attended a hands-on training course. There was no statistically significant difference in complication rates for target sites. The rate of device breakage was higher in this study than previously reported and is an important consideration in the cost analysis of EBUS-TBNA.

This study is limited by recall bias and variable follow up methods, with the potential underestimation of complications. However it is consistent with other studies reporting a low complication rate of EBUS-TBNA. It does show the potential for severe complications and costly device breakage especially for less-experienced operators and highlights the need for guidelines on the safe performance of the procedure.

Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.

Authors: Shaw, A. T. et al.

Reference: N Engl J Med, 2013, 368: 2385-2394.

URL: http://www.nejm.org/doi/full/10.1056/NEJMoa1214886

Comment

This study compared the oral small-molecule anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor Crizotinib with standard chemotherapy in the treatment of patients with non-small cell lung cancers identified as having rearrangements of the ALK gene. Prior single-group studies that have shown Crizotinib to produce marked response rates in patients with advanced ALK-positive NSCLC.

This Pfizer sponsored phase 3, open-label trial randomly assigned patients with locally advanced or metastatic ALK-positive NSCLC (ECOG 2 or less) who had progressed after one prior platinum-based chemotherapy regimen, to treatment with either Crizotinib or intravenous chemotherapy (either Pemetrexed or Docetaxel). Although 227 of the 347 patients in the intention-to-treat population had disease progression or died by the time of data cut off, median progression-free survival was found to favour the Crizotinib group (7.7 months versus 3 months). Response rates were found to be significantly higher in the Crizotinib group also (65% versus 20% in the intention-to-treat population). Median overall survival for Crizotinib was 20.3 months versus 22.8months for chemotherapy although this was only an interim analysis. Sixty-four percent of the chemotherapy group who experienced disease progression subsequently crossed over to receive Crizotinib as part of a separate study, which is a confounding factor in the interpretation of overall survival data. Overall, more adverse events of any cause were reported in the Crizotinib group including elevated aminotransferase levels and interstitial lung disease, although the incidence of grade 3 or 4 adverse events was similar. Despite this, patients in the Crizotinib group reported a significantly greater overall reduction in lung cancer symptoms and global quality of life. Three treatment-related deaths occurred in the Crizotinib group and 1 patient died of hepatic failure after the data cut-off date compared to one treatment-related death in the chemotherapy group.

For the outcomes measured in this study, Crizotinib was found to be more effective than Pemetrexed and even more so Docetaxel as a second-line treatment for patients with advanced ALK-positive NSCLC. However, patient-reported outcomes have to be considered in the setting of an open-label trial. Nonetheless, this is another example of how modern cancer treatment is evolving, with the chance to achieve precision medicine through personalising treatments. Conversely the relative infrequency speaks to the heterogeneity of lung cancer, and the ongoing challenge of finding treatments for small subsets of molecularly defined subsets of lung cancer; nevertheless the sheer numbers of incident lung cancer makes this a very worthwhile pursuit.

Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial.

Authors: Garassino, M. C., O. et al.

Reference: Lancet Oncol., 2013, 14: 981-988.

URL: http://www.mdconsult.com/das/article/body/436990336-2/jorg=journal&source=&sp=26889112&sid=0/N/1182052/s1470204513703103.pdf?issn=1470-2045

Comment

Whilst EGFR tyrosine kinase inhibitors are the favoured treatment choice for patients with advanced non-small cell lung cancer (NSCLC) with EGFR mutations, their efficacy in treating patients with EGFR wild-type tumours is less clear. Erotinib is currently approved, along with Docetazel and Pemetrexed, for second-line treatment of molecularly unselected patients in many jurisdictions based on a previous RCT. This study examined the efficacy of Erotinib compared with standard second-line chemotherapy in patients with EGFR wild-type tumours with overall survival as the primary endpoint.

The design was a multicentre randomised controlled trial involving 52 Italian hospitals. Two-hundred and twenty-two patients with wild-type EGFR tumours (genotyped in two independent laboratories) who failed platinum-based chemotherapy and were ECOG status 2 or less were randomised to treatment with Erotinib (n=112) or Docetaxel (either 75 mg/m(2) every 21 days or 35 mg/m(2) on days 1, 8, and 15, every 28 days) (n=110) on an intention-to-treat basis.

After a median follow up of 33 months, median overall survival was found to be better for the Docetaxel group (8.2 months (95% CI 5.8-10.9)) than for the group treated with Erotinib (5.4months (4.5-6.8)) (adjusted hazard ratio 0.73, 95% CI 0.53-1.00; p=0.05). Median progression-free survival also favoured the Docetaxel group (2.9 months (95% CI 2.4-3.8) versus 2.4 months (2.1-2.6) (adjusted HR 0.71, 95% CI 0.53-0.95; p=0.02)). However patients treated with Docetaxel received a median of 3 cycles whereas those treated with Erotinib received a median of 2 cycles with a large number of patients ceasing treatment due to disease progression or death (196 patients had disease progression and 187 died). Also approximately half of the patients in each group received a third-line treatment with another chemotherapeutic agent and a further 11 patients crossed treatment arms. It was reported that quality of life data had not yet been analysed and would be reported separately. Treatment-related serious adverse events occurred in 4 patients in the Docetaxel group and 2 patients in the Erlotinib group. Of the commonest grade 3-4 toxicities, 20% of the Docetaxel group developed a low neutrophil count (versus nil from the erotinib group) and dermatological side effects were more common with the Erotinib group.

The authors of this study concluded that treatment with Docetaxel is more effective than Erlotinib as a second-line treatment for patients with advanced wild-type EGFR tumours, which further emphasises the targeted nature of Erlotinib therapy. However a small percentage of wild type cases had a partial response to erlotinib, and the reason ie underlying biology is unknown. In practice, docetaxel is a treatment option for EGFR wild type NSCLCs but with the increasing recognition of other actionable mutations eg ALK fusions, the future will be to also undertake molecular testing beyond EGFR to identify patients in whom there may be another effective targeted therapy.

Prediction of survival by [18F]fluorodeoxyglucose positron emission tomography in patients with locally advanced non-small-cell lung cancer undergoing definitive chemoradiation therapy: results of the ACRIN 6668/ RTOG 0235 trial.

Authors: Machtay, M., F. et al.

Reference: J Clin Oncol, 2013, 31: 3823-3830.

URL: http://jco.ascopubs.org/content/31/30/3823.long

Comment

The introduction of [(18)F] fluorodeoxyglucose positron emission tomography (FDG-PET) has been vital to the development of accurate staging systems for NSCLC. Since it is sensitive for detecting metabolically active tumour pre-treatment, it can be hypothesised that FDG-PET would also be useful in assessing response to treatment, which is often difficult with computed tomography, especially post radiotherapy. Using standardized uptake values (SUV), this multi-centre prospective study evaluated the use post-treatment FDG-PET as a predictor of overall survival in stage III NSCLC.

Participants were patients with inoperable stage III NSCLC who were planned for immediate definitive platinum-based doublet chemotherapy with concurrent radiotherapy and had PET within 6 weeks prior to enrolment. 173 enrolled patients from 37 institutions had evaluable post-treatment PET 14 weeks after the completion of radiotherapy or at least 4 weeks after completion of further adjuvant chemotherapy. Higher post-treatment peak and maximum SUVs (SUVpeak and SUVmax) were found to be significantly associated with poorer survival in a continuous variable model but specific cut-off SUVpeak values correlating with overall survival could not be determined.

This prospective study has shown that FDG-PET may have a role in assessing treatment response and predicting the prognosis of patients with NSCLC treated with concurrent chemoradiation. However whether this information could potentially be used to influence treatment decisions and improve clinical outcomes is yet to be determined.

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Results of initial low-dose computed tomographic screening for lung cancer.

Authors: Church, T. R. et al.

Reference: N Engl J Med, 2013, 368: 1980-1991

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3762603/

Results of the two incidence screenings in the National Lung Screening Trial .

Authors: Aberle, D. R. et al.

Reference: N Engl J Med, 2013, 369: 920-931.

URL: http://www.nejm.org/doi/full/10.1056/NEJMoa1208962

Comment

These papers follow the landmark U.S. National Lung Cancer Screening study published in 2011, which was the first to fundamentally show that low-dose CT screening can reduce lung cancer mortality, with a 20% relative reduction in lung cancer mortality compared with radiography.

Church et al describe screening, diagnosis, and limited treatment results from the initial round of screening in the NLST at 33 U.S. centers, from August 2002 through April 2004, during which they recruited 55 to 74 year old asymptomatic participants, with at least 30 pack-years of smoking. The participants were randomly assigned to undergo annual screening, with the use of either low-dose CT or chest radiography, for 3 years; 26,715 to low-dose CT and 26,724 to chest radiography. Of these, 26,309 participants (98.5%) and 26,035 (97.4%), respectively, underwent screening. Sensitivity and specificity of 93.8% and 73.4% for low-dose CT was better than 73.5% and 91.3% for chest radiography respectively, in keeping with the previously reported reduction in lung cancer mortality.

Aberle et al reported on the performance of the two screening tests based on the first two incidence screenings (T1 and T2) in the NLCS study was presented. Low-dose CT was positive for 27.9% of participants at T1 and 16.8% at T2, which was more than three times higher than the number of positive tests in the radiography group (6.2% positive tests at T1 and 5.0% at T2). The Low-dose CT group had 2.7 times more lung cancer diagnoses than radiography, with the sensitivity of low-dose CT found to be 94.4% compared to 59.6% for radiography at T1. However the positive predictive value for low-dose CT at T1 was lower than that for radiography (2.2% versus 4.4%). Positive predictive values for both groups increased at T2. Negative predictive values were similar for both groups (99.9% and 99.8% for low-dose CT and radiography at T1 respectively). The increase in early stage lung cancer diagnoses with low-dose CT was associated with a decrease in late-stage diagnoses over the course of the trial. This study showed

that the mortality benefit observed from annual screening of a high-risk cohort with low-dose CT in the NLST was associated with increased detection of early stage lung cancers and reduction in the number of late-stage lung cancers diagnoses.

Consequently, questions are raised as to whether the performance of low-dose CT may be improved with better selection of high-risk individuals using risk prediction models and the refinement of definitions of positive and negative screens. Determining appropriate screening intervals based on risk is another consideration. Research on novel methods for early detection and screening for lung cancer is also eagerly awaited.

Selection criteria for lung-cancer screening.

Authors: Tammemägi M.C. et al.

Reference: N Engl J Med, 2013; 368:728-736

URL: http://www.nejm.org/doi/full/10.1056/NEJMoa1211776

Probability of cancer in pulmonary nodules detected on first screening CT.

Authors: McWilliams, A. et al.

Reference: N Engl J Med, 2013, 369: 910-919.

URL: http://www.nejm.org/doi/full/10.1056/NEJMoa1214726

Comment

Relatively low positive predictive values reported for low-dose CT (LDCT) screening for lung cancer highlight the need to consider ways to improve the efficiency of LDCT screening by reducing the numbers needed to screen. Moreover, the high false positive rates generally reported translate to a significant burden of medical and participant, physical and psychological costs from current inclusion criteria for LDCT screening.

These Investigators have contributed two significant papers addressing the potential role of risk prediction for LDCT lung cancer screening, addressing both factors in the person as well as making use of data available on the pulmonary nodule once detected for the purposes of ascribing risk of malignancy in that nodule.

Firstly Tammemagi et al modified their 2011 lung-cancer risk-prediction model from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial to develop and then validate the new PLCOM2012 model from the PLCO control and intervention groups who had ever smoked. As compared to the NLST criteria, the PLCOM2012 criteria had improved sensitivity

(83.0% vs. 71.1%, P<0.001) and positive predictive value (4.0% vs. 3.4%, P=0.01), without loss of specificity (62.9% and. 62.7%, respectively; P=0.54). These data showing that this new model performed better than the NLST criteria for identifying appropriate screenees for LDCT have major implications for the implementation of lung cancer screening given the expected improvement in cost-effectiveness from the increased efficiency. Time will tell if policy makers and funders consider such modelling sufficient to effect translation to clinical practice, as it is hard to imagine another large scale trial of the magnitude of the NLST to obtain randomised evidence.

The study by McWilliams et al utilised data from two similar but separate low-dose CT screening cohorts to determine the probability of their screen-detected pulmonary nodules being malignant. The British Columbia Cancer Agency (BCCA) cohort comprised participants from several chemoprevention trials and had more former rather than current smokers and with fewer pack years. More participants in the Pan-Canadian Early Detection of Lung Cancer Study (PanCan) had a family history of lung cancer. In both cohorts, a test was considered positive if it showed “any noncalcified pulmonary nodule or area of nonsolid density at least 1mm in diameter on lung parenchymal windows.” However this study included only participants with at least 1 noncalcified nodule on their baseline scan and without lymphadenopathy. Follow up scans were performed at 3-12 month intervals determined by the maximum diameter of the long axis of the largest nodule.

For the 1871 participants in the PanCan group with nodules, the rate of cancer diagnosis was 5.5% over a median follow up of 3.1 years. The BCCA group had 1090 participants with nodules, of which 3.7% were found to have lung cancer over a median follow up of 8.6 years. The characteristics of study participants shown in univariate analysis to be consistently associated with lung cancer included older age, any emphysema detected on CT and a lower percent of FEV1 predicted. Based on their predictive models, the authors reported that predictors of lung cancer included older age, female sex, family history of lung cancer and presence of emphysema. Nodule characteristics predictive of cancer included larger size, upper lobe location, part-solid nodule type, lower nodule count and spiculation. The probability of perifissural nodules being malignant was zero (0 of 571 nodules). A non-linear relationship between nodule size and cancer was observed. Performance assessments of the model supported its predictive accuracy.

This study has produced a nodule risk-prediction model that may help in the interpretation of low-dose CT scans performed in lung cancer screening programs. It may also help to determine the appropriate management and follow up of pulmonary nodules identified in this setting. We look forward to results of validation studies from around the world to determine the generalizability of these important data.

Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology.

Authors: Lindeman, N. I. et al.

Reference: Arch Pathol Lab Med, 2013, 137: 828-860.

URL: http://www.sciencedirect.com/science/article/pii/S152515781300041X

Comment

Recent major advances in the understanding of genetic alterations in lung cancer and their therapeutic implications have significantly changed our diagnostic and management approach to lung adenocarcinoma in particular. The authors of this study are representatives of the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC) and the Association for Molecular Pathology (AMP). They systemically reviewed data published on Epidermal Growth Factor Receptor-mutated (EGFR) and Anaplastic Lymphoma Kinase-positive (ALK) lung cancer from January 2004 through February 2012 and proposed evidence-based clinical practice guidelines for these lung cancer subgroups.

For clinicians, the main messages from these guidelines are that molecular testing for EGFR mutations and ALK fusions should be used in patients with advanced lung adenocarcinoma or mixed lung cancers with adenocarcinoma components to help guide patient selection for targeted therapies and that patients in this category should not be excluded from molecular testing on the basis of clinical characteristics.

This consensus paper is valuable in helping us translate emerging scientific evidence to improve clinical standards. These recommendations serve to provide relevant guidance to the multidisciplinary lung cancer team. In due course, with the predicted increased in the recognition of somatic lung cancer mutations, particularly actionable mutations combine with the rapid progress in technology such as with next-gen massively parallel sequencing, the recommendations will need to be updated in the context of emerging evidence in this field.

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Virtual bronchoscopic navigation combined with ultrathin bronchoscopy.

Authors: Asano, F. et al.

Reference: Am J Respir Crit Care Med, 2013, 188: 327-333.

URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201211-2104OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed&#.UvBx59GIqUk

Comment

One of the most common problems facing pulmonologists and bronchoscopists is the approach to the assessment of small peripheral lung lesions (often called PPLs). As lung cancer is now dominated by the adenocarcinoma subtype, which typically presents as a peripheral lung lesion, this problem is likely ongoing. Furthermore, as LDCT screening has now been shown to reduce lung cancer mortality and thus increasingly used coupled with increasing use of CTCA and CTPA, the PPLs that we face in the next few years are likely to be smaller than the usual symptomatic lesions, and be even more challenging to diagnose.

Modern bronchoscopy to sample PPLs often makes use of the effective modality endobronchial ultrasound (EBUS) mediated trans-bronchial biopsies. Alternatively, trans-thoracic needle aspiration is also effective but may be difficult in those with severe lung disease, particularly cystic emphysema. Where the lesions are very peripheral, many of us are challenged by difficulty identifying the subsegmental bronchus of interest and also the physical challenge of navigating into the candidate bronchus. Anatomy is a major factor, for example it is well recognised that upper lobe lesions and those with more acute angles can be difficult even for the most experienced bronchoscopists.

Virtual bronchoscopic navigation (VBN) assists the bronchoscopists in navigating to peripheral pulmonary lesions but the physical dimension of conventional bronchoscopes may hinder identifying the precise bronchus to pass the EBUS guide-sheath/biopsy forceps. Some of us resort to using smaller paediatric bronchoscopes and therefore eagerly await improvements in technology as thinner and thinner bronchoscopes are becoming available. In this study of this generation of ultrathin bronchoscopes, despite not increasing the diagnostic yield for PPLs, subgroup analysis showed improvement in the diagnostic yields by VBN for lesions in the right upper lobe, lesions invisible on posterior–anterior radiographs, and lesions in the peripheral third of the lung field. Thus, the bronchosopist's armamentarium is increasing, and bode well for the notion that technological advances, further research and clinical experience will enable us to have the right tool to use at the right time in the right patient to achieve the best outcomes for our patients.

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Mutational heterogeneity in cancer and the search for new cancer-associated genes.

Authors: Lawrence M. S. et al.

Reference: Nature, 2013, 499: 214-8

URL: http://www.nature.com/nature/journal/v499/n7457/full/nature12213.html

Comment

This paper may not be light reading for the clinician but represents one of several important genomic papers discussing one of the fastest moving areas in cancer including lung cancer. International efforts such at The Cancer Genome Atlas (TCGA) and many other groups are using the latest genomic technologies (next generation sequencing or more correctly massively parallel sequencing) methods to identify somatic mutations in human cancer compared to paired constitutional samples.

TCGA is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer from the US NIH and aims to study 500 lung adenocarcinomas and 500 squamous cell carcinomas to identify specific mutations in an attempt to better understand lung cancer biology and also to discover actionable genetic alterations which could be at the DNA, RNA or even epigenome levels.

The study by Lawrence is relevant to human cancers including lung by showing that the discovery of somatic mutations in tumours can be readily influenced by the bioinformatics approach taken to interrogate genomic data due to mutational heterogeneity. While there are several massively parallel platforms, it would seem that the overall performance from these are likely to be largely satisfactory for obtaining the desired coverage of genomic sequences. However, it appears that the bioinformatics pipeline is not as mature, and like other quantitative research, care must be taken to understand strengths and limitations, potential false positives and false negatives, if we are to translate the “genomic revolution” into benefits for our patients. Much more information and resources are available at TCGA’s website at www.cancergenome.nih.gov/.

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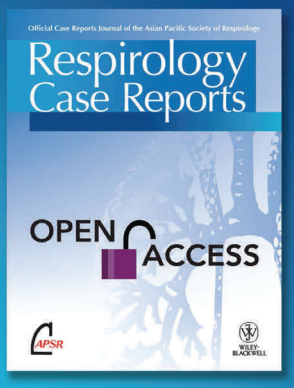

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