



Mediastinoscopy, an invasive procedure requiring general anesthesia, is currently regarded as the diagnostic standard for staging of lung cancer. New research has suggested that endobronchial and transesophageal endoscopic ultrasound-guided fine-needle aspiration (EBUS-FNA, EUS-FNA) are more sensitive than traditional transbronchial needle aspiration in patients with lung cancer. The research, printed in the February issue of the *Journal of the American Medical Association*, demonstrates that by combining these two biopsy methods a less invasive complementary and complete staging of suspected lung cancer patients is possible.

The aim of the study was to compare the diagnostic accuracy of three methods of minimally invasive endoscopic staging, including EBUS-FNA, EUS-FNA and their combinations. Noninvasive staging was performed using computed tomography (CT) or positron emission tomography (PET), but the study notes that CT is associated with high rates of false positives and PET is associated with high rates of false negatives.

Current recommendations set by the American College of Chest Physicians suggest invasive staging with tissue confirmation of suspected metastatic mediastinal lymph nodes, with mediastinoscopy or thoracoscopy being the current diagnostic standard, however, more recently less invasive methods have emerged as potential alternatives.

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The investigation, led by Michael Wallace from the Mayo Clinic in Jacksonville, FL, USA, not only anticipated that combining the two biopsy methods would provide a less invasive procedure for lung cancer staging, but also that the newer endobronchial and transesophageal procedures would prove to be more

accurate than transbronchial needle aspiration.

A total of 138 patients with suspected lung cancer were used in the study and underwent transbronchial needle aspiration, EBUS-FNA and EUS-FNA performed sequentially as a single combined procedure. The researchers found that EBUS-FNA, was more sensitive than EUS-FNA with a detection rate of 69 versus 36% of malignant lymph nodes.

Such procedures are typically limited by 'blind spots' not covered by certain procedures. Wallace explained, "It is a disadvantage that patients require 2 procedures rather than just 1, but we found that all of our 138 patients really benefited from both. Moving forward, it will be interesting to define which patients might be able to have just one procedure."

The combination of EBUS-FNA and EUS-FNA had a higher estimated sensitivity than either method alone. The two procedures also had higher sensitivity and higher negative predictive value for detecting lymph nodes in any mediastinal location and for patients without lymph-node enlargement on chest CT.

"We were able to set up a close collaboration of experts, and our gastro enterologists and pulmonologists were able to work together; this was important" Wallace explained. "Our program is well integrated."

The authors also predicted that advances such as this will be important for other centers as well, and anticipates that a shift will take place in the field, with an increased emphasis on minimally invasive biopsies for patients with suspected lung cancer.

"I think we're going to start seeing more interventionalists specializing in minimally invasive techniques," he said. "I think there will be more surgeons specializing in a couple of these procedures. We are moving from organ-based to more disease-based specialization, and we see evidence of this in the emergence of things like comprehensive cancer centers."

Source: Wallace MB, Pascual JM, Raimondo M *et al.*: Minimally invasive endoscopic staging of suspected lung cancer. *JAMA* 299(5), 540–546 (2008).

In brief...

Post hoc analysis of a randomized, double-blind, placebo-controlled efficacy and tolerability study of tramadol extended release for the treatment of osteoarthritis pain in geriatric patients

Vorsanger G, Xiang J, Jordan D, Farrell J: *Clin. Ther.* 29 (Suppl), 2520–2535 (2007). Discusses the efficacy of tramadol extended release (ER) in osteoarthritis pain. Once-daily tramadol ER was evaluated in a randomized, double-blind, placebo-controlled, parallel-group study in 1020 osteoarthritic patients aged over 65 years, for 12 weeks. The efficacy and tolerability of 100-, 200-, 300- and 400-mg doses of the drug were tested. Results indicated that patients treated with tramadol ER demonstrated a significant improvement in the Western Ontario and McMaster Universities Osteoarthritis Index and pain-related sleep parameters.

A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with Type 2 diabetes.

Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Scherthaner G: *Diabetologia* 51(3), 408–416 (2008).

A 52-week multinational, randomized, open-label, parallel-group, noninferiority trial was performed to compare clinical outcomes following supplementation of oral glucose-lowering drugs. Insulin-naïve adults received either insulin detemir or glargine once-daily to target fasting plasma glucose. Baseline HbA(1c) decreased from 8.6 to 7.2 and 7.1% with detemir and glargine, respectively. Fasting plasma glucose also improved (10.8 to 7.1 and 7.0, respectively). The results indicated that supplementation of oral agents with detemir or glargine achieves clinically important improvements in glycemic control with low risk of hypoglycaemia.

Determination of clopidogrel main metabolite in plasma: A useful tool for monitoring therapy?

Mani H, Toennes SW, Linnemann B *et al.* *Ther. Drug Monit.* 30(1), 8–89 (2007).

This study determines if the analysis of clopidogrel and its main carboxylic acid metabolite in plasma provides information regarding the variability of platelet aggregation inhibition in clopidogrel-treated patients. Clopidogrel carboxylic acid was detected in 95% of the patients. In total 40% displayed a normal range of aggregation response. Further study showed that a large range of carboxylic acid concentrations was detected, indicating a high variability of drug metabolism among patients.

In utero treatment of brittle bones

A new study lead by Imperial College, London, UK, has offered an insight into the use of *in utero* stem cell treatment in babies with brittle bones.

The research has now been moved to The University of Queensland, Australia and is led by Nicholas Fisk who speculated that the work could lead to improvements in the treatment of other disabling conditions such as muscular dystrophy and congenital brain disease.

“Our work suggests that, in the future, it could be possible to take stem cells from an unborn baby carrying the abnormal *OI* gene, manipulate them to correct the errant gene and then put them back into the fetus to allow it to develop properly”

Osteogenesis imperfecta, the inherited form of brittle bone disease, is known to affect babies while still in the womb. The phenotypic properties of the disabling disease are due to collagen being unable to develop properly in the womb. This leads to weak bones and stunted growth and can be detected by DNA testing or ultrasound before birth.

The team led by Fisk studied mouse models of human type III osteogenesis imperfecta. Fetal mesenchymal stem cells were injected through the wall of the uterus into 14-day-old fetuses. At

the age of 3 months, treated mice had suffered just a third of the long-bone fractures compared with untreated mice. It was also discovered that the bones of these mice were stronger, thicker and longer than those with the disease that had not received the transplants.

‘It will help us to understand what it is that leads to such a marked effect after a single transplant of stem cells, so that this can be harnessed to improve the results of stem cell therapy in repairing adult tissues and degenerative conditions.’

Fisk concluded that, “It has significance not only for treating this and other disabling conditions in affected fetuses inside the womb, but also for future related work. It will help us to understand what it is that leads to such a marked effect after a single transplant of stem cells, so that this can be harnessed to improve the results of stem cell therapy in repairing adult tissues and degenerative conditions.

“Our work suggests that, in the future, it could be possible to take stem cells from an unborn baby carrying the abnormal *OI* gene, manipulate them to correct the errant gene and then put them back into the fetus to allow it to develop properly”.

Source: The University of Queensland, Australia: Stem Cell Treatment For Brittle Bones In The Womb [Press release].

About the Bulletin Board

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Safety fears allayed over therapy-induced lymphopenia

Current fears over treatment-induced lymphopenia in patients with rheumatoid arthritis (RA) have been somewhat alleviated. New research into long-term clinical data has shown no increased risk for morbidity or mortality.

The present study led by John Isaacs from Newcastle University (Newcastle, UK), reports the 12-year outcomes of 53 patients treated with the monoclonal antibody alemtuzumab between 1991 and 1994. These patients were compared with 102 patients suffering from RA, but who had not received any form of immunomodulatory therapy.

Alemtuzumab has been in clinical use for RA, and the link between lymphopenia and lymphocytotoxic and other immunomodulatory therapies for RA is

well known, although the clinical relevance is unclear. This led to concerns related to prolonged-therapy-induced lymphopenia.

"Causes of death were similar to those that would be expected in a hospital-based RA cohort."

Closely monitored CD3⁺ CD4⁺, CD3⁺ CD8⁺, CD19⁺ and CD56⁺ at a median follow-up of 11.8 years indicated that lymphopenia persisted in the alemtuzumab-treated patients. Mortality of alemtuzumab-treated patients when compared with controls appeared slightly higher, but these differences did not reach statistical significance.

Issacs added that "Causes of death were similar to those that would be expected in

a hospital-based RA cohort," adding that, "No opportunistic infections were noted, and only three infections were documented following 36 elective orthopedic procedures."

"Despite the profound biologic effects of therapy, findings in our patients have remained typical of those in a cohort of patients with refractory RA." It was concluded that even prolonged lymphopenia is not associated with increased mortality, unusual infection-related morbidity or a lower tolerance of surgery.

Source: Lorenzi AR, Clarke AM, Wooldridge T *et al.*: Morbidity and mortality in rheumatoid arthritis patients with prolonged therapy-induced lymphopenia: twelve-year outcomes *Arthritis Rheum.* 58, 370–375 (2008).

Tissue remodeling and repair genes could be therapeutic targets in COPD

Research published in the *American Journal of Respiratory and Critical Care Medicine* suggests that tissue remodeling and repair genes could be potential therapeutic targets in chronic obstructive pulmonary disease (COPD) and other inflammatory lung diseases.

The authors comment that, "One way of generating new ideas about the pathogenesis of complex genetic disease is to perform genome wide transcriptional analysis on diseased tissue for comparison with normal tissue."

The genes involved in tissue remodeling and repair are differentially regulated in the lungs of smokers with COPD compared with healthy nonsmokers.

The team compared the gene-expression profiles of 48 human lung samples obtained from tissue resected from five nonsmokers, 21 patients with Global Initiative for Chronic Obstructive

"One way of generating new ideas about the pathogenesis of complex genetic disease is to perform genome wide transcriptional analysis on diseased tissue for comparison with normal tissue."

Lung Disease (GOLD) stage 0 COPD, nine with GOLD stage 1, ten with GOLD stage 2 and three patients with GOLD stage 3. Genes were selected on the basis of their involvement with forced expiratory flow. A total of 203 genes were selected and it was discovered that those involved in extracellular matrix synthesis and apoptosis were upregulated, whereas genes that participate in anti-inflammatory responses were downregulated.

Results indicated that urokinase plasminogen activator, urokinase plasminogen activator receptor and

thrombospondin released by alveolar macrophages and airway epithelial cells were all expressed by the candidate genes.

"Genes in this pathway have been shown to be involved in the activation of transforming growth factor (TGF)- β 1 and matrix metalloproteinases, and are subject to inhibition by SERPINE2", the authors note, adding that "Interestingly, both TGF- β 1 and SERPINE2 have been identified as candidate genes in COPD genetic linkage and association studies."

It is argued that the lack of success of traditional therapies points to a need for a new approach to the treatment of COPD.

Source: Wang I-M, Stepaniants S, Boie Y *et al.*: Gene expression profiling in patients with chronic obstructive pulmonary disease and lung cancer. *Am. J. Respir. Crit. Care Med.* 177, 402–411 (2008).