

# NEWS ROUND

Selected reports edited by Janet Fricker

## Expertise counts in diagnostic ultrasound for ovarian cancer

→ The Lancet Oncology

Using expert ultrasonographers over regular operators for diagnosing ovarian cancer results in a significant reduction in the overall number of diagnostic procedures required and reduces length of inpatient hospital stays, according to a recent study.

The established way to distinguish benign from malignant tumours in the region of the uterus, ovary or fallopian tubes (known as adnexal tumours) is assessment of structural features (such as wall structure, blood vessels and presence of fluid) using ultrasound. Ultrasonography, however, is subject to substantial interobserver variability, with experienced operators being significantly more accurate in their diagnosis than the less experienced.

The study set out to assess whether the level of operator skill had a measurable impact on patient management. Overall, 150 patients with suspected ovarian cancer, referred to the regional gynaecological cancer centre at Guy's and St Thomas' NHS Foundation, London, between 3 May 2004 and 15 February 2007, were randomised to level III (expert) ultrasonography ( $n=77$ ) or level II (routine) ultrasonography ( $n=73$ ). Level III ultrasonography was undertaken by gynaecologists with a special interest in gynaecological ultrasound who had more than 10 years' experience in the procedure; while level II ultrasonogra-

phy was undertaken by ultrasonographers trained in gynaecological ultrasonography. For all patients, both transvaginal and transabdominal scans were undertaken to ensure complete assessment of the entire abdominal cavity.

Results showed the number of major surgical staging procedures for presumed ovarian cancer undertaken in women screened by level III ultrasonography was 17 of 77 (22%), compared with 27 of 73 (37%) for those screened by level II ultrasonography ( $P=0.049$ ). There was also a reduction in follow-up procedures after expert sonography, with the median number of follow-up scans being two (range 0–5) in the level II group, compared with one (0–4) in the level III group ( $P=0.0004$ ). "This finding is likely to be the consequence of the greatly increased proportion of patients in whom a conclusive diagnosis of the nature of the adnexal tumour was possible from level III ultrasonography compared with level II ultrasonography," write the authors.

Furthermore, results showed that a histological diagnosis was provided to clinicians for 76 of 77 patients (99%) in the level III group compared with only 38 out of 73 patients (52%) in the level II group ( $P<0.0001$ ). The total number of surgical procedures was similar in the two groups – 35 of 73 (48%) in the level II group versus 33 of 77 (43%) in the level III group ( $P=0.53$ ). However, the number of minimally invasive procedures was higher for the level III group than the level II group. This, write the authors, is likely to have contributed to the significant decrease in the median duration of hospital stay for patients in the expert level III group (5 days; range 1–9 vs 6 days; range 3–13).

The authors add that the effect of expert

scanning might have been even greater if it had been used in the primary assessment of ovarian pathology. "Increased confidence in the diagnosis of benign ovarian lesions is likely to decrease the need for additional diagnostic tests, such as MRI or serum CA-125 concentration, and also decreases the number of referrals to regional cancer centres," they write.

■ Effect of quality of gynaecological ultrasonography on management of patients with suspected ovarian cancer: a randomised controlled trial. J Yazbek, SK Raju, J Ben-Nagi et al. *Lancet Oncol* February 2008, 9:124–131

## PET scans are better than CT for measuring sarcoma response

→ Clinical Cancer Research

Positron emission tomography (PET) – a type of scanning that assesses the activity of cells in the body – is much more sensitive and more accurate than conventional imaging methods in detecting responses to treatment in patients with sarcoma, according to one of the first studies to look at this issue.

The study compared PET scanning with CT in 42 patients with high-grade soft tissue sarcomas. Scans were taken before and after the patients were treated with chemotherapy, prior to surgery to remove their tumours. The researchers measured the metabolic or chemical activity of

the tumour cells using a specific PET probe that assesses glucose metabolism. This allowed them to determine whether the cancer cells were still alive and dividing after treatment. After removing the tumours during surgery, they analysed the cells directly to assess whether chemotherapy had affected their activity.

Assessing the effects of chemotherapy in people with sarcomas has previously been difficult, because the standard measure for response to cancer treatment – Response Evaluation Criteria in Solid Tumors (RECIST) – has proved unreliable in these cancers. Using this method, patients are scanned by CT or MRI to assess whether a tumour has shrunk in response to treatment. Previous research has shown that treatment may change the activity of sarcoma tumour cells in a way that improves a patient's survival, even though a change in tumour size is not apparent using RECIST criteria. This has important implications for patients, because they may be taken off a treatment that is potentially improving their prognosis, because their tumour is not shrinking.

"We knew from our experience with neoadjuvant therapy in sarcoma patients that measuring tumour size correlated poorly with response," explained Fritz Eilber, director of the Sarcoma Program at the Jonsson Comprehensive Cancer Center at the University of California at Los Angeles, and one of the authors of the new study. "We have removed many tumours that have not changed in size with treatment, or have even grown, but are completely dead on pathologic analysis. Just because the tumour doesn't shrink doesn't mean the treatment didn't work," he added.

Results from the study showed that PET scanning was much more accurate in detecting response to chemotherapy in sarcomas than conventional scanning. PET scanning identified all of the patients whose tumour cells responded to treatment. In contrast, using standard tumour-size based criteria (RECIST) identified only one in four patients (25%) whose tumour cells had responded.

The study findings have important implications, say the researchers. "PET should be used to monitor treatment response in patients with high-grade soft tissue sarcomas," they conclude.

■ Reduction of glucose metabolic activity is more accurate than change in size at predicting histopathologic response to neoadjuvant therapy in high-grade soft-tissue sarcomas. V Evilevitch, WA Weber, WD Tap et al. *Clin Cancer Res* 1 February 2008, 14:715–720

### Minimally invasive staging procedure works in lung cancer

→ JAMA

An evaluation of several methods of endoscopic biopsy suggests a minimally invasive approach can accurately stage suspected lung cancer. A combined approach using two different endoscopic procedures has been shown to provide the most accurate method of diagnosis.

Accurate staging of lung cancer is recognised as critical for the selection of optimal therapy. Patients without evidence of mediastinal lymph node metastases are generally offered surgical resection, whereas those with metastases are treated with chemoradiotherapy (with or without surgery).

Noninvasive staging with chest CT or PET has been associated with high rates of false-positive and false-negative results. The American College of Chest Physicians therefore recommends invasive staging of the metastatic mediastinal lymph nodes, a surgical procedure requiring general anaesthesia that carries a 2% risk of major morbidity.

More recently, less invasive methods have emerged, including blind transbronchial needle aspiration, endobronchial ultrasound-guided fine-needle aspiration, and transoesophageal endoscopic ultrasound-guided fine-needle aspiration.

In the *JAMA* study, Michael Wallace and colleagues, from the Mayo Clinic College of Medicine in Florida, compared the diagnostic accuracy of each of these endoscopic staging procedures. The study involved 138 suspected lung cancer cases seen consecutively between November 2004 and October 2006, with each patient undergoing the three procedures sequentially in a single combined procedure. Pathologic confirmation and clinical follow-up took place at 6–12 months.

Results showed that 42 patients (30%) had malignant lymph nodes. The endobronchial ultrasound-guided aspiration method was more sensitive than the blind transbronchial procedure, detecting 29 (69%) versus 15 (36%) of the 42 malignant lymph nodes ( $P=0.003$ ). Transoesophageal aspiration also detected 29. Combining the ultrasound-guided endobronchial and the transoesophageal endoscopic procedures detected 10 more malignant nodes than either method used alone.

If mediastinoscopy had been performed only when the results of the endobronchial and transoesophageal endoscopic procedures were negative, write the authors, an invasive procedure could have been avoided in 28% of patients (39/138).

"If these data are confirmed by other studies, they thus suggest that endoscopic ultrasound-guided fine-needle aspiration plus endobronchial ultrasound-guided fine-needle aspiration... may be an alternative method for surgical staging of the mediastinum in patients with suspected lung cancer," they conclude.

■ Minimally invasive endoscopic staging of suspected lung cancer. M Wallace, JMS Pascual, M Raimondo et al. *JAMA* 6 February 2008, 299:540–546

### Ki-67 does not predict response to adjuvant breast cancer treatment

→ Journal of the National Cancer Institute

In breast cancer, having a high percentage of tumour cells expressing the proliferation antigen Ki-67 – a high tumour Ki-67 labelling index – has been found to be associated with poor disease-free survival but, according to a retrospective analysis, it does not predict response to adjuvant treatment.

Expression of the Ki-67 antigen indicates cells in the active phase of the cycle. Several small studies have reported that a high Ki-67 labelling index predicts better response to neoadjuvant chemotherapy.

To investigate whether the Ki-67 labelling index could also be used to predict response to adjuvant chemoendocrine therapy, Giuseppe Viale

and colleagues from the European Institute of Oncology, Milan, undertook a retrospective assessment of Ki-67 expression in tumour samples from the International Breast Cancer Study Group trials VIII and IX. The two large randomised trials, conducted between 1988 and 1999, compared endocrine therapy alone versus CMF chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil) followed by endocrine therapy among pre/perimenopausal (trial VIII) and postmenopausal (trial IX) breast cancer patients with node-negative, hormone-receptor-positive disease.

The team assessed 1,924 formalin-fixed paraffin-embedded samples for Ki-67 labelling index, using the mouse monoclonal antibody MIB-1. They found Ki-67 levels could not be used to predict which patients benefited from the addition of chemotherapy to endocrine therapy in the adjuvant setting. Results did show, however, that a high Ki-67 labelling index was associated with a worse disease-free survival among both postmenopausal women (trial IX; recurrence or death HR 1.60, 95% CI 1.26–2.03,  $P < 0.001$ ) and pre/perimenopausal women (trial VIII; HR 1.66, 95% CI 1.20–2.29,  $P = 0.002$ ).

Other biomarkers are needed to define which women with endocrine-responsive node-negative early breast cancer benefit from the addition of adjuvant chemotherapy to endocrine therapy, the authors conclude.

In an accompanying editorial, Matthew Ellis from Washington University, St Louis, Missouri, wrote, "This result is striking because it indicates that patients with aggressive node-negative hormone-receptor-positive breast tumours who have a high growth fraction – the patients most in need of additional therapy – obtain no extra benefit from the addition of cyclophosphamide, methotrexate, and 5-fluorouracil to their endocrine regimen."

■ Predictive value of tumor Ki-67 expression in two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. G Viale, MM Regan, MG Mastropasqua et al, on behalf of the International Breast Cancer Study Group. *J Natl Cancer Inst* 6 February 2008, 100:207–212

■ Improving outcomes for patients with hormone receptor-positive breast cancer: back to the drawing board [editorial]. MJ Ellis. *ibid* pp159–161

## Sorafenib patients require monitoring for hypertension

→ The Lancet Oncology

Patients taking sorafenib (Nexavar) need close monitoring and treatment for high blood pressure to prevent cardiovascular complications, according to a recent study.

Sorafenib is a multikinase inhibitor used to extend survival in patients with advanced renal cell cancer (RCC) and hepatocellular cancer. Hypertension has been noted in trials, with an incidence ranging from 16% to more than 42%. Other angiogenesis inhibitors, including bevacizumab (Avastin) and sunitinib (Sutent), have also been associated with hypertension.

With the aim of understanding the overall risk for hypertension in patients on sorafenib, Shenhong Wu and colleagues from The University of New York conducted a systematic review and a meta-analysis using databases including MEDLINE, the Web of Science and abstracts presented at ASCO meetings. Overall the team identified nine studies, including a total of 4,599 patients with RCC or other solid tumours meeting the criteria of patients being assigned single-drug sorafenib at 400 mg twice daily, with data on hypertension available.

Results showed that the incidence of all-grade hypertension was 23.4% in patients receiving sorafenib, with a 5.7% incidence of high-grade hypertension. Sorafenib treatment was associated with a six-fold increased risk of developing all-grade hypertension compared with controls.

Initially the authors had speculated that RCC would be associated with a greater risk of hypertension than non-RCC malignancies, on account of previous nephrectomy and renal dysfunction. This, however, was not found to be the case. "A possible explanation... is that the increase in blood pressure and hypertension induced by sorafenib is so prominent that the risk associated with RCC is not evident in this setting," write the authors.

Early detection and effective management of hypertension might allow for safer use of sorafenib, conclude the authors. "The hypertensive and cardiovascular side effects of sorafenib need thorough post-marketing surveillance and reporting, and future studies will be needed to identify the

mechanism and appropriate treatment of sorafenib-induced hypertension," they add.

■ Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. S Wu, J J Chen, A Kudelka et al. *Lancet Oncol* February 2008, 9:117–123

## Androgen suppression therapy does not benefit patients with comorbidity

→ JAMA

Adding androgen suppression therapy (AST) to external radiation treatment increases overall survival in men with high-risk locally advanced prostate cancer, but, according to a recent study, the benefits are not seen in patients with comorbidities.

Several randomised trials have documented increased survival when AST is combined with external beam radiation therapy (RT), compared to RT alone, in localised and locally advanced prostate cancer. As a result, combination treatment has become the standard of care. However, pooled analyses of randomised studies suggest that, in older men, AST administration can be associated with an increased risk of cardiovascular events.

Anthony D'Amico and colleagues from Brigham and Women's Hospital and Dana Farber Cancer Institute, Boston, Massachusetts, set out to investigate whether survival benefits in men undergoing AST in combination with RT varied according to their comorbidity illness profiles.

In all, 206 men (median age 72.5 years) with clinically localised or locally advanced non-metastatic prostate cancer and at least one unfavourable prognostic factor were randomised to treatment with RT or RT plus AST. Each patient was assigned a baseline comorbidity score, graded on a scale of 0 (none) to 3 (severe).

After a median follow-up period of 7.6 years, results showed a significant increase in the risk of all-cause mortality in patients receiving RT alone compared with the group receiving both RT and AST (44 vs 30 deaths, HR 1.8, 95% CI 1.1–2.9,  $P = 0.01$ ).

When a subgroup analysis was undertaken, the

increased risk in all-cause mortality for men receiving RT alone applied only to those with no or minimal comorbidity (31 vs 11 deaths, HR 4.2, 95% CI 2.1-8.5,  $P=0.001$ ). Among men with moderate or severe comorbidity, 13 of those randomised to RT alone died, compared with 10 randomised to RT plus AST (HR 0.54, 95% CI 0.27-1.10,  $P=0.08$ ).

"The clinical significance of this finding is that preexisting comorbid illness may increase the negative effects of specific anticancer treatments such as AST," conclude the authors. "Therefore, future randomised studies evaluating the impact on survival of adding novel therapies to the current standards of practice in men with clinically localised or locally advanced non-metastatic prostate cancer should consider a pre-randomisation stratification by comorbidity score."

■ Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. AV D'Amico, MH Chen, AA Renshaw et al. *JAMA* 23 January 2008, 299:289-295

## The breast cancer personality is laid to rest

→ Journal of the National Cancer Institute

Studies in the 1980s suggested that women who had difficulty expressing emotions might be more prone to breast cancer. However, a recent 13-year follow-up study looking at breast cancer incidence and personality traits has found no evidence of any association.

The study was conducted by Eveline Bleiker and colleagues, from the Netherlands Cancer Institute in Amsterdam. It followed an earlier study by Bleiker, conducted in 1996, which had found a weak association between breast cancer and a high score on the 'anti-emotionality scale' (indicating an absence of emotional behaviour or a lack of trust in one's own feelings). One limitation of that study, reported by the authors, was that follow-up was for a maximum of five years after the psychological assessment, so the assessment could have been detecting the sub-clinical effects of tumour growth.

In the current study, involving the same cohort of women, Bleiker and colleagues followed, for 13

years, 9,705 women attending a population surveillance programme in the Dutch city of Nijmegen between 1 January 1989 and 31 December 1990. All the women were asked to complete a personality questionnaire assessing anxiety, anger, depression, rationality, anti-emotionality, understanding, optimism, social support, 'emotional expression in' (feelings held in or suppressed), 'emotional expression out' (feelings directed toward other people or subjects) and emotional control (control of outward expression of feelings). Information on medical risk factors, like having a first-degree relative with breast cancer, was also collected.

A total of 217 women subsequently developed breast cancer, between 17 May 1995 and 1 January 2003. When their personality profiles were compared with 868 age-matched controls, none of the personality factors examined showed any significant association with increased risk of breast cancer – a result, say the authors, that may help reassure some patients.

"Our finding that no psychological risk profile was associated with the incidence of breast cancer may help oncologists to reassure patients that their personality appears to have played no role in the development of their breast cancer," they conclude.

■ Personality factors and breast cancer risk: a 13-year follow-up. E Bleiker, J Hendriks, J Otten et al. *J Natl Cancer Inst* 6 February 2008, 100:213-218

## Oxygen does not help cancer patients with dyspnoea

→ British Journal of Cancer

Use of oxygen therapy fails to improve symptoms of dyspnoea in cancer patients, according to a systematic review and meta-analysis.

Dyspnoea, defined by the American Thoracic Society as a "subjective experience of breathing discomfort", is experienced by 50%-70% of patients with advanced cancer. The use of oxygen therapy is widespread, despite there being little evidence that it works. Treatment should not be undertaken lightly, since the patient's quality of life can be limited as a result of functional restrictions; psycho-

logical distress can arise from being reliant on a machine, and use of nasal cannulae can increase the risk of nose bleeds. Furthermore, home oxygen is expensive, with many patients forced to fund treatment themselves.

In an attempt to improve understanding of the use of palliative oxygen, Hope Uronis and colleagues from Duke University Medical Center in Durham, North Carolina, undertook a systematic review in MEDLINE and EMBASE of studies published between 1966 and December 2006. Altogether the team identified four blinded, randomised, crossover trials of cancer patients treated with non-invasive oxygen (nasal cannula, mouth-piece or face mask), where direct comparisons could be made between oxygen therapy and medical air (used as a placebo).

In the studies, dyspnoea ratings were measured using the modified Borg 0-10 numerical rating scale (NRS) or a 100-mm or 300-mm visual analogue scale (VAS). These were converted into standardised mean differences (SMDs). Altogether 134 patients were included in the meta-analysis.

Results showed that oxygen failed to improve dyspnoea in mildly or non-hypoxaemic cancer patients (SMD -0.09; 95% CI -0.22-0.04;  $P=0.16$ ). This, say the authors, translates to a 0.22-point reduction in dyspnoea on a 0-10 numerical rating scale. Most clinicians would consider a 1-point reduction on a 0-10 NRS to be clinically significant.

Patient preferences were also studied, because dyspnoea is subjective and patients often have difficulty describing the sensation – and it is also known that not all patients who benefit from oxygen want to receive it.

Two of the four studies demonstrated statistically significant patient preferences for oxygen. "The data... suggest that there is a population of patients who experience less dyspnoea while receiving oxygen as compared with medical air," write the authors, adding that further research is needed to identify this subgroup. Until that time, decisions regarding palliative oxygen should be made on an individual basis.

■ Oxygen for relief of dyspnoea in mildly or non-hypoxaemic patients with cancer: a systematic review and meta-analysis. H Uronis, D Currow, D McCrory et al. *Br J Cancer* 22 January 2008, 98:294-299