NEWSROUND

Selected reports edited by Janet Fricker

Combined PET–CT avoids futile surgery in NSCLC

➜ New England Journal of Medicine

Preoperative lung cancer staging using combined PET–CT imaging allows some patients with non-small-cell lung cancer (NSCLC) to avoid futile surgery, a Danish study has found.

Since 2001, combined PET–CT has replaced standalone PET due to superior diagnostic capability, with the advantage based on a more accurate assignment of tumour stage and to a lesser extent lymph-node stage. Accurate staging is key to identifying patients who are candidates for surgery. If preoperative staging fails to identify patients with advanced disease, these patients may undergo futile surgery – surgery that is of no benefit.

In the current study, Barbara Fischer and colleagues from Odense University Hospital (Odense, Denmark) set out to determine whether improved diagnostic accuracy improves management of the disease. The team recruited patients from three Danish hospitals, with participants aged between 18 and 80 years, with newly diagnosed or highly suspected NSCLC considered operable after conventional staging procedures such as blood tests, bronchoscopy, and contrast-enhanced CT scans of the chest and upper abdomen.

Between January 2002 and February 2007, 189 patients were randomly assigned to conventional staging plus PET–CT (n=98) or conventional staging alone (n=91). Afterwards, a pulmonologist and thoracic surgeon agreed on the TNM (tumour-node-metastasis) stage before deciding whether to operate, using all available information.

All patients with stage I to stage IIB NSCLC were offered surgery, while those with involvement of mediastinal lymph nodes or distant metastases were considered to have inoperable cancer and were offered chemotherapy with or without radiotherapy. The primary endpoint for the study was the frequency of futile thoracotomies, with the criteria including benign lung lesions, pathologically proven mediastinal lymph node involvement (stage IIIA [N2]), stage IIIB or IV disease, inoperable T3 or T4 disease, or recurrent disease or death from any cause within one year after randomisation.

Following staging, 60 out of 98 patients in the PET–CT group and 73 out of 91 patients in the conventional staging group underwent thoracotomy. Results showed that 35% of patients in the PET–CT group had a futile thoracotomy, compared with 52% of patients in the conventional staging group (P=0.05). After exclusion of the 11 patients in the PET–CT group who did not undergo PET–CT and the 1 patient who underwent PET–CT but declined further procedures, 16 of 55 patients in the PET–CT group (29%) underwent a futile thoracotomy, as compared with 38 of 73 patients (52%) in the conventional staging (P=0.009). The results equated to one less unnecessary surgery for every five PET–CT scans performed. Additionally, the results showed that PET–CT had no effect on survival.

The researchers note that the trial was closed prematurely due to slow patient accrual. Despite this, the investigators conclude: "adding a PET–CT examination to the diagnostic regimen for patients with NSCLC improves sensitivity in preoperative staging. The addition of a PET–CT examination reduces the frequency of futile thoracotomies and the total number of thoracotomies, with no effect (negative or positive) on overall survival."

The significantly higher number of early deaths and relapses in the conventional staging group than in the PET–CT group, write the authors, was not due to chance or more successful surgery in the PET–CT group, but instead reflects a better selection of patients for surgery in the PET–CT group.

■ Preoperative staging of lung cancer with combined PET–CT. B Fischer, U Lassen, J Mortensen et al. *N Engl J Med* 2 July 2009, 361:32–39

Telangiectasiae predict cardiac complications

→ British Journal of Cancer

A relationship between the development of skin telangiectasiae following radiotherapy and long-term risk of cardiovascular disease has been shown in a study of breast cancer patients. The UK authors suggest that the presence of telangiectasiae might in future be used to predict cardiac complications following radiotherapy.

Overall, 5% of patients show late normal-tissue damage following radiotherapy. Studies have shown increased risk of cardiovascular disease for irradiated patients compared with non-irradiated ones, and for those irradiated to the left breast or chest wall compared to those treated on the right.

Radiation-induced heart disease is thought to result from damage to both micro and macrovasculature. Damage to the microvasculature is initiated by endothelial cell damage within cardiac structures, followed by ischaemia that appears secondary to capillary swelling and progressive obstruction of the vessel lumen, with the damaged area replaced by fibrous tissue. Macro vascular damage results from injury to larger vessels, leading to exacerbation of atherosclerotic lesion formation. The functional consequence is diffuse interstitial myocardial fibrosis, contributing to diastolic dysfunction.

Telangiectasiae – focal dilations of post-capillary venules and occasionally of the capillaries and arterioles of the subpapillary plexus – can develop as a late tissue injury, from six months to many years after completion of radiotherapy. Telangiectasiae, which occur in an atrophic dermis under a thin epidermis and present as areas of reddish discolouration, have to date only been regarded as a cosmetic burden.

In the current study, in an attempt to associate genotype with phenotypes, George Tanteles and colleagues from the University of Leicester, UK, set out first to examine the relationship between late normal-tissue radiation injury in breast cancer patients and phenotype.

Altogether, 149 patients treated more than four years previously with radiotherapy and/or surgery were examined for cardiovascular disease. A total of 15 patients with cardiac disease requiring referral or investigation were identified, six of whom were found to have already documented cardiovascular disease and were initially excluded from the analysis.

As part of the study, the presence or absence of telangiectasiae was documented, scored by the SOMA scale, using sight and/or palpation. Scores of 1 were excluded from the study to try to reduce interexaminer bias, resulting in a denominator of 137 for study analysis. Thirty-two of the patients had a telangiectasia score greater than 1, of whom 17 had received right-sided and 15 left-sided breast irradiation.

Altogether, five of the 32 patients (15.6%) in the telangiectasiae group had developed heart disease, compared to three out of 105 (2.9%) patients in the non-telangiectasiae group (OR 6.3, 95% CI 1.4–28.0, P=0.017).

When a second study was undertaken including the patients previously excluded on the basis of pre-existing cardiac disease, the difference between those with telangiectasiae exhibiting heart disease and those without was found to be even greater (OR 6.4, 95% CI 2.1–19.9, P=0.004).

In this study, no association was found between cardiovascular disease and different alleles previously linked to radiation-induced telangiectasiae.

"We observed a statistically significant association between the long-term risk for cardiovascular disease and the presence of cutaneous telangiectasiae. Interestingly, the significance of this correlation was maintained and became even greater when we included all the identified CVD [cardiovascular disease] patients with no exclusions. Although telangiectasiae in most cases are only unsightly, our findings could suggest a novel use as a marker and a predictor of future cardiac-related complications," write the authors, adding that the conclusions are based on a small cohort and need to be replicated.

The most likely explanation, they write, is that propensity for the development of telangiectasiae and cardiovascular disease are part of a common biological pathway on the basis of a genetically predisposed endothelium. "If this conclusion is correct, we would expect identification of genes that prove the association. Further studies are required to explore the potential mechanisms and identification of individuals at increased risk of radiation induced heart disease to maintain a reasonable therapeutic benefit for radiotherapy in breast cancer."

■ Can cutaneous telangiectasiae as late normal-tissue injury predict cardiovascular disease in women receiving radiotherapy for breast cancer? GA Tanteles, J Whitworth, J Mills et al. *Br J Cancer* 14 July 2009, 101:403–409

Ovarian cancer risk clarified for HRT use

→ JAMA

Women who have taken hormone replacement therapy (HRT) – regardless of duration, formulation or route of administration – are at increased risk of ovarian cancer, a Danish study has reported.

Primary prevention of ovarian cancer is challenging, since little is known about the cause. Previous studies have suggested an increased risk of ovarian cancer among women taking postmenopausal hormone therapy. Some studies have suggested that ovarian cancer risk is higher among users of oestrogen therapy alone than with oestrogen plus progestin therapy, while the UK Million Women Study found no significant difference between the effects of the two types of therapy.

In the current study, Lina Steinrud Mørch and colleagues, from Copenhagen University, Denmark, set out to provide more data to clarify the risk of ovarian cancer associated

with different HRT formulations, regimens and routes of administration.

Using the Danish Sex Hormone Register Study, which was initiated in 1995 to explore the influence of sex hormones on the risk of cardiovascular diseases and different female cancers, the investigators were able to use the Danish personal identification number to link the women to other national registries. Altogether the investigators followed a cohort of 910,000 women aged 50 to 79 for an average of eight years (equivalent of 7.3 million women-years). During this time 3068 incident ovarian malignancies were diagnosed (2681 of which were epithelial cancers).

The results showed that, compared to women who never took HRT, current users of hormones had a higher risk of developing ovarian cancer – with a relative risk of 1.38 for all ovarian cancers and 1.44 for epithelial ovarian cancer. The risk was equivalent to one extra case of ovarian cancer for 8300 women taking HRT each year. The risk declined with years since last use, with the relative risk for all ovarian cancers being 1.22 for 0–2 years, 0.98 for 2–4 years, 0.72 for 4–6 years, and 0.63 for more than 6 years.

The risk was found to be similar among women who took oestrogen-only HRT and those who took oestrogen plus progestin, with the type of progestin making no difference. However, among women who took oestrogen-only HRT, the oral method , but not the transdermal method, was linked to a much higher relative risk than never users (relative risk 1.34 for oral and 1.13 for transdermal). Vaginal oestrogen was also linked to a marginally higher risk (relative risk 1.23 compared with never users).

"Regardless of the duration of use, the formulation, estrogen dose, regimen, progestin type, and route of administration, hormone therapy was associated with an increased risk of ovarian cancer," write the authors, adding that their study was in agreement with the findings from the Million Women Study.

Hormone therapy, they estimate, may have caused roughly 140 extra cases of ovarian cancer in Denmark during the study period, or 5% of the ovarian cancers. "Even though this share seems low, ovarian cancer remains extremely fatal, so consequently this risk justifies consideration when deciding whether to use hormone therapy," the authors concluded.

Limitations of the study, they say, include the fact that they were not able to adjust for age at menopause and use of oral contraceptives. Women with early natural menopause are more likely to use hormones compared with women with late natural menopause, they write, but because natural early menopause decreases the risk of ovarian cancer, more women taking HRT could have a decreased risk of ovarian cancer. They also did not take into account the confounder of women with a family history of cancer being less likely to use hormone therapy, and lacked information on hormone exposure prior to study entry.

■ Hormone therapy and ovarian cancer. L Steinrud Mørch, E Løkkegaard, A Helms Andreasen et al. *JAMA*, 15 July 2009, 302:298–305

Conference abstracts often at odds with final results

➜ Journal of Clinical Oncology

Abstracts presented at cancer meetings frequently show discordance with the articles that are subsequently published in journals, according to a study by the National Cancer Institute of Canada. Given the potential for non-final analyses to be both misleading and to introduce bias into the conduct of trials, the investigators urge caution with the interpretation of abstract results.

In the literature there have been many examples of inconsistency between randomised control trial abstracts presented at meetings and the final results published in journals. Christophe Booth and colleagues, from the National Cancer Institute of Canada Clinical Trials Group, Queen's University (Kingston, Ontario), set out to design a study comparing randomised control trial (RCT) abstracts and eventual article publications, in order to evaluate the potential implications of abstract publications based on non-final analysis.

For the study, all RCTs involving outcomes of systemic therapy for lymphoma, breast, colorectal or non-small-cell lung cancer published between 2000 and 2004 in six major journals were included. The six journals covered were: the *Journal of Clinical Oncology, Journal of the National Cancer Institute, Blood, New England Journal of Medicine, Lancet* and the *Journal of the American Medical Association*. The target diseases were selected because they represent the most common malignancies treated with systemic therapy. Abstracts relating to these primary articles were identified by searching the proceedings of seven major cancer meetings between 1990 and 2004, using the names of the first and last authors. The meetings were: the American Society of Clinical Oncology (ASCO), ASCO Gastrointestinal Cancers Symposium, American Society of Hematology, San Antonio Breast Cancer Symposium, International Association for the Study of Lung Cancer World Conference, European Society for Medical Oncology Congress, and the European Cancer Conference (ECCO).

Altogether, the investigators identified 138 RCTs from searching the six targeted journals, which went on to yield 303 related abstracts from conference proceedings, of which 106 were deemed ineligible because they did not relate to primary efficacy outcomes. Of the 197 abstracts finally reviewed, discordance with the related article was found in 124 abstracts (63%). Discordance was more common with non-final analyses abstracts – 78% for non-final analyses compared to 51% for final analyses (P=0.0001). When compared with final articles, the authors' conclusions were found to be substantively different in 17 abstracts (10%). The factors that were most associated with data discordance were lymphoma trials (OR 3.8, 95% CI 1.5–10.8), cooperative group trials (OR 2.8, 95% CI 1.4–

5.6) and presentation of a non-final analysis (OR 2.9, 95% CI 1.5–5.8).

"We have shown that the majority of RCT abstracts presented at major oncology conferences include important data discrepancies compared with subsequent published articles, suggesting that reporting of non-final analyses is common. Given the potential for NFA to be misleading and to introduce bias to trial conduct, clinicians, investigators and conference organizers should be cautious when interpreting results of RCTs in abstract format," conclude the authors, who went on to identify three potential risks for presenting non-final analyses at meetings. Firstly, preliminary data are potentially unstable and risk misinforming consumers. Secondly, there is a higher probability of observing false results when there are multiple "looks at the data". Thirdly, there is a risk that the subsequent conduct of an ongoing trial may be altered when results are released before completing accrual or before a sufficient number of patients have completed protocol therapy.

Limitations of the study, write the authors, include the fact that only four disease sites were considered and that, by limiting the search to six journals, they did not capture all RCTs published during the study period.

■ Presentation of nonfinal results of randomized controlled trials at major oncology meetings. CM Booth, A Le Maître, K Ding. *JCO* 20 August 2009, 27:3938–3944

Surgery plus chemotherapy/radiotherapy option in lung cancer

➜ The Lancet

Radiotherapy plus chemotherapy, with or without surgery, both represent treatment possibilities for patients with stage IIIA (N2) non-small-cell lung cancer, a study by the Radiation Therapy Oncology Group (RTOG) in Chicago has concluded. The phase III study showed no difference in overall survival between the two groups, but found a difference in progression favouring the surgical group.

Earlier studies have demonstrated that the addition of chemotherapy to radiotherapy administered concurrently as opposed to sequentially significantly improves survival in patients with stage IIIA non-small-cell lung cancer with ipsilateral mediastinal nodal metastases (N2), making this the standard of care. Furthermore, phase II pilot studies to test the role of surgical resection after induction treatment with chemotherapy alone or concurrent chemotherapy and radiotherapy have provided controversial results, producing higher long-term survival rates than expected, at the expense of substantial toxicity, postoperative morbidity and mortality.

In the current study, Kathy Albain and colleagues from Loyola University (Chicago, Illinois), set out to assess whether resection resulted in significant improvements in survival compared with just chemotherapy plus radiotherapy.

Between March 1994 and November 2001, patients with stage T1-3pN2M0 non-small-cell lung cancer underwent induction chemotherapy (two cycles of cisplatin [50 mg/m² on days 1, 8, 29, and 36] and etoposide [50 mg/m² on days 1–5 and 29–33]) plus radiotherapy (45 Gy) in multiple academic and community hospitals. If no progression was evident, patients were randomly assigned on a 1:1 ratio to resection (n=202) or to continued radiotherapy uninterrupted up to 61 Gy (n=194).

Results showed that median overall survival was 23.6 months for the group who underwent radiotherapy, versus 22.2 months for the group who did not (HR 0.87, 95% CI 0.70–1.10; P=0.24). Progression-free survival was 12.8 months in the surgical group, compared to 10.5 months in the non-surgical group (HR 0.77, 95% CI 0.62–0.96, P=0.017).

Neutropenia and oesophagitis were the main grade 3 or 4 toxicities associated with chemotherapy plus radiotherapy, with rates of 38% and 10% respectively in the surgical group, and 41% and 23% in the non-surgical group. In the surgical group, 16 deaths (8%) were treatment related compared to four (2%) in the non-surgical group. In an exploratory analysis, overall survival was improved for the subgroup of patients who underwent lobectomy (but not pneumonectomy), compared to chemotherapy plus radiotherapy.

The most likely reason for the absence of an effect of surgery on overall survival, suggest the authors, is the increased mortality following pneumonectomy, mainly due to acute respiratory distress syndrome and other respiratory causes. The sub-study demonstrated that the patients who appeared to have a major benefit from surgery were those who had lobectomy as opposed to removal of the entire lung.

"Chemotherapy plus radiotherapy with or without resection (preferably lobectomy) are options for patients with stage IIIA (N2) non-small-cell lung cancer... medically healthy patients with stage IIIA (N2) non-small-cell lung cancer should be assessed by a team skilled in multimodality treatment, and treatment options can be considered during assessment," conclude the authors, adding that on the basis of their study patients should be counselled about the risks and potential benefits of definitive chemotherapy plus radiotherapy with and without a surgical resection (preferably by lobectomy).

In an accompanying comment, Wilfried Eberhardt, from the University Duisburg-Essen (Essen, Germany), wrote: "Can we undertake surgery in patients with stage IIIA (N2) NSCLC after induction chemoradiotherapy from now on? Yes, we can – selectively in patients with less extensive resection (eg, lobectomy) than pneumonectomy."

■ Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. KS Albain, RS Swann, VW Rusch et al. *Lancet* 1 August 2009, 374:379–396

■ Surgery in Stage III non-small-cell lung cancer. WEE Eberhardt, G Stamatis, M Stuschke. *ibid* pp 359–360