NEWSROUND

Selected reports edited by Janet Fricker

Study helps define melanoma tumour margins

→ The Lancet

For cutaneous melanomas thicker than 2 mm resection margins of 2 cm are sufficient and safe, a collaborative study between the Swedish Melanoma Study group and the Danish Melanoma Group has found. The study, say investigators led by Peter Gillgren from the Karolinska Institute (Stockholm, Sweden), represents the largest randomised controlled trial of resection margins for thick melanomas.

Surgery is the key treatment for patients with localised cutaneous melanoma, with the standard procedure being removal of the tumour with a safety margin from the edge of the tumour border. A trade-off exists between a wide excision, with consequent surgical difficulties, and the relapse-risk with a narrow excision, which could compromise disease-free survival or overall survival. Complications of wide excisions, however, include bad cosmetic results, lymphoedema, long hospital inpatient stays, frequent need for skin grafts and complicated skin flap reconstructions.

In the current study, between January 1992 and May 2004, 936 patients with cutaneous melanoma thicker than 2 mm at clinical stage IIA–C were randomised 1:1 to have either a 2-cm (n=465) or a 4-cm (n=471) surgical resection margin. The patients, who were aged 75 years or younger, were recruited from 53 hospitals in Sweden, Denmark, Estonia and Norway.

After a median follow-up of 6.7 years, 181 patients in the 2-cm margin surgery group had died versus 177 in the 4-cm margin surgery group (HR 1.05, 95%CI 0.85–1.29; P=0.64). The five-year overall survival was 65% in the 2-cm group versus 65% in the 4-cm group (P=0.69).

"Our data lend support to the hypothesis that a 2-cm margin is safe but a 1-cm margin might be insufficient for patients with a cutaneous melanoma thicker than 2 mm," write the authors.

The advantage of a 2-cm surgical margin, they add, is that the skin can be closed in most cases without skin grafting or skin flaps. A meta-analysis, they conclude, should now be undertaken of all randomised trials of cutaneous melanoma thicker than 2 mm.

In an accompanying editorial, John Thompson, from the Melanoma Institute Australia (Sydney), and David Ollila, from the University of North Carolina (Chapel Hill, North Carolina), wrote, "These conclusions need to be tempered by the knowledge that the originally planned equivalence trial design had a target accrual of 2000 patients, yet fewer than 1000 were enrolled. Thus, the statistical power required for an equivalence trial was lacking."

The next question to be addressed, they say, is whether a 2-cm margin is preferable to a 1-cm margin or whether a 1-cm margin would be sufficient and safe. Another area of importance, they write, is "proper understanding" of the inherent tumour biology necessary for safe excision margins, adding that assessment of margins using haematoxylin and eosin staining is a relatively crude pathological technique.

■ P Gillgren, K Drzewiecki, M Niin et al. 2 cm versus 4 cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicentre trial. *Lancet* 5 November 2011, 378:1635–42

■ J Thompson, D Ollila. Optimum excision margins for melanoma. *ibid* pp 1608–10

Treatments help breast cancer hot flushes

→ Journal of Clinical Oncology

Venlafaxine and clonidine offer effective treatments in the management of hot flushes in patients with breast cancer, a Dutch study has found.

Therapies for breast cancer in pre- and post-menopausal women, such as systemic endocrine therapy and chemotherapy, can result in symptoms of hot flushes that affect compliance and treatment outcomes. Both venlafaxine, a selective serotonin-norepinephrine reuptake inhibitor, and clonidine, a centrally acting alpha-adrenergic agonist, are prescribed to moderate hot flushes. However, trials have not been undertaken comparing them with placebo.

Jan Schellens and colleagues, from the Netherlands Cancer Institute, initiated a randomised double-blind placebo-controlled multicentre trial of venlafaxine and clonidine treatment in women with a history of breast cancer. Between October 2005 and August 2009, 102 patients being treated for breast cancer were enrolled from three Dutch hospitals and randomly assigned (2:2:1) to venlafaxine 75 mg, clonidine 0.1 mg or placebo daily for 12 weeks. The hot flush scores recorded combined both the severity (scored on a scale of 1–4) and frequency (number of five-minute periods experienced over a day) in a single measure.

Results show that during week 12, hot flush scores were significantly lower in the clonidine group versus placebo (P=0.03), while for venlafaxine the difference was borderline not significant (P=0.07).

In contrast, analysing the impact over the entire 12 weeks, the reduction compared with placebo in hot flush scores in the venlafaxine group was 41% (P<0.001), but only 26% (P=0.045) in the clonidine group. The frequencies of treatment-related adverse effects were higher in the venlafaxine group.

"Venlafaxine and clonidine are effective treatments in the management of hot flashes in patients with breast cancer," the authors conclude. "The results of this trial agree with the results of earlier trials in which both venlafaxine and clonidine have been studied. However, to the best of our knowledge, this is the first time that venlafaxine and clonidine were compared with placebo in patients with breast cancer over a period of 12 weeks of treatment."

The authors add that the occurrence of more adverse effects in the venlafaxine group may have been related to the dose of 75 mg daily, somewhat higher than previous studies, which started at 37.5 mg.

In an accompanying editorial, Charles Loprinzi, Debra Barton and Rui Qin, from the Mayo Clinic (Rochester, Minnesota), write that the primary weakness of the study is that the patient numbers were too small to reliably identify suspected differences between the two active study arms. "With the currently reported sample size of 40 patients per arm, the power of detecting a 10% difference (effect size −0.32) is only 29%," they write.

■ A Boekhout, A Vincent and O Dalesio. Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomised, double-blind, placebo-controlled trial. *JCO* 10 October 2011, 29:3862–68

■ C Loprinzi, D Barton and R Quin. Nonestrogenic management of hot flashes. *ibid*, pp 3842–44

Call for changes to NSCLC treatment paradigm in the elderly

→ The Lancet

Platinum-based doublet chemotherapy was associated with survival benefits compared with vinorelbine or gemcitabine monotherapy in elderly patients with non-small-cell lung cancer (NSCLC), the Intergroupe Francophone de Cancérologie Thoracique (IFCT) 0501 phase III trial has found.

Increases in life expectancy in the general population have led to a notable rise in the incidence of lung cancer in elderly people, leading to a median age of diagnosis of lung cancer in developed countries of between 63 and 70 years. The 2004 ASCO guidelines recommend platinum-based doublet chemotherapy to treat advanced NSCLC in fit, non-elderly adults, but monotherapy for patients older than 70 years. However most *post hoc* subgroup analyses of elderly patients enrolled in clinical trials with no upper age limit have shown similar outcomes in younger and older patients, suggesting that platinum-based doublet chemotherapy increases survival in elderly patients.

In the current study, Elisabeth Quoix and colleagues from the Strasbourg University Hospitals in France, investigated whether patients aged between 70 and 89 years fared better on double therapy. Between April 2006 and December 2009, 451patients with locally advanced or metastatic NSCLC and WHO performance status scores of 0–2 were enrolled from 61 centres and randomised in a 1:1 ratio to receive either four cycles of carboplatin plus paclitaxel (n=225) or five cycles of vinorelbine or gemcitabine monotherapy (n=226). In the monotherapy group 62 patients received vinorelbine and 164 gemcitabine. The median age of patients in the trial was 77 years.

Results showed that median overall survival was 10.3 months for the doublet chemotherapy group versus 6.2 months for the monotherapy group (HR 0.64, 95%CI 0.52–0.78; P<0.0001). Furthermore, one-year survival was 44.5% for the doublet chemotherapy group versus 25.4% for monotherapy.

Toxic effects, however, were more frequent in the doublet chemotherapy group. For example, 48.4% of patients in the doublet chemotherapy group experienced decreased neutrophil counts versus 12.4% with monotherapy; and 10.3% of patients in the doublet group experienced asthaenia versus 5.8% taking monotherapy.

"We saw a survival benefit with doublet chemotherapy of such magnitude that we believe the treatment paradigm for elderly patients with advanced NSCLC should be reconsidered," write the authors.

In an accompanying editorial Karen Reckamp, from the City of Hope Comprehensive Cancer Center (Duarte, California), writes, "Older patients dominate the lung cancer population, but continue to be under-represented in clinical trials. Additional studies are needed that enrol adequate numbers of older adults, and include a comprehensive geriatric assessment to provide the knowledge required to properly assess the risk–benefit ratio in treatment decisions, so that a personalised approach can be taken."

■ E Quoix, G Zalcman, J Oster. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. *Lancet* 17 September 2011, 378:1079–88

■ K L Reckamp. Combination chemotherapy for older adults with advanced non-small-cell lung cancer. *ibid*, pp 1055–57

Intraoperative MRI improves glioma resection

➜ Lancet Oncology

Intraoperative MRI guidance in glioma surgery helps surgeons provide the optimum extent of resection, a German study has found.

Intraoperative MRI systems were developed to help visualise tumour remnants that would otherwise remain unresected. Depending on the type of intraoperative MRI system, installation costs $3–8 million, with surgery reported to be more time-consuming than conventional treatment, adding further to costs. But the true value of intraoperative MRI guidance in modern neurosurgery has not been scientifically validated, with only retrospective cohort series studies undertaken showing the positive effects of such guidance according to the extent of remaining tumour tissue.

In the current study, Christian Senft and colleagues, from the Goethe University (Frankfurt, Germany), set out to test whether the additional expense was justified by prospectively assessing whether use of intraoperative MRI guidance resulted in higher rates of radiologically complete tumour resection than did conventional microsurgical tumour resection. The study represents the first randomised controlled trial to be undertaken in the area.

Between October 2007 and July 2010, 58 patients with contrast-enhancing gliomas amenable to radiologically complete resection were assigned in a 1:1 ratio to undergo intraoperative MRI-guided surgery (n=29) or to the conventional microsurgery control group (n=29). The primary endpoint was rate of complete resections established by early postoperative high-field MRI. Surgeons and patients were not masked to the treatment group assignment, but the neuroradiologists who analysed the MRI data were.

Results showed that 96% of patients in the intraoperative MRI group (23 out of 24) had complete tumour resection versus 68% (17 out of 25) in the control group (P=0.023). The postoperative rates of new neurological deficits did not differ between patients in the intraoperative MRI group and the control group (13% vs 8%, P=1.0). No patients for whom use of intraoperative MRI led to wider resection of residual tumour experienced neurological deterioration.

The investigators found intraoperative imaging led to wider resection of contrast-enhancing tissue in a third of patients in the experimental group, and that MRI-guided surgery added around one hour to the procedure over conventional surgery.

"Our study shows that intraoperative MRI is an appropriate method to improve the extent of resection of malignant brain tumours, comparable to the use of 5-aminolaevulinic acid [used for fluorescent imaging of tumour tissue]," write the authors. The enhanced resection, they add, was not achieved at the cost of increased surgical morbidity.

Whether resection control is best implemented by use of an intraoperative MRI device or by visualisation of tissue fluorescence, write the authors, remains to be seen. Future trials of extent of resection and outcome in brain tumour surgery should not be undertaken without use of either intraoperative MRI or 5-aminolaevulinic acid as a control, they conclude.

■ C Senft, A Bink, K Franz et al. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. *Lancet Oncol* October 2011, 12:997–1003

PET scan avoids neck dissection

➜ Clinical Oncology

Neck dissection can be avoided in patients with head and neck squamous cell carcinoma (HNSCC), with two positive lymph nodes at presentation (N2), if post-treatment fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) has been shown to be negative, finds a UK study.

The role of planned neck dissection after chemotherapy and radiotherapy (CRT) in patients with N2 HNSCC remains controversial due to a lack of randomised clinical trial data. Some clinicians advocate neck dissection after CRT for all patients with N2 neck disease regardless of treatment response, while others support its use only in selected cases with residual neck disease. They argue that post-CRT neck dissection benefits only those patients destined to develop nodal recurrence, while in others it represents an unnecessary procedure associated with high rates of postoperative complications.

Evidence is now accumulating supporting use of post-treatment PET in the identification of patients with residual nodal disease after CRT, who would benefit from post-treatment neck dissection. The idea is to spare patients who would not benefit from the procedure. FDG PET is a functional imaging tool that exploits the increased glucose metabolism in malignant tissues, which accumulate higher

concentrations of FDG relative to the surrounding normal tissues.

In the current study, Tom Roques and colleagues, from Norfolk and Norwich University Hospitals NHS Foundation Trust (Norwich, UK), set out to assess neck control in patients with N2 HNSCC in whom neck dissection was omitted for those who showed negative post-treatment FDG PET-CT results

In the study, 34 consecutive patients with N2 HNSCC were treated with radical intent using sequential chemoradiotherapy, 27 of whom received concomitant platinum-based chemotherapy with their radiotherapy.

FDG PET-CT was undertaken three months after completion of the radical radiotherapy, with neck dissection carried out only in those found to have increased FDG uptake in the neck post-treatment. In the study, 33 patients were observed not to show any increase in FDG uptake and therefore avoided neck dissection.

The results showed that in the 33 patients no regional recurrence occurred after a median follow-up of 39.1 months, leading to a negative predictive value (NPV) of post-treatment FDG PET-CT of 100%.

"A negative post-treatment PET-CT seemed to predict the absence of residual tumour in the neck, with an NPV of 100%, allowing us to safely withhold adjuvant neck dissection," write the authors.

If planned neck dissection had been carried out on their entire cohort of patients by virtue of their N2 disease status at presentation, they add, all of them would have undergone a procedure, with its attendant morbidities, without any improvement to their regional disease control.

The current observations, they write, will need to be confirmed in a larger patient cohort involving multiple institutions.

■ SW Loo, K Geropantas, C Beadsmoore, et al. Neck dissection can be avoided after sequential chemoradiotherapy and negative post-treatment positron emission tomography-computed tomography in N2 head and neck squamous cell carcinoma. *Clin Oncol (R Coll Radiol)* October 2011, 23:512–517

Anthracycline alternative reduces cardiac toxicity in HER2-positive breast cancer

➜ New England Journal of Medicine

Replacing anthracyclines with docetaxel- and carboplatin-based chemotherapy in patients treated with trastuzumab (Herceptin) for HER2-positive early breast cancer reduces cardiac complications while maintaining survival, the Breast Cancer International Research Group (BCIRG) 006 study has found.

The significant efficacy shown by trastuzumab in treating first-line metastatic HER2-positive breast cancer prompted its evaluation in early-stage disease. Studies have, however, shown increased cardiac dysfunction when trastuzumab is used in combination with anthracycline-based chemotherapy.

In the current study, lead investigator Dennis Slamon, from the University of California Los Angeles, together with investigators from 41 countries, set out to test trastuzumab with and without anthracyclines to determine whether oncologists could provide effective treatments without resulting toxicities.

In the BCIRG 006 study, between April 2001 and March 2004, 3222 women with early-stage HER2-positive breast cancer were randomised to one of three arms. The first arm received doxorubicin and cyclophosphamide followed by docetaxel (the non-trastuzumab group); the second arm received the same regimen plus 52 weeks of trastuzumab (the anthracycline group); and the third arm received docetaxel and carboplatin plus 52 weeks of trastuzumab (the non-anthracycline group). The primary endpoint was disease-free survival, with overall survival and safety as secondary endpoints.

Results show that at five years the estimated disease-free survival rates were 75% for the non-trastuzumab group, 84% among the anthracycline and trastuzumab group and 81% among the non-anthracycline and trastuzumab group.

The overall survival rates were 87% in the non-trastuzumab control group, 92% with the anthracycline and trastuzumab containing regimen (HR 0.63 vs control, $P<0.001$), and 91% for the non-anthracycline and trastuzumab regimen (HR 0.77 vs control, $P=0.04$)

Altogether there were 21 cases of congestive heart failure in the anthracycline and trastuzumab arm versus four cases in the non-anthracycline and trastuzumab arm ($P<0.001$), and seven cases of acute leukaemia in the anthracycline and trastuzumab arm versus one case in the non-anthracycline and trastuzumab arm. There were also significant differences favouring the non-anthracycline group for arthralgias, myalgias, hand-foot syndrome, nail changes, stomatitis, vomiting and sensory and motor neuropathies.

"Our findings show that we can further exploit this new translational knowledge to optimize efficacy while simultaneously minimizing acute and chronic toxic effects in the adjuvant treatment of HER2-positive breast cancer," write the authors.

In an accompanying editorial Daniel Hayes, from the University of Michigan Comprehensive Cancer Center in Ann Arbor, writes, "Taken together, these data do not clearly favour one regimen over the other. Hence, this trial establishes the non anthracycline regimen as 'another' (but not 'the') standard of care for adjuvant treatment of HER2 positive early stage breast cancer."

The risk for secondary leukaemia or irreversible congestive heart failure from anthracyclines, he adds, is arguably similar to the small but insignificant benefit of the anthracycline regimen over the non-anthracycline regimen (about one to two additional lives saved per 100 patients).

■ D Slamon, W Eiermann, N Robert, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *NEJM* 6 October 2011, 365:1273–83

■ D Hayes. Steady progress against HER2-positive breast cancer. *ibid*, pp 1336–38