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Selected reports edited by Janet Fricker

Mohs' micrographic surgery shows benefit in recurrent basal cell carcinoma

→ Lancet Oncology

Significantly fewer recurrences happen after Mohs' micrographic surgery (MMS) than after standard surgical excision in treatment of recurrent basal cell carcinoma (BCC), a five-year Dutch study has concluded. But no such differences were found for primary BCC.

A recent Cochrane review noted a "paucity" of published randomised controlled trials on treatment of BCC, although studies have suggested that MMS appears to be a better option than standard surgical excision. The method of histological assessment is thought to be the main reason for differences in recurrence – in MMS complete surgical margins are examined in horizontal sections, whereas in surgical excision, margins are examined in random vertical sections, known as the 'bread loaf technique'.

Klara Mosterd and colleagues, from Maastricht University Medical Centre, the Netherlands, undertook the first prospective randomised controlled trial comparing the effectiveness of surgical excision with MMS versus standard surgical excision for treatment of primary and recurrent facial BCC. Between October 1999 and February 2002, 408 patients with primary BCC (pBCC) and 204 patients with recurrent BCC (rBCC), from seven hospitals in the Netherlands, were randomly assigned to one of the two treatments. Patients were assessed visually for recurrence at six months, 18 months, and then annually through to five years.

Results show that, of the 11 recurrences in patients with pBCC, seven (4.1%) occurred in patients treated with surgical excision and four (2.5%) occurred in patients treated with MMS (log-rank test χ^2= 0.718; *P*=0.397). For patients with rBCC, two (2.4%) recurred in patients treated with MMS, versus 10 (12.1%) in patients treated with surgical excision (log-rank test χ^2= 5.958; *P*=0.015).

For pBCC, total treatment costs were €1,248 for MMS and €990 for surgical excision, whereas for rBCC, total treatment costs were €1,284 and €1,043, respectively. The incremental cost-effectiveness ratio (ICER), which represents the additional cost of one unit of outcome gained by a healthcare intervention, was calculated by dividing the mean difference in total treatment costs between MMS and surgical excision by their difference in effectiveness, and led to an ICER of €23,454 for pBCC and €3,171 for rBCC.

"Our findings show that treatment with MMS leads to a significantly lower number of recurrences than treatment with surgical excision in facial rBCC," conclude the authors, adding that recurrence differences might be explained by the difference in results obtained from examining surgical margins in horizontal and vertical sections. In addition to recurrence, costs and cosmetic outcomes, say the authors, factors such as age and comorbidity need to be considered when choosing treatments for individuals.

In an accompanying editorial, Steve Feldman and colleagues from Wake Forest University Health Sciences (Winston-Salem, North Carolina, USA) write, "Despite the quality of this prospective study, questions remain about the recurrence rates of surgical excision versus MMS for BCC. In the trial . . .16% of assessed tumours were not randomised because of a preference by the patient or referring physician, which could have introduced a considerable bias." Moreover, the intention-to-treat allocation was not fully informative, they added, since several tumours treated with surgical excision were rescued by Mohs' surgery.

"Because of the complexity of BCC management, physician judgement and consideration of each patient's unique circumstances are still essential," they concluded.

■ Surgical excision versus Mohs' micrographic surgery for primary and recurrent basal-cell carcinoma of the face: a prospective randomised controlled trial with 5-years' follow-up. K Mosterd, G Krekels, F Nieman et al. *Lancet Oncol* December 2008, 9:1149–1156

■ Surgical decision making for basal-cell carcinoma of the face. S Feldman, D Pearce and P Williford. *ibid*, pp 1119

Tamoxifen adherence below 80% impacts on survival

→ British Journal of Cancer

Low adherence to tamoxifen results in increased all-cause mortality for women with breast cancer, a Scottish study has concluded.

In 2005, the Early Breast Cancer Trialists' Collaborative showed tamoxifen reduced mortality by 31% in women with oestrogen-receptor-positive early breast cancer. Non-adherence to prescribed medication represents a major public health issue for patients with chronic conditions, including breast cancer. One recent study showed 49% of patients stopped taking tamoxifen before the end of the recommended five-year treatment period; another study found that 17% of women aged 65 and over had stopped treatment within two years. Earlier studies have considered duration of tamoxifen therapy, persistence (the period over which patients continue to take medication without a break) and whether patients take their medication persistently on a daily basis.

In the current study, Colin McCowan and colleagues from the University of Dundee, Scotland, undertook a retrospective cohort analysis of all women with incident breast cancer in the Tayside region of Scotland between 1993 and 2002, to see whether women prescribed tamoxifen after surgery adhered to their prescriptions and whether their adherence patterns influenced survival. The study intentionally included all women with breast cancer, including those with clinical metastases, and those who were oestrogen-receptor negative. The 10-digit Community Health Index number (CHI) issued for each patient allowed the team to combine dispersed prescribing information with clinical data at the individual patient level. Duration of tamoxifen therapy was calculated from the number of days between the first and last prescription and the coverage of the last prescription. The adherence index for each patient was calculated by summing the coverage for all prescriptions for each patient, dividing it by the duration, and then converting this to a percentage. Patients with an adherence index less than 80% were defined as having 'low adherence'.

Overall, 2,080 women were analysed in the study, with tamoxifen prescribed as therapy for 1,633 patients (79%), of whom 414 (25%) died during the course of the study. Patients were generally highly adherent to their medication during the course of treatment, with a median adherence of 93% (interquartile range 84%–100%). Results show that low adherence was associated with poorer survival in the 315 patients (19%) who had a low adherence at the median duration of tamoxifen use of 2.4 years (HR 1.10, 95%CI 1.001–1.21). Restricting the analysis to cover only patients whose oestrogen-receptor status was positive or unknown changed the hazard ratio for low adherence to 1.13 (95%CI 1.01–1.26).

The study found no difference in low adherence according to social class (P=0.96), but revealed there was a trend for a higher proportion of young women to have low adherence (P<0.001).

Results also showed that 411 patients (33%) prescribed tamoxifen discontinued their medication before completing five years of treatment. Within one year of commencing tamoxifen, 10% had discontinued treatment. Within two years, this had risen to 19%; at three and half years, 32%; and at five years plus, 51%. Duration of tamoxifen use was also associated with better survival, with the hazard ratio at any given time calculated from using the equation hazard ratio = exp (-0.065 x follow-up time).

"Patients need to be encouraged to continue their medication for the full five-year recommended period to ensure their best chance of survival," conclude the authors, adding that, for tamoxifen, the relatively long half life may mean that the occasional missed tablet is less of an issue. "Aromatase inhibitors are increasingly used as adjuvant therapy but have a shorter half life than tamoxifen and so strict adherence to this medication regimen should be emphasized as the occasional missed dose may have a greater detrimental effect on survival," write the authors.

Commenting on the shortcomings of the study, McCowan and colleagues write that measuring adherence to medication by looking at the "encashment of prescriptions" means that you cannot tell for certain if breast cancer patients have taken their medication.

■ Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. C McCowan, J Shearer, PT Donnan et al. *Br J Cancer*, 25 November 2008, 99:1763–1768

Gefitinib shows potential in non-small-cell lung cancer

→ The Lancet

Gefitinib (Iressa) shows survival 'non-inferiority' to docetaxel in previously treated patients with non-small-cell lung cancer, the international INTEREST study has concluded.

Earlier, two phase II trials (IDEAL 1 and 2) suggested that, in patients with previously treated advanced non-small-cell lung cancer, gefitinib – an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor – was both efficacious and less toxic than chemotherapy. Furthermore, the SIGN trial and Japanese phase III V-15-32 trial, both showed no significant difference between gefitinib and docetaxel in overall survival and progression-free survival, and also noted similar or improved response rates, improved quality of life and a more favourable toxicity profile for gefitinib.

In the Iressa NSCLC Trial Evaluating Response (INTEREST) study, Edward Kim and colleagues recruited 1,466 patients with histologically or cytologically confirmed locally advanced or metastatic non-small-cell lung cancer that had progressed or recurred after at least one previous platinum-based chemotherapy regimen. Between March 2004 and February 2006, patients were recruited from 149 centres in 24 countries in Europe, Asia, and North, Central and South America. In the open-label phase III study, patients were randomly assigned with dynamic balancing to receive gefitinib (250 mg per day orally; n=733) or the standard of care – docetaxel (75 mg/m^2 intravenously in one-hour infusion every three weeks; n=733).

Results show the overall survival hazard ratio for gefitinib versus docetaxel was 1.020 (96%CI 0.905–1.150). Median overall survival was 7.6 months in the gefitinib group versus 8.0 months in the docetaxel group, and one-year survival was 32% and 34% respectively.

Gefitinib was associated with lower rates of treatment-related adverse events than docetaxel (72% vs 82%), lower rates of serious adverse events (4% vs 18%) and lower rates of adverse events, leading to discontinuation of therapy (4% vs 11%).

The investigators were surprised to find no difference in overall survival between gefitinib and docetaxel, irrespective of a patient's EGFR protein expression, EGFR gene mutation, or K-Ras gene mutation status. The biomarker analyses were undertaken on archived tissue samples, taken at diagnosis, and the authors speculate that these variables might have changed with time, or under the influence of first-line therapy.

INTEREST showed unexpectedly that, although never smokers, women, people of Asian ethnic origin, and those with adenocarcinoma lived longer than did smokers, men, people of non-Asian ethnic origin, and those without adenocarcinoma, respectively, they had similar survival times on both gefitinib and docetaxel. This, say the authors, implies that such groupings are prognostic factors that are not related to treatment.

"The clinical management of advanced non-small-cell lung cancer remains challenging, but an oral agent that has similar efficacy, has a more favourable tolerability profile, and results in better quality of life than intravenous chemotherapy is an important shift in the treatment paradigm for this disease, and presents an alternative option for patients," conclude the authors, adding that, on the basis of these data, gefitinib is a valid treatment option for patients with pretreated advanced non-small-cell lung cancer.

In an accompanying comment, Michael Cullen (University Hospital Birmingham, UK) and Nicholas Thatcher (Christie Hospital, Manchester, UK) expressed disappointment with the results. "Our hope was that this trial would also guide prescribing by reinforcing our growing belief… that some patients with non-small-cell lung cancer can be clinically and biologically identified as being likely to benefit more from gefitinib than from docetaxel, or vice versa," they write, adding that such a finding would have allowed selection of the best treatment for different subsets of patients.

"Nevertheless, from INTEREST, we now have more than one option to offer patients after first-line chemotherapy," write Cullen and Thatcher. "While our understanding of predictive biomarkers develops, the choice of drug is likely to be influenced by patients' views and performance status as well as previous adverse effects," they conclude.

■ Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. ES Kim, V Hirsh, T Mok et al. *Lancet* November 2008, 372:1809–1818

Lymphadenectomy and EBRT do not affect survival in endometrial cancer

➜ The Lancet

There is no survival advantage to be gained by adding either lymphadenectomy or external beam radiotherapy (EBRT) to surgery, two separate studies of early endometrial cancer have concluded.

The mainstay of surgical treatment for early endometrial cancer, including stage I and stage IIA, is total hysterectomy and bilateral salpingo-oophorectomy (THBSO). With the intention of improving locoregional tumour control, THBSO can be supplemented with lymph-node dissection, adjuvant EBRT and vaginal brachytherapy. Although both are widely applied and recommended in practice guidelines, there is little evidence to support the belief that such therapies have beneficial effects on survival or quality of life. Furthermore, lymph node dissection and EBRT have been shown to increase treatment-related morbidity, and might aggravate comorbidities associated with older age and obesity.

ASTEC (A Study in the Treatment of Endometrial Cancer) was designed to address the question of whether additional benefits might be obtained from lymph-node dissection and adjuvant EBRT. Two separate studies were undertaken, both funded by the UK Medical Research Council – a surgical study looking at lymph-node dissection, and a radiotherapy study looking at adjuvant EBRT.

In the surgical study, 1,408 women from 85 centres in four countries with histologically proven endometrial cancer were randomly allocated to standard surgery (n=704), or standard surgery plus lymphadenectomy (n=704), which consisted of systematic dissection of the iliac and obturator nodes.

In the radiotherapy study, 905 women with intermediate- or high-risk early-stage endometrial cancer from 112 centres in seven countries were randomly assigned after surgery to observation (n=453) or to EBRT (n=452). EBRT consisted of a target dose of 40–46 Gy in 20–25 daily fractions to the pelvis, five times per week.

For the radiotherapy analysis, 789 of the subjects came from the ASTEC trial, and 116 from the earlier National Cancer Institute of Canada's EN.5 trial. The EN.5 study, which first started in 1996, was unable to recruit sufficient numbers to complete the study. Additionally, a meta-analysis combining the ASTEC and EN.5 data with two previously published trials (PORTEC 1 and GOG99) was undertaken, providing a total analysis including more than 2,000 patients.

Results of the ASTEC surgical study, after a median follow-up of 37 months, show 88 women in the standard surgery group had died versus 103 in the lymphadenectomy group (HR 1.16, 95%CI 0.87–1.54; P=0.31). At five years, after adjustment for baseline characteristics and pathology details, the HR for overall survival was 1.04 (95%CI 0.74–1.45; P=0.83) and for recurrence-free survival was 1.25 (95%CI 0.93–1.66; P=0.10).

The ASTEC surgical trial investigators concluded, "Our results suggest that lymphadenectomy in itself has no therapeutic effect and is therefore not justified as a therapeutic procedure in its own right." One limitation of the study, they add, was that the lymphadenectomy specified in the protocol was not comprehensive, and did not include all pelvic and para-aortic nodes.

Results of the radiotherapy study show that, after a median follow-up of 58 months, 68 women in the observation arm and 67 in the EBRT arm had died, providing no evidence for any overall survival benefit with EBRT (HR 1.05, 95%CI 0.75–1.48; P=0.77). The updated meta-analysis of the effect of EBRT on overall survival produced an HR of 1.04 (95%CI 0.84–1.29; P=0.38). Late toxicity (predominantly gastrointestinal or urogenital), was more commonly reported after EBRT. Results show 202 women

(45%) in the observation arm experienced late toxicity compared to 274 (61%) in the EBRT arm. "In conclusion, adjuvant external beam radiotherapy cannot be recommended as part of routine treatment to improve survival for women with early endometrial cancer at intermediate or high risk of recurrence, and brachytherapy might be preferred for local control," write the radiotherapy study authors.

In an accompanying commentary to the two papers, Michael Hockel and Nadja Dornhofer, from the University of Leipzig, Germany, consider why these treatments may not have been beneficial. Both the surgical and radiotherapeutic treatments tested in the two randomised trials, they say, were confined to the pelvis and would therefore only have been therapeutic with curative intent for the approximately one-third of node-positive patients whose metastases were exclusively located in the high peri-aortic lymph-node basins.

Addressing the question of where should we go from here, Hockel and Dornhofer write, "Appropriate studies need to explore whether locoregional tumour control can be improved and distant metastases prevented by better surgery and different systemic therapies," adding that the different therapies might include modified THBSO, including resection of the vaginal cuff with techniques that minimise tumour dissemination.

Additionally, for postoperatively established high-risk cases, adjuvant chemotherapy with paclitaxel-carboplatin might be offered.

■ Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. The ASTEC/EN.5 writing committee. *Lancet* published online 13 December 2008, doi:10:1016/S0140-6736(08)61767-5

■ Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Writing committee on behalf of the ASTEC study. *Lancet ibid*, doi:10.1016/S0140-6736(08)61766-3

■ Treatment of early endometrial carcinoma: is less more? M Hockel and N Dornhofer. *Lancet ibid*, doi:10.1016/SO140-6736(08)61768-7

Gene expression shows importance of tumour micro-environment

➜ New Engl J Med

Three gene expression profiles are associated with survival in diffuse large-B-cell lymphoma, two of which demonstrate the importance of tumour micro-environment, a US National Cancer Institute study has found.

The addition of rituximab immunotherapy to cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) has been shown to improve overall survival among patients with diffuse large-B-cell lymphoma by 10%–15%. Although phenotypically uniform, diffuse large-B-cell lymphoma is heterogeneous at the molecular level, leading Louis Staudt and colleagues from the metabolism branch of the Center for Cancer Research (Bethesda, Maryland) to hypothesise that rituximab might improve survival only in certain subgroups of diffuse large-B-cell lymphoma patients.

In the current study, investigators obtained preclinical tumour biopsy specimens and clinical data from 414 patients with newly diagnosed diffuse large-B-cell lymphoma being treated at 10 institutions in North America and Europe. In the study, 181 patients received CHOP (known as the training group), and 233 received R-CHOP (known as the validation group). Staudt and colleagues then looked for new survival-associated signatures at the $P>0.01$ level in the CHOP training group.

Results showed that three gene expression signatures – germinal-centre B-cell, stromal-1 and stromal-2 – predicted survival in both patients who received CHOP and patients who received R-CHOP. Furthermore, the stromal-1 signature, associated with a favourable outcome, contained genes encoding components of extracellular matrix and the monocytic lineage found in T cells and natural killer cells. In contrast, the stromal-2 signature, associated with poor outcomes, contained genes encoding molecules related to angiogenesis.

"The stromal-2 signature may be an 'angiogenic switch' in which the progression of a hyperplastic lesion to a fully malignant tumor is accompanied by new blood-vessel formation," speculate the authors, adding that diffuse large-B-cell lymphomas with high relative expression of the stromal-2 signature were observed to be associated with increased tumour blood-vessel density and adverse outcomes.

Using the CD19 status of cells, Staudt and colleagues sorted the malignant component from the non-malignant tumour stroma, and showed stromal-1 and stromal-2 gene expression signatures were more highly expressed in the non-malignant fraction, while the germinal-centre B-cell signature was more highly expressed in the malignant fraction.

Ultimately, combined treatments targeting oncogenic mechanisms in the malignant cell as well as interactions in the tumour micro-environment may prove synergistic, suggest the authors.

Bevacizumab (the monoclonal antibody to VEGF) is currently being investigated in several phase II and phase III clinical trials involving patients with diffuse large-B-cell lymphoma. "On the basis of our results, it is possible that only a subgroup of such patients – those with diffuse large-B-cell lymphoma characterized by high relative expression of the stromal-2 signature and increased tumor blood-vessel density – may benefit from this angiogenesis inhibitor," write the authors.

In an accompanying editorial, Charis Eng, from Case Western Reserve University (Cleveland, Ohio) wrote that somatic profiling of the neoplasia should now be taking into account the tumour micro-environment. "The challenge in all these integrative endeavours is that genetic data are only as good as the documentation and annotation of the clinical phenotype and outcome," writes Eng.

■ Stromal gene signatures in large-B-cell lymphomas. G Lenz, G Wright, SS Dave et al. *N Engl J Med* 27 November 2008, 359:2313–2323

■ Microenvironmental protection in diffuse large-B-cell lymphoma. C Eng. *ibid*, pp 2379–2381