NEWSROUND

Selected reports edited by Janet Fricker

Shorter radiotherapy courses may not increase risk of breast cancer relapse

➜ Lancet Oncology

Giving a lower total dose of radiotherapy, delivered in fewer, slightly higher-dose treatments over a shorter period of time is as effective in reducing local relapses in women with early breast cancer as standard radiotherapy of a higher total dose delivered over a longer time, and has no more side-effects, according to a large UK study. However, specialists have cautioned that longer-term follow-up is needed to ensure that this radiotherapy regimen achieves a sustained reduction in the risk of breast cancer relapse.

Radiotherapy after surgery for breast cancer has been shown to reduce local recurrence. This is important, as previous research has shown that avoiding four local recurrences saves one woman from dying of breast cancer. The treatment is traditionally given in 25 daily doses (called fractions) of 2.0 Gy, achieving a total dose of 50 Gy over five weeks. However, hospitals in the UK and Canada have been delivering a lower total dose in fewer, larger fractions – termed hypofractionation – for some time, and retrospective studies have shown that it appears to be as effective as standard radiotherapy in reducing the risk of relapse, without increasing adverse events.

UK researchers have now carried out two prospective studies randomly allocating women to different radiotherapy regimens and following them up for five to six years to assess the rate of recurrence of breast cancer and the adverse effects associated with the different approaches.

In the first study, the UK Standardisation of Breast Radiotherapy (START) Trial A, researchers randomly allocated 2,236 women who had undergone surgery for early breast cancer to receive the standard radiotherapy schedule (50 Gy in 25 fractions of 2.0 Gy over five weeks), or a lower total dose of 41.6 Gy (13 fractions of 3.2 Gy over five weeks) or 39 Gy (13 fractions of 3.0 Gy over five weeks). After an average follow-up of just over five years, the results showed that the rate of locoregional tumour relapse in women given 41.6 Gy (3.5%) was similar to that in women given 50 Gy (3.6%). However, it was slightly higher in women given the lowest total radiotherapy dose of 39 Gy (5.2%).

In the second study, START Trial B, a further 2,215 women with early breast cancer were randomly allocated, following surgery, to the standard radiotherapy schedule or a hypofractionated schedule (40 Gy in 15 fractions of 2.67 Gy over three weeks).

Results showed similar rates of local-regional tumour relapse after five years: 3.3% of women given standard radiotherapy and 2.2% of those given the hypofractionated regimen. A significant reduction was also seen in the rate of distant metastasis and overall risk of death at five years among women treated with the hypofractionated schedule, as well as lower rates of late side-effects.

"The results suggest that a high total dose given in 25 small treatments is no better than simpler schedules, using fewer exposures to a total dose," said John Yarnold, chief investigator for the two studies. "Shorter therapies giving fewer, larger treatments are obviously convenient for patients. These results support the current use of shorter schedules in the UK and in other countries," he added.

Other breast cancer specialists, however, have questioned the findings, arguing that increasing the radiation dose per fraction would be expected to increase normal tissue damage and reduce the therapeutic benefit. They point out that the results from the START trials seemed to be contrary to those seen in studies in head and neck cancer, which show that reducing the radiation dose per fraction at the same time as increasing the number of fractions (hyperfractionation) and the total dose leads to better tumour control and survival without increased toxicity. Much longer follow-up is needed, they argue, to see if the apparently similar reduction in rate of relapse with hypofractionated radiotherapy to standard radiotherapy is maintained over time.

■ The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation

for treatment of early breast cancer: a randomised trial. The START Trialists' Group. *Lancet Oncol* 4 April 2008, 9:331–341

■ The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. The START Trialists' Group. *Lancet* 29 March 2008, 371:1098–1107

Delays in adjuvant chemotherapy worsen ovarian cancer outcomes

➜ British Journal of Cancer

Ovarian cancer patients who start chemotherapy more than six weeks after debulking surgery and those receiving an abbreviated course of treatment are more likely to die than those starting therapy within six weeks and completing the full course of treatment, according to an analysis of two US cancer registries.

Previous studies in ovarian cancer examining the time from surgery to initiation of adjuvant chemotherapy have produced varying results. A theoretical basis for the benefits of early administration of cytotoxic agents was suggested by a mouse mammary tumour model, where removal of primary lesions resulted in increased tumour proliferation.

Dawn Hershman and colleagues, from the Herbert Irving Comprehensive Cancer Center, used the US National Cancer Institute's SEER cancer registry and the linked Center for Medicare and Medicaid Services (CMS) data base to identify 6,047 women aged 65 years or older with stages III–IV epithelial ovarian cancer. A total of 3,585 women underwent surgery and 2,558 (71%) received at least one cycle of chemotherapy. Of these, 1,712 (67%) started chemotherapy within six weeks of debulking surgery, while 846 (33%) began treatment at least six weeks after debulking surgery.

Results show the median survival for women initiating treatment within six weeks of surgery was 34 months compared to 28 months for those beginning therapy after six weeks. Women who initiated treatment after six weeks had poorer overall survival (P<0.0001) and ovarian cancer-specific survival (P=0.009) than women who did not delay treatment.

A second analysis, which looked at duration of treatment, showed that women treated for three to seven months had 16% lower mortality than women treated less than three months.

"Prospective studies of factors that influence the quality of care in women with OC [ovarian cancer] are needed," write the authors, "but until such studies are completed, efforts should be made to facilitate prompt initiation and full completion of adjuvant chemotherapy."

■ Variability in chemotherapy delivery for elderly women with advanced stage ovarian cancer and its impact on survival. JD Wright, T Doan, R McBride et al. *Br J Cancer* 1 April 2008, 98:1197–1203

Lymphadenectomy advised for nodal metastasis from an unknown primary melanoma

➜ Journal of Clinical Oncology

Overall survival is significantly better for patients with melanomas of unknown primary origin than for patients where the primary melanoma is of known origin, according to a recent US study.

For 10%–20 % of patients presenting with palpable evidence of regional metastatic melanoma, no primary lesion can be identified. Proposed causes of unknown primary melanoma (MUP) include failure to recognise the primary lesion during clinical examination, prior removal of the primary lesion during traumatic injury or by excision without pathologic diagnosis, and the unrecognised primary lesion undergoing spontaneous regression.

Some studies have reported poorer outcomes for MUP compared to known primary melanoma (MKP), while others have reported equivalent or better outcomes. The need for clarification prompted Chris Lee and colleagues, from the John Wayne Cancer Institute in Santa Monica, to review clinical records for 13,000 melanoma patients registered on a prospective melanoma database between 1 April 1971 and 31 December 2005.

The study identified a subgroup of 1,571 patients in the database managed with regional lymphadenectomy for palpable nodal metastases within three months of presentation. Of these, 262 had MUP and 1,309 had MKP. For each patient, age (whether they were under or over 60), sex, site of tumour involvement, number of tumour nodes, decade of diagnosis, status of primary (MUP or MKP) and clinical outcome were recorded.

Results show that five-year overall survival was significantly better for the 262 patients with MUP than for the 1,309 patients with MKP (55% ±6% vs 44% ±3%, P=0.0021). Computerised matching of MUP and MKP by four significant covariables (age, sex, nodal tumour burden and decade of diagnosis) yielded 221 matched pairs. Median and five-year overall survival rates were 165 months and 58% ±7% for MUP, compared with 34 months and 40% ±7 % for MKP (P=0.0006).

The most likely explanation for MUP, say the authors, is that an unrecognised primary lesion has undergone spontaneous regression mediated by an endogenous immune response. "Our data strongly suggest that the initial treatment of MUP with nodal metastasis should be regional lymphadenectomy," they write, stressing the importance of an accurate staging work-up that includes complete imaging to rule out distant disease.

"Unless the results of this work-up are positive for metastasis beyond the regional basin, patients should undergo therapeutic (and potentially curative) regional lymphadenectomy as the standard of care."

■ Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. C Lee, M Faries, L Wanek et al. *J Clin Oncol* 1 February 2008, 26:535–541

One in four do not adhere to aromatase inhibitor prescription

→ Journal of Clinical Oncology

Around one-quarter of early-stage breast cancer patients taking the aromatase inhibitor (AI) anastrozole do not adhere to treatment, according to the largest study of adherence to adjuvant endocrine therapy ever undertaken outside a clinical trial. The US study suggests that a substantial proportion of women with early-stage breast cancer receive suboptimal treatment.

In 2001 the ATAC study showed a statistically significant improvement in disease-free survival for postmenopausal women taking initial anastrozole compared with initial tamoxifen as adjuvant therapy for hormone-receptor-positive early-breast cancer. Previous studies have suggested adherence to tamoxifen among women with early stage breast cancer in the range of 25%–96%. This is important because, across all disease types, adherence has been cited as the single most important modifiable factor compromising treatment outcomes.

In the present study, Ann Partridge and colleagues from the Dana-Farber Cancer Institute in Boston looked at whether similar patterns of non-adherence occur in women prescribed AIs for early-stage breast cancer. The study focused on anastrozole, since it was the only AI approved for early-stage breast cancer during the study period.

Investigators used longitudinal claims data from three large commercial US health programmes: Plan A, Plan B and the Market Scan, which included information on 1,111 women, 1,587 and 4,434 women respectively. For the purposes of the study, receiving medication on less than 80% of days was defined as 'non-adherence'.

Results show the number of days a patient took anastrozole, known as the medication possession ratio (MPR), declined from year 1 to year 3 of the study. For patients in Plan A, in year 1 the mean MPR was 86%, declining to 79% in year 3. For those in plan B, mean MPR decreased from 78% to 62%, while for those in the Market Scan it fell from 84% to 72%. Across all three data sets the proportion of women considered non-adherent ranged from 22% to 31% in year 1, rising to 32% to 50% in year 3.

The results of the study have important implications, say the investigators. "Patients who are non-adherent to adjuvant endocrine therapy may be compromising their care. Oncologist and patient awareness of the problem of non-adherence, and communication regarding the importance of adherence to therapy, may improve health outcomes," they write, adding that future research should focus on identifying patients at risk for non-adherence and on developing interventions to improve adherence.

■ Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. AH Partridge, A LaFountain, E Mayer et al. *J Clin Oncol* 1 February 2008, 26:556–562

Better survival for HPV-positive squamous cell head and neck cancer

→ JNCI

Patients with human papillomavirus- (HPV)-positive head and neck squamous cell carcinoma (HNSCC) show better survival than patients with HPV-negative tumours, according to a US study. The authors are calling for cancer staging systems to reflect these differences.

Previous analyses of HNSCC tumours have suggested HPV-positive oropharyngeal tumours are clinically and molecularly distinct from HPV-negative tumours, and are associated with different prognostic outcomes. In a prospective multicentre study, Carole Fakhry and colleagues from the John Hopkins Medical Institutions in Baltimore evaluated the association of tumour HPV status with response to treatment and survival among 96 patients with stage III or IV HNSCC of the oropharynx or larynx. The subjects – who were participants in an Eastern Cooperative Oncology Group (ECOG) phase II trial – had been administered two cycles of induction chemotherapy with intravenous paclitaxel and carboplatin, followed by concomitant weekly intravenous paclitaxel and standard fractionation radiation therapy. For each subject, formalin-fixed and paraffin-embedded biopsy specimens were evaluated for the presence of HPV16 DNA by *in situ* hybridisation.

Results show that, compared with patients with HPV-negative tumours, patients with HPV-positive tumours have a significantly better rate of response following induction chemotherapy (82% vs 55%; 95%CI 9.3% –44.7%, P=0.01), and following chemoradiation treatment (84% vs 57%; 95%CI 9.7%–44.3%, P=0.007). Furthermore, patients with HPV-positive tumours showed an overall two-year survival of 95% compared with 62% for HPV-negative tumours (95% CI 18.6%–47.4%, P=0.005).

The association of tumour HPV status with survival and response to treatment, say the authors, is sufficiently strong to warrant consideration in the design and analysis of future head and neck cancer clinical trials. "Our data suggest that the risks and benefits of intensive combined modality therapies should be considered separately for HPV-positive and -negative patients," they write, adding that failure to take such differences into consideration could lead to confounding results.

■ Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. C Fakhry, WH Westra et al. *J Natl Cancer Inst* 20 February 2008, 100:261–269

No difference between sequential and concomitant chemotherapy and hormonal therapy in breast cancer

→ Annals of Oncology

No difference in overall survival is evident between pre- and post-menopausal breast cancer patients given sequential or concomitant

hormonal therapy with adjuvant chemotherapy, according to an Italian study. A slight advantage, however, was noted for concomitant treatment in pre-menopausal patients.

Adjuvant chemotherapy and hormonal therapy are currently administered sequentially, with hormonal therapy following chemotherapy. The study by Lucia Del Mastro and colleagues, from the Istituto Nazionale per la Ricerca sul Cancro in Genova, set out to clarify optimum timing for treatments. A potential advantage of concomitant administration, say the authors, is the possibility of avoiding detrimental effects of delaying tamoxifen. Preclinical studies, however, have suggested negative interactions between tamoxifen and chemotherapy when given concomitantly. So far, randomised clinical trials have reported conflicting results: two trials found no difference between sequential and concomitant treatment, while sequential therapy was found to be better in a third trial. The current study is the first to include pre-menopausal women.

The study retrospectively analysed outcomes for 1,096 patients entered into two phase III trials receiving adjuvant chemotherapy and tamoxifen either concomitantly or sequentially.

In the MIG-1 study, patients had been randomly assigned to receive either six courses of FEC21 (5-fluorouracil, epirubicin and cyclophosphamide every 21 days) or six courses of dose-dense FEC14 (same as FEC21 but given every 14 days, with granulocyte colony-stimulating factor support).

In the MIG-5 study, patients had been randomly assigned to receive either the FEC21 treatment or four courses of epirubicin and paclitaxel every 21 days. In both trials, tamoxifen was given either after completion of chemotherapy or concomitantly at the physician's discretion.

Of the total population of eligible patients from the two trials, 507 had received concomitant tamoxifen and 589 sequential tamoxifen.

Results show no significant difference in overall survival between the two groups (P=0.384). The cumulative overall survival at five years was 94% (95%CI 92%–96%) in both the concomitant and the sequential groups. By 10 years, however, the survival rate had fallen to 83% in the concomitant group (95%CI 78%–88%) and 80% (95%CI 74%–86%) in the sequential group.

The cumulative 10-year event-free survival was 63% (95%CI 56%–70%) in the concomitant group and 54% (95%CI 42%–66%) in the sequential group (P=0.570).

In terms of overall survival, a significant decreasing trend in the hazard ratio for death or reoccurrence was observed with increasing age, indicating that concomitant therapy, as compared with sequential therapy, might be more effective in younger patients. "A potential explanation of this finding is that the early commencement of tamoxifen could counterbalance the bad prognosis reported in young pre-menopausal patients with ER-positive tumors who are treated with chemotherapy alone," write the authors. The potential advantage of concomitant tamoxifen in young patients needs to be further addressed in prospective trials, they add.

■ Timing of adjuvant chemotherapy and tamoxifen in women with breast cancer: findings from two consecutive trials of Gruppo Oncologico Nord-Ovest–Mammella Intergruppo (GONO-MIG) Group. L Del Mastro, B Dozin, E Aitini et al. *Ann Oncol* February 2008, 19:299–307

Quality of life changes in prostate cancer

➜ New England Journal of Medicine

Each of the three common primary therapies for prostate cancer – radical prostatectomy, brachytherapy and external beam radiotherapy – produce unique quality of life changes in patients relating to urinary symptoms, sexual and bowel function, vitality and hormonal function, according to a recent American study.

Quality-of-life outcomes are important for prostate cancer patients. Early studies reviewing outcomes following prostatectomy or conventional radiotherapy raised concerns about urinary incontinence, bowel function and sexual activity. Less is known, however, about quality of life after brachytherapy and androgen-suppression therapy.

Martin Sanda and colleagues from Harvard University, in Boston, sought to identify determinants of health-related quality of life after primary treatment for prostate cancer and to determine how quality of life relates to overall satisfaction with the outcome of treatment for patients and their partners. Patients who underwent elected prostatectomy, brachytherapy or external-beam radiotherapy between March 2003 and March 2006 were enrolled in the study. In phone surveys, 1,201 patient and 626 partners responded to questionnaires, including the Expanded Prostate Cancer Index Composite (EPIC-26) and Service Satisfaction Scale for CancerCare (SCA). Responses were obtained before treatment and at 2, 6, 12, and 24 months after starting treatment.

Results show adjuvant hormone therapy exacerbated the adverse effects of radiotherapy or brachytherapy, whereas nerve-sparing surgical procedures mitigated the adverse effects of prostatectomy. Factors associated with worse patient-reported outcomes were obesity, a large prostate size, a high pretreatment prostate-specific antigen (PSA) score, and older age. At one year, 5% of partners reported being bothered by the patient's incontinence after prostatectomy or brachytherapy, while 7% of partners in the brachytherapy group and 3% each in the radiotherapy and prostatectomy groups reported being bothered by the patient's symptoms of urinary obstruction, such as urinary frequency.

Black patients reported lower satisfaction with the degree of overall treatment outcomes than other patients. "We could not determine whether these differences in outcome reflected disparities in the quality of care, in the expectations of patients, or in cancer biology," write the authors, adding that further study will be required to answer these questions.

■ Quality of life and satisfaction with outcome among prostate-cancer survivors. MG Sanda, RL Dunn, J Michalski et al. *N Engl J Med* 20 March 2008, 358:1250–1261