NEWSROUND

Selected reports edited by Janet Fricker

Functional limitations following breast cancer treatment influence mortality

→ JNCI

Physical limitations following breast cancer treatment, defined as reported difficulties in the completion of tasks of everyday living, can have far-reaching effects on how long women live, a US study has found. Older breast cancer patients in particular, and those who are overweight, are more likely to experience functional impairments for at least 18 months after treatment. The research indicates that the health of breast cancer survivors could be greatly improved with simple modifications in habits, such as becoming more physically active.

Breast cancer survivorship is increasing due to improvements in early detection and adjuvant therapy. Since overall survival is considered the most therapeutically relevant outcome for cancer patients, little attention has been paid to the physical limitations and other health problems affecting women who have had breast cancer. But the recent US Institute of Medicine report emphasised the need to identify high-risk breast cancer populations who could be targeted with interventions to promote quality and length of life.

To determine how physical limitations following initial breast cancer treatment affect morbidity and mortality among women who have had breast cancer, Dejana Braithwaite and colleagues from the University of California, San Francisco, studied 2202 women diagnosed with stage I, II or III breast cancer between 1997 and 2000. The women were followed for up to 11 years after diagnosis.

Baseline questionnaires, completed on average 21 months after diagnosis, asked participants about endurance, strength, muscular range of motion and small muscle dexterity following initial treatments such as chemotherapy, radiation therapy or hormone therapy. The study then explored the extent to which the impact of functional limitations on survival differed as a function of age, body mass index (BMI), tumour stage and other lifestyle characteristics.

Results show that at least one functional limitation was present in 39% of study participants. The authors found that functional limitations increased with age - 39.3% of women with one or more functional limitation were aged 65 to 79 versus 23.8% of those without any functional limitation ($P<0.001$). Women with limitations were also more likely to be overweight or obese – 35.7% of women with one or more functional limitations had a BMI of at least 30, versus 21.4% of women without limitations ($P<0.001$).

More women with functional limitations died from causes other than breast cancer – 8.9% of women with versus 2.7% without limitations ($P<0.001$). In contrast, similar proportions of patients with and without functional limitations died of breast cancer ($P=0.99$)

"A new finding from this analysis among longer-term breast cancer survivors is that functional limitations following initial adjuvant treatment primarily affect overall and competing-cause survival, but not breast cancer-specific survival," write the authors. The study, they add, underscores the need to track long-term effects and explore whether they are amenable to interventions. "...functional status may be an important addition to clinical screening among breast cancer patients to identify groups that are at high risk of poor prognosis, allowing the targeting of functionally impaired patients to improve quality and length of life."

Limitations of the study include the fact that information on physical impairments was available only after initial treatment so that functional limitations prior to cancer diagnosis could not be evaluated. The lack of a control group also meant that the effect of physical limitations on mortality could not be compared between women with and without breast cancer.

In an accompanying commentary, Harvey Jay Cohen from Duke University Medical Center (Durham, North Carolina), writes that the study's conclusions could be incorporated into a cancer survivorship plan, especially for elderly survivors. "Such an evaluation could guide therapy regarding underlying co-morbidities and other reasons for functional decline, such as obesity and decreased physical activity."

■ D Braithwaite, WA Satariano, B Sternfeld et al. Long-term prognostic role of functional limitations among women with breast cancer. *JNCI* 6 October 2010, 102:1468–1477

■ HJ Cohen. Functional assessment and the cancer survivor: something old, something new. *ibid*, pp 1450–1451

Reduced-intensity treatment delivers similar benefits to standard therapy in early Hodgkin's lymphoma

→ New England Journal of Medicine

Patients with early-stage Hodgkin's lymphoma showed similar rates of disease control regardless of whether they were treated with standard or reduced-intensity chemotherapy and radiation, a study from the German Hodgkin

Study Group (GHSG) has concluded.

The integration of the chemotherapy regimen consisting of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) with radiation therapy resulted in greater efficacy and allowed the radiation field and dose to be reduced, leading to widespread use of the combined approach in patients with early-stage Hodgkin's lymphoma and a favourable prognosis. Four cycles of ABVD followed by 30 Gy of involved-field radiation therapy is now regarded as the standard of care by many groups.

In 1998 the GHSG initiated the HD10 study to investigate whether fewer cycles of chemotherapy and lower doses of radiotherapy could be delivered while maintaining high rates of disease control in patients with early-stage Hodgkin's lymphoma and a favourable prognosis.

Between May 1998 and January 2003, GHSG investigators, led by Andreas Engert, from the University Hospital of Cologne (Germany) randomly assigned 1370 patients with newly diagnosed Hodgkin's lymphoma and a favourable prognosis in a 1:1:1:1 ratio to one of four treatment groups – four cycles of ABVD followed by 30 Gy radiation (group 1, *n*=346), four cycles of ABVD followed by 20 Gy radiation (group 2, *n*=340), two cycles of ABVD followed by 30 Gy radiation (group 3, *n*=341), or two cycles of ABVD followed by 20 Gy of radiation therapy (group 4, *n*=343). Patients were recruited and treated at 329 hospitals and outpatient practices in Germany, Switzerland, the Netherlands, the Czech Republic and Austria. The primary outcome was freedom from treatment failure, with secondary endpoints including progression-free survival, complete response and treatment toxicity.

Results show that, at five years, rates of freedom from treatment failure were 93.0% for the four-cycle ABVD regimen versus 91.1% for the two-cycle regimen (*P*=0.39). Among patients randomised to four cycles of ABVD, five-year rates of freedom from treatment failure were 92.8% with 20 Gy compared with 93.1% with 30 Gy. Patients treated with two cycles of chemotherapy had 90.9% freedom from treatment failure with 30 Gy and 91.2% with 20 Gy. The intention to treat analysis showed no significant differences between the two chemotherapy groups for the secondary endpoints of overall survival (*P*=0.93) and progression-free survival (*P*=0.28).

Grade 3 to 4 adverse events occurred in 51.7% of patients treated with four cycles of ABVD versus 33.2% receiving two cycles (*P*<0.001). Additionally, grade 3 to 4 adverse events occurred in 8.7% of patients who received 30 Gy versus 2.9% who received 20 Gy (*P*<0.001).

"In summary, the HD10 trial showed that in patients with early-stage Hodgkin's lymphoma and a favourable prognosis, treatment with two cycles of ABVD followed by 20 Gy of involved-field radiation therapy is as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy," write the authors.

The overall survival rate of 94.8% at eight years for all patients in the study, add the authors, may suggest that some patients are still being overtreated. The introduction of positron-emission tomography, they add, might help identify patients who can be cured with even less treatment.

■ A Engert, A Putsches, HT Each et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *NEJM* 12 August 2010, 363:640–652

Ovarian cancer strategies demonstrate similar survival

➜ New England Journal of Medicine

Neoadjuvant chemotherapy followed by interval debulking surgery was shown to be non-inferior to primary debulking surgery followed by chemotherapy in patients with bulky stage IIIC or IV ovarian cancer, a collaborative study by researchers from the EORTC Gynaecological Cancer Group and the Clinical Trials Group of the Canadian NCI has reported.

Primary debulking surgery followed by adjuvant chemotherapy is the standard of care for patients with advanced ovarian cancer. However, in several prospective studies investigators have evaluated outcomes with neoadjuvant chemotherapy before cytoreductive surgery as an alternative approach. One meta-analysis of such trials showed worse outcomes for those receiving neoadjuvant chemotherapy compared with those undergoing primary surgery.

Between September 1998 and December 2006, 632 patients from 59 centres in eight countries with stage IIIc or IV epithelial ovarian carcinoma, fallopian tube carcinoma or primary peritoneal carcinoma were randomised to primary debulking surgery followed by platinum-based chemotherapy (*n*=336) or to neoadjuvant platinum-based chemotherapy followed by debulking surgery (*n*=334). The primary endpoint was overall survival with the trial statistically powered to evaluate non-inferiority of the neoadjuvant chemotherapy versus primary surgery.

After a median follow-up of 4.7 years, results show that patients with neoadjuvant chemotherapy had a median overall survival of 30 months versus 29 months for patients receiving primary surgery. Subgroup analysis failed to identify any patient or tumour characteristics that were associated with better outcomes with one treatment than the other.

For both treatment groups the strongest predictor of overall survival was complete resection of all macroscopic disease. For the primary surgery group, median overall survival was 45 months for patients who had no residual tumours, 32 months for patients with residual tumours measuring 1–10 mm, and 26 months for patients with residual tumours greater than 10 mm. For the group receiving neoadjuvant therapy, the corresponding figures were 38, 27 and 25 months respectively.

"In conclusion, among patients with advanced (stage IIIC or IV) ovarian, fallopian-tube, or peritoneal ovarian carcinoma, survival after neo adjuvant chemotherapy followed by interval debulking surgery is similar to survival after primary debulking surgery followed by chemotherapy," write the authors, led by Ignace Vergote from Leuven University Hospitals (Belgium).

Given these findings and the results of other studies, the authors suggest that the goal of therapy should be the elimination of all macroscopic residual disease, rather than the elimination of lesions larger than 1 cm in diameter. "A potential drawback of neo adjuvant

chemotherapy followed by debulking surgery is that the occurrence of fibrosis after chemotherapy may make complete resection of macroscopic disease more difficult," write the authors.

The standard of care for women with stage IIIB or earlier-stage epithelial ovarian cancer (a group with a better prognosis) remains primary cytoreductive surgery, say the authors, adding that it is also important to rule out primary tumours of gastrointestinal origin when selecting patients for neoadjuvant chemotherapy.

■ I Vergote, CG Tropé, F Amant et al. Neo adjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *NEJM* 2 September 2010, 363:943–953

Less-invasive lymph node surgery is safe in breast cancer

➜ Lancet Oncology

Breast cancer patients with biopsies detecting no cancer cells in the sentinel lymph nodes who avoided axillary lymph node dissection (ALND) showed the same overall survival at eight years as women who underwent ALND, reports the largest ever randomised trial of breast cancer surgery.

Sentinel lymph node (SLN) surgery was designed to minimise the side-effects of lymph node surgery but still offer equivalent outcomes to ALND. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial, led by David Krag from the University of Vermont (Burlington, Vermont), set out to establish whether SLN resection achieves the same survival and regional control as ALND.

Between May 1999 and February 2004, the phase III trial enrolled 5611 women with invasive breast cancer and randomly assigned them in a 1:1 ratio to either group 1 (*n*=2807), who received SLN biopsy plus ALND, or to group 2 (*n*=2804) who received SLN biopsy alone (with ALND only if the SLNs were positive). The women were operated on by more than 200 surgeons from 80 centres in Canada and the US. Outcomes analyses were undertaken in patients who were assessed as having pathologically negative sentinel nodes and for whom follow-up data were available.

Altogether 3989 of participants in the study had pathologically negative sentinel nodes. Results show that the eight-year Kaplan–Meier estimates for overall survival were 91.8% (95% CI 90.4%–93.3%) in group 1 and 90.3% (95% CI 88.8%–91.8%) in group 2.

Eight-year Kaplan–Meier estimates for disease-free survival were 82.4% (95% CI 80.5%–84.4%) in group 1 and 81.5% (95% CI 79.6%–83.4%) in group 2.

Additional results show that there were eight regional node recurrences as first events in group 1 and 14 in group 2 (*P*=0.22). The most common adverse events were allergic reactions, mostly related to the administration of the blue dye.

"Our trial shows that overall survival, disease-free survival, and regional control were all statistically equivalent in SLN-negative patients who had an ALND (group 1) or SLN surgery alone (group2)," conclude the authors, adding that results published earlier from the trial have already shown that patient-reported outcomes and morbidity related to range of motion, oedema, pain and sensory defects were lower for the SLN group than the ALND group.

"NSABP B-32 results suggest that when the SLN is negative, SLN surgery alone with no further ALND is an appropriate, safe, and effective therapy for patients with breast cancer," the authors conclude.

In an accompanying commentary, John Benson from the University of Cambridge (UK) wrote, "The paper from Krag and colleagues constitutes a seminal publication on the primary endpoints of loco regional recurrence and overall survival for the largest randomised trial of SLN biopsy. It vindicates contemporary practice of SLN biopsy and provides support for a reduction in extent of axillary surgery for most patients with breast cancer."

However, Benson cautioned that longer follow-up is required, and highlighted the fact that there were almost twice as many regional recurrences in the SLN biopsy only group. "Low volume axillary disease might arguably be clinically relevant if it translates into overall survival differences with longer-term follow-up," he writes.

■ DN Krag, SJ Anderson, TB Julian et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* October 2010, 11:927-933

■ JR Benson An alternative to initial axillary-lymph-node dissection. *ibid* pp 908–909

Study helps define metastatic breast cancer patients benefitting from phase I trials

➜ British Journal of Cancer

Around one-fifth of patients with metastatic breast cancer (MBC) entered for phase I clinical trials show a measurable benefit after four months, a single-institution UK study has reported.

Despite recent advances in drug development, most women with MBC have a limited median survival time of approximately 18–24 months, with only around 20% alive five years after diagnosis of metastatic disease. Patients who remain sufficiently well may be offered early experimental phase I trials, but appropriate advice for patients remains uncertain due to limited studies documenting outcomes. A recent retrospective analysis reviewing outcomes for patients with MBC participating in phase I clinical trials at MD Anderson Cancer Center (Houston, Texas) found patients had a median overall survival of 6.7 months. In the current study, Charles Swanton and colleagues performed a similar retrospective analysis on MBC patients at the Royal Marsden Hospital (Sutton, UK) entering phase I clinical trials, to further characterise this cohort of patients.

In the study, outcomes for 70 patients with MBC treated between October 2002 and October 2009 in 30 phase I trials in the Drug Development

Unit at the Royal Marsden Hospital were analysed. For those women who had participated in more than one trial, only the first trial entry was considered for the analysis.

Results show that the median overall survival was 8.7 months and the median time to progression was 7.0 weeks. In all, eight women (11.4%) obtained a partial response, 12 (17.1%) had stable disease, and 50 (71.4%) had progressive disease at first radiological assessment. The overall clinical benefit rate (defined as partial response plus stable disease) at four months was 20%.

Patients with triple-negative breast cancer showed greatest clinical benefit rate, at 30.7%, while HER2-positive patients showed a clinical benefit rate of 19% and oestrogen receptor (ER)-positive/HER2-negative patients showed a clinical benefit rate of 8.7%.

In a multivariate analysis, abnormal lactate dehydrogenase levels, serum albumin less than 35mg per 100 ml, more than five previous treatment lines, liver metastases and ECOG (Eastern Cooperative Group) performance status greater than 2 at study entry were significantly associated with poor overall survival. In addition, the multivariate analysis showed that patients treated in trials based on a PARP inhibitor had a significantly longer time to disease progression (Cox regression HR 0.45, 95% CI 0.23–0.86; *P*=0.015). No patients discontinued the trials due to treatment-related toxicities.

"Early patient referral in selected tumour types and chemo-refractory disease may augment the chance of benefit to experimental therapies. In addition, selection of patients based on prognostic tools can assist go-no-go decisions on trial participation for those least likely to benefit," write the authors.

The shorter median overall survival found in the MD Andersen patients, add the authors, probably results from patient heterogeneity and the inclusion of greater numbers of poor prognostic patients.

■ AT Brunetto, D Sarker, D Papadatos-Pastos, et al. A retrospective analysis of clinical outcome of patients with chemo-refractory metastatic breast cancer treated in a single institution phase 1 unit. *Br J Cancer* 24 August 2010, 103 607–612

Advanced GIST patients should remain on imatinib

➜ Lancet Oncology

Interrupting imatinib (Glivec) after three years in responders with advanced gastrointestinal stromal tumours (GIST) leads to a high risk of rapid progression, the BRF14 trial by the French Sarcoma Group has reported.

Imatinib mesylate – a small-molecule inhibitor targeting mutations of the KIT or PDGFRA genes that encode tyrosine kinase receptors – has greatly improved outcomes for patients with advanced GIST, increasing survival from 25% in the era before imatinib to 75% after its introduction. Resistance to imatinib, however, begins to occur after 20– 24 months, due largely to the acquisition of additional mutations.

Since the effect of imatinib discontinuation on progression-free survival and overall survival in long-lasting responders with advanced GIST was unknown, Axel Le Cesne and colleagues, from the Institut Gustave Roussy (Villejuif, France), undertook the current study.

For the open-label, multicentre phase III trial, the investigators identified 50 patients with non-progressive GIST (according to RECIST criteria) who had been taking imatinib 400 mg/day for three years, and randomised them to either continue (*n*=25) or stop taking the drug (*n*=25).

Results show that after a median follow-up of 35 months, two-year progression-free survival was 80% in the continuation group versus 16% in the interruption group (*P*<0.0001). The median time to progression was nine months after randomisation in the treatment interruption group, and had not been reached among the group that remained on imatinib (*P*<0.0001).

All but three patients in the discontinuation group relapsed, most (68%) within a year of stopping therapy. Of the three patients who did not relapse, one had refused to stop imatinib and the other two had their tumours resected.

Among 21 patients in the interruption group with progressive disease, 20 resumed treatment with imatinib at the time of progression. Tumour control (complete response, partial response or stable disease according to RECIST) was obtained in all cases three months after the imatinib re-challenge. Re-introduction of imatinib upon tumour progression in 20 patients was associated with 100% tumour control after three months according to RECIST criteria.

One important issue to be explored was whether imatinib interruption affects the emergence of resistance. Results showed no difference in mutations between the two groups (*P*=0.826).

"Our findings show that imatinib interruption in the setting of advanced disease results in rapid progression in most patients," write the authors, adding that the time to secondary resistance was similar in the two groups. "[This] shows that imatinib interruption neither prevents nor promotes the emergence of imatinib resistance in GIST," they conclude. The absence of any effect of imatinib interruption on overall survival, write the authors, could allow imatinib-free intervals in cases of prolonged and uncomfortable side-effects related to the drug.

They note that similar findings have been reported in chronic myeloid leukaemia (CML), where a pilot phase II trial showed that imatinib interruption resulted in a rapid molecular relapse in 50% of patients judged to be in complete response.

In an accompanying commentary, Michael Heinrich from Portland VA Medical Center (Portland, Oregon), wrote that these findings support the need for continuous treatment with tyrosine kinase inhibitors in GIST, CML and by extension in other cancers responsive to such drugs. "These findings also suggest that current efforts to improve the potency of TKIs against the activated oncogenes in CML and GIST might improve the duration of disease control, but will not be sufficient to achieve a cure," writes Heinrich, adding that therapies with the ability to eradicate the initiating stem cells are needed for a cure.

■ A Le Cesne, I Ray-Coquard, B N Bui, et al. Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial. *Lancet Oncol* October 2010, 11:942–949

■ MC Heinrich. Imatinib treatment of metastatic GIST: don't stop (believing). *ibid* pp 910–911