newsround

Selected reports edited by Janet Fricker

Health risks continue into middle age for childhood cancer survivors

Journal of Clinical Oncology

Elevated risks for morbidity and mortality among survivors of childhood cancers increase beyond the fourth decade of life. An analysis of the retrospective Childhood Cancer Survivor Study (CCSS) shows survivors of childhood cancers aged 35 years and older are five times more likely to experience new onset of severe, disabling, life-threatening, or fatal health conditions than their same-age, same-sex siblings.

Health outcomes research conducted over the last three decades has established that survivors of childhood cancer are at increased risk for morbidity and mortality during their childhood and young adult years, largely as a result of adverse effects of the therapies that cured their primary malignancies. What has not been clear, however, is whether such adverse health conditions continue as this population ages.

In the current study Gregory Armstrong and colleagues, from St Jude Children's Research Hospital, Memphis, Tennessee, set out to address the risk of future serious health problems for survivors of childhood cancers, and whether survivors who reach their third decade without developing serious conditions still have elevated risks.

Investigators compared the occurrence of, severe, disabling, life threatening and fatal health conditions for 14,359 survivors and 4,301 siblings. The survivors had all been diagnosed before the age of 21 years and were still alive after five years. The data were drawn from the Childhood Cancer Survivor Study, a retrospective cohort study with longitudinal follow-up of the survivors of childhood cancer from 26 institutions in the US and Canada.

Results showed that the cumulative incidence of suffering a severe, disabling, life-threatening, or fatal health condition by the age of 50 years was 53.6% for survivors, versus 19.8% for their siblings. The hazard ratio (HR) for experiencing severe, disabling, life-threatening or fatal events was 6.8 for the 15- to 19-year-old age group, 3.8 for the 20- to 34-year age group and 5.0 for the >35-year age group. Among survivors who reached 35 years of age without a previous grade 3 or 4 condition, 25.9% experienced a subsequent grade 3 to 5 condition within 10 years, compared with 6.0% of siblings ($P<0.001$).

"We now identify that elevated risk for severe, disabling, life-threatening, or fatal health conditions extends across the aging spectrum into the fourth and fifth decades of life, increasing significantly beyond age 35 years versus a sibling comparison population," write the authors, adding that these findings have important implications for cancer screening and prevention.

Exposure to systemic chemotherapy or focal radiotherapy, the authors suggest, may accelerate the aging process. Indeed, mechanisms for aging, such as telomere shortening or free-radical mediated injury, have been hypothesised to occur in cancer survivors. "These data ... highlight the need for longitudinal, risk-based follow-up; and identify the increasing health burden on this population as they age," write the authors.

■ G Armstrong, T Kawashima, W Leisenring et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the Childhood Cancer Survivor Study. *JCO* 20 April 2014, 32:1218–27

CML patients fare better in teaching hospitals

Blood

Patients with chronic myeloid leukaemia (CML) have a better survival if they are treated in teaching hospitals compared with treatment in municipal hospitals or by office-based physicians, the German CML Study Group has reported. The results showed that patients with blast crisis in particular show superior outcomes.

With the introduction of tyrosine kinase inhibitors (TKIs), treatment of patients with CML profoundly changed. Not only have their prognosis and quality of life improved remarkably, but treatment has become less complex. One consequence is that treatment of CML patients has shifted from

teaching hospitals to municipal hospitals and office-based physicians. In the current study Michael Lauseker and colleagues, from the Ludwig-Maximilians University of Munich, Germany, set out to investigate whether healthcare settings have an impact on patient outcomes.

For the study, outcomes were considered for the 1,491 patients enrolled into the German CML Study IV. For the analysis each study centre was classified into one of three categories: teaching hospital, municipal hospital, or office-based physician. Survival times were calculated from the date of diagnosis to the date of last observation, unless the patient had already died. Cox models were estimated to assess the impact of study centre type and experience with CML, with models adjusted for European Treatment and Outcome Study (EUTOS) score prognostic group, calendar year of diagnosis, age at diagnosis, and Karnofsky performance status (KS). Furthermore, the models were stratified according to randomised treatment.

Results showed a significant survival advantage for patients treated at teaching hospitals. When this group of patients was compared with patients treated in municipal hospitals, the HR was 0.633 (95% CI 0.414–0.966; *P*=0.034); and when they were compared with patients treated by office-based physicians, the HR was 0.609 (95%CI 0.363–1.024; *P*=0.060). Survival for the 73 patients who suffered a blast crisis was statistically significantly better for those treated at teaching hospitals. After two years, 47.7% of blast crisis patients treated at a teaching hospital were alive compared with 22.3% of blast crisis patients treated at a municipal hospital (*P*=0.015) and 25% of blast crisis patients treated by an office-based physician (*P*=0.012).

"Our data indicate a survival advantage for CML patients treated initially at a TH [teaching hospital] compared with those that were treated at an MH [municipal hospital] or OBP [office-based physician]," write the authors. Because the differences in the outcomes between the three groups were "not negligible", they add, further research should try to replicate such an analysis in an independent data set and explore potential reasons for the observed differences.

■ M Lauseker, J Hasford, M Pfirrmann et al. The impact of health care settings on survival time of patients with chronic myeloid leukemia. *Blood* 17 April 2014, 123:2494–96

Stereotactic radiosurgery effective for multiple brain metastases

■ Lancet Oncology

Stereotactic radiosurgery without whole brain radiotherapy (WBRT) for patients with five to ten brain metastases was found to be non-inferior in terms of overall survival to that for patients with two to four metastases. The prospective, observational study, funded by the Japan Brain Foundation, also showed that the number of treatment-related adverse events did not differ between the two groups.

The American Society of Radiation Oncology guidelines state that level 1 evidence only supports stereotactic radiosurgery without concurrent WBRT for patients with up to four brain metastases. Debate continues as to how many tumours can or should be treated by stereotactic radiosurgery alone. Stereotactic radiosurgery is considered to have several benefits, including the fact that it can be repeated and done after WBRT, and that it does not prevent radiation therapy to other parts of the body, chemotherapy, or major surgery for another lesion.

In the study Masaaki Yamamoto, from Hospital Moto Gamma House, Ibaraki, Japan, and colleagues from the Japanese Leksell Gamma Knife (JLGK) Society, set out to examine whether stereotactic radiosurgery without WBRT as the initial treatment for patients with five to ten brain metastases was non-inferior in terms of overall survival to that for patients with two to four brain metastases.

Between March 2009 and February 2012, 1,194 patients from 23 facilities in Japan with one to ten newly diagnosed brain metastases were enrolled. The patients, who had all types of original malignant tumours except sarcoma, were split into groups based on the number of tumours observed on initial MRI. The primary endpoint was overall survival defined as the interval between stereotactic radiosurgery and death due to any cause, or the day of last follow-up.

Results showed that the median overall survival after stereotactic radiosurgery was 13.9 months (95%CI 12.0–15.6) in the 455 patients with one tumour; 10.8 months (9.4–12.4) in the 531 patients with two to four tumours; and 10.8 months (9.1–12.7) in the 208 patients with five to ten tumours. Overall survival did not differ between the patients with two to four tumours and those with five to ten tumours (HR 0.97, 95% CI 0.81-1.18, *P*=0.78, and for non-inferiority *P*<0.0001). The proportion of patients who had one or more treatment-related adverse event of any grade was 9% for patients with two to four tumours versus 9% for patients with five to ten tumours (*P*=0.89).

"This result challenges the practice of inconsistent use of stereotactic radiosurgery for patients with five or more brain metastases, in whom most treatment guidelines still strongly recommended WBRT, and provides evidence in favour of offering stereotactic radiosurgery to patients with multiple brain metastases. Existing treatment guidelines for the management of patients with brain metastases might need to be revised in the near future," write the authors.

■ M Yamamoto, T Serizawa, T Shuto et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* April 2014, 15:387–395

Radiotherapy benefits patients with N1–N3 breast cancer

■ The Lancet

For women with breast cancer and one to three lymph nodes testing positive for cancer, radiotherapy is beneficial after mastectomy and axillary dissection, reports a meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).

Prior meta-analyses have shown that post mastectomy radiotherapy (PMRT) reduces the risk of dying of breast cancer and of recurrence in patients with node-positive disease. But whether PMRT benefits patients with only one to three positive nodes has been controversial, with most studies concluding that there is insufficient evidence to make firm recommendations for this group.

In the current study Paul McGale and colleagues, from the EBCTCG group in Oxford, UK, performed a meta-analysis of individual data on 8,135 patients with node-positive disease enrolled in 22 randomised trials between 1964 and 1986. From this larger group, they identified 3,786 women who had undergone mastectomy and axillary lymph node dissection and been randomly assigned to receive radiation to the chest wall and surrounding regions or no radiation.

The women fell into three categories: those with no cancer in the lymph nodes (n=700); those with cancer in one to three lymph nodes (n=1,314); and those with cancer in four or more lymph nodes (n=1,772).

Results showed that for women with axillary dissection and no positive nodes, radiotherapy had no significant effect on locoregional recurrence (two-sided significance level [2p]>0.1), or overall recurrence (2p>0.1), or dying of breast cancer (2p>0.1). For women with axillary dissection and one to three positive nodes, radiotherapy did reduce locoregional recurrence (2p<0.00001), overall recurrence (2p=0.00006), and deaths from breast cancer (2p=0.01). Of these 1,314 women, 1,133 were in trials in which systemic therapy (cyclophosphamide, methotrexate and fluorouracil, or tamoxifen) was given in both trial groups. For this group of patients radiotherapy again reduced locoregional recurrence (2p<0.00001), overall recurrence (2p=0.00009), and deaths from breast cancer (2p=0.01). In women with axillary dissection and four or more positive nodes, radiotherapy was also found to have reduced locoregional recurrence (2p<0.00001), overall recurrence (2p=0.0003), and death from breast cancer (2p=0.04).

In an accompanying commentary Philip Poortmans, from the Institute Verbeeten, in the Netherlands, writes, "The results of this EBCTCG meta-analysis clearly confirm that post mastectomy radiotherapy should be considered equally for patients with one to three involved axillary lymph nodes as it should be for patients with four or more affected axillary lymph nodes. The same considerations concerning regional radiotherapy also seem to be valid for patients treated with breast-conserving therapy."

Since the absolute risks of breast cancer recurrence and dying of breast cancer have been reduced in many countries due to advances in detection and treatment, he adds, the absolute benefits from post mastectomy radiotherapy today are likely to be less than those reported in the study.

■ EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomized trials. *Lancet* published online 19 March 2014, doi:10.1016/S0140-6736(14)60488-8

■ P Poortmans. Postmastectomy radiation in breast cancer with one to three involved lymph noeds: ending the debate. *Lancet* published online 19 March 2014, doi:10.1016/S0140-6736(14)60192-6.

Exercise guidelines unrealistic for cancer survivors

■ British Journal of Cancer

Expecting the majority of sedentary cancer survivors to achieve current exercise guidelines is likely to prove unrealistic, concludes a UK systematic review. The study did, however, show that aerobic exercise tolerance was improved at both eight to twelve weeks and six months follow-up.

Over the last decade exercise interventions for cancer survivors have received increased attention as an effective way to improve health-related quality of life and physical function and to reduce fatigue. Furthermore, an association with a reduced risk of disease recurrence has been suggested. The current exercise guidelines indicate that cancer survivors should achieve 150 minutes per week of aerobic exercise and twice weekly resistance (strength) training (Rock et al., *CA Cancer J Clin* 2012, 62:242–274). However, the Quality Health 2012 survey from the UK Department of Health found only one quarter of cancer survivors achieved such levels.

In the current study Liam Bourke and colleagues, from Queen Mary University of London, UK, set out to systematically review the effects of interventions to improve exercise behaviour in sedentary people living with and beyond cancer. From a review of electronic databases including the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, AMED, CINAHL, PsycINFO, SportDiscus, and PEDro, the authors identified 14 trials (11 for breast, 2 for colorectal and 1 for

prostate cancer) involving a total of 648 participants.

Results showed that none of the trials included in the review reported an adherence of 75% or more for a set prescription that would meet the Rock et al. (2012) aerobic exercise guidelines, and only three trials reported an adherence of 75% or more to a lower aerobic exercise goal. Notably, write the authors, all three of these trials incorporated both a supervised and independent exercise component as part of their interventions.

For the seven trials reporting change in aerobic tolerance as an outcome, a meta-analysis showed that, at eight to twelve weeks, aerobic exercise tolerance was significantly better in the exercise group than the control group (standard mean difference [SMD]=0.73, 95%CI 0.51–0.95), and continued to improve at six months (SMD=0.70, 95%CI 0.45–0.94).

"The review findings indicate that currently there is a lack of convincing evidence to suggest that existing exercise interventions are useful for achieving the Rock et al. (2012) guidelines ... in sedentary cancer cohorts," write the authors.

The study, they add, suggests that interventions combining the supervision of exercise training in tandem with a requirement of independent exercise are likely to promote better adherence.

In an accompanying commentary Clifford Hudis, from Memorial Sloan Kettering Cancer Center, and Lee Jones, from Duke Cancer Institute, write that large clinically meaningful reductions in disease risk can be achieved when moving from the least active (or low fitness) group to a moderately active (fit group). "In other words, only small changes in exercise behaviour may be required in sedentary individuals to produce meaningful reductions in disease recurrence or risk of other chronic diseases," they write.

■ L Bourke, K Homer, M Thaha et al. Interventions to improve exercise behaviour in sedentary people living with and beyond cancer: a systematic review. *Br J Cancer* 18 February 2014, 110:831–841

■ C Hudis, L Jones. Promoting exercise after a cancer diagnosis: easier said than done. *ibid* pp 829–830

Radical prostatectomy shows continued survival benefits

■ NEJM

Extended follow-up of the Scandinavian Prostate Cancer Group-4 trial (SPCG-4) up to 23 years shows men with early prostate cancer undergoing radical prostatectomy have reduced risk of all-cause mortality, prostate cancer-specific mortality, and distant metastases and reduced need for androgen deprivation therapy in comparison to those undergoing 'watchful waiting'. The benefits of surgery with respect to death from prostate cancer were found to be largest in men less than 65 years of age.

In the SPCG-4 study, between 1989 and 1999, Anna Bill-Axelson and Lars Holmberg, of Uppsala University Hospital, Sweden, randomly assigned 695 men from 14 centres in Sweden, Finland and Iceland, with early prostate cancer, to radical prostatectomy (*n*=347) or 'watchful-waiting' (*n*=348). The study, which was funded by the Swedish Cancer Society, was undertaken before the era of PSA (prostate specific antigen) testing.

Results showed that, during 23.2 years of follow-up, 200 of 347 men in the surgery group and 247 of 348 men in the 'watchful waiting' group died. Of the deaths, 63 in the surgery group and 99 in the 'watchful waiting' group were due to prostate cancer (RR 0.56, 95%CI 0.41–0.77; *P*=0.001). Androgen deprivation therapy was used in 145 patients who underwent prostatectomy versus 235 who underwent 'watchful waiting' (RR 0.49, 95%CI 0.39–0.60, *P*<0.0002). Other palliative treatments, such as radiation therapy, were less common in the radical prostatectomy group than in the 'watchful waiting' group (49 vs 63).

The benefit of surgery with respect to death from prostate cancer were most marked in patients younger than 65 years, where 31 deaths occurred in the radical prostatectomy group versus 58 in the 'watchful waiting' group (RR 0.45, 95%CI 0.29–0.69, *P*=0.002); and in those with intermediate-risk prostate cancer, where 24 deaths occurred in the radical prostatectomy group versus 50 in the 'watchful waiting' group (RR 0.38, 95%CI 0.23–0.62, *P*<0.001).

In the interval from 10 to 18 years of follow-up, the number needed to treat to prevent one death decreased from 20 to 8 in the whole cohort, and from eight to four among men younger than 65 years of age. By December 2012, 294 men in the 'watchful waiting' group had not received curative treatments.

"Extended follow-up confirmed a substantial reduction in mortality after radical prostatectomy; the number needed to treat to prevent one death continued to decrease when the treatment was modified according to age at diagnosis and tumor risk," write the authors. However, they add that a large proportion of long-term survivors in the 'watchful-waiting group' have not required any palliative treatment.

"The overall long-term disease burden is also a reminder that factors other than survival should be considered when counselling men with localized prostate cancer; the risk of metastases and ensuing palliative treatments also affect quality of life," write the authors.

■ A Bill-Axelson, L Holmberg, H Garmo et al. Radical prostatectomy or watchful waiting in early prostate cancer. *NEJM* 6 March 2014, 370:932–942