NEWSROUND

Selected reports edited by Janet Fricker

Quality of colon cancer surgery is important in survival

➜ Lancet Oncology

A research study has suggested for the first time that the quality of surgery for colon cancer is associated with patient survival. On analysis of the tissue removed during cancer surgery in nearly 400 patients, UK researchers found marked variability in the plane of surgery – the directions in which dissection is carried out – in operations to remove colon cancers, with direct impact on survival.

Previous studies have shown that the quality of rectal cancer surgery improves patient outcomes, and total mesorectal excision (TME) for rectal cancer has now become the standard surgical procedure for this cancer type. The researchers in this study wanted to see whether the quality of colon cancer surgery could have a similar effect on patient outcomes. They decided to examine whether the removal of an intact colonic mesentery, or mesocolon (the folds of peritoneum that attach the colon to the posterior wall of the abdomen), might minimise the risk of cancer spread. To test this, they carefully examined all resections for primary colon adenocarcinoma carried out at one UK hospital, Leeds General Infirmary, between 1 January 1997 and 30 June 2002. They photographed all of the specimens of tissue removed during surgery and graded them according to the plane of mesocolic dissection, and followed up the patients to see if this was associated with five-year survival.

The study identified a total of 521 cancers. Nearly one-quarter of these (122 specimens) were excluded because there were no photographic images or insufficient images to allow grading of the surgery, leaving 399 specimens for analysis. The researchers graded the surgery using a system initially developed for the Medical Research Council trial of Conventional versus Laparoscopic Assisted Surgery In patients with Colorectal Cancer (CLASSIC).

This system classified surgery as being either in the muscularis propria plane, which was considered a 'poor' plane of surgery, with little bulk to the mesocolon and disruptions extending down into the muscularis propria (the inner circular and outer longitudinal muscle layers of the colon wall); or in the intramesocolic plane, which was judged 'moderate', with moderate bulk to the mesocolon with irregularity but incisions not reaching down to the muscularis propria; or in the mesocolic plane, which was considered a 'good' plane of surgery, giving an intact mesocolon with a smooth peritoneal-lined surface.

The new results revealed marked variation in the proportion of each plane of surgery used. Dissection had been carried out along the muscularis propria in just under one-quarter (24%) of the specimens; it was intramesocolic in nearly half (44%) and mesocolic in nearly one-third (32%) of specimens. The average cross-sectional area of tissue outside the muscularis propria was significantly higher with mesocolic plane surgery (2,181 mm^2) than with the intramesocolic (1,273mm^2) or the muscularis propria plane (1,447mm^2).

Survival results showed that patients undergoing mesocolic plane surgery had a 15% overall survival advantage at five years when compared with those who had surgery in the muscularis propria plane (HR 0.57, 95% CI 0.38–0.85; P=0.006) when analysed in univariate analysis.

This association was no longer significant in the multivariate model, which took account of other factors with a significant effect of survival (HR 0.86, 95% CI 0.56–1.31; P=0.472). However, it remained significant for patients with stage III cancers, who showed a 27% survival advantage at five years if their surgery was carried out in the mesocolic plane (HR 0.45, 95% CI 0.24–0.85; P=0.014). Overall, the planes of surgery and the amount of mesocolon removed were better in left-sided resections than right-sided procedures, which were better than transverse resections (P<0.0001).

The researchers, led by Nicholas West from the Leeds Institute of Molecular Medicine at the University of Leeds, said, "We have shown that good quality colon cancer surgery by use of mesocolic plane dissection removes more tissue around the tumour, which is associated with a 15% survival advantage at five years, rising to 27% in stage III disease. Improving the plane of dissection might improve survival, especially in patients with stage III disease." They added, "Our study suggests that in stage III disease, twice as many patients will be alive at five years if they are operated on in the mesocolic plane compared with the muscularis propria plane."

The research group concluded, "If this is confirmed by clinical trials, improvement of the plane of dissection might be a new cost-effective method of decreasing morbidity and mortality in patients with colon cancer." The plane of dissection is one of the measures currently being evaluated in the ongoing National Cancer Research Institute FOxTROT trial (Fluoropyrimidine, Oxaliplatin and Targeted Receptor pre-Operative Therapy for colon cancer) in patients with advanced resectable colon cancer.

In an accompanying editorial, Marcel Den Dulk and Cornelis van de Velde, from Leiden University Medical Centre, in the Netherlands, considered that the findings on the quality of surgical resection in colon cancer were 'alarming'. They agreed with the study authors that, as for rectal cancer, the quality of surgery seemed to be a very important factor in the prognosis of patients with colon cancer. They suggested that standardised pathological quality assessment of resection specimens of all solid cancers should be implemented in all new oncological trials and in daily clinical practice to provide feedback to surgeons to continuously improve the number of radical resections in the future.

■ Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. NP West, EJ Morris, O Rotimi et al. *Lancet Oncol* September 2008, 9:857–865

■ Time to focus on the quality of colon-cancer surgery. M Den Dulk and CJH van de Velde. *ibid* pp815–817

Genetic 'signature' in healthy liver cells predicts cancer recurrence

➜ New Engl J Med

Researchers have found a gene 'signature' – a specific set of genes – in the healthy, non-cancerous cells in the liver of people who have had liver cancer, which is associated with better chances of survival. A second gene signature has been found that is associated with late cancer recurrence. The findings emanate from an international study that has shown for the first time that tissue samples preserved by traditional methods can be used for genetic analysis.

The researchers analysed the genetic profiles of liver samples from 307 people with liver cancer who had taken part in clinical studies in four countries – Japan, the US, Italy and Spain. The liver samples had been preserved using traditional methods of fixing tissue with formalin and embedding in paraffin, rather than being frozen. Some had been stored for more than 24 years.

Current methods of genome-wide expression profiling require frozen tissue for analysis. This has – until now – limited efforts to study the genetic profile of liver cancer cells, because tissue banks from most clinical trials have collected formalin-fixed, paraffin-embedded specimens.

The researchers used a new method for gene profiling that was able to reconstruct the thousands of genes that are cut into tiny pieces when tissue samples are treated with a chemical fixative and stored in wax. They used DNA microarrays (DNA chips) to analyse the gene expression simultaneously of 6,000 genes across the human genome, and found it was successful in 90% of the specimens.

When they used the gene profiling technique to look at the tissue samples from people with liver cancer, they were surprised to find that the genetic profile of the tumour tissue was not predictive of outcome, survival or late recurrence (defined as a further tumour occurring more than two years after the first cancer). However, when they analysed apparently normal liver tissue samples surrounding the patients' tumours, they found a gene signature of 186 genes that was highly correlated with survival (P=0.04).

This 'good prognosis' signature contained genes associated with normal liver function, including genes coding for plasma proteins and for several drug-metabolising enzymes. In contrast, the 'poor prognosis' signature – found in patients at higher risk of liver cancer recurrence – contained gene sets associated with inflammation, including those related to interferon signalling, activation of nuclear factor-κB, and signalling by tumour necrosis factor α (TNFα).

The findings fit with the 'field defect' theory, in which researchers have previously suggested that factors in the entire liver may predispose a person to liver cancer. There may be genetic abnormalities in liver tissue that appears normal, which could give rise to new tumours after an initial tumour has been removed.

The lead author of the study, Yujin Hoshida, from the Broad Institute of MIT (Massachusetts Institute of Technology) and Harvard University, Cambridge, USA, said, "These findings indicate that we might be able to identify patients at high risk of recurrence and target those patients to prevent it." Although the treatment of hepatocellular carcinoma is evolving, hepatic resection remains the treatment of choice for most patients. Resection is associated with a five-year survival rate of 50%, but the recurrence rate remains 70%. For most patients, resection is not a cure.

Hoshida added, "The fact that the predictive information comes not from the tumour but from surrounding tissue could offer important insights into the mechanism of liver cancer."

In an editorial accompanying the report of the results, Morris Sherman, from the University of Toronto, Canada, agreed that the new findings added to the understanding of the development of liver cancer. "The research has opened the door to identifying the relevant gene expression in the pathogenesis of hepatocellular carcinoma as it evolves from non-tumourous liver, as well as initiating research into a molecular method for determining more precisely who is

at risk for the development of hepatocellular carcinoma." He added that these findings "bring the possibility of individualised therapy for hepatocellular carcinoma one step closer."

The researchers suggested that, in future research, the new gene profiling technique could potentially be used in any type of cancer. "We don't know whether there will be a recurrence signature in the non-tumour tissue of breast cancer. But it is now possible to explore that possibility."

■ Gene expression in fixed tissues and outcome in hepatocellular carcinoma. Y Hoshida, A Villanueva, M Kobayashi et al. *New Engl J Med* 6 November 2008, 359:1995–2004

■ Recurrence of hepatocellular carcinoma. M Sherman. *ibid* pp2045–2047

Fatigue in patients with early cancer

→ British Journal of Cancer

Between 14% and 28% of cancer patients experience severe fatigue prior to starting treatment, a Dutch study has found.

Fatigue is recognised as a common symptom during cancer treatment, occurring in 25%–99% of patients according to different studies. Generally, symptoms of fatigue are thought to arise as a consequence of both the cancer itself and the treatments patients receive. Psychological distress, including depression, anxiety and poor sleep quality, has also been shown to be related to fatigue.

In the current study, Martine Goedendorp and colleagues, from the Expert Centre Chronic Fatigue in Nijmegen, the Netherlands, set out to investigate the prevalence of severe fatigue immediately after diagnosis, and prior to initiation of treatment. Altogether 179 patients with a range of malignancies (including 109 with breast cancer, 57 with prostate cancer and 76 with other cancers) were assessed between November 2005 and August 2007, prior to starting treatment with curative intent. Studies undertaken included the Checklist Individual Strength, Sickness Impact Profile, Beck Depression Inventory for Primary Care, Symptom Checklist-90, and six numeric rating scales to measure fatigue, pain and physical activity. Finally, to test which factors contributed to severe fatigue, a logistic regression analysis was undertaken.

Overall results show 23.5% of cancer patients were severely fatigued, but that this percentage varied according to the diagnosis. The presence of severe fatigue was lowest in patients with prostate cancer (14%), higher in those with breast cancer (20%) and gastrointestinal cancer (28%) and highest in patients with other cancers (33.3%).

Four factors were found to influence severe fatigue prior to cancer treatment: more fatigue one year prior to diagnosis, evaluated retrospectively (P=0.005), lower current physical activity (P=0.013), more depressive mood (P=0.014) and impaired sleep and rest during day and night (P=0.045).

"This study showed that a large number of cancer patients already experience severe fatigue before initiation of cancer treatment. One might expect that the course of fatigue during and after cancer treatment could be different for patients with severe fatigue or patients without severe fatigue before cancer treatment," write the researchers, adding that a major topic for further research is whether patients with severe fatigue prior to cancer treatment should receive early fatigue intervention.

Limitations of the study, say the authors, are that the reliance on cross-sectional data makes it difficult to draw conclusions about causality between fatigue and the related factors – impaired sleep and rest, depressive mood and physical activity. Furthermore, asking people to estimate their level of physical activity has limitations, with studies showing lack of correspondence between self-reported physical activity and objective physical activity.

■ Severe fatigue and related factors in cancer patients before the initiation of treatment. MM Goedendorp, MFM Gielissen, CAH Verhagen et al. *Br J Cancer* 28 October 2008, 99:1408–1414

Hot flushes: a good omen in breast cancer

→ Lancet Oncology

The appearance of new vasomotor or joint symptoms in the first three months of treatment for breast cancer indicates a greater response to endocrine therapy (both tamoxifen and anastrozole) in comparison to women who do not experience these side-effects, according to a Cancer Research UK study.

Vasomotor symptoms, such as hot flushes, night sweats and cold sweats, are common side-effects of endocrine treatment in women with early breast cancer. Treatment with aromatase inhibitors also increases the incidence of arthralgia and other joint symptoms. Both side-effects are known to be related to decreases in oestrogen concentration.

In the retrospective analysis, Jack Cuzick and colleagues from the Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, in London, set out to investigate whether women with hormone-receptor-positive tumours who reported vasomotor or joint symptoms at their first three-month follow-up visit in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial showed any differences in recurrence compared to women who did not report these symptoms.

Results showed that the 37.5% of those who reported vasomotor symptoms at the three-month follow-up visit (1,486 out of 3,964) had a lower breast cancer recurrence rate after nine years (18%) compared to women who did not report new vasomotor symptoms (23%; HR 0.84, 95% CI 0.71–1.00; P=0.04). Furthermore, the women who reported new joint symptoms at the three-month visit (31.4% of the sample) had a 14% rate of cancer recurrence, compared to 23% for those women who did not report such symptoms (HR 0.60, 95% CI 0.50–0.72, P<0.0001). Overall, patients with and without these symptoms who received anastrozole had lower recurrence rates than those who received tamoxifen.

"This analysis supports an inverse associ-

ation between the occurrence of vasomotor symptoms and breast cancer recurrence previously reported for tamoxifen, and extends this association to the aromatase inhibitor anastrozole and also to the presence of joint symptoms," write the authors, who add that the results have important implications for communication between healthcare professionals and patients.

"Several reports have documented poor adherence to long-term endocrine therapy, and an appreciation that endocrine symptoms indicate a stronger treatment effect should help to encourage better symptomatic management and improve adherence for women receiving endocrine treatment."

The findings also raise questions about the effect drugs aimed at easing endocrine symptoms might have on the efficacy of endocrine treatment if they target the same mechanism of action.

■ Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: a retrospective analysis of the ATAC trial. J Cuzick, I Sestak and D Cella. *Lancet Oncology*, published online 30 October 2008, doi:10.1016/S1470-2045(08)70259-6

New era for tailored kidney cancer treatment

➜ Cancer

A study from the University of California, Los Angeles (UCLA), is being heralded as laying the foundations for personalised kidney cancer therapy and ending the treatment era of 'one size fits all'.

Arie Belldegrun and colleagues, from the UCLA Jonsson Comprehensive Cancer Center, believe that their results show that patients with low-risk, localised renal cell carcinoma (RCC) can be treated with surgery alone, and still expect excellent outcomes, sparing them side-effects from radiation or immunotherapy. Patients with high-risk localised kidney cancer, however, should consider additional therapy. In contrast, in metastatic disease, patients with low-risk cancer should get aggressive treatment because they stand a good chance of success, while high-risk patients are less likely to experience benefit.

The UCLA research was inspired by rapidly evolving treatment paradigms for RCC. Improvements in imaging have given rise to increased use of partial nephrectomy or minimally invasive or ablative treatments, while the US regulators, the FDA, recently approved three targeted agents (sorafenib, sunitinib and temsirolimus). "The field of kidney cancer is undergoing dramatic changes, and it is as yet still unclear how these changes are affecting patient outcome," write the authors, adding that no phase III trials have evaluated new targeted agents against interleukin-2 (previously the only FDA-approved drug for metastatic RCC) or compared resection and ablation.

"It is imperative to evaluate the efficacy of new treatments in relation to an established benchmark," write the authors.

To this end, Belldegrun and colleagues undertook a comprehensive analysis of 1,632 patients treated at the UCLA for RCC between 1989 and 2006, with treatments including radical surgical resection and aggressive use of immunotherapy. The investigators analysed patient outcomes in relation to an integrated staging system developed by the UCLA. The staging system combines ECOG PS, TNM stage and Fuhrman grade to stratify patients into six groups based on risk of death from RCC.

Results show that patients with localised cancer identified as low risk have an expected five-year survival rate of 97%, while their 10-year survival rate is 92%. Patients with localised disease of intermediate risk have a five-year survival rate of 81% and a 10-year survival rate of 61%. Patients at high risk, however, have a five-year survival rate of 62% and a 10-year survival of 41%.

For patients with metastatic disease, the five-year survival rate for low-risk patients is 41%, compared to 3% for intermediate groups and 18% for high-risk groups. The 10-year survival was 7%, 8% and 0% respectively.

The authors hope their results will serve as a benchmark to compare the results of emerging medical and surgical treatments. "For advanced disease, newer targeted and potentially less-toxic treatments should be at least as effective as those achieved with aggressive surgical resection and immunotherapy," they conclude.

In a press release, Belldegrun commented that this was the most important work that the Kidney Cancer Program at UCLA has undertaken. "We outline the foundation for personalized kidney cancer therapy. We have shown that not all kidney cancer patients are the same, not all localized kidney cancers are the same, and not all metastatic kidney cancers are the same," he said. "Our paper identifies very precisely, which patients should get which therapies."

Although the single institutional study might be viewed as a limitation, the authors say it can also be seen as a strength, since the clinicians involved followed a consistent therapeutic approach of aggressive surgical resection and immunotherapy.

■ Cancer-specific survival outcomes among patients treated during the cytokine era of kidney cancer (1989–2005): a benchmark for emerging targeted cancer therapies. AS Belldegrun, T Klatte, B Shuch et al. *Cancer* 1 November 2008, 113:2457–2463

Benefits of exercise defined in breast cancer

➜ Breast Cancer Research

Vigorous exercise protects women against breast cancer after menopause, but only if they are of normal weight, a US study has found. No associations, however, were found between non-vigorous activity and breast cancer or between vigorous activity and breast cancer among women who were overweight or obese.

Michael Leitzmann and colleagues, from the US National Cancer Institute, set out to elucidate which aspects of physical activity contribute most towards decreasing women's risk of breast cancer.

Researchers analysed questionnaires answered between 1987 and 1998 by 32,269 post-menopausal women enrolled in the Breast Cancer Detection Demonstration Project Follow-up Study. Physical activity during the previous year was assessed by asking subjects to estimate the number of hours per typical weekday and weekend day they spent engaging in moderate and vigorous physical activities.

Vigorous activity was judged to include heavy housework (scrubbing floors, washing windows, heavy yard-work, digging, chopping wood) and strenuous sports or exercise (running, fast jogging, competitive tennis, aerobics, bicycling on hilly ground and fast dancing).

Activities rated as 'moderate' included light housework (vacuuming, washing clothes, painting, home repairs, lawn mowing, general gardening) and light sports or exercise (walking, hiking, light jogging, recreational tennis, bowling, golf and bicycling on level ground). All the women were free of chronic disease at the start of the study, with an average age of 61 years at 'baseline'.

Results show that, during 269,792 person-years of follow-up (over an 11-year period), 1,506 new cases of post-menopausal breast cancer were identified. Overall, the volunteers who exercised most were 13% less likely to have developed breast cancer than the volunteers who exercised least. The reduced risk for women who exercised most increased to 32% when researchers compared only women who had a body mass index (BMI) less than 25.0 kg/m^2.

In contrast no association was found among women who had a BMI greater than 25.0 kg/m^2.

"A non-causal explanation for a stronger inverse relation of vigorous activity among lean women compared with overweight women is that heavier women may not exercise as intensely as lean women. Moreover, non-vigorous activities performed by overweight women, such as light house work, general gardening and light sports, may be misreported as vigorous activities among overweight individuals," write the authors.

Possible mechanisms through which physical activity may protect against breast cancer that are independent of BMI, say the authors, include reduced exposure to growth factors, enhanced immune function and decreased chronic inflammation.

Notable strengths of the study, say the authors, include the large sample size, prospective design, high follow-up rate and availability of relevant known or suspected breast cancer risk factors. The main limitation of the study was a reliance on self-reported physical activity, a method prone to both systematic and random errors, and the fact the cohort comprised predominantly Caucasian women, so that findings may not be relevant to all women.

■ Prospective study of physical activity and risk of postmenopausal breast cancer. MF Leitzmann, SC Moore, TM Peters et al. *Breast Cancer Res*, published online 31 October 2008, doi:10.1186/bcr2190

Glycaemic control alert for diabetic patients taking sunitinib

➜ British Journal of Cancer

Glycaemic control needs to be carefully evaluated in diabetic patients receiving treatment with sunitinib, a French study has concluded.

Sunitinib, a multitargeted tyrosine-kinase inhibitor, extends survival of patients with metastatic renal cell carcinoma (mRCC) and gastrointestinal tumours.

Recently a case study of remission of type I diabetes following treatment with sunitinib was reported by Templeton et al. in the *Annals of Oncology* (vol 4, pp824–825).

In the current study, Betrand Billemont and colleagues from Pitié-Salpêtrière Hospital and Georges Pompidou Hospital, in Paris, undertook a retrospective review of variations in blood glucose levels in 200 patients being treated with sunitinib for mRCC in both a phase III study and an expanded access programme between October 2005 and March 2007.

Overall, 19 patients were identified with type II diabetes, five of whom had pancreatic metastases. All 19 patients showed a decrease in blood glucose levels (mean 1.77 mmol/l) after four weeks of treatment. This was followed by an increase of blood glucose levels during the rest period (mean 0.93 mmol/l)

After two cycles of sunitinib, two patients were able to stop taking glucose-lowering drugs, and five other patients had normalised their blood glucose levels. In comparison, blood glucose levels from nine non-diabetic 'control' patients were analysed, and non-significant decreases in mean levels were observed, from 5.89 to 5.26 mmol l/l.

While the exact mechanism in the observations remains to be elucidated, the authors speculate that the phenomenon might be related to capillary regression in pancreatic islets, or that sunitinib treatment could interfere with the IGF-1 pathway, having a subsequent impact on insulin resistance, or that drug-to-drug interactions between sunitinib and blood-glucose-lowering drugs may occur.

"Our data suggest that sunitinib lowers blood glucose level. The indications for and the dose of blood glucose lowering drugs should be evaluated during both the active treatment period and the rest period," write the authors, adding that to avoid severe hypoglycaemia, oral blood-glucose-lowering drugs should be carefully monitored.

■ Blood glucose levels in patients with metastatic renal cell carcinoma treated with sunitinib. B Billemont, J Medioni, L Taillade et al. *Br J Cancer* 28 October 2008, 99:1380–1382