NEWSROUND

Selected reports edited by Janet Fricker

Treatment by gynaecologic oncologists improves outcome in endometrial cancer

➜ Journal of Clinical Oncology

Patients with endometrial cancer treated by gynaecologic oncologists were more likely to undergo staging surgery and receive adjuvant chemotherapy in advanced cancer, a US study has found. The researchers also reported a higher five-year disease-specific survival among endometrial cancer patients with stage II–IV disease who were treated by gynaecologic oncologists.

Over the last decade the number of annual deaths from endometrial cancer has doubled in the US. Studies of patients with ovarian cancer have shown that those receiving care from gynaecologic oncologists underwent more thorough staging surgery and received more chemotherapy in high-risk disease. This, in turn, led to improved survival outcomes. Despite a lack of evidence for survival benefit for patients with endometrial cancer, the American College of Obstetrics and Gynecology recommends that these patients should also be referred to gynaecologic oncologists.

In the current study, John Chan and colleagues from the University of California at San Francisco, undertook to determine the influence that care by gynaecologic oncologists had on both the type of treatment and the survival of patients with endometrial cancer. Between 1988 and 2005 the investigators obtained data from the Medicare data bases and from the Surveillance, Epidemiology and End Results (SEER) programme. The speciality of the treating surgeon was found by linking their unique provider identification numbers in the data bases to information collected by the American Medical Association. Kaplan–Meier and Cox proportional hazard methods were used for analyses.

Results show that of the 18,338 women identified with endometrial cancer in the data bases, 21.4% received care from gynaecologic oncologists (defined as group A); while 78.6% were treated by other clinicians (defined as group B).

Women in group A were older, with 49.6% in group A aged over 71 years compared to 44% in group B (P=0.001); they had more lymph nodes removed, with 22% in group A having more than 16 nodes removed compared to 17% in group B (P<0.001) they presented with more advanced cancer, with 21.9% in group A having stage III–IV cancers versus 14.6% in group B (P<0.001); they had higher-grade tumours (P<0.001) and they were more likely to receive chemotherapy for advanced disease, with 22.6% in group A receiving chemotherapy versus 12.4% in group B (P<0.001).

For women with stage II–IV disease, the five-year disease-specific survival (DSS) of group A patients was 79% versus 73% for group B (P=0.001). For stage III–IV disease, women in group A had a five-year DSS of 72% versus 64% in group B (P<0.001). However, no association with DSS was identified among women with stage I cancers. On multivariable analysis, younger age, early stage, lower grade, and treatment by gynaecologic oncologists were all found to be independent prognostic factors for improved survival.

"Directed care by gynecologic oncologists was associated with more extensive lymph node resection and subsequent adjuvant therapy. Most importantly, care provided by gynecologic oncologists improved the survival of those with high-risk (stages II to IV, grade 2 and 3, and high-risk histologies) disease," write the authors, adding, that to their knowledge this is the first population-based study to have analysed the impact that gynaecologic oncologist care has on endometrial cancer patients.

Nearly 80% of endometrial cancer patients in the study, stress the authors, did not receive care from gynaecologic oncologists. "Clearly, further research is needed to identify the

disparities in endometrial cancer treatment and potential barriers to accessing subspecialty care," they write.

Limitations to the study included a lack of information on the extent of residual disease after cytoreductive surgery for advanced disease, lack of central pathology review, unknown types and cycles of adjuvant chemotherapy and unspecified treatment for recurrent disease. "Without central pathology review, it is possible that a change in grade of disease may affect the results of this study," write the authors.

■ J K Chan, AE Sherman, DS Kapp et al. Influence of gynecologic oncologists on the survival of patients with endometrial cancer. *JCO* doi 10.1200/JCO.2010.31.2124, published online 24 January 2011

Choice of surgeon is a significant influence on outcome in DCIS

→ JNCI

The most important determinants of outcomes for women with ductal carcinoma *in situ* (DCIS) are associated with tumour margins, whether or not they received radiotherapy, whether or not they underwent mastectomy, and the treating surgeon, a retrospective US study has found.

"An important implication of our work is that surgeons may play a critical role both in the surgical treatment choices made by patients (and in the receipt of radiation therapy). Because these are the most important factors in predicting outcomes the substantial variation by surgeon suggests that the quality of DCIS care could be improved," write the authors Andrew Dick and colleagues from the RAND Corporation (Pittsburgh, PA), a non-profit-making institution, with the remit to improve policy and decision making through research and analysis.

The goal for treating DCIS, or non-invasive breast cancer, is to reduce the likelihood of developing invasive breast cancer while respecting patient preferences for treatment options, which include breast conserving surgery alone, breast conserving surgery followed by radiation, and mastectomy. Since DCIS is non-lethal, physicians' attitudes regarding optimal management and patient preference may play a role in treatment decisions.

To determine the comparative effectiveness of treatment strategies, and identify key factors associated with variations in outcomes, Dick and colleagues conducted a retrospective study of 994 women diagnosed with DCIS between 1985 and 2000. The investigators identified subjects through two large tumour registries: the Monroe County (New York) tumour registry, and the tumour registry at the Henry Ford Health System in Detroit. Margins were defined as positive (when cancer cells extended to the edge of the resected tissue); negative (when cancer cells were more than 2 mm away from the edge of the tissue); or close (when cancer cells were present within 2 mm of the edge).

Results showed that the overall differences in predicted five-year disease-free survival rates were 0.993 for mastectomy, 0.945 for breast-conserving surgery with radiation therapy and 0.824 for breast-conserving surgery without radiation therapy, with all the differences found to be statistically significant (*P*diff <0.001 for each of the differences). Similarly, each of the differences at 10 years was statistically significant (*P*<0.001).

In all the treatment groups, except breast conserving surgery without radiation therapy, the rates of recurrence were statistically significantly different according to margin status, with positive margins found to be associated with substantially higher recurrence rates. Furthermore, variation by surgeon accounted for 15%–35% of the subsequent ipsilateral five-year recurrence rates, and for 13%–30% of 10-year recurrence rates.

"Although variation by surgeon could be generated by patients' preferences, the extent of variation and its contribution to long-term health outcomes are troubling," write the authors, adding that further work is required to determine why women with positive margins receive no additional treatment and why margin status and receipt of radiation therapy vary by surgeon. Additionally, they add, there is currently no consensus on what constitutes a negative margin.

In an accompanying commentary, Beth Virnig and Todd Tuttle of the University of Minnesota ask how patients should go about selecting health providers, in the knowledge that up to 35% of the variation in outcomes is based on their choice of physician, but that there are no actionable characteristics that can be taken into account.

One solution, they suggest, would be to publish the scores for all physicians performing breast cancer surgery in a particular area. "With this approach, it would not matter why one physician had higher or lower recurrence rates or positive margin rates, the rates would simply be reported so that women could take this into account when selecting a provider," they write.

The challenge, they add, will be for the professional community to identify factors that are associated with the unexplained physician variability and to use that information to promote identification of high-quality providers or quality improvement activities.

■ AW Dick, MS Sorbero, GM Ahrendt et al. Comparative effectiveness of ductal carcinoma in situ management and the roles of margins and surgeons. *JNCI* 19 January 2011, 103:92-104

■ B Virnig, TM Tuttle. Random physician effect and comparative effectiveness of treatment for ductal carcinoma in situ. *ibid*, pp 81–82

Protocols needed to cut delays in giving antibiotics for febrile neutropenia

→ British Journal of Cancer

A study providing detailed insights into the management of chemotherapy-induced febrile neutropenia in a UK Cancer Network shows that while the condition is generally recognised early and managed appropriately,

improvements are needed in the timely administration of antibiotics. The prospective study, the authors believe, highlights the need for introducing network-wide clinical care pathways to improve outcomes.

Febrile neutropenia (the development of fever in patients with abnormally low levels of neutrophil granulocytes) is a complication of chemotherapy associated with considerable morbidity and mortality. The UK National Chemotherapy Advisory Group (NCAG) – set up to provide advice on the delivery of high-quality chemotherapy services to the National Cancer Director and Department of Health – have produced guidelines on febrile neutropenia, recommending 'treat and transfer' arrangements (if hospitals do not have appropriate facilities), and an arrival to delivery time of antibiotic administration for neutropenic sepsis of less than one hour.

"The NCAG recommendations provide a framework for a process of assessment, decision to treat, informed consent and prescription of chemotherapy, and emphasise the importance of detailed standardised consent forms and the involvement of senior trained oncology medical staff ," write the authors of the study, Simon Chowdhury and colleagues from Guy's & St Thomas' NHS Foundation Trust (London, UK).

In this study, Chowdhury and colleagues undertook a prospective study of all the cases of chemotherapy-induced febrile neutropenia in the South West London Cancer Network between May and August 2007. Data recorded at seven hospitals serving a population of 1.4 million people included demographics, treatment histories, management of febrile neutropenia and outcomes.

Results showed that, in all, 71 admissions for febrile neutropenia were reported, involving 64 patients, with seven patients admitted on two separate occasions. Fifty-nine per cent of patients (*n*=38) were female and 41% (*n*=26) male, with a median age of 60 years. Of note, one-third of patients with febrile neutropenia in the study were older than 65 years, which the authors suggest supports the notion "that increasing age is an independent predictor of development of febrile neutropenia." The seriousness of the condition was underlined by the fact that three of the patients (4.2%) died as a direct consequence of neutropenic sepsis.

Forty-five patients (63%) were admitted directly to a specialist oncology or haematology ward, while 21 (30%) were seen first in the accident and emergency departments. The median time from arrival to nursing assessment was 10 minutes (range 0–135 mins), and the median time to first assessment by a clinician was 40 minutes (range 0–230 mins). The median time from arrival to administration of an antibiotic was 135 minutes (range 15–550 mins), with only 9 out of 50 patients receiving antibiotics within 60 minutes.

"Our study has provided an important and detailed insight into the incidence and management of chemotherapy-induced febrile neutropenia in a representative cancer network in the United Kingdom," write the authors, adding that the area that most needs to be addressed is the time interval between arrival at the hospital and treatment.

"To achieve this, physician and nursing protocols to standardise and streamline clinical care pathways for the whole network are under consideration," write the authors, adding that it is hoped that the recommendation for NICE to provide a nationwide policy for management of neutropenic sepsis will lead to the introduction of a standardised approach both within and across networks.

One issue, add the authors, is that peripheral hospitals may not be staffed with 24-hour oncology services, making it crucial that these sites have access to well-designed protocols and expert consultant advice. Furthermore, patient education regarding what to do in the event of a chemotherapy-induced complication is fundamental to ensuring people receive prompt appropriate care.

■ M Okera, S Chan, U Dernede. A prospective study of chemotherapy-induced febrile neutropenia in the South West London Cancer Network. Interpretation of study results in light of NCAG/NCEPOD findings. *Br J Cancer* 1 February 2011, 104:407–412

IMRT spares head and neck cancer patients dry mouth symptoms

➔ Lancet Oncology

Sparing the parotid glands of patients with head and neck cancer by using intensity modulated radiotherapy (IMRT) reduces the incidence of xerostomia (a dry mouth due to lack of saliva), reports the phase III UK PARSPORT study.

While radiotherapy is the main non-surgical treatment for squamous-cell carcinoma of the head and neck, radiation-induced xerostomia is a commonly reported late side-effect. Lack of saliva affects speech and swallowing, and can accelerate dental caries. In comparison with conventional radiotherapy, IMRT, which allows focused radiation delivery to tumours, can reduce irradiation of the parotid glands.

In the current study, which took place at six UK centres between January 2003 and December 2007, Christopher Nutting and colleagues from the Institute of Cancer Research (Sutton, UK), randomised 94 patients with histologically confirmed squamous carcinoma (T1–T4, N0–N3, M) to parotid sparing IMRT (*n*=47) or to conventional radiotherapy (*n*=47). In both groups, the primary tumour and involved lymph nodes were treated with 65 Gy, delivered in 30 daily fractions, five days a week. The investigators undertook measurement of salivary flow prior to radiotherapy, at week 4 of treatment, and then at 2 weeks and 3, 6, 12, 18 and 24 months after radiotherapy.

Results at 12 months show that grade 2 or worse xerostomia symptoms occurred in 74% of patients given conventional radiotherapy versus 38% of patients given IMRT (P=0.0027). At 24 months, grade 2 or worse xerostomia occurred in 83% of patients given conventional radiotherapy versus 29% given IMRT (P<0.0001).

At 12 months, unstimulated saliva flow from the contralateral parotid glands was noted in 47% of patients treated with IMRT versus none treated with conventional radiotherapy (P<0.0001), while at 24 months unstimulated saliva flow occurred in 44% of patients in the

IMRT group versus none in the conventional therapy group (P=0.0068).

The only recorded acute adverse event of grade 2 or worse that differed significantly between the treatment groups was fatigue, which occurred in 41% of patients given conventional radiotherapy versus 74% given IMRT (P=0.0015). Significant differences were also noted in stimulated saliva flow from the contralateral parotid at 12 months (P<0.0001). The estimated two-year overall survival was 76% with conventional radiotherapy versus 78% with IMRT.

"Our trial has shown a clinically and statistically significant reduction in xerostomia, improved salivary flow, and improved quality of life, and this strongly supports a role for IMRT in head and neck squamous cell carcinoma," conclude the authors, adding that the results of the PARSPORT trial are likely to be generalisable to all head and neck tumours for which conventional radiotherapy is used. It is possible, they say, that further reductions in severe xerostomia could be achieved by additionally sparing the submandibular and mucosal minor salivary glands.

Fatigue was unexpectedly found to be greater in patients treated with IMRT. This, say the authors, could be due to greater radiation doses being delivered to non-tumour tissues.

One limitation of the study, they add, is that it was not possible to mask the treatment from patients or clinicians due to the differences in treatment delivery. "However, results that relate to multiple secondary endpoints support the primary analysis and the size of the observed effect is unlikely to be due entirely to assessment or reporting bias."

In an accompanying commentary, Andy Trotti from the Moffitt Cancer Center (Tampa, Florida) and Avi Eisbruch from the University of Michigan Medical Centre (Ann Arbor) say that future work should systematically explore the prioritisation of different components of the salivary gland system, since a clinical benefit of sparing the submandibular glands can be obtained over the parotid glands. "The parotid glands provide watery saliva during eating, which is largely replaceable by consuming more water or lubricants. The submandibular, sublingual, and minor salivary glands provide mucinous saliva, associated with the resting sense of moisture and dry mouth symptoms." Further possibilities, they add, include gland repair or regenerative strategies with stem cells, acupuncture, or acupuncture-like stimulation.

■ CM Nutting, JP Morden, KJ Harrington et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* February 2011, 12:127–136

■ A Trotti, A Eisbruch. Reducing xerostomia through advanced technology. *ibid* pp 110–111

Cannabis improves cancer patients' appetites and sense of taste

➔ Annals of Oncology

The active ingredient of cannabis improved the appetite and sense of taste of patients with advanced cancer, but had no effect on their calorie intake, a US proof of principle study has found.

Loss of appetite is common among cancer patients, both due the cancer itself and to treatment affecting people's sense of taste and smell. As a result, they experience decreased enjoyment of food, which in turn can lead to weight loss, anorexia, reduced quality of life and decreased survival. For a long time health professionals thought nothing could be done and advised cancer patients to 'cope' with chemosensory problems by eating bland, cold and odourless food. More recently, however, the potential of delta-9-tetrahydrocannabinol (THC) – the main psychoactive ingredient in cannabis, which is thought to increase appetite via endocannabinoid receptors – has been recognised. Studies have shown that THC increases appetite in animals, healthy humans and patients with acquired immunodeficiency syndrome (AIDS), but its ability to have an effect in cancer patients has not been consistently reported.

In the current study – conducted in two Canadian cancer centres in Edmonton and Montreal – Wendy Wismer and colleagues from the University of Alberta (Edmonton, Canada) hypothesised that THC may favourably alter the chemosensory perception of cancer patients.

In the randomised placebo-controlled phase II double-blind pilot study, which took place between May 2006 and December 2008, 21 patients with advanced cancer (excluding brain cancers) who had been eating less as a result of their illness for two weeks or more, were randomised to receive THC (n=11) or to placebo (n=10). The active capsules contained 2.5 mg of THC, with patients asked to take them once a day for the first three days, then twice a day thereafter, with the option to increase the dose to a maximum of 20 mg a day. Treatment ran for 18 days. Questionnaires were conducted before, during and at the end of the trial.

From questionnaires, researchers found that 73% of THC-treated patients reported an increased overall appreciation of food compared with 30% of patients receiving placebo, and that 55% said that the medication "made food taste better", compared with 10% taking placebo (P=0.04). Half of the patients who reported odours to be unpleasant at baseline no longer found odours offensive with THC treatment (P= 0.083).

Although no difference was found in the total number of calories consumed by the two groups, the THC-treated patients tended to increase the proportion of protein they ate, and 55% reported that savoury foods tasted better, whereas no patients in the placebo group reported an increased liking for these foods. In addition, THC-treated patients reported better quality of sleep (P=0.025) and relaxation (P=0.045) in comparison the placebo group.

"Our pilot study demonstrates that THC, compared with placebo, improved and enhanced chemosensory perception, altered micronutrient preference, appeal of savory foods, appetite, relaxation, and quality of sleep for advanced cancer patients with chemosensory alterations," write the authors, adding that the data will assist in the development of larger phase II trials by facilitating sample size calculations.

Inevitably, they add, questions are raised about the ability to blind THC treatment based on

its well-known psychoactive characteristics. "However, the timed administration of low doses and the lack of differences in AEs [adverse events] between treatment groups suggest that this problem was likely minimal," write the authors.

■ TD Brisbois, IH deKock, SM Watanabe et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol* doi:10.1093/annonc/mdq727, published online 22 February 2011

Study shows occult metastases have little effect on outcome

➜ New England Journal of Medicine

No additional clinical benefit is obtained by evaluating women with breast cancer for occult metastases, a US study has concluded. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial found that the detection of occult metastases could not be regarded as a discriminatory predictor of cancer recurrence.

Clinicians have debated for some time whether breast cancer patients whose lymph nodes initially test negative for disease, but who have occult metastases (detected after further evaluation), are at greater risk of recurrence and might benefit from more aggressive treatment. The standard approach, endorsed by ASCO and the American College of Surgeons, is to slice sentinel nodes at 2.0-mm intervals and stain samples with haematoxylin and eosin (H&E). However, controversy continues over whether pathologists should be looking at more frequent intervals in order to find hidden cancers.

Donald Weaver and colleagues from the University of Vermont College of Medicine (Burlington, USA) undertook the B-32 trial in which 5611 women with no clinical evidence of metastatic disease in the armpit were randomly assigned to sentinel lymph node biopsy plus axillary dissection or sentinel lymph node biopsy alone.

In the current sub-study, the 3887 patients in whom metastases were not detected underwent further evaluation. Tissue blocks from the negative sentinel nodes were sent to a central laboratory for evaluation of additional sections that were 0.5–1.00 mm deeper in the block relative to the original surface. The deeper analysis included routine use of (H&E) testing and immunohistochemical staining.

Occult metastases were detected in 15.9% of the patients whose initial sentinel node biopsy tested negative for cancer. Isolated tumour cells (≤0.2 mm) accounted for 11.1% of the metastases followed by micrometastases (>0.2–≤2.0 mm, 4.4%), and macrometastases (>2.0 mm, 0.4%).

Log-rank tests indicated a significant decrease in overall survival (P=0.03); disease-free survival (P=0.02); and distant-disease-free interval (P=0.04) between patients in whom occult metastases were detected and patients in whom occult metastases were not detected.

However, the five-year Kaplan–Meier survival estimates for overall survival were 94.6% for patients in whom occult metastases were detected versus 95.8% for patients in whom occult metastases were not detected; for disease-free survival they were 86.4% versus 89.2%; and for distant-disease-free survival were 89.7% versus 92.5%.

The multivariable analysis identified several other factors that influenced outcomes: older age and larger primary tumour size adversely affected outcomes, whereas systemic chemotherapy, endocrine therapy and radiation therapy significantly improved outcomes.

Perhaps the most interesting interaction, say the authors, was with endocrine therapy, indicating that occult metastases are associated with oestrogen-receptor-positive tumours (considered a favourable prognostic factor) and that endocrine therapy markedly reduces the risk of a poor outcome.

"Occult metastases were an independent prognostic variable in patients with sentinel nodes that were negative on initial examination; however, the magnitude of the difference in outcome at five years was small (1.2 percentage points)," write the authors, adding that their findings argue against analysis of additional tissue levels or routine immunohistochemical analysis for sentinel-lymph-node evaluation.

One limitation of the study, they say, is that no analysis would be able to detect all the occult metastases.

Although the difference in survival between women with and without occult metastasis was small at five years' follow-up, the investigators believe the study "warrants continued follow-up and analysis".

■ DL Weaver, T Ashikaga, DN Krag et al. Effect of occult metastases on survival in node-negative breast cancer. *NEJM* 19 January 2011, 364:412–421

Corrections and clarifications

ISOPP's founders

In the cover story on Klaus Meier, published in the Jan-Feb issue, we reported that Meier founded the International Society of Oncology Pharmacy Practitioners (ISOPP).We would like to clarify that it was Helen McKinnon of New Zealand who came up with the idea of founding ISOPP in 1988, and she was elected ISOPP's first president in 1997. Meier was part of the board that initiated and developed the notion of ISOPP becoming an incorporated society in 1993, and he turned that notion into reality, setting up ISOPP as an incorporated society under German law in 1996.

Myriad's gene patents

It was a federal district court that overturned some of Myriad's BRCA patents in March last year, and not the Supreme Court, as was incorrectly reported in the article on Promoting genetic literacy, in the Jan-Feb issue of *Cancer World*. Myriad is now appealing the decision in a hearing that started on April 4th. It's chances of succeeding will have been dented by a re-evaluation of past policy conducted by the US Justice Department, which has filed a brief asking the appeal judges to uphold parts of the ruling that overturned several of Myriad's patents on the BRCA genes.