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Nadia Harbeck

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ECCO–ESMO: a powerful partnership

Alexander MM Eggermont and José Baselga ■ GUEST EDITORS

Bridging the bench-to-bedside gap and promoting multidisciplinarity are pivotal to advancing research and improving patient treatment and care.

The implementation and measurable outcomes of both ideals in everyday practice generally translate into increased dialogue and debate between professional specialties and communities. In the battle to eliminate cancer much more can – and will – be done.

The recently announced collaboration between ECCO, the European CanCer Organisation, and ESMO, the European Society for Medical Oncology, was welcomed by the oncology community as a turning point in uniting forces, efforts and professionals across Europe.

ECCO exists to uphold the right of all European cancer patients to the best possible treatment and care and promote interaction between all organisations involved in cancer research, education, treatment and care. ESMO represents one of the specialties most concerned in such interaction, since medical oncology demands a scientific and academic base, a vision towards developing and evaluating novel treatment methodologies and an involvement in total cancer care.

To deliver on multidisciplinarity and provide equal access to quality care, neither ECCO nor ESMO can stand alone. ESMO's decision to join ECCO represents a further step forward in shaping a united front – the convergence of specialty organisations that share a determination to promote a coherent, concise and harmonised approach to tackling the second leading cause of death in Europe.

One critical outcome of the collaboration is that the two leading educational opportunities in European oncology, the ECCO and ESMO congresses, have been combined every other year. By fusing excellence and expertise to create all-encompassing comprehensive programmes of the highest calibre, the biennial joint multidisciplinary congresses are set to draw record attendances.

Setting the standard for the future, the first ECCO–ESMO congress will take place in Berlin, Germany, 20–24 September 2009. Thereafter they will take place on uneven-numbered years, while ESMO will continue to organise its standalone congress in even-numbered years.

Unlike many other fields, cancer incorporates multiple interrelated disciplines, which naturally poses a challenge. Efforts to strengthen policies on cancer will succeed only by standing united. Divided we will fail.

ESMO's membership of ECCO will be crucial in the campaign to build awareness of patients' needs and encourage progressive thinking in cancer policy, training and education at the EU level. The oncology community is now better positioned than ever to improve care and research interactivity across Europe.

Alexander Eggermont is the President of ECCO and José Baselga is the President of ESMO

Nadia Harbeck:

breaking with convention

Marc Beishon

Gynaecologists don't win top awards at ASCO. German oncologists don't make it on the international stage. Women who want large families can't expect to be leaders in their field. Nadia Harbeck's high-flying career and relaxed leadership style demonstrate the great possibilities that open up if you refuse to let conventional wisdom and prejudices stand in your way.

Those who would like to see rigid career structures for oncologists and conformity concerning the organisation of cancer centres would do well to pay a visit to the department of obstetrics and gynaecology at the Technical University Hospital in Munich. Not only is the department a leading clinical trials centre for breast cancer – an unexpected finding for an ob/gyn unit for those who do not know the German system – but it is also part of a growing network of translational research and breast care excellence in Germany, a country that has the dual challenges of a fragmented public/private healthcare system and a pretty rigid hierarchy in the medical professions.

One of the key agents of change in Munich is Nadia Harbeck, ostensibly an associate professor of obstetrics and gynaecology, but actually more or less full time on one of her 'subtitles', namely head of breast cancer systemic therapy and the clinical trials unit in the department. "In Germany it is traditional that gynaecologists have always treated breast cancer," she says. "From the woman's point of view it makes sense as we see them when they are healthy and then if they do contract breast cancer and other diseases we carry out all the diagnosis, treatment and follow-up care – it's a continuum in one clinic."

Harbeck, though, has gone much further than most gynaecologists in making the switch to oncology, including participating in research that has brought her to international attention on the largest possible stage – at the American Society of Oncology (ASCO) meeting in the US. What's more, the work for which she is best known – a prognostic biomarker for breast cancer – has been made possible largely because the continuum of care in her clinic has provided the opportunity to collect fresh tumour samples and conduct translational research that is more difficult at present in countries such as the US, thanks to different medical practices. And overall she says Germany now has an advantage in being able to carry out neoadjuvant work, in particular, because of this 'all in one' structure. This biomarker work continues in her department, together with other trials across the spectrum from prevention to metastatic treatment, while she also promotes holistic care for the cancer journey, with

TOBIAS HASE/DPA

strong interest in areas such as breast awareness and psychosocial support for women with cancer.

But, as in other fields where specialists can dominate, in particular urology, Harbeck recognises that there can be tension between the role of general medical oncologists and specialists such as herself. The picture across Germany varies: at the Technical University Hospital there is a separate medical oncology department, while in other hospitals medical oncology leads on breast cancer, she notes. Further, many physicians in Germany, including gynaecologists, work as private practitioners in their own offices and clinics, and it can be challenging to integrate them with major centres.

Other specialists, in particular radiologists, are also free to practise separately. Harbeck comments on one group that recently set up its own breast unit in Munich, in part to carry out screening in line with Germany's recent rollout of a national programme. "But this means they are apart from the already established multidisciplinary 'all under one roof' breast centres such as ours – and it is not clear if this will be to the benefit of the patient. This is a hot political topic in Germany right now."

Germany has only just announced a national cancer plan – health minister Ulla Schmidt announced in June a programme for improving early detection, treatment and care, access to drugs, patient information and the communications skills of doctors. Early announcements include the establishment of more oncology 'excellence centres' and free skin cancer screening for those over 35. The

"This was really unusual – a European, a German and a gynaecologist getting this award"

country has also been late in establishing its breast screening programme, and is still in the process of ensuring breast units conform to recent national guidelines and those from EUSOMA (the European Society of Breast Cancer Specialists). The country has a relatively low number of patients recruited into clinical trials; only a few regions, such as Bavaria, maintain high-quality cancer registries (Harbeck regrets that a good registry in East Germany was allowed to run down after reunification); and much to do in providing better palliative care services.

This might seem surprising given the perception of Germany as a high-quality medical provider, and indeed a high spender per head on cancer services, but healthcare is driven by a network of devolved and expensive public and private insurance systems that more closely resemble the situation in the US than most other nations. Meanwhile, adds Harbeck, there is still much to do in improving research networks both among German centres and among researchers in the neighbouring German-speaking countries of Austria and Switzerland.

Indeed, as she says, because of lack of confidence in speaking English, fear of being out alone as 'one of the first', and with so much to do at home, German cancer specialists have also not ventured onto the international stage as much as they could. That certainly does not apply to Harbeck – she is already a veteran of the conference circuit, attending all the key breast events such as the San Antonio Breast Cancer Symposium, the European Breast Cancer Conference, the St Gallen consensus event and also the ASCO meeting. It was at the latter in 2001 that she received the fellowship merit award as lead author for the highest ranking abstract, which was for long-standing work on the prognostic breast cancer biomarker. "This was really unusual – a European, a German and a gynaecologist getting this award. It had never happened before and created a lot of publicity."

Harbeck could also have added being a women to that list, for not only has she carved out an unofficial specialism within gynaecology, one of Germany's core medical disciplines, she also started out at a time when men dominated this and other German medical fields – and still do to a large extent, especially at the top. "My head of department in ob/gyn here at the Technical University is a woman, Marion Kiechle, but she was the only woman director of gynaecology in any university hospital in all the German speaking countries when she was appointed in 2000, and this has not changed since," she says.

Women, adds Harbeck, do have a different leadership style, in her experience. "In my department, at least, hierarchies are not so rigid, and that makes it easier for me to travel and network, without which it would be very hard to progress with work such as our trials portfolio." Elsewhere in Germany, she says, department heads tend to run everything and take all the credit, and also give little scope for younger staff to learn the administrative side of running a unit, which can be very demotivating.

Harbeck left school with the qualifications to study medicine. Unsure what to do, she spent a year in Canada with a relative learning photography and film skills, but not wanting to end up as a wedding photographer she returned to Munich to enter medical school, with a desire to specialise in ob/gyn firmly embedded. "I always wanted to work with women – you work with both healthy and sick women, carry out surgery, administer endocrine treatments and so on – the many different disciplines make you think. It also touches women from a psychological point of view, as some diseases affect them very personally."

She duly worked her way to a full ob/gyn qualification. Choosing to combine her career with having a sizeable family – she has four children – this took her at least three years longer than her male colleagues. "It is not surprising then that a lot of women gynaecologists go off to private practice where they can work part time to accommodate

family life," she notes. "It is especially difficult for women with families to get to the top in surgical specialities."

Needing an MD thesis, Harbeck chose an oncology topic involving monoclonal antibodies that could be carried out in the clinic. It was about detecting tumour cells in the bone marrow of breast cancer patients and was supervised by Wolfgang Eiermann at Munich's other university hospital, Ludwig-Maximilians. This sparked her interest in breast cancer research, especially in early spread of the disease, and she switched to the Technical University as the then head of the ob/gyn department, Henner Graeff, was setting up a translational research unit with a dedicated laboratory. The lab is still run today by the same biochemist, Manfred Schmitt, who is one of Harbeck's key mentors and colleagues.

"Henner Graeff had the vision of a role for a physician/scientist, which was intriguing and why I came here, and he liked my background. But I was on a short-term contract – and when I left to have my first child he kept a tenured position open for me, which was very unusual then. You can't have a family and plan research if you only have two-year contracts. This was a decisive point in my career – my husband is American and I was open to anything then, including going to work in the States."

So Harbeck's research career was safeguarded – and has continued through three more children. About 10 years ago she also moved full time in the clinic away from surgery and day-to-day ob/gyn work to focus on systemic therapy and building up the department as a top breast unit.

As she says, there can't be too many internationally known oncologists who have delivered babies and carried out breast cancer surgery and many other procedures such as hysterectomies, and who are now investigating novel therapies. The experience, she feels, gives her a more profound insight into the needs of women, which helps in her work with breast cancer patients of all age-groups.

Her main achievements, then, fall into the two camps of research and trial work, and building up the department as one of Germany's main cancer centres, especially for breast cancer. As trial work is a parameter for accreditation, the two reinforce one another. "In 2005 we were certified as a breast centre by the German authorities – two organisations have jointly drawn up specifications, namely the German Cancer Society and the Society of Senology, but they differ from EUSOMA's guidelines. We do struggle with EUSOMA because it requires that medical oncologists be part of the unit and does not accept that I have the expertise." Harbeck herself sits on Germany's AGO breast cancer gynaecology guidelines group.

The breast centre accreditation does, of course, include the usual multidisciplinary structures such as tumour boards – Harbeck and colleagues run no fewer than four early morning meetings a week, mostly for breast but also for other cancers such as ovarian, which a colleague specialises in. Medical oncologists from elsewhere, she says, would feel superfluous most of the time, "But we consult with them on difficult cases, and in our phase II trials we also work with them closely – I try to partner a medical oncologist with a gynaecologist as investigators, to help bridge the gap and avoid confrontation.

"It is sometimes hard to explain to colleagues abroad how we do things here and that

TOBIAS HASE/DPA

"You can't have a family and plan research if you only have two-year contracts"

"I don't think it is what you did 10 years ago but what you specialise in now that counts"

I don't want to export our system – but I do want the recognition that I am an equal in the medical oncology field in breast cancer, even though I did a different specialist degree. I don't think it is what you did 10 years ago but what you specialise in now that counts." In fact, Harbeck also faces some opposition from within the ob/gyn world too – not all are too keen to see their field extended and sub-specialised so far in the direction of systemic treatment of early and metastatic breast cancer.

Meanwhile, she considers the introduction of certified breast centres will radically change the landscape of breast care in Germany. "The estimate is we need 200 centres to provide good care – we are at around 150 now. Smaller hospitals that see only a low number of cases should not carry on with breast cancer work – but it will probably be the insurance companies that decide the issue as they won't offer reimbursement to non-conforming places."

It is important also, she adds, to implement a structure where the patients of private practitioners are referred to breast centres, but are then returned to the care of the referring physician.

Harbeck's department also carries out a good deal of second opinion work, seeing patients directly – but she feels that moves to implement a mandatory second opinion system where only the paperwork is received, which is partly driven by insurance companies seeking to avoid expensive therapies, is politically controversial. "Who is going to take responsibility if the patient relapses – and can you really give second opinions for individual patients just by following guidelines and published evidence?" That said, guidelines are critical: "We have seen changes in treatment patterns and better outcomes in both breast and ovarian cancer for those who follow guidelines, and overall, despite what some of our journalists like to say, treatment in experienced German centres is not any worse than in the US. You do not have to go to America to get the best care."

The research that has captured Harbeck's attention is on the plasminogen activator system – a complex enzyme system where it has been found that increased levels of an activator, uPA, and also its inhibitor, PAI-1, in primary breast cancers correlate with aggressive tumours and poor outcomes. As she explains, work on uPA goes back to the 1980s, where Joe Duffy, of St Vincent's University Hospital, Dublin, demonstrated the effect of high uPA activity, while Manfred Schmitt in Munich developed an ELISA (Enzyme Linked ImmunoSorbent Assay) to measure the levels of uPA and PAI-1. The uPA enzyme degrades the extracellular matrix and so tumour cells can escape and metastasise – and the inhibitor also has a similar effect and helps tumour cells migrate, which is counter-intuitive, but was shown to be true.

"Various groups around Europe, helped by the then Receptor and Biomarker Group [now Pathobiology Group] of the European Organisation for the Research and Treatment of Cancer [EORTC], also found the same bad prognosis, and Fritz Janicke, then here in Munich, led the first clinical trial of these biomarkers, (Chemo N0). The results were published in 2001 in the *Journal of the National Cancer Institute*."

That trial should sound familiar in its aim to *Cancer World* readers, as it concerns selecting which women with node-negative breast cancer would best benefit from adjuvant chemotherapy, through risk stratification – the same aim of the much discussed MINDACT and TAILOR*x* trials, which instead use gene signatures to help distinguish high- and low-risk groups. But the uPA/PAI-1 work relies on a simpler and cheaper protein measurement that Harbeck says is easier to replicate and now has a robust quality control methodology.

"When Fritz Janicke left, I took over as clinical lead on the project and did my professorial thesis on the system," says Harbeck. "The ASCO merit award was for a meta-analysis on behalf of the EORTC

A familiar face on the international stage. Harbeck gave the Emmanuel van der Schueren lecture at the opening ceremony of the Sixth European Breast Cancer Conference in Berlin this April

FRANK NÜRNBERGER/EVENT-PHOTO.BIZ

Receptor and Biomarker Group, where we showed that uPA and PAI-1 were ready for routine testing of primary breast cancer as level 1 evidence. No one had ever done such an analysis of a prognostic factor on over 8,000 patients – it was the first in any cancer I think – and the ASCO organisers emailed me twice to check the details were true." So far these biomarkers are the only ones proved in a prospective trial in breast cancer. As an aside, she also mentions the support she's received from Martine Piccart-Gebhart, current president of the EORTC, in developing her international work.

As she adds, the uPA/PAI-1 work is also an excellent example of translational research in action. "We went from bed to bench and back again. We had the clinical indication first, the scientist explained how it worked, and then we did the trial that proved that high levels of these factors are bad for patients. We have been a step ahead of the gene signature work with level 1 evidence – i.e. ready for use in the clinic – and we also have a second clinical trial (NNBC-3) now in train with 3,000 patients in 150 centres that will be finished early next year."

"So far these biomarkers are the only ones proved in a prospective trial in breast cancer"

Role model. Harbeck – pictured here with children (from the left) Lara, Julian, Emma and Daniel, and husband Ronald – is living proof that, with a bit of give and take, it is perfectly possible to combine family with a successful career in oncology

The uPA/PAI-1 biomarker system is, says Harbeck, now routinely used in clinics in Germany and elsewhere (about half of the current trial sites use the system in the clinic). As a consequence, about 35%–40% of node-negative breast cancer patients are spared adjuvant chemotherapy, but wider application is constrained by the need for medical oncologists to access fresh tumour tissue and also have available the ELISA. "The Americans don't have it – after the surgeon takes out the tumour, samples end up in formalin, and the company making the ELISA test has not marketed it heavily." The fresh tissue constraint is shared with the MINDACT gene signature trial, but not with TAILORx, which is designed to work with formalin-fixed, paraffin-embedded tissue specimens.

Further, because it is deemed 'impractical', the biomarker is acknowledged but not recommended in the influential St Gallen breast cancer treatment consensus, nor is it used by the Adjuvant Online resource (www.adjuvantonline.com), according to Harbeck, who is in discussion with Adjuvant Online on how to integrate her data.

"Some say, 'If your biomarker is so good how come it's not in St Gallen?' But half of the St Gallen panel come from the US so it's not surprising they don't yet recommend it. We had a big boost last year, though – uPA/PAI-1 is now in ASCO's guidelines, which shows how scientifically independent they are. And the company making the ELISA is looking for approval from the US Federal Drug Administration based on our German data."

The portfolio of trials in Munich – some 15 currently – is keeping Harbeck very busy; paperwork and organising and motivating junior doctors and remote participants in outlying clinics is an exhausting business, even though she has the help of her colleagues and a university trials centre. One of her key achievements is turning the trials work in her department from an informal, after-hours approach into a fully fledged functional trials unit with study nurses and a growing portfolio. She would like to see more clever trials that target subgroups such as those with hard-to-treat triple-negative disease, and she is also an investigator for therapies such as Avastin (bevacizumab), which are starting to be used more widely across several tumour types. "But companies need to invest more in predictive biomarkers so we can see what compounds are best used in which patient," she says. She has recently applied for a large grant for combining targeted therapy with molecular imaging in line with this need to develop markers for drugs such as Avastin.

"I try to be as patient-oriented as I can, but it is hard, as we have to raise outside funds for much of this"

"Now I write at the top of my CV that I have four kids, so women can ask me how I did it"

She adds that one other reason to travel so much – especially to the US – is to meet top industry and academic decision makers to discuss clinical trials and biomarkers.

But a few German oncologists making international commitments is not sufficient to raise the bar generally for German oncology, she feels. She is pleased to report that there is now a national translational research network for gynaecological cancers (TRAFO), for which she is deputy chair, while she is also the scientific co-chair of a new translational research meeting for breast cancer, COMBAT, which has been deliberately set up as a German-speaking networking event (its inaugural event is in Frankfurt this November).

Naturally, though, she sits also on the scientific committee of the ASCO-NCI-EORTC Annual Meeting on Molecular Markers in Cancer, which will be held in Florida this year, having had its first meeting in Nyborg, Denmark, in 2000. She also told the uPA/PAI-1 story this year at the Breast Cancer Conference in Berlin as an invited lecturer at the opening ceremony. Harbeck is also one of the editors in chief of *Breast Care*, a journal set up in 2006 that has both English and German contributions, and she seems tireless in writing up treatment standards and new developments.

Harbeck is keen to stress that she is not single-minded about treatment and survival. "I do try to be as patient-oriented as I can, for example by introducing counselling and a specialist breast care nurse to the clinic, but it is a struggle, as we have to raise outside funds for much of this. I'm also researching breast self-awareness – women need to learn about self-examination and we are evaluating what this brings to their awareness. A technique called MammaCare, which comes from the US, can help them do it better, and we are also doing this with breast cancer patients – they don't like to touch themselves, but they need to feel a new lump.

She is firmly on the side of the screening programme, feeling that its late introduction has cost women's lives in Germany, and comments that the old trials that have been criticised need to be interpreted within the time they were initiated, and some of their flaws may not be relevant any more, given the introduction of digital mammography and a thorough double-reading procedure.

Harbeck has a close non-medical colleague in Renate Haidinger, a breast cancer survivor who first set up a support group in Munich and then co-founded Brustkrebs Deutschland (Breast Cancer Germany). Haidinger gives counselling sessions at the Munich clinic and has also worked with Harbeck on writing up patient experiences with treatments such as Femara (letrozole) (*Breast Can Res Treat* 105:91–103). There are other breast cancer advocacy groups in Germany, and Harbeck's wish is that they would collaborate more closely and also look outside the country, in an echo of the situation on the medical side.

The pan-European advocacy group, Europa Donna, does not have a big local presence in Germany, she says, despite German MEP Karin Jöns being a past Europa Donna president.

For her own part, Harbeck is determined to be a role model for younger women wanting to pursue a clinical research career. "There was no one like me when I was starting out – now I write at the top of my CV that I have four kids, so women can ask me how I did it." Those children are aged 16, 14, 9 and 4, and husband Ronald Kates, who was a relativity physicist in the US, works now as freelance mathematician and indeed is a co-author on many of Harbeck's papers. "He does my bio-maths," she says.

Harbeck's immediate plans are to continue to develop the breast unit part of the clinic, and she indicates she might move to head up her own breast centre if there was an opportunity to set up a genuinely holistic facility. She will of course be at every major breast meeting in the next few years – and if you see her, some words of warning: don't ask who is looking after her children…

The modern approach to managing locally advanced rectal cancer

The traditional approach to managing locally advanced rectal cancer has shifted to the concept of total mesorectal excision and the use of MRI for local staging and selecting patients for multimodal therapy. This case report highlights the key role of the pathologist, the benefits of preoperative concurrent chemoradiation and the importance of multidisciplinary discussion.

The last few years have seen some major changes in the management of rectal cancer. The old standards developed by the US National Institutes for Health in 1990 have now largely been left behind. The classical approach was to carry out surgical resection, followed by a pathology assessment of penetration of the tumour into the bowel wall, and the involvement of lymph nodes. This allowed us to estimate the stage and risk. Treatment was based on classical TNM factors, as recommended by the NIH consensus conference (Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990, 264:1444–1450). Surgery would be followed by postoperative concurrent chemoradiation, which had been shown to improve survival.

The modern approach

MRI staging

The first major change in the approach currently taken to rectal cancer is MRI staging before surgery. The mesorectum – the

European School of Oncology
e-grandround

The European School of Oncology now presents fortnightly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues with leading European experts in the field, from controversial areas and the latest scientific developments to challenging clinical cases. One of these will be selected for publication in each issue of *Cancer World*.

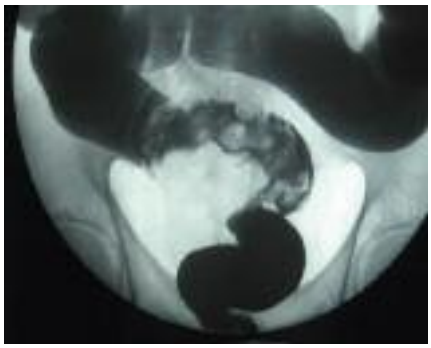
In this e-grandround, Andrés Cervantes, associate professor of medicine at the Hospital Clinico Universitario, Valencia, Spain, reviews a challenging case of locally advanced rectal cancer. His presentation was summarised by Sue Mayor.

The recorded version of this e-grandround, together with 25 minutes of discussion, is available at http://tiny.cc/rectalcancer

THE CASE

Presenting symptoms

A 55-year-old man presented with: constipation and rectal bleeding; false diarrhoea; increased urinary frequency; 20 kg weight loss in the last three months; performance status of 1.



Diagnostic tests

Physical examination detected no peripheral lymph nodes and no signs of ascitis or pleural effusion. A digital rectal exam detected a tumour at 10 cm from the anal edge with fixity of the surrounding tissues from 5 cm.

Rigid rectoscopy confirmed a fixed tumour at 10 cm from the anal verge completely obstructing the rectum.

Biopsy showed poorly differentiated invasive adenocarcinoma of the rectum.

Colonoscopy detected a tumour at 15 cm. The flexible colonoscope was not able to pass the rectal mass.

Endoscopic ultrasonography was not performed because it was not possible to go through the rectal mass.

Blood tests showed no anaemia or leucocytosis.

Biochemistry was within normal range, and there were no liver alterations.

Carcinoembryonic antigen was 2.9 ng/ml.

Chest and abdominal CT scans showed no evidence of metastatic disease.

Barium enema showed the tumour starting 10 cm from anal verge. It was extensive, going up the colon for a considerable length.

fascia surrounding the rectum – can be visualised clearly by MRI (see p17).

The MRI scans show this patient has a bulky rectal tumour above the levators and located at 10 cm from the anal verge. There are several lymph nodes with suspected neoplastic involvement above the tumour. There is invasion of the presacral space and of the mesorectal fascia (circumferential resection margin) at the lateral left side. There was also suspected involvement of the right ureter and an extramural invasion of more than 10 mm, but no vascular invasion.

Multidisciplinary team discussion

The next step after MRI staging is multidisciplinary team (MDT) discussion. One of the main tasks for the MDT is to select patients for preoperative therapy. This includes systemic staging, which would usually include CT of the thorax and abdomen. However, the patient did not have metastatic disease. Local staging was performed using rectoscopy, endorectal ultrasound and digital rectal examination.

After local staging, MRI has a key role in defining:

- the circumferential resection margin (CRM) involvement – if it is T3-4 or is arising at, or below, the level of origin of the levator muscles. This is more or less the lower third of rectum and should be considered high risk
- extramural spread of more than 5 mm
- extramural vein invasion
- peritoneal involvement. If this is in the upper third of rectum, patients are at risk of the CRM being involved, and we would recommend preoperative treatment.

There are essentially three different groups of patients in terms of preoperative treatment strategies (see table below).

For group A, the risk is very low. This includes patients with T1, T2 or even T3 tumours, but less than 5 mm in diameter and no affected lymph nodes, or very small ones. For this group, we predict the CRM will be negative, so the patient can go to surgery. In contrast, for patients in group C, we predict that the CRM is going to be involved, so preoperative chemoradiation is indicated. In the middle group, it is safer for patients to have preoperative chemoradiation.

The impact of MDTs on surgery outcomes

The importance of MRI data being discussed with the MDT is illustrated by data published by Royal Marsden Hospital in the UK (Burton et al. *Br J Cancer* 2006, 94:391–397). From a total of 298 patients with rectal cancer, 76% of the 259 patients considered to be potentially curative were discussed in a MDT. Of these, 81 (41%) were considered to require preoperative therapy. Of those going to surgery alone, 97% had negative margins indicating that decision making was generally correct.

SELECTION OF PATIENTS FOR PREOPERATIVE THERAPY

Treatment group	MRI features	Treatment strategy
A	T1-2, T3 <5 mm, N0-1, Predicted CRM–	TME surgery
B	T3>5 mm, T4 N2 Predicted CRM–	Pre-op chemoradiation
C	Predicted CRM+	Pre-op chemoradiation

However, in the 62 patients not discussed by an MDT, where decisions were reached on an individual basis, 100% were sent on to surgery alone. A very high proportion – 26% – were found to have histological involvement of the margin, posing a high risk of local and systemic relapse.

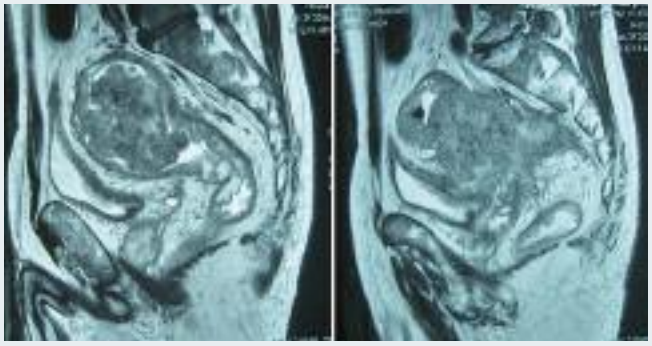
These data support a MDT discussion before taking decisions. Benefits include:

- improved coordination of care
- each case considered from the variety of perspectives provided by the MDT
- patients more likely to be offered a range of types of treatment at appropriate times
- a supportive environment where professionals can share their concerns
- feedback to the surgeons from histopathologists and other team members on the results of their work
- an optimal setting for clinical research.

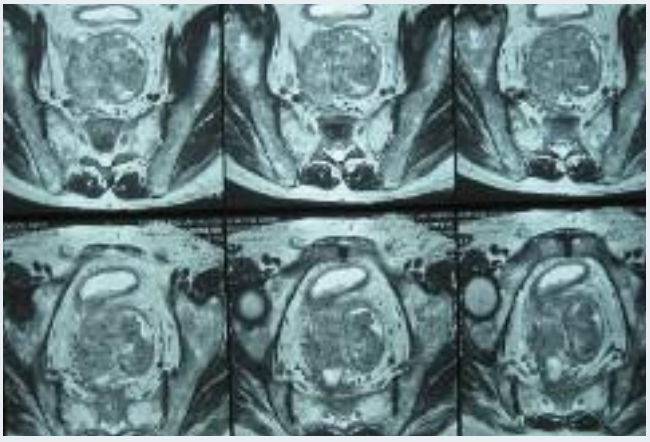
Preoperative chemoradiation

The MDT agreed that chemoradiation was indicated in the patient being considered in this e-grandround. The treatment plan was capecitabine (1,300 mg/m^2 per day from day 1 to the end of radiotherapy. Radiotherapy was 6 MeV photons at a dose of 45 Gy (180 cGy/day for

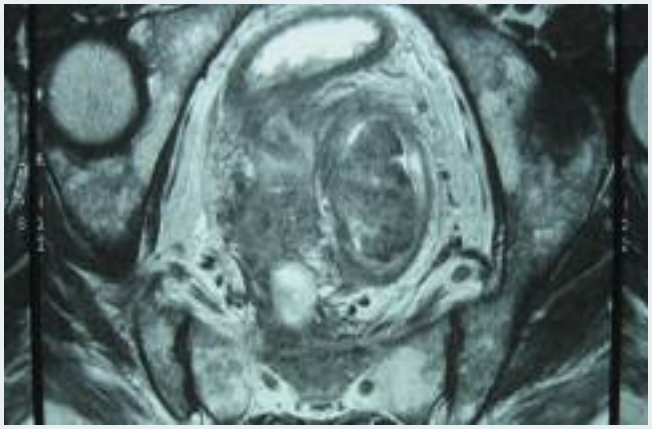
Magnetic resonance imaging



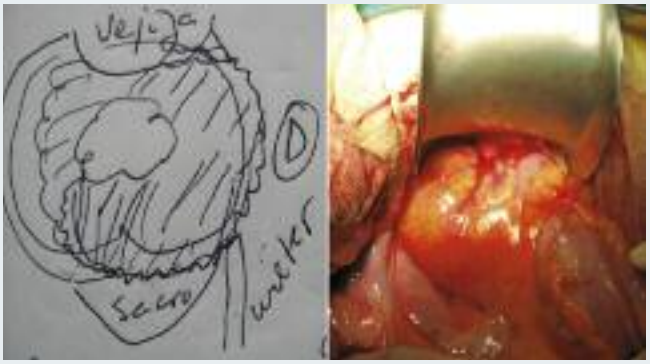
1. In this patient, MRI shows a very extensive tumour almost invading the sacrum, which is also pressing on the urinary bladder. This explains the urinary frequency that the patient was experiencing



2. The axial views depict the circumferential fascia as a straight line. The fact that the left part of this line is not well depicted indicates that the tumour is invading the pelvic wall



3. On the left side, the tumour can be seen completely invading the mesorectal fascia



4. The diagram drawn by the surgeon in the surgical report indicates that the tumour could not be resected because it was firmly adherent to structures in the pelvic wall

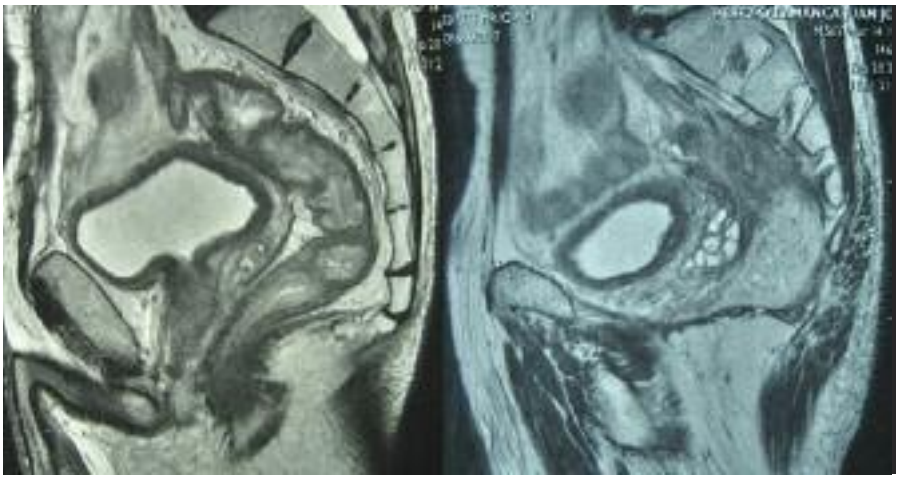
5 days/week), which took five weeks. Surgery was indicated 5–6 weeks after.

Side-effects included grade 1 diarrhoea and grade 1 cystitis with some urinary symptoms. There were no delays in dose due to toxicity, and radiotherapy was given as planned, over a five-week period.

TME surgical resection

MRI was performed before proceeding to total mesorectal excision (TME) surgical resection. This showed clear shrinkage of the tumour, with the bladder no longer being constricted by the tumour. However, despite this shrinkage, the tumour was still in contact with the presacral area towards the spine. The margin on the lateral right side was involved. We had to discuss the case very carefully with the surgeons, who, because of a lack of previous experience in operating on what had been considered a completely unresectable tumour, were reluctant to go ahead with surgery, but we considered that it was justified.

Surgery was performed six weeks after radiotherapy ended. A TME was performed with a sphincter-saving procedure (anterior resection); the levators were not involved. The patient also underwent a temporary ileostomy.



MRI assessment after chemoradiation. Shrinkage is clear, and the bladder is no longer pressed by the tumour. However, at the back, the tumour is still in contact with the presacral area

Pathology and risk assessment after surgery

The next step is a pathological assessment and estimation of risk. The classical pathology approach would be to assess bowel wall invasion, regional lymph node involvement and distant metastasis. The current pathological approach includes three further important assessments:

- the macroscopic integrity of the mesorectum
- the distance to CRM
- staging after preoperative chemoradiation.

The pathologist also audits the surgical skills applied, assessing the macroscopic of the excised mesorectum. Pathologists should define planes of surgery as follows:

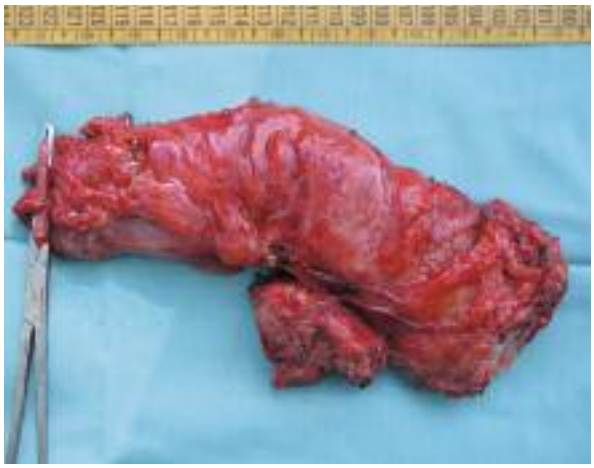
Mesorectal plane: intact mesorectum with only minor irregularities of a smooth mesorectal surface; no defect deeper than 5 mm; no coning; smooth CRM on slicing.

Intramesorectal plane: moderate bulk to mesorectum, but irregularity of the surface; moderate distal coning; muscularis propria not visible; moderate irregularity of the CRM.

Muscularis propria plane: little bulk to mesorectum with defects down onto muscularis propria and or very irregular CRM (Quirke et al, ASCO 2006).

Macroscopic assessment of the resected mesorectum showed an irregular area in the front section, in front of the sacrum, close to the presacral space. Ink staining showed that the mesorectal surface was smooth, with no mesorectum in the pelvic wall.

The pathology report showed that the rectosigmoidectomy specimen was 16 cm in length. The quality of the anterior mesorectum was complete, but the posterior mesorectum was partially complete.



Macroscopic assessment of the resected specimen

The tumour was located at 7 cm from one of the borders. The distal and circumferential margins were free, with the circumferential margin (macroscopically) at 7 mm from the tumour edge.

Microscopic assessment showed that there was extensive fibrosis. The tumour had completely regressed. There was some indication of postradiation angeitis. None of the 23 lymph nodes examined were involved (ypT0 ypN0) – this was a good number to analyse as it is not easy to obtain a large number in surgical resection after radiation. Overall, the specimen indicated pathologically complete remission.

Postoperative chemotherapy

The patient should receive postoperative chemotherapy if this is indicated. Randomised trials over the last 28 years have shown major achievements in control of local relapse. In the early 1980s, 25%–30% of patients had local relapse, but recent trials with TME plus chemotherapy show this rate has fallen to 5%.

In contrast, the proportion of patients presenting with distal metastases has shown almost no change from the early 1980s to today.

There is currently no consensus on the use of adjuvant chemotherapy in patients with resected rectal cancer, but its use is widespread. Recent data from the UK QUASAR study (*Lancet* 2007, 370:2020–2029) for patients with an uncertain indication showed significant improvement in five-year survival with chemotherapy (P=0.02). In the subgroup of patients with rectal cancers, the benefit was marginal but almost significant (P=0.06).

Follow up

The patient had an intraoperative colonoscopy, which showed the absence of metachronic tumour or polyps. He was not given postoperative chemotherapy because he had a presacral abscess and slow recovery after surgery. The ileostomy was reversed after six months. At two-year follow-up, his CEA was 1.9 ng/ml, which was within normal levels. Thoracic, abdominal and pelvic CT scans showed no evidence of metastatic disease and no local relapse.

Conclusions

In this patient, who presented with unresectable rectal cancer but no metastatic disease, multidisciplinary discussion was essential in optimising the treatment strategy, as for all rectal cancer cases. Successful multimodality treatment was given, with an R0 resection (complete resection with no microscopic residual tumour), and there was no relapse at two years. This case was the first I have had in which a patient underwent a colostomy in order to avoid obstruction during chemoradiation.

In conclusion, unresectable rectal cancer should be treated with concurrent chemoradiation using a multidisciplinary team approach.

Robert Glynne-Jones (RG-J), of the Mount Vernon Centre for Cancer Treatment, Northwood, UK, put questions to Andrés Cervantes (AC) about the case.

RG-J: *You must have been delighted that you started off with a bulky tumour and got such a fantastic response. Is there more risk of an anastomotic leak with advanced tumours?*

AC: Not with our surgical team. They always proceed to protective ileostomy and then close the ileostomy 4–6 months after treatment is complete to avoid leaks.

RG-J: *In terms of the regression grades, a complete pathological response is very clear. How reproducible are the other regression grades?*

AC: This requires some experience. We have gained experience discussing all our cases and we try to reproduce the recommendation of Philip Quirke in having at least 20 slides of the specimen revised. If the pathologist is not careful, the probability of regression may be higher.

I think that sometimes it may be complicated to have the five grades, as proposed by Dvorak. However, good regression grades are related to better outcome – this is the best validity of the grading system.

RG-J: *What about the standardisation of preoperative chemoradiation for all patients, even T1 and local excision? You would not usually give preoperative chemoradiation for all patients?*

AC: No. I do not like the approach of ignoring the patient in front of you and going straight to preoperative chemoradiation, because there are long-term toxicities, including sexual problems, urinary problems and problems with the sphincters after radiation. I prefer to select patients with MRI, because this reveals tumours that are involved or close to the margin, making it clear when we should give preoperative chemoradiation. ▶

Even if people do not feel that surgery is safe, I would consider preoperative chemoradiation, because with a mesorectal margin involved, it is difficult to put things back in the right way. I think people should think about it, but I would not consider preoperative therapy for all.

RG-J: *The original surgeon defunctioned the patient because of fear of obstruction. Right at beginning you could not introduce ultrasound because it was a very bulky tumour. Do you have a policy of when you defunction patients routinely?*

AC: In our series of 120 patients over the last seven years, we have defunctioned only two or three patients – those presenting with impending obstruction. It is important that the surgeon should not remove the tumour in these patients, which are locally advanced cases. Instead, a defunctioning colostomy should be performed. This takes one week – then you can start preoperative chemoradiation. However, this problem is very infrequent.

RG-J: *We saw the value of MRI in relation to the circumferential margin. What about lower down, below the levator? Does your MDT feel as confident in that?*

AC: In T3 and T4, we go directly to preoperative chemoradiation. However, the surgical team tries to confirm if the levators are involved with the tumour. If they are, and MRI is very clear on that, then a sphincter-preserving procedure may not be indicated.

RG-J: *You routinely operate 5–6 weeks after completion of chemoradiation. Do you restage patients with another CT to make sure they haven't developed disease outside the pelvis?*

AC: Yes, especially in trials, we always do. When we give preoperative chemoradiation this adds 5–6 weeks, making 12 weeks in all. This is not a long time. But we do MRI just before surgery. Sometimes, we recommend restaging the liver or lung.

RG-J. *What about giving chemotherapy after surgery? This is an area where it can be difficult to make decisions. In a patient with a pathological complete response, are you going to give more chemotherapy?*

AC: Treating patients with locally advanced disease, there is no level 1 evidence, but I consider that adjuvant postoperative therapy may be beneficial. It is difficult to differentiate patients with colon cancers from those with rectal cancers. We have achieved major improvements in colon cancer. But if the control of systemic disease in patients with rectal cancer is not good, the situation is more difficult. In our programme, we favour postoperative chemotherapy for these patients. But the patient presented in our case study had mild chemotherapy – just capecitabine and radiation, and no oxaliplatin. It would be useful to have randomised controlled trials showing the effect of adding oxaliplatin.

RG-J: *What happens when patients don't respond to chemoradiation?*

AC: Assessment has to be done in the pathology report. If the pathology report after surgery indicates a bulky tumour, positive lymph nodes and vascular invasion, these are very negative signs indicating a high risk of relapse. There are several options. If the patient has had chemotherapy with 5-FU or an oral fluoropyrimidine, I would go ahead with oxaliplatin plus 5-FU. If the patient has had an R0 resection but is resistant to chemotherapy, they are probably OK and we would follow them up and give chemotherapy when they relapse. I am not sure of the role of chemotherapy in patients who are resistant to chemoradiation.

RG-J: *In the UK, we give a short course of chemoradiation. Is there any role for short-course radiotherapy? We argue about this a lot, with concerns about morbidity for early tumours which MRI suggests are resectable.*

AC: The evidence is there, with three randomised controlled trials showing better local control. Before the use of MRI, I think it had a definite role. In patients who cannot tolerate chemoradiation, short-course radiation is a possibility. The problem is that it doesn't downsize tumours, so I am reluctant to give it for locally advanced tumours by MRI.

RG-J: *On another issue, how much do surgeons like having the quality of the mesorectum documented?*

AC: In our team, the surgical group is quite sensitive about this point. They have performed a lot of studies on this issue. Especially in the lower third, the results show they should check carefully. Reporting gives them feedback, improving the final result. It has been good to see the quality of surgery improving over the years. Now, we have 100% data on sphincters in pathology reports, which were almost absent five years ago. So we are sure the levators are in the specimen and analysed by the pathologist. These are points of quality. The way forward is for the surgical group to understand that feedback from pathology improves quality.

RG-J: *It's also a way of validating the MRI decision – you need the report on quality to validate this. If after surgery there is 20% involvement of the circumferential resection margin, you know that the decision was not well founded. Pathology helps us to move in the right direction.*

Stopping trials prematurely: sorting the right decisions from the wrong

Anna Wagstaff

Allegations that commercial pressures may be leading to cancer drug trials being halted prematurely hit the news on both sides of the Atlantic last April. Industry leaders are pleading 'not guilty'. But how can we judge when calling an early halt to a trial is the right thing to do?

Are commercial pressures prompting pharmaceutical companies to stop trials prematurely? A group from the Italian drug regulatory agency, AIFA, and the Mario Negri Institute in Milan, suggest that this may be the case in an article widely reported on both sides of the Atlantic. They draw attention to the sharp increase in the number of cancer trials stopped early on the basis of benefit shown in interim analyses, pointing out that the vast majority were registration trials, aimed at getting marketing approval for a new drug or a new indication.

Their article in the *Annals of Oncology* (2008, 19:1347–1353) surveyed all clinical trials of anti-cancer drugs published from January 1997 to October 2007 that were stopped early 'for benefit' (i.e. excluding those stopped due to lack of efficacy or unacceptable toxicity). There were 25 trials in this category.

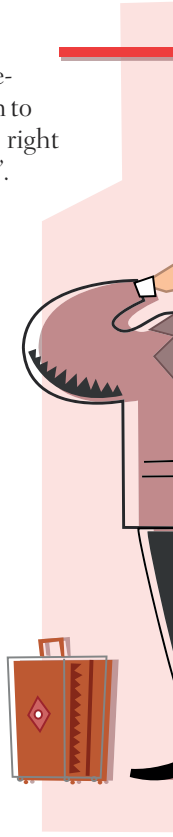
The survey, say the authors, highlights, "a consistent increase (>50%) in prematurely stopped trials in oncology during the last 3 years in comparison to the whole period analysed." They point out that, of those stopped prematurely in the last three years, more than 78% were used for registration purposes. "This suggests a commercial component in stopping trials prematurely."

Senior figures from the industry strongly deny the allegations and are unhappy about the tone of the media coverage prompted by the *Annals* article, which, they feel, fuelled a climate of suspicion and failed to spell out how companies insulate decisions on clinical trials from inappropriate influence.

Stopping a trial early is generally considered undesirable. It is likely to result in losing information of relevance in evaluating efficacy in the longer term, depriving physicians, patients and researchers of important knowledge. The chance to gather statistical data on disease recurrence and progress, drug resistance, metastasis or adverse events may be lost forever.

An early halt has also been shown to lead to a systematic exaggeration of benefit because, in any randomised trial, the smaller the number of outcomes or events, the greater the likelihood that the difference between the arms of the trial at a given moment will represent a 'random spike'. If the interim analysis shows low benefit, researchers have an incentive to continue the trial as planned to see whether the early results readjust upwards as more results come in. However, if the analysis coincides with a spike that exaggerates the benefit, the question of stopping early may be raised – hence the bias.

The more interim analyses done in a single trial, the greater the likelihood of hitting a random benefit spike, leaving trial sponsors open to accusations of looking for the right moment to 'quit while they're ahead'.



Why stop early?

There are of course very good reasons for stopping a trial that shows benefit early – particularly where lives are at stake and there are no therapeutic alternatives. An interim analysis may reveal evidence so strong that it would be unethical to continue to randomise patients to the control arm of the trial and to delay access to the new therapy among the wider patient population.

Stuart Pocock, professor of medical statistics at the London School of Hygiene and Tropical Medicine, has written extensively on this subject. "Good practice should be that you stop

"You risk inflicting an apparently superior but toxic treatment on lots and lots of future patients"

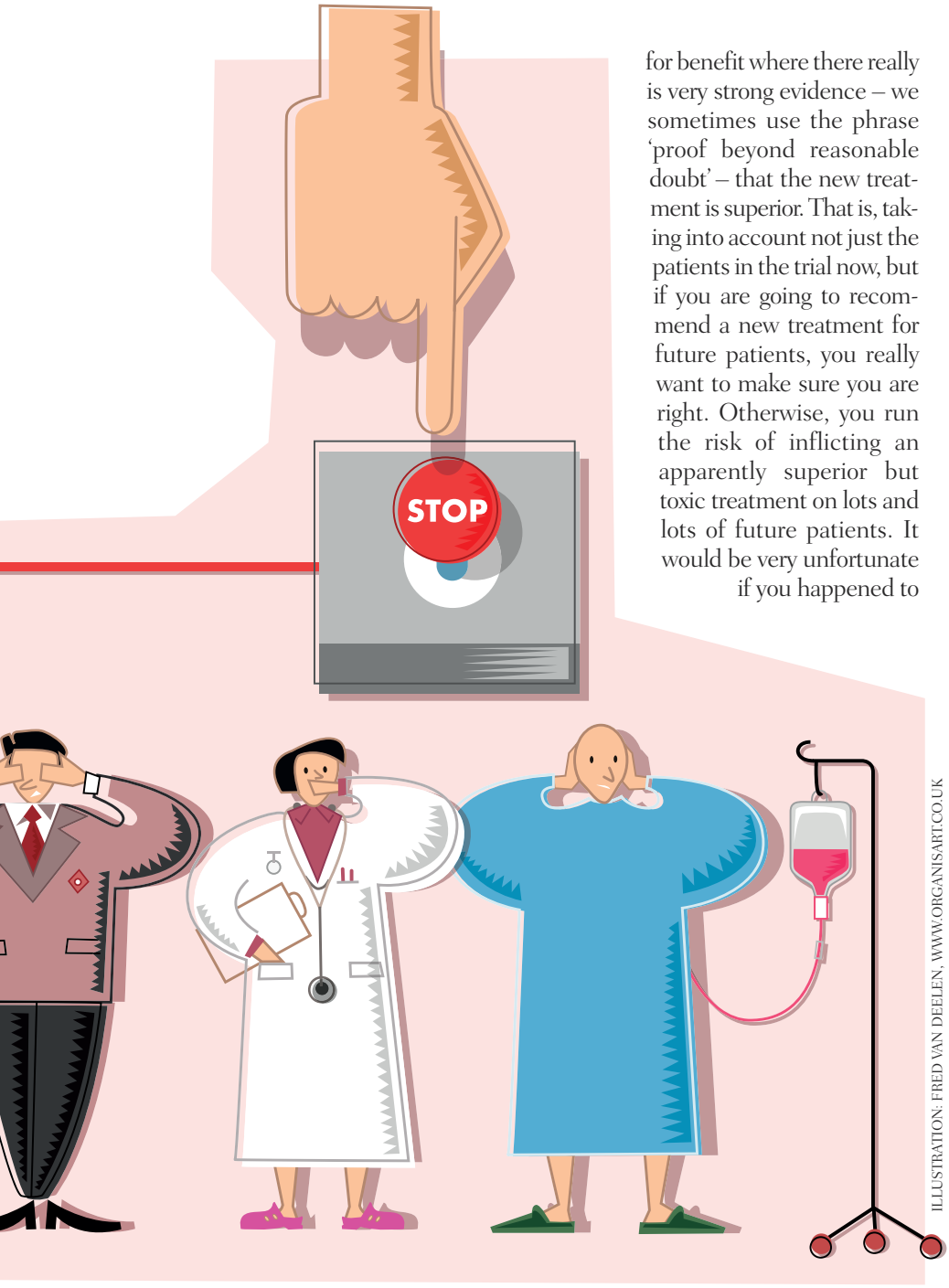


ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

for benefit where there really is very strong evidence – we sometimes use the phrase 'proof beyond reasonable doubt' – that the new treatment is superior. That is, taking into account not just the patients in the trial now, but if you are going to recommend a new treatment for future patients, you really want to make sure you are right. Otherwise, you run the risk of inflicting an apparently superior but toxic treatment on lots and lots of future patients. It would be very unfortunate if you happened to have stopped on lesser evidence, when in truth the treatment is not superior."

Establishing sensible statistical stopping boundaries before the trial starts adds objectivity to any subsequent decision to stop early, but the final judgement needs to be based on a wise interpretation of the total evidence available, says Pocock. For example, the leaders of the HERA trial into trastuzumab (Herceptin) as an adjuvant – one of the trials listed in the *Annals* article – justified sacrificing data on side-effects when they stopped the trial early by pointing to the strong data already available from widespread use of the drug in the metastatic setting.

Wise judgement is also needed in balancing the interests of future patients and the patients on the trial. Roger Wilson, a patient advocate who works with the UK national cancer research network (NCRN) expresses the dilemma. "I feel trapped between the two sides, because I really do want to see unequivocal evidence that patients will benefit. At the same time, as a patient, I want to benefit at the earliest possible opportunity should that present itself."

Wilson regrets the loss of potentially important information about development of resistance that resulted from a recent decision to halt prematurely the ACOSOG trial into imatinib (Glivec) as an adjuvant in GIST patients. He also believes that stopping early the sunitinib (Sutent) trial for GIST patients who don't respond to imatinib sacrificed important data on overall survival, making it very difficult for some patients to get the treatment reimbursed.

"In terms of treating patients now – 2006 when they did it – it was

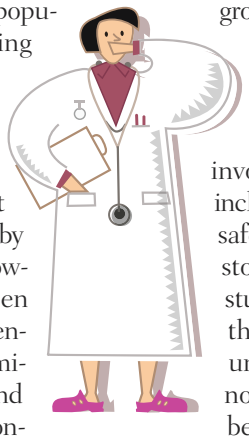
absolutely the right thing to do. But we are going to have to live with the consequences. All we've got at the moment is about a median of eight months progression-free survival on Sutent for patients who relapsed on imatinib. We haven't got any data to say that patients going onto Sutent live for an extra two to three years. It's just not possible to produce it."

"Patients do benefit in the short term, and that is something we mustn't ignore," says Wilson, adding that crossover trial designs can help resolve the conflict, although they too entail some loss of data. In the end, he says, researchers have to balance the potential short-term benefits to current patients of stopping a trial early, against the long-term disservice to future patients from the loss of data. "You have to operate some sort of balance mechanism, whereby you put the evidence into a pot and come up with a view."

For patients or profit?

Given the complexity of the issues in deciding to stop early, the seven-page overview of 25 trials in the *Annals* article is not sufficient to show whether the decision was justified on ethical grounds in each case. The authors nonetheless point to a number of factors they say might indicate that commercial concerns played a role – possibly to save the costs of continuing the trial or to steal a march on companies with rival products in the pipeline.

- More than 78% of all trials stopped early for benefit in the last three years were used to support an application for marketing authorisation at the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA).
- The average time to publication was around two years, suggesting that disseminating information for the benefit of a wider patient population was not the driving force.
- In all, only around 3,300 patients/events out of a planned 8,000 were studied. The authors accept that this could be accounted for by ethical considerations, "However, the relation between sparing patients [from potentially unnecessary randomisation] and saving time and trial costs is also unquestionable, and indicates that there is also a market-driven intent."



Alan Barge, head of Clinical Oncology at AstraZeneca, strongly denies that commercial pressures play any role in his company's decisions about how to take a trial forward, and he says it is also highly unlikely that this happens in other major pharmaceutical firms. "There is not a shred of evidence to show this is the case."

Like most pharmaceutical companies, AstraZeneca uses independent data monitoring committees (DMCs – also known as data safety monitoring committees) to ensure that decisions on stopping early are independent of inappropriate influence – whether from commercial pressures, from enthusiastic principal investigators or from anxious patients. DMC members are appointed according to strict criteria. "They must be completely independent of the study, and independent of any pecuniary interests of AstraZeneca. Second, the DMC must be an independently scientifically credible group of people. Third, they must be accepted by the principal investigators as an appropriately qualified group to monitor the study. We then make everyone involved aware of the names, including the regulatory agencies."

The DMC then becomes involved in the study design, including defining the efficacy and safety criteria and the statistical stopping boundaries. Once the study has started, no-one outside the DMC has access to unblinded data (without which no comparisons can be made between treatment arms).

Barge says that this insulates the trial from commercial pressure. "Knowing as I do the degree to which DMCs jealously guard their independence, and also the view that regulatory agencies take of clinical trials stopping early, I cannot envisage a situation where my commercial colleagues would try to put me or, more importantly, the independent physicians conducting the study and the DMC under pressure to stop a trial early, or in any way influence their view about the medical rationale or ethics for continuing."

Barge argues that the pharmaceutical industry is second only to the nuclear industry in its level of regulation. "If a company were to decide to stop a trial based on commercial considerations or otherwise conduct a trial in a way that would not be considered appropriate, those actions are discoverable when the dossier is filed with the regulatory agency. Any company that were to do that runs the risk of being found out, which would fundamentally damage their credibility."

"The authors point to a number of factors they say might indicate that commercial concerns played a role"

"People need to understand that there are significant safeguards built into the design of these trials"

Academic trials, he adds, are subject to far less scrutiny.

Diane Young, head of global medical affairs at Novartis Oncology, says she and her colleagues were disappointed by the press coverage, given the weaknesses of the *Annals* article. "In order to do the type of analysis they are trying to do, they would have to look at all the protocols for each study, and understand the statistical model, and why an interim analysis was built in… You can't just look at it on a surface level and say they did or did not do the right thing."

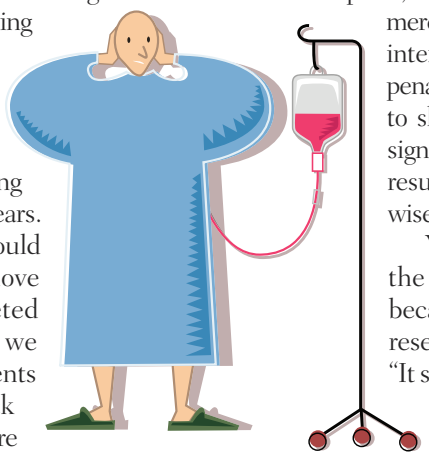
She accepts that pharmaceutical companies could improve the way they report decision-making processes when they publish trial results. "Maybe there is an educational opportunity here, that people need to understand that there are significant safeguards built into the design of these trials. We do it in collaboration with a lot of independent people as well as the regulators."

One of the 25 trials listed in the *Annals* article was the letrozole (Femara) trial, stopped after one-third of the planned events. Young points out that, although this was a registration trial for a Novartis therapy, it was initiated, designed and conducted entirely by an independent trials group, led by the Clinical Trials Group of the National Cancer Institute of Canada and including the North American Breast Intergroup and the Breast International Group.

The trial was studying the therapy in an adjuvant setting in a population of women who had already received five years of tamoxifen, so that 'events' regarding the primary outcome measure of disease-free survival, took a long time to accrue. Carrying that trial to its planned conclusion, Young argues, would have delayed access to a beneficial treatment for years. She also denies that the decision to stop early saved money; the women are still being followed up, even though the trial has stopped.

The ACOSOG trial, she adds, was also entirely in the hands of a cooperative group of investigators, who have their own procedures. "We got the phone call the day before they were going to announce they were going to stop the study".

Both Barge and Young believe that the increasing number of trials being stopped early may simply reflect the surge in the number of cancer trials being carried out in recent years. They also suggest it could be linked to the move towards novel targeted therapies. "Because we are using targeted agents we are often able to pick populations where there aren't other therapies available. In these populations, if you have solid data at the interim analysis that the drug is beneficial to patients, because you have patients on the trial and out in the world too who don't have any alternative, it is important to make that information available," says Young.



Interim analyses also have a much more important role to play in developing drugs aimed at specific targets, says Barge. "In the past you might have been taking forward a cytotoxic drug that was slightly different to a previous version of the same drug, where you already had phase II data showing that it shrank tumours. The same is true of hormonal agents developed in the '70s and '80s. Proof of concept was already established. There was no need to look for early evidence of efficacy in a large trial. The issue was all about safety."

By contrast, when developing a drug based on a new concept, and trying to find the appropriate dose and patient population, the rationale for interim analyses is much greater. However, it is not an easy option, says Barge, because the mere fact of conducting an interim analysis incurs a penalty – you have in effect to show a higher level of significance in your final results than would otherwise have been the case.

Young takes issue with the assumption that because a trial ends early, research comes to a halt. "It simply isn't possible to answer every question and do it well in one study. But it's important to have a programme of research that answers the questions."

Barge agrees. He has spent years trying to figure out why dramatic phase II responses to AstraZeneca's non-small-cell lung cancer (NSCLC) drug gefitinib (Iressa) were not replicated in the phase III trial. "It's a rather simplistic view to say you will never know those things if you stop clinical trials early. You set out on a series of clinical trials to answer different questions."

He points out that clinical trials are

"With targeted agents we are often able to pick populations where no other therapies are available"

designed to much more robust standards than used to be the case. "The initial approval for taxotere in NSCLC was based on only around 100 patients. In one of our drugs recently, we have done a direct head to head comparison with taxotere, and we studied 1,400 patients, just to demonstrate that our drug, which is a well-tolerated oral drug, is as good as taxotere."

An important issue

Pocock, who has been following the issue for many years, says: "Practice is better than it was in terms of sensible choices as to when to stop trials, but there is still a problem and we need to improve. Certain trials do stop too soon – it's a question of educating investigators and sponsors."

Pocock feels that the *Annals* survey "went slightly beyond what we can conclude" in singling out commercial interests. "I think it's probably a mix of industry motivation of getting to profit fast, over-enthusiasm of investigators and over-enthusiasm of DMCs to stop trials too quickly."

He suggests that pseudo-ethical arguments can often lead to decisions to call a premature halt. "Many will stop because they think it is ethical to stop, but their judgement may not be the wisest one on that paticular issue. If you have some evidence, and you are passionate about your treatment anyway, whether as an investigator or as a sponsor, you may feel, 'Ooh it's heading in that direction, I always knew it would, therefore I should stop early.'

"One can speculate, but it is dangerous ground to think you can tell what the specific motives are in a particular circumstance."

However, the underlying concern raised by the *Annals* article – that a trend towards stopping trials early is resulting in unclear and poorly defined risk/benefits – stands regardless of the motivation. It is a concern that urgently needs to be addressed, as physicians struggle to use appropriately a stream of new therapies about which too little is known.

Francesco Trotta, lead author of the *Annals* article, says he and his co-authors would like to see action on three fronts. They want DMCs used in all clinical trials (there were no DMCs in almost a quarter of the trials in the *Annals* survey) and greater transparency over who sits on them. Names should be made publicly available either in the clinical trial registers (when the trial is ongoing) or in the published articles (when the trial terminates).

They want trial patients to be made fully aware when they sign consent forms that the primary purpose of research is to reach robust conclusions. "Before the trial starts, investigators should inform patients that interim results should be considered as partial, and that only completing the trial allows the achievement of the study objectives." Wilson, with his experience as a patient advocate, points out that consent forms usually do make this point. "The trouble is that people who have never been exposed to the clinical trials environment don't ever actually get that message."

Above all, they want to explore ways of improving the methodology governing the early truncation of trials to ensure that trials only stop early when this is demonstrably appropriate, and that they are followed up with confirmatory trials wherever possible.

This is one of the big challenges of current drug development. Finding solutions will require constructive dialogue involving not just academic researchers and statisticians, but the regulators, patient advocates… and the industry – commercial interests and all.

TRIALS STOPPED EARLY

The *Annals* article listed 25 trials into anti-cancer therapies that were halted early between 1997 and 2007. Among them were registration trials for:

- sunitinib (Sutent) in (i) metastatic renal cell carcinoma, and (ii) advanced gastrointestinal stromal tumour (GIST)
- sorafenib (Nexavar) in advanced clear-cell renal cell carcinoma
- bevacizumab (Avastin) in (i) a combination regimen for non-small-cell lung cancer; (ii) various combinations for metastatic colorectal cancer; and (iii) metastatic renal cell cancer
- lapatinib (Tykerb) + capecitabine for HER2+ metastatic breast cancer
- trastuzumab (Herceptin) for early HER2+ breast cancer
- letrozole (Femara) for receptor-positive early breast cancer
- irinotecan (Camptosar) + cisplatin for metastatic small-cell lung cancer

Balancing cure and care

One surgeon's multidisciplinary quest to raise standards across the board

➜ Janet Fricker

Cornelis van de Velde went into cancer because he loved the complexity. Throughout his career he has grasped each new development across the disciplines to see how it could help resolve the difficult balance between curing a patient and preserving their quality of life. Spreading excellence in surgery, he says, is the single most important thing Europe can do to improve outcomes.

When Cornelis van de Velde's youthful ambition of becoming a fighter pilot was thwarted by a Dutch air force's freeze on recruitment, he was forced to turn to his second career choice – medicine. From the outset there was no question he would do anything other than surgery – it required the same macho 'action hero' outlook on life, love of gadgets and gizmos, and hand–eye coordination skills as flying.

Throughout his career as a surgical oncologist, flying has been a recurring theme, helping him transfer the disciplines of quality assurance to the operating theatre. "If your Captain tells you that your flight to Heathrow had a 10% chance of crashing into the North Sea, you don't accept that level of risk. Yet in cancer surgery, every day patients accept much higher levels of risk without question," says van de Velde, who has dedicated his career to minimising those risks and raising standards of care particularly in breast, gastric and colorectal cancer.

"By conducting well-controlled clinical trials in surgery we have been able to make simple improvements that dramatically change outcomes and make a real difference to patients' quality of life," he says. It has often been an uphill battle, however, as surgeons – surgical oncologists in particular – have been slow to accept the feasibility of conducting clinical trials in their specialty. "There was a real feeling that you could not compare different surgical procedures, since surgery was more of an art than a science, and impossible to control… But we have found that by introducing a rigid system of checklists it is possible to control for the individual skills of different surgeons and introduce proper clinical trials," he says, adding that widespread introduction of good evidence-based surgical techniques has greater potential to improve cancer care across Europe than any new pharmaceutical agent.

Van de Velde appreciates the historical irony that it was a French surgeon barber, Ambroise Paré (1510–1590), who performed the first clinical trials in medicine. Cauterising the wounds of amputees at the siege of Villaine, in 1537, Paré 'randomised' patients between tar and an ointment combined with ligatures – the latter proving to be better for both survival rate and comfort. It's an example van de Velde, who was appointed professor of surgery at Leiden (Netherlands) in 1987, and has headed the

KATHALIJN VAN DE VELDE

Department of Surgical Oncology at Leiden University Medical Center since 1999, is proud to follow. Indeed it was van de Velde who developed the protocol for the first clinical trial ever in the Netherlands for breast cancer, as part of his PhD.

Cornelis van de Velde was born in 1951 in Zevenbergen, a rural community in the south of the Netherlands. The family settled in the area at the end of the Second World War, when his father, Jo, moved to a dental practice. The quiet environment particularly suited his mother, Lien, who had been badly injured in the allied bombing, and lost most of her immediate family. "My mother was the sole survivor when her family home was bombed – her parents and brother, after whom I was named, died just metres from her. The experience was something she never spoke of."

As a teenager, van de Velde describes himself as a real 'dare-devil', not in the least interested in anything academic. "I started flying at 14, and did my first solo flight at 16, and remember literally screaming with delight. Flying gave me such a wonderful sense of freedom and power, and also opportunities for travel. One summer I did a student exchange with the Israeli air force," he remembers. There was, however, a more artistic side – in his spare time the young Cornelis also enjoyed playing the piano and painting landscapes in the style of the impressionists.

In 1968 he started his medical studies at the University of Leiden, not far from Amsterdam. As a

student he enjoyed rowing, and backpacking around Europe and North and South America, and he met his wife Kathalijn, who was studying law.

A job administering anaesthetics, in his fourth year of studies, exposed him to many different types of surgery, and he picked up on the challenge of cancer. "The complexity of oncology really appealed to me, particularly the balance you need to strike between doing extensive surgery to enhance cure and limiting procedures to offer patients the best quality of life. The different facets of cancer surgery offered access to so many different areas of medicine," he says.

The year he turned 25, Van de Velde married, started his residency and gained his PhD. His thesis in breast cancer, looking at the role of lymph nodes, the extent of their removal and the value of adjuvant chemotherapy, set the tone for a career in which investigating the concept of preoperative chemotherapy, hormone therapy and radiotherapy has been a dominant theme.

Action hero. Van de Velde, seen here on a student exchange with the Israeli air force (front row, second from left), is so busy nowadays that he cannot clock up sufficient hours to maintain either his flying licence or his right to perform certain tricky surgical procedures

The future is neoadjuvant

Last May, he published the 10-year survival results of the EORTC study of preoperative chemotherapy in primary operable breast cancer. The study demonstrated no survival differences (for either overall or disease-free survival) between breast cancer patients who received chemotherapy preoperatively and those receiving it postoperatively. The use of preoperative chemotherapy, however, was accompanied by an increase in the rate of breast conserving surgery.

Chemotherapy and hormone therapy prior to surgery makes 'intuitive sense', he says, as it permits less extensive surgery and helps to prevent tumour spread. "Tumour manipulation can lead to a shower of tumour cells, and animal studies have also shown that, following surgery, metastatic cells divide faster and have a higher labelling index."

The general theme is one he has taken beyond breast cancer into gastric and rectal cancer. He hasn't always found it easy to convince his fellow surgeons, however. At times, says van de Velde, he has felt like a 'failed comedian' when he has done the lecture circuits trying unsuccessfully to persuade other clinicians to change their practice. "Breast and gastric cancer surgeons still find it really difficult to delay surgery," he says.

In gastric cancer he was a co-investigator of the MAGIC trial (Medical research council Adjuvant Gastric Infusional Chemotherapy), published in 2006, which showed that chemotherapy prior to surgery improved the resectability of stomach

"Striking that balance between enhancing the cure and preserving quality of life really appealed to me"

The five-year survival for stage III disease was 13% in the West compared to 44% in Japan

tumours by 10% and improved five-year survival by 13%, making it the new standard of care.

In rectal cancer he showed that, although total mesorectal excision (TME) combined with preoperative radiotherapy resulted in increased local control, there was more long-term bowel dysfunction in irradiated patients. "But I'm increasingly hopeful that the advent of more tailored therapy will soon allow us to select the patients who'll benefit most from treatment," he says.

Most recently he has been advocating preoperative chemotherapy and hormone therapy in breast cancer prior to sentinel node biopsy, since it leads to significantly less lymph node dissection and morbidity for patients.

In 1980 van de Velde and his wife spent six months in the US, where he worked at the MD Anderson (Houston, Texas), and the National Cancer Centre (Bethesda, Maryland). This proved a particularly creative period, most notably pursuing his idea for developing the technique of isolated liver perfusion for patients with metastatic colorectal cancer. He got the idea from hearing about isolated limb perfusion in malignant melanoma.

Isolated liver perfusion is a procedure in which a catheter is placed into the artery providing blood to the liver, and a second is placed in the vein taking blood away from the liver, thereby temporarily separating the liver's blood supply from the blood circulating throughout the rest of the body. The technique allows four times the maximum tolerated dose of chemotherapy to be directed to the liver. Van de Velde also developed a safety valve, giving labelled erythrocytes with the treatment to spot any leaks. If a problem developed, the chemotherapy could immediately be flushed from the body.

First he performed the procedure on pigs, often sleeping in the lab with his animals, until finally moving on to trials in patients. Results showed that survival could be increased from seven months before isolated perfusion to 24 months for patients exposed to prior chemotherapy and 34 months for chemotherapy naïve patients. But there was disappointment that the technique did not have more potential for cure, as can sometimes be achieved in surgery for liver metastases.

"The logistics of the procedure were extremely complex, since in addition to surgical teams we needed separate teams to monitor for leakage," says van de Velde, adding that with improved chemotherapy now allowing survival with metastases to 20 months, it is likely that the hey day of isolated liver perfusion has passed.

A TRIAL OF TECHNIQUES

In the mid-1980s, van de Velde became aware that Japanese surgeons were producing dramatically better outcomes in gastric cancer surgery than surgeons in the West. After surgery, the five-year survival for stage II disease was 29% in the West, compared to 72% in Japan, and the five-year survival for stage III disease was 13% in the West compared to 44% in Japan. The difference, he found, was that Japanese surgeons undertook more extensive removal of lymph nodes and used wider surgical margins than the standard of care employed in the West. "It seemed

Who says clinical trials don't work in surgery? Van de Velde, age 25, with his PhD thesis, which included the protocol for the first breast cancer trial ever conducted in the Netherlands

obvious that we needed to teach our surgeons to operate like the Japanese, but we needed to show that survival differences were due to technique and not some fundamental racial difference in disease," he says.

In 1985 van de Velde visited the National Cancer Centre in Tokyo, working with Keiichi Maruyama, and the Seoul National University Hospital, South Korea, working with Jin Pok Kim, to learn for himself the Japanese way of performing the technique. With a better understanding of the procedure, he initiated a project to bring Japanese surgeons to the Netherlands, to teach Dutch surgeons how to perform the operation. In a randomised controlled trial – where the surgeons were randomised to the different hospitals – they were able to compare outcomes for the Japanese and Dutch approaches to performing the surgery in the same racial population.

But to undertake the trial they first needed to standardise the Dutch approach to surgery. "Studies showed that patients died from recurrent disease when the tumour margins were not big enough, but that more extensive surgery increased the likelihood of their dying from complications," says van de Velde, who over the past 20 years has organised many additional trials to define the optimum extent of surgery.

One notable feature of the Japanese–Dutch randomised trial was that the investigators banked the tissue – a very uncommon practice in those days. This means they are now able to look for candidate markers for selecting patients most likely to benefit from more aggressive surgery.

Despite his wealth of experience, new ideas still have the potential to excite van de Velde. One of his PhD students has just discovered that damage to the levator ani nerve – responsible for motor innervation to the levator ani muscle – explains why faecal incontinence often occurs following surgery for rectal cancer. The nerve was isolated when the researcher correlated common areas of damage in patients who developed incontinence after surgery, and mapped these directly to intact nerves in dissections of cadavers who had died from other causes. "It's so inspiring that in an old discipline like anatomy we can still be making discoveries in 2008 that have the potential to make a real difference to patients' quality of life," he says.

Van de Velde is also involved with an innovative project using a special camera system that can identify light emitted by injected dyes capable of specifically targeting tumour cells. "This project has two potential applications: it allows the visualisation of tumour margins, thereby promoting more accurate surgery, and it also allows clinicians to see whether sentinel nodes have been invaded by cancer cells without having to open patients up," he says.

A strategic surgeon

Today van de Velde leads a packed life, sitting on numerous national advisory and clinical boards, teaching, lecturing, and pursuing his research activities. He still operates one day a week and sees outpatients on another day, although he no longer takes the lead on more complex surgery. One of the ironies of his quest for improving surgical standards is that he cannot himself always undertake enough annual procedures for quality control purposes. But he is happy to take more of a back seat in surgery, aware that through his international committee work and coordination of trials he can make a more strategic contribution.

He also exerts an influence in supervising PhD students – to date he has supervised more than 50 theses, ranging from surgery to immunology. "My students are the potential surgery leaders of the future, and educating them well is one of the best ways of improving standards," he says, adding that he is achieving an even wider sphere of influence on the next generation through editing the Dutch standard textbook on oncology *Leerboek Oncologie*.

On the national scene, he has been president of the medical section of the Royal Academy of Sciences of the Netherlands, where he chairs a group of 23 medical leaders from the Netherlands who come together to prioritise medical developments and inform the Minister of Health. He has also been

They can now look for markers for selecting patients most likely to benefit from more aggressive surgery

"Colorectal cancer survival differs by 10% according to the country in which people are operated"

largely responsible for initiating national groups for breast, gastric and colorectal cancer, that help to translate the results from clinical trials into national standards of care, and has played a key role in the recent creation of the virtual Centre for Molecular Medicine – a joint initiative between academia and industry that allows the sharing of resources such as tumour banks.

In Europe, he is set to become president of the European Society of Surgical Oncology (ESSO) in September, and is in the process of setting up a quality assurance programme for Europe. The scheme, starting first with colorectal cancer, aims to ensure that all patients get access to the best treatments. "In the past protocols have just stated 'surgery', without appreciating that surgery is not all the same. For colorectal cancer, for example, there is a 10% difference in survival according to the country in which people are operated," he says.

At the European CanCer Organisation (ECCO), where he is a board member, he has been promoting interactive workshops, involving international experts. "Oncologists attending these workshops can be really inspired to introduce significant improvements in their day-to-day care of patients," he says.

Life is undoubtedly hectic. "I don't have any time for a golf handicap, but I keep fit by walking my Labrador and cycling to work," says van de Velde, who unwinds at weekends by tinkering with his old Ferrari. Solo flying is no longer feasible, he says with regret, as in recent years he has not had time to put in the required number of flying hours to guarantee his safety.

Holiday time is particularly precious, though far from relaxing. Van de Velde uses his annual leave to indulge his love of travel and try experiences that are as removed from his daily existence as possible. Last year he was ship's doctor on a Russian cruise ship to the North Pole, and next January he plans to repeat the experience on a trip to Antarctica. Other recent trips have included skiing in Canada with his wife and their two adult sons, Jan Willem, aged 27, who works with an oil company and Michiel, aged 26, a lawyer, and they have just returned from a trip to Botswana, where they hired a four-wheel drive to view elephants. His flying days may be over, but van de Velde remains above all an action man, both in his professional and personal life.

Family time. With holidays like this one, watching elephants in Botswana, it's little wonder that sons Jan Willem and Michiel opt to come along (the holiday he spent as ship's doctor on a Russian cruise to the North Pole, however, was just him and wife Kathalijn)

The neglected magic bullet

UK health reporter asks: why the obsession with new cancer drugs?

Surgery still offers by far the best hope of a cure in solid tumours. Yet patients are being let down by too great a focus on drugs at the expense of investment in surgical equipment and training, argues **Simon Crompton**, in an article for the *The Times* that won him a Best Cancer Reporter Award, and is reprinted below.

Simon Crompton

The operating theatre is dimly lit and completely silent apart from the gentle beep of the heart monitor. The patient lies strangely angled with his feet in the air, his head near the ground. Around him are seven nursing and medical staff and three raised video screens, revealing the intimacies of his organs. And above him looms a large spider-like object wrapped in transparent plastic, its arms passing into small holes in his abdomen.

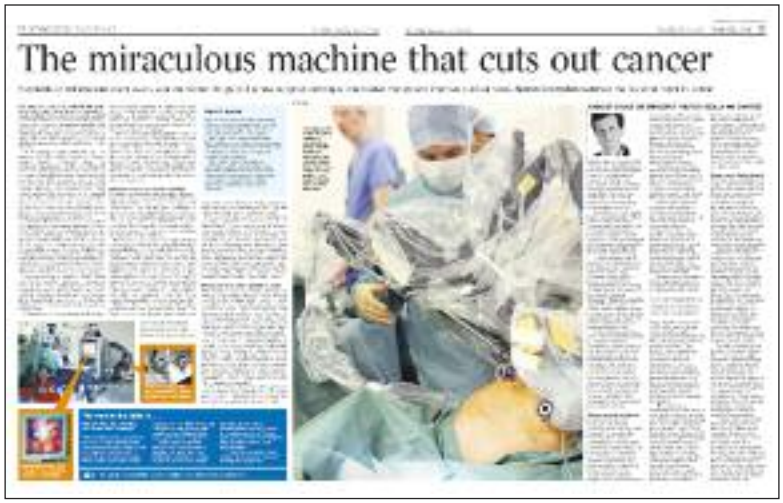
I'm witnessing surgery conducted by the amazing Da Vinci robotic surgeon at Addenbrookes Hospital, Cambridge. Despite its forbidding appearance, it is the most advanced piece of surgical equipment in the UK, offering the man on the table a chance of recovery from prostate cancer that he would never have had five years ago. He is having his prostate gland removed because of a cancerous growth. But there is no need for the patient to be 'opened up'. The three abdominal holes accommodate Da Vinci's camera arm and two operating arms. To the side of them, two more abdominal holes allow nurses to drain fluids, feed in clips to stem bleeding and push organs out of the way.

Controlling the robot at a console four metres from the patient is the cancer surgeon Professor David Neal, his head pressed against stereoscopic eyepieces conveying 3-D pictures of the abdomen's contents from the central camera leg of Da Vinci: the robot's eyes are his eyes throughout the surgery. Professor Neal tells me it's like having your head inside the patient. His hands are swivelling, tweaking and pinching joystick-style controls, controlling the tiny robotic hands at the end of Da Vinci's two other arms. He looks more like a seamstress than a surgeon.

Every movement he makes is scaled down into the far smaller, shakeless, movements made by the 7-mm, multijointed pincers, deep inside the patient's abdomen. You can see everything in high magnification on those screens above, though to the untrained eye it's hard to tell bladder from bowel, a bit of fatty tissue from a major vein.

Professor Neal, a Cancer Research UK professor of surgical oncology, is working his way down from the middle of the abdomen, past the bladder, to its deepest recesses in the pelvis, where the prostate is located. Gravity has pushed the upside-down patient's

THE TIMES


The miraculous machine that cuts out cancer

Discussion point: Articles like this one help promote public debate and political accountability around the best use of limited health resources. Video footage of the operation gave readers the chance to see the operation for themselves http://www.timesonline.co.uk/tol/life_and_style/health/article3728811.ece

bowels out of the way, up under the ribcage.

There's the occasional magnified whoosh of red as Professor Neal nicks a blood vessel and, more surprisingly, little puffs of smoke. The little robotic hands have super-heated edges, which mean they burn through tissue (rather than actually cutting it) and cauterise veins as they go. It's quite overwhelming on the senses. The burning tissue looks like pork crackling and there's a whiff of burnt meat. My vision starts to bleach and my head begins to whirl. I have to sit down for a minute.

Eventually, an hour into the operation, the prostate is revealed, a crimson globe sitting behind a deflated bladder. Now comes the tricky bit. Traditionally, one of the great problems of removing a prostate gland affected by cancer is that the nerves controlling urination and penile erection are tightly and intricately wrapped around it. Removing the prostate the conventional way means cutting nerves, often resulting in impotence or incontinence.

But so dextrous are Da Vinci's cutting hands, and so clearly visible is the noodle-like mesh of nerves attaching to the prostate, that it can be detached intact before the prostate is removed. "Outcomes aren't great when you remove the prostate using conventional open surgery," says Professor Neal. "After four years, half of men will have lost erections, or continence, or their cancer will have returned. But with this type of surgery, 90% of patients are completely dry. The finer dissection that robotic surgery allows means that patients are more comfortable after the operation, there are fewer complications and they get better more quickly."

Professor Neal has conducted 230 radical prostatectomies at Addenbrookes using Da Vinci since it was bought three years ago. Remarkably, half of Professor Neal's prostate operation patients go home the next day. "My star patient was back on his tractor in a week."

This is one of only six Da Vinci machines in the NHS [UK National Health Service], compared with 350 operating in the United States. If such surgery were to become more widely available, the

THE MAN ON THE OPERATING TABLE WAS...

...Michael Mills, 65, a building contractor from Cambridge.

"The prostate cancer was picked up after a routine health check. The specialists said I might be OK for 15 years and there didn't seem to be any spread outside the prostate, but I didn't want it hanging over me. When I was told that recovery was quicker with robotic surgery, I thought that was a good reason to go for it.

"I went in to hospital on Monday, had the operation on Tuesday, and went home on Wednesday lunchtime. I've had no pain at all and not a single painkiller. It was a little uncomfortable where the holes in my abdomen were. The only problem I've had is controlling my urine, but that seems to be getting better.

"I was back to work in three weeks. To be honest, I feel as if nothing has happened."

implications for men with prostate cancer could be profound. On diagnosis, only 20% of men opt for prostate removal. Because many tumours are slow growing, specialists often recommend watching and waiting, and not risking the permanent sexual and urinary problems that surgery can bring. But this causes uneasiness in many men, who simply want to be rid of the cancer. Da Vinci changes the odds, and makes prostate removal a more feasible 'play it safe' option.

Now Professor Neal is pushing, dabbing and stroking the prostate as he cuts it away, detaching it from the urethra (which passes through it), pushing it away from the big veins coming up from the penis. Finally, it's released. "Just pop it up under the ribs for now," he tells the nurses, and using keyhole probes, they manipulate it into a plastic bag, and push it up out of sight of the camera. (After the operation, they will pull it out, through one of the keyholes.)

Meanwhile, Professor Neal has more intricate work to do. He has to remove lymph tissue in case there are any cancer cells there and, finally, stitch the bladder back to the urethra. It's incredibly fiddly work, but the tiny robotic hands, holding a needle and winding thread into loops and knots, work fast. Robotic surgery minimises blood loss and transfusions are rarely required. The patient lying in front of me has lost less than 100ml of fluids – just a small wine glass full – during the operation.

After an intense two hours, the operation over, Professor Neal takes me for a cup of tea and a biscuit – his lunch before the next Da Vinci operation begins in just over an hour.

Cancer drugs or surgery? There really is no contest

Why are we so obsessed with new cancer drugs? Surgery is the real and unacknowledged hero in the battle against cancer, according to an increasing number of experts, including the [UK] Health Minister Lord Darzi. They point out that only 10% of cancers are cured by drugs, while surgery cures half.

Currently, the £700 million [€885 million] spent annually by the National Health Service on cancer drugs dwarfs the amount spent on surgery. Yet innovative techniques such as robotic surgery not only improve survival and quality of life for people with cancer but give more bang to the NHS buck than expensive drugs.

"Local therapies such as surgery and radiotherapy cure ten times as many people as chemical means," says Professor Gordon McVie, a senior consultant at the European Institute of Oncology in Milan and former director of the Cancer Research Campaign. "Medical oncologists get all the money spent on them, but the surgeons are the unsung heroes. Surgery is more cost-effective and, if done well, it has a significant effect on improved quality of life."

In the past decade there have been vast improvements in surgery. Increasing expertise in cancer surgeons, the development of keyhole (laparascopic) surgery and, perhaps most spectacularly, the rise of the robot have meant that cancers can be removed far more cleanly, with less trauma, than ever before. There's evidence that this is having an impact not just on how long people are living but, arguably more importantly, on the quality of the rest of their life.

In prostate cancer, for example, the pinpoint accuracy of the Da Vinci robot in removing the prostate gland without damaging surrounding veins, nerves and tissue means that patients are free to get on with their lives within days and are considerably less likely to suffer the disabling side-effects that often accompanied traditional surgery, such as incontinence and impotence. The success of this, and other new keyhole surgery techniques, has contributed to a 335% rise in prostate cancer surgery rates in the past ten years. Recent trials have also indicated the efficacy of Da Vinci at performing radical hysterectomies for gynaecological cancers.

In bladder cancer there has been a drop in mortality rates of about 10% in the past 15 years, partly as a result of more advanced surgical techniques being used to remove lymph nodes that may carry cancer cells.

And the fact that more surgeons are choosing to specialise in operating on particular types of cancer has also had a wide effect on cancer mortality and complication rates. The number of patients dying in hospital after removal of oesophageal cancer halved between 1997 and 2005, largely because the surgery was increasingly performed by specialists rather than generalists, according to the Department of Health.

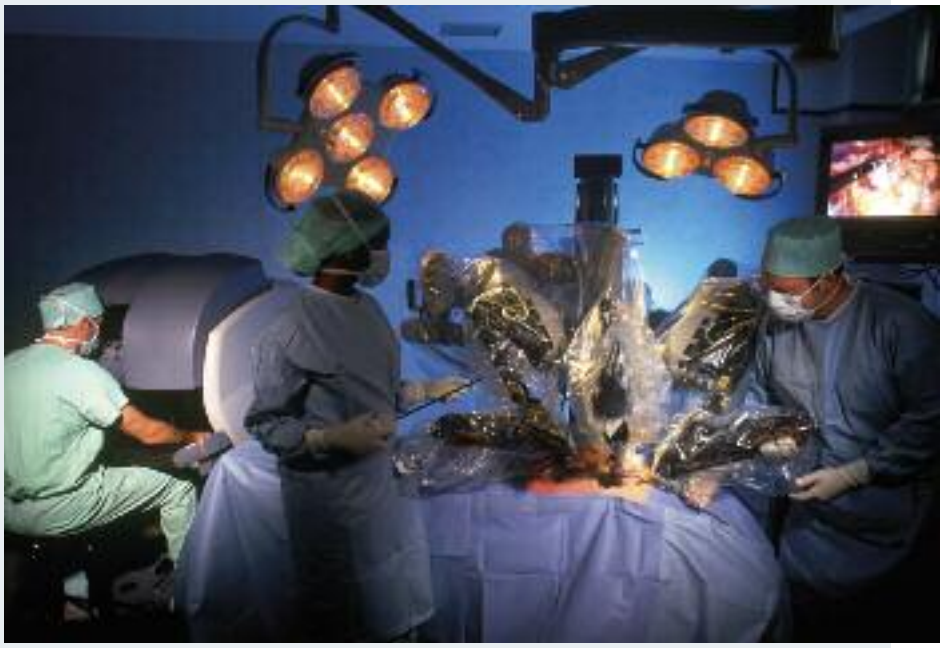
Yet the money allocated to advancing surgical practice can pale into insignificance compared with new cancer drugs. The NHS spent about ▶

£100 million [€125 million] on the breast cancer drug Herceptin in 2006, but some estimates say that only about 500 patients actually benefited. That kind of money could train hundreds of surgeons to specialise in the latest techniques, or transform research into new surgical techniques each benefiting thousands of people. One Da Vinci machine costs £1 million [€1.25 million] to buy and maintain over five years, helping hundreds of cancer patients in that time.

"The thing that is improving cancer cure rates is specialised surgeons focusing on particular operations, doing them more often and getting better at them," says David Neal, the Cancer Research UK Professor of Surgical Oncology at Addenbrookes Hospital, which houses one of the six Da Vinci robots in the UK. "But until five years ago there weren't the surgeons here trained to do prostate removal properly. Surgery needs an investment of time for training in the latest techniques.

"I get fed up with the current emphasis on cancer drugs. It gets forgotten that surgery is the single most effective treatment for cancer. The NHS has fallen behind on equipment. In the US, 65% of radical prostatectomies are done using a robot. In Europe it's one in three. But here it's just 1% or 2%."

Professor Neal has high-level support. Cancer experts such as Professor McVie and Karol Sikora, a professor of cancer medicine and honorary consultant oncologist at Hammersmith Hospital, in West London, point out that the days of discovering blockbuster drugs helping millions of people are gone, and drug development is becoming increasingly focused on specialist drugs that will help ever-smaller groups of people.



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There are signs that the contribution of surgery to curing cancer may finally be acknowledged. Lord Darzi, the consultant surgeon at St Mary's Hospital, London, who introduced the Da Vinci robot to the UK, is a Health Minister. His input is clear in the Government's new Cancer Plan, with proposals to establish a new programme to train more surgeons in laparascopic surgery. The Department of Health has promised a £250 million [€315 million] investment in 'capital equipment' for cancer over the next three years, but how much of that will be spent on surgery is as yet unclear.

As both a minister and a director of the new Hamlyn Centre for robotic surgery research at Imperial College London, Lord Darzi has to tread a careful line. But he says he agrees that the amount invested in surgery is "minuscule".

He would like to see much more money going into research into the effectiveness of new surgical techniques, then the case for investing in robotic and laparascopic techniques would be unanswerable.

"People don't realise that their only chance of a cure from cancer is through an operation that removes it completely," he says. "There has always been more emphasis on drugs because the pharmaceutical lobby is so strong. We've got to remember that in pharmaceuticals we have yet to find a magic bullet that has the potential to cure most cancers. But in surgery we already have that."

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Adjuvant EBRT improves survival in patients with lymph-node-negative pancreatic cancer

Lisa Hazard, Jonathan Tward and Dennis Shrieve

Though the role of radiation therapy in the adjuvant treatment of pancreatic cancer remains controversial, a recent large retrospective study indicates that radiation is associated with improved survival.

The role of adjuvant external-beam radiotherapy (EBRT) for the treatment of pancreatic adenocarcinoma remains controversial. A randomised trial by the Gastrointestinal Study Group demonstrated a survival benefit with the addition of chemoradiotherapy to surgery, and a randomised trial by the European Organisation for Research and Treatment of Cancer also showed a trend towards improved survival with adjuvant chemoradiotherapy.[1,2] On the other hand, a randomised trial by the European Study Group for Pancreatic Cancer (ESPAC), which comprised four adjuvant treatment arms (observation, chemotherapy alone, radiotherapy with concurrent chemotherapy, and radiotherapy with concurrent chemotherapy followed by maintenance chemotherapy),[3] revealed that the survival of patients who received radiotherapy (with or without maintenance chemotherapy) was inferior to that of patients who did not receive radiotherapy. The authors of this report concluded that radiotherapy had deleterious effects on survival.

The reasons for the decrease in survival in patients receiving radiotherapy on the ESPAC trial remain unclear. Radiation was not reported to increase treatment-related mortality, but late radiation toxicity is difficult to report accurately because it can be difficult to differentiate from symptoms of a progressive tumour, and patients may be lost to follow-up. The ESPAC trial did not describe radiation field size and technique, and central review of radiation plans was not required. The Radiation Therapy Oncology Group (RTOG) has reported that a major deviation from the protocol-defined radiation therapy plan was associated with inferior survival for patients with pancreatic cancer enrolled on the RTOG 97-04 trial, suggesting that radiation technique is important.[4]

The current study based on the SEER registry by Artinyan et al. (see opposite) demonstrates that the addition of radiotherapy to surgery in patients with T1–3N0M0 pancreatic adenocarcinoma is associated with improved survival. Limitations of the SEER registry include its retrospective nature and lack of information regarding surgical-margin status and the use of chemotherapy. In addition, it is not possible to determine any bias in the

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selection of patients for radiotherapy. For example, patients who do not have major health problems could be more likely to receive radiation, thereby biasing survival rates in favour of patients who receive radiation. Alternatively, patients who have high-risk features not assessed in the SEER study may be more likely to receive radiation, biasing results against radiation.

Given the limitations of the SEER registry, the results of this study do not answer the question of whether the addition of radiotherapy to chemotherapy improves survival.

The study does, however, suggest that, at a minimum, radiation is not detrimental to survival, as suggested by the ESPAC study.

In the current study, improvement in survival with radiotherapy was observed regardless of T stage on multivariate analysis, although improvement in survival was limited to patients with T3 disease on univariate analysis. Using the SEER registry data, Hazard and co-authors did not detect a survival benefit of radiotherapy and surgery in patients with T1–2N0M0.[5]

It is possible that T3 disease is associated with a higher probability of margin positivity, and the benefits of radiotherapy are, therefore, greater. It is also possible that patients with T1–2N0 disease who receive radiotherapy are more likely to have high-risk features, thereby limiting the potential survival benefit of radiotherapy.

In summary, this study indicates that adjuvant radiotherapy is an acceptable treatment for pancreatic adenocarcinoma that warrants continued investigation; only a randomised trial can determine whether or not the use of radiotherapy improves survival.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

Synopsis

Avo Artinyan, Minia Hellan, Pablo Mojica-Manosa et al. (2008) **Improved survival with adjuvant external-beam radiation therapy in lymph node-negative pancreatic cancer: a United States population-based assessment.** *Cancer 112:34–42*

Background. The prognosis for patients with lymph-node negative (N0) pancreatic cancer is very poor, with low survival rates after curative resection. Adjuvant treatment regimens consisting of chemotherapy, radiotherapy or a combination of both have been used to improve survival; however, the role of adjuvant radiation therapy is unclear.

Objective. To assess the benefit of adjuvant external-beam radiation therapy (EBRT) in patients with locally confined lymph-node-negative pancreatic cancer.

Design and intervention. This study used the Surveillance, Epidemiology and End Results (SEER) registry to identify patients who had undergone surgery for histologically confirmed, node-negative, invasive pancreatic cancer during the period 1988–2003. Patients whose tumours were excised or who had extensive pancreatic and multiorgan resections were included. Patients who had undergone biopsies, exploratory surgeries or lymph-node dissections alone and patients with no lymph nodes were excluded. A total of 1,930 patients were included in the analysis. Kaplan–Meier analysis was used to compare the survival rates of patients who received EBRT with those of patients who did not. Multivariate Cox regression analysis was used to determine the prognostic significance of adjuvant EBRT.

Outcome measures. The primary end point was overall survival (OS). The administration of adjuvant EBRT was the main prognostic factor of interest.

Results. The median OS for the whole study population was 17 months. Patients who received adjuvant EBRT had significantly better survival than patients who did not (median OS 20 months vs 15 months; $P<0.001$). Univariate regression analysis revealed that adjuvant EBRT was significantly associated with survival (hazard ratio [HR] 0.75, 95% CI 0.67–0.84; $P<0.001$). Age at diagnosis, and tumour location, grade and classification were all associated with survival. Multivariate analysis revealed that EBRT was associated with an approximately 30% reduction in the risk of death (HR 0.72, 95% CI 0.63–0.82; $P<0.001$). With each year of increasing age there was an approximate 1% increase in the risk of death (HR 1.01, 95% CI 1.004–1.016; $P<0.001$). Kaplan–Meier survival curves showed that after the exclusion of patients with less than 3 months survival, there was no difference in OS between patients who did and patients who did not receive adjuvant EBRT (median 20 months vs 19 months; $P=0.14$); however, multivariate analysis showed that adjuvant EBRT was an independent predictor of improved OS (HR 0.87, 95% CI 0.75–1.00; $P=0.044$).

Conclusion. Adjuvant EBRT provided a survival benefit to patients with operable, node-negative pancreatic cancer and should be considered as adjuvant treatment in this group of patients.

Acknowledgement: The synopsis was written by Mandy Aujla, Associate Editor, *Nature Clinical Practice.*

Lenalidomide plus dexamethasone is efficacious in patients with relapsed or refractory multiple myeloma

Nikhil Munshi, Constantine Mitsiades, Paul Richardson and Kenneth Anderson

Two recent studies have shown that lenalidomide in combination with high-dose dexamethasone is significantly more effective than high-dose dexamethasone alone in patients with relapsed multiple myeloma.

Lenalidomide is a more potent analogue of thalidomide that directly induces apoptosis of multiple myeloma (MM) cells and inhibits interactions between MM cells and bone-marrow-stromal cells. In addition, lenalidomide blocks both the constitutive production of cytokines and the production of cytokines induced by the binding of MM cells to bone-marrow-stromal cells. In blocking cytokine production, lenalidomide mediates MM-cell growth and survival, inhibits angiogenesis, and upregulates natural killer and T-cell responses against MM cells.[1] On the basis of preclinical efficacy, phase I and II clinical trials have demonstrated that 25 mg lenalidomide given for 21 days of a 28-day cycle is well-tolerated and induces responses in over 30% of patients with relapsed MM. Moreover, these responses are enhanced by the addition of dexamethasone.[2] On the basis of these exciting results, two randomised phase III trials were conducted that compared lenalidomide plus high-dose dexamethasone with high-dose dexamethasone plus placebo in patients with relapsed or refractory MM. Both the North American study by Weber et al. (n=353)[3] and the international study by Dimopoulos et al. (n=351; see opposite) confirmed that the combination regimen was significantly superior to dexamethasone in terms of response rate, time to progression and overall survival.

In the North American study,[3] those receiving lenalidomide had significantly improved partial and complete response rates (61% and 14.1%, respectively) and time to progression and overall survival were significantly prolonged (11.1 months and 29.6 months, respectively). The corresponding partial and complete response rates in those receiving dexamethasone were 19.9% and 0.6%, respectively, and time to progression and overall survival were 4.7 months and 20.2 months. The results of the Dimopoulos study were very similar. Oral lenalidomide plus dexamethasone was active in patients who had previously received bortezomib, high-dose therapy and stem-cell transplantation, or thalidomide. A tolerable toxicity profile was observed in both studies. These studies provided the basis for the rapid approval of lenalidomide plus dexamethasone by the FDA and the European Medicines Agency for the treatment of patients with relapsed MM following initial induction therapy.

Notably, the study by Dimopoulos et al. confirmed that deep vein

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Synopsis

M Dimopoulos, A Spencer, M Attal et al. (2007) **Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma.** *N Engl J Med 357:2123–2132*

Background. Lenalidomide is a more-potent and less toxic derivative of thalidomide. When lenalidomide is combined with dexamethasone this combination is more effective than either agent alone in the treatment of refractory myeloma.

Objective. To investigate the efficacy of lenalidomide plus dexamethasone in patients with relapsed or refractory myeloma.

Design. This multicentre, randomised, placebo-controlled phase III trial recruited 351 patients with multiple myeloma (MM) from centres in Europe, Israel and Australia between September 2003 and September 2004. All patients had received at least one previous antimyeloma treatment. Other eligibility criteria included age at least 18 years, an Eastern Cooperative Oncology Group performance status of 2 or less and an absolute neutrophil count of at least 1,000 mm^3. Patients who experienced disease progression while being treated with high-dose dexamethasone or who had hypersensitivity to previous treatment with thalidomide or dexamethasone were excluded.

Intervention. Patients were randomly assigned to receive either 25 mg oral lenalidomide (n=176) or placebo (n=175) on days 1 to 21 of a 28-day cycle. All patients received 40 mg oral dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for four cycles; after the fourth cycle, dexamethasone was administered on days 1 to 4 only. Patients continued to receive the assigned regimen until disease progression or the development of unacceptable toxic effects.

Outcome measures. Time to disease progression was the primary endpoint of this trial. Secondary endpoints included overall survival, rate of response and safety.

Results. The median time to progression was significantly longer in patients treated with lenalidomide plus dexamethasone than in patients treated with placebo plus dexamethasone (11.3 months vs 4.7 months; P<0.001; hazard ratio for time to progression 2.85). In total, 106 patients in the lenalidomide group achieved at least a partial response, compared with 42 patients in the placebo group (P<0.001). A complete response was achieved in 28 patients receiving lenalidomide and in 6 patients receiving placebo (P<0.001). The median duration of response in the lenalidomide group was 16.5 months compared with 7.9 months in the placebo group (P=0.02). Patients who received lenalidomide had significantly improved overall survival (hazard ratio for death 0.66; P=0.03). A higher incidence of grade 3 neutropenia, grade 3 or 4 thrombocytopenia and venous thromboembolism was reported in the lenalidomide group than in the placebo group.

Conclusion. The combination of lenalidomide plus dexamethasone is more effective than high-dose dexamethasone alone in the treatment of relapsed or refractory MM.

Acknowledgement: The synopsis was written by Mandy Aujla, Associate Editor, *Nature Clinical Practice.*

thrombosis is an important side-effect of lenalidomide and that optimum prophylactic anticoagulation is required.[4] In this study, high-dose dexamethasone was used at 40 mg on days 1–4, 9–12 and 17–20 for the first four cycles of treatment. A recent Eastern Cooperative Oncology Group study in patients with newly diagnosed MM has shown a survival advantage with the combination of lenalidomide plus low-dose dexamethasone (40 mg once a week) versus lenalidomide plus high-dose dexamethasone.[5] This finding raises the question as to whether a weekly dose of dexamethasone could be used in combination with lenalidomide to treat relapsed MM.

Ongoing studies are evaluating the use of lenalidomide as maintenance therapy after induction therapy or transplantation. Moreover, it is now being combined with melphalan and prednisone to treat newly diagnosed patients who are not transplantation candidates.[6] Lenalidomide is also being combined with monoclonal antibody therapy to enhance antibody-dependent cellular cytotoxicity. Finally, preclinical studies showing induction of dual apoptotic signaling and synergistic cytotoxicity have led to investigations into the combination of lenalidomide with bortezomib. The current study provides further clinical validation of the novel treatment paradigm – targeting the MM cell in its bone marrow microenvironment to overcome drug resistance to conventional therapy. These studies represent a key advance in the treatment of MM and an extraordinary example of rapid, collaborative bench-to-bedside research to improve patient outcome in MM.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

NEWSROUND

Selected reports edited by Janet Fricker

Prognostic scores can guide treatment in some pancreatic cancers

→ Annals of Surgery

Prognostic scores can be used to predict outcomes and guide adjuvant treatment in pancreatic neuroendocrine tumours (PNETS), concludes a US study.

PNETs – also known as neuroendocrine carcinomas or islet cell neoplasms – have a poorly defined natural history. In contrast to pancreatic adenocarcinoma, PNETs (which account for just 3% of all pancreatic neoplasms) have a more indolent tumour biology, are more amenable to resection, and show better long-term survival. However, the relative rarity of the disease has limited the identification of factors affecting survival after resection. Single-institution studies have identified conflicting factors associated with outcomes after resection, with the result that a widely accepted staging system to provide prognostic information does not currently exist for PNETS.

In the current study, Karl Bilimoria and colleagues from Northwestern University (Chicago, Illinois), identified 3,851 patients from the National Cancer Data Base who had undergone resection of PNETs between 1985 and 2004. The objective of the study was to assess the clinicopathologic features of resected patients, determine long-term survival and examine the patient, tumour, treatment and hospital characteristics predicting outcome after resection. Ultimately, the team looked to develop prognostic scores based on these predictive factors.

Results showed that the five-year overall survival for the 3,851 patients who underwent pancreatectomy for PNETs was 59.3% and that the 10-year survival was 37.7%. Five-year survival varied according to histologic subtype – 58.3% for neuroendocrine carcinoma, 67.3% for insulinoma, and 51.4% for glucagonoma. In the PNET post-resection prognostic score, the team found that age, tumour grade and distant metastases were the most powerful prognostic factors for patients undergoing resection.

Tumour functionality and the type of resection were also found to be independent predictors of survival after resection, but gender, race, socioeconomic status, tumour size, nodal status, margins, adjuvant chemotherapy and hospital pancreatic surgery volume were not found to be associated with survival. From these data the team developed a PNET post-resection prognostic score taking into account age, grade and distant metastases.

For patients with complete information on age, tumour grade and distant metastases, a prognostic score was calculated, with five-year survivals for three score groups. The five-year observed survival was 76.7%, 50.9% and 35.7 % for each of the three groups; this produced a *P*-value of <0.0001 for each pairwise comparison.

"The prognostic score will provide information regarding expected survival, assist in adjuvant treatment decisions and allow for patient stratification for clinical trials," write the authors.

■ Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors. Analysis of 3851 patients. KY Bilimoria, MS Talamonti, JS Tomlinson et al. *Ann Surg* March 2008, 247:490–500

Percutaneous radiofrequency ablation shows promise in lung tumours

→ Lancet Oncology

Percutaneous radiofrequency ablation – a minimally invasive treatment technique that heats and destroys cancer cells – achieves a high rate of sustained complete response in selected patients with lung tumours, according to results from the first prospective study of patients treated with the technique.

Surgical resection, the standard of care for early-stage non-small-cell lung cancer, achieves five-year survival rates greater than 50%. Patients unfit for surgery may be treated with radiotherapy, with five-year survival rates of up to 27%.

Surgical resection of pulmonary metastases has been shown to improve survival in selected patients. However, only a few patients can undergo resection because of the extent and location of tumours in the lungs, tumours elsewhere in the body or concurrent medical conditions. The high risk of cancer recurrence and the need to remove functioning lung tissue together with the cancerous tissue further restricts the use of surgery for lung cancers,

so new treatment techniques are needed.

Percutaneous radiofrequency ablation uses imaging techniques such as ultrasound or CT to guide a needle electrode into a tumour. High-frequency electrical currents are then passed through the electrode, generating heat that destroys the abnormal cells.

Researchers assessed the effects of percutaneous radiofrequency ablation in a series of 106 patients with 183 small lung tumours. The tumours included non-small-cell lung cancers in 33 patients, metastases from colorectal carcinoma in 53 patients and metastases from other types of cancers in 20 patients. All of the patients were considered by their doctors to be unsuitable for surgery, radiotherapy or chemotherapy.

The patients were treated with radiofrequency ablation and followed up for two years. A complete response in target tumours lasting at least one year was achieved in 75 of the 85 assessable patients (88%). Overall survival at one year was 70% (95% CI 51%–83%) and at two years was 48% (95%CI 30%–65%) in patients with non-small-cell lung cancer. Cancer-specific survival was higher – 92% at one year and 73% at two years, meaning that most people who died during the study died due to causes other than cancer.

Survival was similar in the patients with colorectal metastases (89% at one year and 66% at two years) and in those with other metastases (92% at one year and 73% at two years). Cancer-specific survival at two years was 68% and 67% for these two groups, respectively.

The safety profile of the procedure was considered acceptable, with no deaths or life-threatening complications associated with radiofrequency ablation. The major complications included pneumothorax in 27 patients and pleural effusion needing drainage in four patients. None of the patients suffered significant worsening of lung function.

The researchers, led by Riccardo Lencioni, associate professor of radiology in the Division of Diagnostic and Interventional Radiology at the University of Pisa, Italy, said: "Percutaneous radiofrequency ablation yields high proportions of sustained complete responses in properly selected patients with pulmonary malignancies and is associated with acceptable morbidity." They commented that the 92% two-year cancer-specific survival achieved in patients with stage I non-small-cell lung cancer was promising, and comparable with the rate achieved with radiotherapy. "A randomised controlled trial comparing radiofrequency ablation with standard non-surgical treatment options is now warranted to prove the clinical benefit of this approach," they conclude.

■ Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). R Lencioni, L Crocetti, R Cioni et al. *Lancet Oncology* July 2008, 9:621–628

Physiotherapy-guided pelvic floor training aids continence after prostate surgery

➜ European Urology

Pelvic floor muscle training helps regain urinary incontinence significantly better when guided by a physiotherapist than when patients train on their own, concludes a Norwegian study in men who had undergone radical prostatectomy.

Postprostatectomy urinary incontinence, which occurs in between 7% and 87% of men undergoing prostatectomy, is most often caused by dysfunction of the urethral sphincter from injury of either the striated muscle fibres or the innervating nerve fibres. Increasing the strength of the pelvic floor muscles can support the voluntary sphincter muscle and increase blood supply.

An earlier study showed that 88% of men with postprostatectomy urinary incontinence participating in a pelvic floor re-education programme (involving active pelvic floor muscle exercises, biofeedback and additional electrical stimulation) were continent three months after surgery, compared to 56% in a control group who did not undergo treatment. This raised the question of whether the same results could have been achieved from interventions with less time-consuming follow-up by physiotherapists.

In the current study, Mari Overgard and colleagues from St Olav's Hospital and Trondheim University Hospital (Trondheim, Norway), set out to assess the effects of intensive and frequent pelvic floor muscle training, both with and without follow-up instructions from a physiotherapist.

In the study, 85 men with clinically localised prostate cancer, operated on between September 2005 and December 2006 at St Olav's Hospital, were randomly allocated to two intervention groups.

The 42 patients randomised to group A followed a pelvic floor muscle exercise course consisting of intensive pelvic floor muscle training guided by a physiotherapist for 45 minutes once a week. Patients were instructed to perform three sets of 10 contractions daily at home.

The 43 patients randomised to group B received oral and written descriptions of the postoperative training programme, with encouragement to perform three sets of 10 pelvic floor muscle contractions daily. The primary outcome measure of the study was self-reported continence/incontinence at three months after surgery, with continence defined as the absence of use of continence pads.

Results at six months showed a clinically relevant difference in continence status – 79% of patients in group A were continent compared to 58% in group B (P=0.061). At 12 months 92% of patients in group A were continent, compared with 72% in group B (P=0.028).

"Our findings suggest that in patients with postoperative incontinence, follow-up instructions by a physiotherapist increase long-term adherence to pelvic floor muscle training and thereby improve continence rates over time more than information provided to patients for training on their own," conclude the authors.

■ Does physiotherapist-guided pelvic floor muscle training reduce urinary incontinence after radical prostatectomy? A randomised controlled trial. M Overgard, A Angelsen, S Lydersen et al. *European Urology* August 2008, 54:438–448

Five biomarkers best at identifying basal-like breast cancer

→ Clinical Cancer Research

Including markers for epidermal growth factor receptor (EGFR) and cytokeratin 5/6 (CK5/6) in addition to the 'triple-negative phenotype' in microarray panels results in a significantly better identification of basal-like breast cancer, concludes a Canadian study.

Basal-like breast cancer – which accounts for approximately 15% of all breast cancers – is associated with mitotically active high-grade invasive tumours, which affect younger patients and have a poor prognosis. Identifying these tumours would help target a cohort of breast cancer patients who require more aggressive systemic therapy.

Clinically, a triple-negative phenotype (TNP) – i.e. testing negative for oestrogen receptor (ER), progesterone receptor (PR), and HER2 – has been used to identify basal-like breast cancer. While the TNP is convenient, since it uses biomarkers routinely ordered during the clinical work-up of breast cancer biopsies, the addition of EGFR and CK5/6 has been shown to identify basal-like tumours from gene microarrays with 100% specificity and 76% sensitivity. The current study by Maggie Cheang and colleagues, from the Vancouver Coastal Health Research Institute (British Columbia, Canada) and the University of North Carolina (Chapel Hill, North Carolina, USA), set out to compare the prognostic value of the three and five biomarker panels in identifying basal-like breast cancer.

In the study, tumours from 4,046 women referred to the British Columbia Cancer Agency between 1986 and 1992 were assembled into tissue microarrays. All were accompanied by information on staging, pathology, treatment and outcome, with a median follow-up of 12.5 years.

Among 3,744 interpretable cases, 17% were found to be basal using the triple-negative definition (with a 10-year breast cancer death specific survival of 67%) while the five marker definition found 9% to be basal (with a 10-year breast cancer death specific survival of 62%). Likelihood ratio tests of multivariate Cox models including standard clinical variables show that the five marker panel was significantly more prognostic than the three marker panel.

"Our results provide strong evidence to support the use of a five-biomarker surrogate to define the basal-like subtype, a finding of immediate relevance to prognostication and clinical trial design," write the authors. "Drawing on readily available inexpensive diagnostic tools already in clinical use, this immunopanel provides a more specific definition of this aggressive form of breast cancer for which there is a particular need to improve therapeutic options."

■ Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. MCU Cheang, D Voduc, C Bajdik et al. *Clin Cancer Res* 1 March 2008, 14:1368–1376

Relief for opioid-induced constipation

→ New England Journal of Medicine

Subcutaneous methylnaltrexone is safe and effective at relieving opioid-induced constipation, concludes a multicentre phase III trial of patients with advanced illness.

Clinicians often use opioids to treat moderate to severe pain, but in advanced illness, opioid-induced constipation often rivals the distress caused by pain. Treating opioid-induced constipation can prove challenging, since opium antagonists (such as naloxone) cross the blood–brain barrier, resulting in opioid withdrawal. In contrast, methylnaltrexone is a peripherally acting μ-opioid-receptor antagonist that has restricted ability to cross the blood–brain barrier.

In the study, Jay Thomas and colleagues from San Diego Hospice and the Institute for Palliative Medicine (San Diego, California) determined the safety and efficacy of methylnaltrexone in 133 chronically ill patients from 27 US and Canadian nursing homes, hospices and palliative care centres. The patients – all of whom had opioid-induced constipation that was unresponsive to a median of two classes of laxatives – were randomised to methylnaltrexone (at a dose of 0.15 mg/kg body weight) or an equal volume of placebo administered subcutaneously on alternate days for two weeks. Cancer was the primary diagnosis in 58% of patients studied.

Results show that, within four hours of the first dose, 48% of methylnaltrexone-treated patients had a bowel movement, compared with 15% of patients given the placebo ($P<0.001$). The corresponding rates within four hours of the second, third or fourth doses were 52% for methylnaltrexone-treated patients and 8% for placebo-treated patients ($P<0.001$). The response to methylnaltrexone was rapid; among patients who had a response within four hours after receiving a dose, half experienced defaecation within one hour. Overall methylnaltrexone was well tolerated, with the most frequent adverse events being abdominal pain and flatulence.

"Our study showed that in this population methylnaltrexone rapidly induced laxation without compromising analgesia. Methylnaltrexone may represent an important therapeutic option for patients with advanced illness who are suffering from opioid-induced constipation," conclude the authors.

In an accompanying editorial, Charles Berde and Samuel Nurko, from the Children's Hospital Boston and Harvard, write that although methylnaltrexone was more effective than placebo, "it was somewhat disappointing that in both phases of the study, the drug produced rescue-free laxation [i.e. laxations without the use of a rescue laxative such as an enema or suppository] in only about half of patients." The explanation, they suggest, is that constipation could have been caused by the effects of other drugs or disease processes, or that the central actions of opioids – not the peripheral ones, which would be blocked by methylnaltrexone – might have caused the constipation.

■ Methylnaltrexone for opioid-induced constipation in advanced illness. J Thomas, S Karver, GA Cooney et al. *N Engl J Med* 29 May 2008, 358:2332–2343

■ Opioid side effects – mechanism based therapy. C Berde and S Nurko. *ibid* pp2400–2402

Stellate-ganglion blockade relieves hot flushes in breast cancer survivors

➜ Lancet Oncology

Stellate-ganglion blockade significantly decreases the number and intensity of hot flushes and decreases night awakenings in breast cancer survivors, a US pilot study has concluded.

Hot flushes and sleep dysfunction are a frequent side-effect of pharmacological breast cancer treatments, including oestrogen-synthesis inhibitors, oestrogen antagonists and aromatase inhibitors. "Hot flushes can have a debilitating effect on daily living, by disrupting sleep and causing fatigue and irritability during the day," write study authors, Eugene Lipov and colleagues from the Advanced Pain Centers (Hoffman Estates, Illinois, USA). In severe cases they can substantially increase the risk of sleep deprivation, depression, sexual dysfunction, and other medical conditions.

Earlier studies have suggested that the stellate ganglion interacts with several key structures in the brain known to modulate core body temperature. One study using functional MRI on postmenopausal women experiencing hot flushes showed the stellate ganglion provided neural input into the insular cortex, an area of the brain known to be activated during a hot flush. The studies suggested to Lipov and colleagues the possibility of relieving hot flushes by interrupting the stellate ganglion's input to the sympathetic system.

In the study, 13 women in remission from breast cancer, who were experiencing severe hot flushes and night awakenings, underwent stellate-ganglion block at the anterolateral aspect of the C6 vertebra on the right side. For one week prior to the procedure, and 12 weeks after, subjects kept a daily record of the number of night awakenings and the frequency and severity of hot flushes. The decision to repeat the block was made by the patient if she thought her symptoms were returning.

Five patients had one stellate-ganglion block and eight had two blocks.

Results show that the total number of hot flushes decreased from a mean of 79.4 per week prior to the procedure to 49.0 per week during the first two weeks after the procedure (P=0.0002). Over the remaining 3–12 weeks, the number of hot flushes continued to decrease, stabilising at a mean of 8.1 per week (P<0.0001). Severe hot flushes decreased from 26.5 per week at the outset to 5 per week by the end of the study (P<0.0001).

Night awakenings also decreased, from a mean of 19.5 per week prior to the procedure to 7.3 per week during the first few weeks after the procedure (P<0.0001), stabilising at a mean of 1.4 per week by the end of the study (P<0.0001).

"The findings of this pilot study suggest that a properly done stellate-ganglion blockade might be a highly effective treatment for both hot flushes and night awakenings in survivors of breast cancer, but more studies are needed," conclude the authors, adding that some continued to experience relief from hot flushes for more than two years after a single block.

■ Effects of stellate-ganglion block on hot flushes and night awakening in survivors of breast cancer: a pilot study. EG Lipov, JR Joshi, S Sanders et al. *Lancet Oncology* June 2008, 9:523–532

Treatment groups defined in locally advanced breast cancer

➜ British Journal of Cancer

Locally advanced breast cancer (LABC) patients with tumours testing negative for oestrogen receptor (ER), progesterone receptor (PgR) and HER2 show the lowest levels of recurrence-free survival (RFS), an Italian study has concluded. The investigators, who also found that a high Ki-67 labelling index and the presence of peritumoral vascular invasion (PVI) correlates with poor RFS, hope that their findings will help to define distinct biological entities that require a differentiated approach.

LABC defines a heterogeneous group of diseases, including tumours with locoregional lymph node metastases, primary breast carcinomas infiltrating skin or chest wall – known as non-inflammatory breast cancer (NIBC) – and inflammatory breast carcinoma (IBC). Limited information is available, however, on prognostic and predictive parameters for both IBC and NIBC.

In the current prospective study, Emilia Montagna and colleagues from the European Institute of Oncology (Milan, Italy), evaluated the clinical and pathological features of 504 consecutive patients with NIBC and IBC operated on at the Institute between 1999 and 2006. The data were collected from patients who were treated with multimodal treatments, including neoadjuvant chemotherapy followed by radical surgery and radiotherapy. Tumour samples obtained at surgery were evaluated using standard immunohistochemical methods. Patients with recurrent tumours, metastatic disease at presentation, previous tumours, no primary chemotherapy, male breast cancer and those who received trastuzumab therapy were excluded from the study.

Altogether, 248 patients were deemed eligible, of whom 107 (43%) were diagnosed with IBC and 141 (57%) with NIBC. The investigators did not observe any differences in RFS (P=0.72), disease-free survival (P=0.98) and overall survival (P=0.35) between patients with IBC and NIBC.

In a multivariate analysis, patients with ER- and PgR-negative disease showed significantly worse RFS than patients with ER- and PgR-positive disease (HR 2.47, 95%CI 1.33–4.59, P<0.001). The worst RFS was found in the subgroup of patients with endocrine non-responsive breast cancer and HER2-negative breast cancer. Here the two-year RFS was 57% in both NIBC and IBC. In addition, a high Ki-67 labelling index (>20% of the invasive tumour cells) and the presence of peritumoral vascular invasion (PVI) significantly correlated with poorer RFS. Tumours with a Ki-67 >20% had a hazard ratio for RFS of 2.69 (95%CI 1.61–4.50, P<0.001), while presence of PVI gave a hazard ratio of 2.27 (95%CI: 1.42–3.62, P=<0.001).

"This study confirms the value of prognostic parameters assessed at final surgery, including ER and PgR expression, Ki-67 expression and presence of vascular invasion," conclude the authors.

■ Factors that predict early treatment failure for patients with locally advanced (T4) breast cancer. E Montagna, V Bagnardi, N Rotmensz et al. *BJC* 27 May 2008, 98:1745–1752

Why 'plenty of bed rest' could be bad advice

Survivors to be prescribed exercise as cancer care 'catches up' with cardiology

➜ Peter McIntyre

Evidence from a growing number of robust studies points incontrovertibly towards the benefits of regular, moderate activity not just in preventing cancer, but in rehabilitation for survivors and protection against recurrence. The question, as ever, is how to help those who need it most to get the message and act on it.

Not everyone can be like Lance Armstrong. Following treatment for testicular cancer with lung and brain metastases, he famously went on to win the *Tour de France* seven times, and now he has retired from competitive cycling, he runs marathons.

"I view running as a hobby and a necessity," he said in April 2008, just before completing the Boston marathon in 2 hours 50 minutes and 58 seconds.

Nor can all cancer patients be like Jane Tomlinson from Leeds in England, who, given six months to live at the age of 36, swam, ran marathons, cycled to Rome and back, and cycled across America raising £1.75 million (€2.2 million) for cancer care.

Jane died in September 2007, having outlived her six-month prognosis by nearly seven years, and having achieved her ambition to see her children through their early childhood – her youngest was 12 when Jane died.

These are exceptional people. One is still alive and the other is not, but in both cases exercise represented a focus of the will to win and the will to live.

However, a growing tide of research shows that the benefits of exercise for cancer patients do not depend on running marathons. Even 'moderate' daily exercise – such as brisk walking or energetic housework – is important in the rehabilitation of cancer patients. Doctors are increasingly advising their patients to take moderate exercise five times a week, to speed their recovery, improve their quality of life and help prevent the return of the cancer.

Fernando Dimeo runs a specialist referral centre for cancer patients with fatigue at the Charité Universitätsmedizin in Berlin. He says simply, "If there is no clear contraindication for exercise, all cancer patients should exercise. That means that we are putting the argument on its head. Usually doctors recommend their patients not to exercise, unless they have a good reason to do so."

Anna Campbell has researched the effects of exercise on patients with cancer in Scotland and now runs cancer rehabilitation training courses across the UK (www.canrehab.co.uk). She is focusing on how to introduce into cancer care packages evidence-based practice on exercise.

"There is something protective about being active post diagnosis. For people who have already had a

"Racing dragon boats is physically and mentally demanding, which makes you focus and forget your problems momentarily. Every woman rises to the challenge. You gain your confidence back and are able to face life again, head-on. Perhaps the most important thing is the fun – whether it is sunny, raining, hail or snow, we go out on the water and have a laugh!"

Wendy de Corte, Pool of Life

WILF HOLDEN

Rowing back to health. Dragon boat racing is becoming a very popular form of exercise among breast cancer survivors. Pictured here is the UK Pool of Life team (www.pooloflife.net) from Liverpool, on a 42-km paddle along the Leeds/Liverpool Canal this May, to raise awareness about the importance of early detection

cancer diagnosis, 30 minutes of moderate exercise five days a week will cut by half the risk of colorectal or breast cancer compared with someone who has a very sedentary lifestyle. There is no patient who could not incorporate some kind of physical activity, whether home-based or in a group setting or a one-to-one programme into their daily life."

Both specialists say that exercise improves quality of life and can often begin during treatment, though there are caveats for patients who suffer exercise-related pain, poorly controlled hypertension or diabetes, unstable heart disease, or other comorbidity.

Cancer care is taking time to catch up with cardiovascular medicine in understanding the beneficial role of exercise, says Dimeo. "For 20 years now, we have recommended patients with cardiovascular disorders or lung disorders to start exercising or increase physical activity. But for cancer patients, some doctors recommend that patients do not exercise during anaemia or immunosuppression. If you ask them why, they cannot give you a reason."

Exercise is now becoming an issue wherever the number of cancer survivors is increasing, such as in colorectal or prostate cancer. There is increasing interest in encouraging children with leukaemia to exercise and there are studies showing benefits for patients with myeloma and non-Hodgkin's lymphoma. There is also evidence that exercise improves quality of life for patients receiving palliative care.

The evidence is stacking up

The evidence showing the benefits of exercise before and after diagnosis is stacking up fast. It is estimated that inactive lifestyles could account for up to 5% of all cancer deaths, 13–14% of all bowel cancer cases

Exercise is now becoming an issue wherever the number of cancer survivors is increasing

and 11% of breast cancer cases. A recent study from Poland, where 9,000 women are diagnosed with breast cancer every year, showed that women who were in the most active group were 20% less likely to develop breast cancer than women in the lowest activity group. Beata Peplonska and colleagues at the Nofer Institute of Occupational Medicine in Łódź, found particularly strong benefits for women who increased activity levels in their 50s.

The benefits of exercise post diagnosis is also becoming clear. One of the most dramatic results was shown in a study by Meyerhardt and colleagues in the *Journal of Clinical Oncology*. They followed 573 women with stage 1–3 colorectal cancer, and found that cancer-specific death was 60% lower in women who exercised six or more hours a week (walking at average pace) than in those who exercised for less than one hour a week. The reduction in deaths from all causes was almost as large. A second study of more than 800 patients with stage 3 colon cancer showed that mortality was reduced by half in the group that had exercised six hours a week or more.

Exercise can also help with the fatigue that many patients suffer long after treatment. A Cochrane review published in April found that "exercise can be regarded as beneficial for individuals with cancer-related fatigue during and post cancer therapy". It called for further research to decide the best type, intensity and timing of exercise.

Dimeo's group in Berlin enrolled 32 cancer patients with mild-to-severe persistent fatigue in a research programme that involved 30-minute sessions on a treadmill with resistance exercises for the major muscle groups. After three weeks, the patients showed a significant increase in physical performance and reduced overall fatigue scores by a mean average of 25%.

However, when Dimeo analysed detailed fatigue scores, he found no significant effect on cognitive fatigue, depression or anxiety.

"I have had patients here working out for six or eight weeks, and we observe a very clear improvement in their physical performance, but at the end, some go on feeling mentally tired. Why do they continue to feel lack of motivation and have cognitive problems? The first idea was exercise – we were very ecstatic about exercise and the improvement in physical performance. Now we are certain that the problem of fatigue is much more complex than that, and that the patient also has problems in other areas."

Dimeo says that we need better definitions of mental fatigue to distinguish, for example, between patients who feel run down and lacking in motivation and those who become forgetful and unable to

The studies

Examples of the growing body of literature testifying to the importance of exercise in survivor quality of life, primary prevention and preventing recurrence include:

- *Adulthood lifetime physical activity and breast cancer.* B Peplonska, J Lissowska, TJ Hartman et al. *Epidemiology*, March 2008
- *Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial*. N Mutrie, A Campbell, F Whyte et al. *BMJ*, 16 February 2007
- *Effects of an endurance and resistance exercise program on persistent cancer-related fatigue after treatment*. F Dimeo, S Schwartz, N Wesel et al. *Ann Oncol* published online 1 April 2008
- *Exercise for the management of cancer-related fatigue in adults.* F Cramp and J Daniel, *Cochrane Database of Systematic Reviews 2008* Issue 2 Art. No. CD006145, April 2008
- *Exercise for women receiving adjuvant therapy for breast cancer.* M Markes et al. *Cochrane Database of Systematic Reviews* 2006 Issue 4 Art. No. CD005001, October 2006
- *Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB* 89803. JA Meyerhardt, D Heseltine, D Niedzwieckiet al. *JCO,* 1 August 2006
- *Physical activity and survival after colorectal cancer diagnosis,* JA Meyerhardt, EL Giovannucci, MD Holmes et al. *JCO,* 1 August 2006

"Inactive lifestyles could account for up to 13–14% of colorectal cancers and 11% of breast cancers"

Even patients who do not seem to have made progress exercising during treatment often feel the benefits later

concentrate when reading a book or watching a film.

"The instruments we have are very unspecific. We have to ask the patient: what exactly do you mean when you feel mentally tired? You cannot concentrate or you are forgetful or what? The next step is to define the limitations of the patient, and after that we can start to evaluate different therapeutic approaches."

Late effects

However, Campbell says that even patients who do not seem to have made progress during the exercise programme during treatment often feel the benefits later. She was involved in research in Glasgow, Scotland, that randomised 203 women with early-stage breast cancer to a 12-week exercise programme during their treatment or a control group, and then followed them up six months later.

The women attended two 45-minute exercise classes a week and were encouraged to do one other exercise session at home. After 12 weeks they showed physical and psychological benefits compared to the control group. However, the difference in general quality of life first emerged at the six-month follow-up. Of cost–benefit interest is that the exercise group spent fewer nights in hospital and made fewer visits to their doctor, compared with the control group.

This was the first randomised controlled trial of exercise in breast cancer patients in the UK, and, like Dimeo, Campbell thinks there is a complex story underneath the figures.

"When you look at any group studies post-treatment, when you give them a physical exercise programme they not only get fitter, able to be more active and stronger, but their quality of life improves. We found that when you are doing an intervention with physical activity during chemo- or radiotherapy, it is much more difficult to see an overall improvement in quality of life. We think that during the treatment there are other issues and side-effects of treatment, which perhaps mask the overall improvement. The interesting thing is that when we followed up the women six months later, when they finished their treatment, surprise, surprise, the women who have been given exercise, their quality of life has improved, compared with the women who haven't been given the exercise."

Group exercise appears to have some extra benefits

CATHY MCINTYRE

Long-term benefit. These survivors are part of the 203-strong randomised clinical trial that demonstrated a significant impact of the CATS (Cancer and Tiredness Support) exercise programme on quality of life. Lead researcher, Anna Campbell is pictured leading the class, in Renfrew, Scotland

FRANTISEK HONZAC

Group dynamics. The Czech Dracice team (www.dracice.org) is one of the more recent additions to the European breast cancer survivor dragon boat racing scene. They are pictured here (centre) taking part in the Prague Dragon Boat Festival this June

over exercising alone, according to Campbell. "Definitely the group dynamics did have some effect, so there were two plusses. But it came out very strongly that the women were not interested in just sitting around the table talking about their cancer. The physical functioning improved and they showed reduced fatigue and a greater range of movement."

One manifestation of this group effect is the success of dragon boat racing amongst breast cancer survivors, as a way of combining exercise with fun and group support. This is a huge sport in Canada, North America and Australia, and has spread to Europe, with teams in the Czech Republic, Germany, Italy, Poland and the UK. This September, the European Dragon Boat Racing championships, hosted in Sabaude, Italy, will feature for the first time a race for breast cancer survivor teams.

Learning from cardiac care

Campbell is involved in trying to get physical exercise into routine cancer rehabilitation care as part of NHS treatment in the UK, working with healthcare and exercise professionals to develop properly validated training and educational courses. She too believes that cancer care professionals should learn from cardiac care.

"Cardiac rehab is a fantastic example of where the patients, after a triple bypass or whatever, have a 12-week structured programme with exercise and are also given information on health lifestyle such as diet, smoking and alcohol consumption. At the end of the 12 weeks they are straight into community-based programmes near them in the local gym. That is what I would love to see take place for cancer rehabilitation."

Making exercise part of rehabilitation care would be a great help in getting people started. But as every health club knows, it is one thing to start exercise and another thing to make it a part of your daily life. A study in Alaska showed that breast cancer patients who were given step counters and encouraged to walk "like they were late for an appointment" were taking more exercise after three months than those who were simply given verbal encouragement, but after six months the difference was no longer significant.

Campbell says that those setting up exercise programmes have to pay close attention to the motivators and the barriers to taking part, especially to attract the patients who may be the least likely to attend.

"You may find that younger women weren't coming in after a diagnosis of breast cancer compared to older women. The main factors may be things like childcare, or they are keen to get back to work and the timing does not suit them, or the treatment they are getting is slightly more aggressive and they are finding it harder to cope. I am looking at how to overcome the barriers so you can incorporate people who maybe cannot travel to a local gym or who have comorbidities. Like everything else, the first to take it up are the more socially and educationally advantaged people. You really want to target the people who are not coming along, but need it the most. But many health professionals would like more training in helping patients to change behaviour."

"Many health professionals would like more training in helping patients to change behaviour"

Why is cancer killing more men than women?

Marc Beishon

A rising focus on men's health issues, more sophisticated registry data and new techniques for investigating the biology of cancers are fuelling interest in unravelling what lies behind gender differences in cancer incidence and mortality. Getting answers could boost prevention and early detection and could even lead to better targeted therapies.

When it comes to the differences between men and women, publicity about cancer tends to focus on the tumours specific to each sex – in the main, prostate and testicular for men and cervical, ovarian and breast for women (although of course men also get breast cancer – and there is rising incidence in some countries). But there are striking differences between adult men and women in some cancers common to both sexes, which are starting to receive more attention – and which raise a wide range of biological, social and environmental issues concerning cancer incidence, survival and mortality.

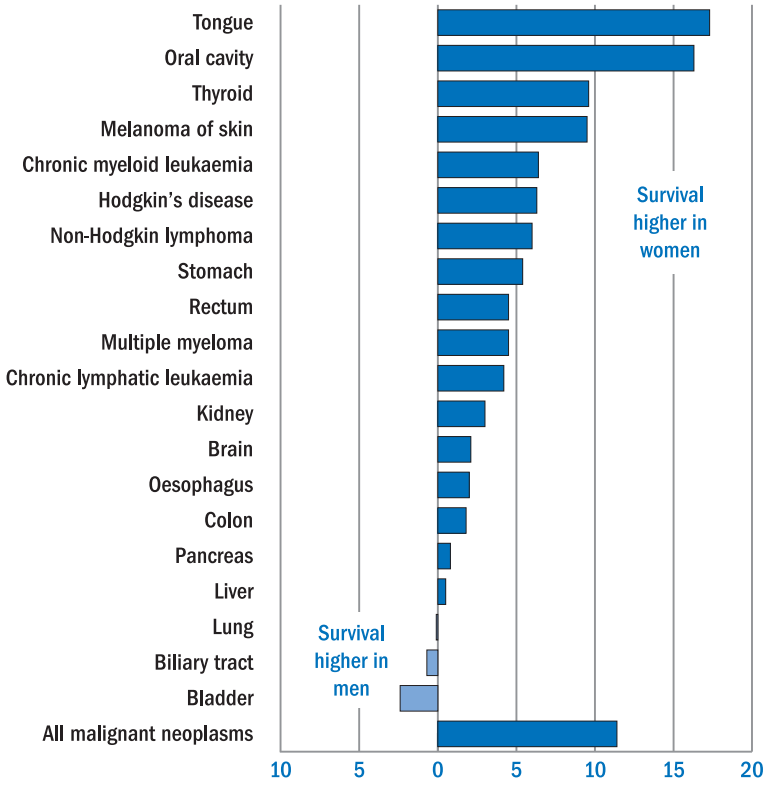
As Jan Willem Coebergh, professor of cancer surveillance at the Department of Public Health, Erasmus Medical Centre in Rotterdam, points out, there are two cancer sites which currently stand out as significantly different in cancer survival and which are hard to explain. Melanoma has a higher incidence in women, but more men proportionately die from the disease. But the reverse is true in bladder cancer, where the prognosis for women is poorer despite a lower incidence. Trying to unpick the reasons for these disparities can involve everything on the 'gender' side, from when men and women present to health services, to what doctors do that may be different, to lifestyle risk factors such as smoking and obesity, and also the 'sex' factors – possible differences in male and female biology.

However, for some cancers common to men and women the big differences, in incidence at least, are relatively straightforward to explain, according to Coebergh. "Tobacco exposure in particular and also alcohol explain the higher rates in men in many countries in tumour sites such as lung, larynx, bladder and to some extent pancreas, and we have of course seen a decline in these cancers in northern Europe as smoking rates have decreased, although there is a lag of 0–25 years in the data." As male and female smoking rates have become more equal across Europe, so too has the cancer incidence difference narrowed in those tumours where tobacco is a major risk factor.

"We are also seeing the rates of colorectal cancer in older men going up in some countries – this could be the result of a longer latency time of 30–40 years for smoking, but the data is much less robust," he adds. He points out that survival and mortality rates in older age groups are also heavily influenced by comorbidity with other diseases, especially cardiovascular conditions and chronic obstructive pulmonary disease – again where smoking makes a major impact.

But as Coebergh adds, the wider statistical picture of male and female differences around Europe is very mixed and complex. An analysis of the latest Eurocare-4 data shows that, for Europe as a whole, the regionally weighted mean

DIFFERENCE IN RELATIVE SURVIVAL (%) BETWEEN WOMEN AND MEN



Age-standardised data for adults diagnosed in the period 1990–1994.
Source: MP Coleman et al, Eurocare-3 Summary, Ann Oncol 2003, vol 14 (suppl 5), v135

five-year cancer survival is about 55% for women, but just 45% for men for all tumours, and those countries that spend the least on healthcare per head have notably lower scores.

It is notable too that the US has much higher survival figures than Europe and men actually do better – about 66% for men and 63% for women. But as Franco Berrino and Riccardo Capocaccia point out, in *Responding to the challenge of cancer in Europe* (available from WHO Europe), men in the US have a lower incidence of lethal cancers such as lung and stomach, and an exceptionally high incidence and survival for prostate cancer, thanks to widespread screening.

Those wanting to delve deeper into gender patterns could look at a recent paper in the *European Journal of Cancer* (Henrike Karim-Kos et al, 2008, 44:1345–89), in which Eurocare and other sources are mined for 17 cancer types across Europe. This lengthy report gives detailed figures for men and women on incidence, survival and mortality for several cancers, including colorectal, pancreatic and lung, and summaries of trends in various countries. There is also some discussion on possible reasons for the gender patterns. A more detailed gender paper, by Andrea Micheli and colleagues at the Eurochip health indicator project in Milan, will be published in the *EJC* this year .

Unravelling the causes

It has been ten years since Micheli et al published their last gender paper, which looked at earlier Eurocare data. In 'The prognostic role of gender in survival of adult cancer patients' (*EJC* 1998, 34:2271–78), which was put forward as the first such examination of gender in cancer survival, they suggested that "women may be intrinsically more robust than men in coping with cancer." The better overall survival in women, they noted, could result from one or more factors – women paying more attention to their bodies, resulting in earlier diagnosis; the impact of different risk factors on the cancer case mix; and a "biological superiority in women in responding to disease, treatment or both". They also note the figures may be skewed by different corrections for comorbidity between men and women.

For Alan White, probably the first professor of men's health in any country, based at Leeds Metropolitan University in the UK, the data on worse incidence and outcomes for many male cancers is a huge issue that absolutely requires more detailed analysis. "In 2003 the European Men's Health Forum commissioned a study of men's health across Europe, the first time we had looked across all health issues for men, and it emerged that men seemed to be developing and dying from all sorts of conditions at a greater rate than we thought. We assumed that cardiovascular disease would be the major condition – but cancer emerged as a higher cause than we anticipated."

White has also assembled data from various sources. Looking for example at the differences in England and Wales between the sexes he finds that, although cancer accounts for a greater proportion of female deaths in younger age groups, removing breast and genital cancers reveals that "63% more men in England and Wales in the 15–64 age group succumb to cancers that should be affecting men and women equally".

"For Europe as a whole, five-year cancer survival is about 55% for women, but just 45% for men"

He has since spent a good deal of time analysing the causes for the excess male cancer mortality, including organising an expert symposium on the issue ('Tackling the excess incidence of cancer in men'), held in 2006 in Leeds. At this event, David Forman, of the Centre for Epidemiology and Biostatistics at the University of Leeds, noted that the received wisdom of men presenting later is not sufficient to explain the discrepancy in mortality rates. He also commented that the drop in smoking among men and the lower rates of lung cancer, while cutting overall male rates could still mask differences in other cancers, and indeed in most other tumour sites there doesn't appear to be any single explanation for the higher incidence in men, though a simple combination of smoking and alcohol is associated with male oral cancers.

White considers that while later presentation is a factor, it has to be added in with a wide range of lifestyle factors including smoking, diet, physical exercise, body fat and obesity. Socioeconomic inequality also plays a part – in England, social disadvantage worsens outcomes for men more than for women. (The Eurocadet project – www.eurocadet.org – is currently examining the major lifestyle and socioeconomic factors affecting the incidence of cancer around Europe.)

Melanoma stands out, as Coebergh and White comment, because of the worse outcome for men coupled with lower incidence – one of the few cancers, in fact, where incidence is higher in women. Identifying the reasons may help point researchers in promising directions. At the Leeds expert symposium, Forman presented data that showed that even after controlling for stage at presentation and the location of the tumour, there is still a 31% survival advantage for women, which can partly but not wholly be explained by factors such as age and socioeconomic status. Similar results have been written up by colleagues of Coebergh in the Netherlands, led by Esther de Vries at the Erasmus Medical Centre, where again an unexplained gap in male/female survival was found in a sample of more than 10,000 Dutch melanoma patients.

"Hypotheses about the difference include looking at the role of the immune system," comments Coebergh. "And there is also evidence about obesity as a cancer risk for men and melanoma – we do not see the same risk in obese women – so the underlying factors that determine obesity in men may also determine the progression of melanoma." He points to a recent meta-analysis in the *Lancet* that reinforced the obesity link. He adds that his group is cooperating with the European Organisation for the Research and Treatment of Cancer (EORTC) in looking at melanoma trial data, where there is more detailed pathology, in the search for prognostic factors for men and women. Other research he mentions is led by Alan Spatz, chair of the EORTC melanoma group, on the role of the X and Y chromosomes in protection and tumour progression. "An interesting point is if we can explain the male/female difference it might lead to new therapeutic approaches, as nothing seems to work so far with melanoma."

Meanwhile, in bladder cancer, which stands out as a cancer in which women face a worse prognosis, Coebergh says he is not aware of systematic efforts to explain the reasons, but there are various explanations, including underlying biological causes, while urologists have, he says, traditionally investigated men earlier and more thoroughly than women, where in any case the tumour has been rare.

Cultural factors

Differences in treatment and wider cultural factors are of great interest to White. "My concern is that we start seeing a marked rise in incidence of diseases such as cancer and heart disease after the age of 35 in men, which is also the time when they are least likely to be seen by health services. We need to target men more effectively in the workplace so that we can identify those men who are reluctant to come forward and are missing the benefits of early diagnosis."

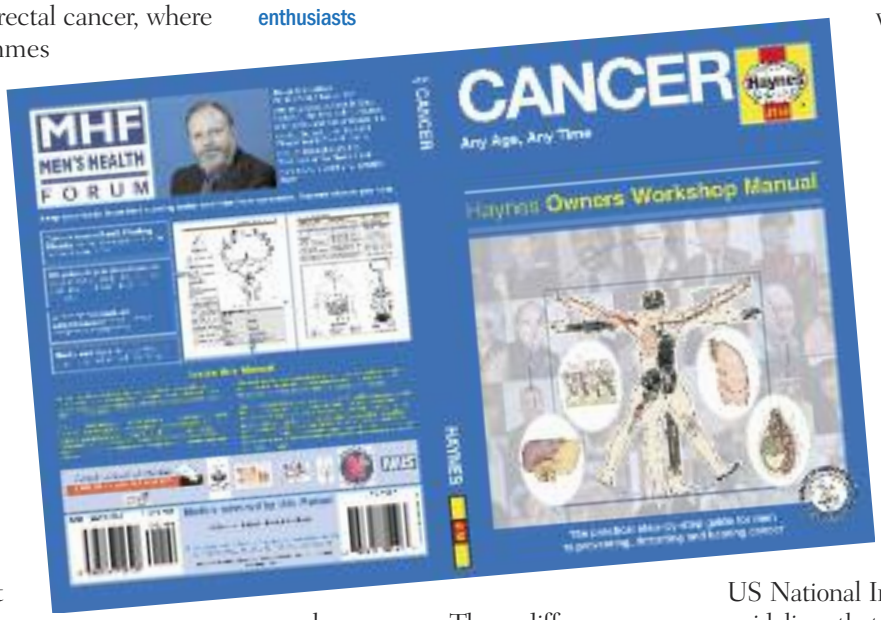
The European Men's Health Forum (EMHF) leads on many activities like this around the region, and this year made the workplace the theme for the International Men's Health Week. It issued a 'Lung cancer in the workplace' document in June, which highlights the need for health policies for migrant workers.

The EMHF's president, Ian Banks, is a pioneer of men's health in Europe, and now a visiting professor at Alan White's department. The site www.emhf.org has copious resources, including a download of the proceedings of the Leeds expert symposium – this event, White is pleased to report, is referenced in England's recent reform of its national cancer strategy. "It is clear that more research is needed if we are to fully understand how gender impacts on cancer," the strategy notes.

Indeed, the EMHF and professionals such as Banks and White are also calling for far more research about men and

cancer. As White says, "No systematic study of men's increased risk of cancer has yet been undertaken." There could, he adds, be major implications for healthcare policy makers in the sex and gender differences. Take colorectal cancer, where screening programmes are now starting to be implemented in several countries: if there is evidence that men are developing and dying from the tumour earlier than women – which indeed there is – does it make sense to start everyone at the same age? It may be more effective and cost-effective to bring forward the age of first screening for men, or put back the first female screen.

Coebergh points to another factor with colorectal cancer, this time in favour of men. "Men tend to have spouses to look after them and so are more likely to receive adjuvant chemotherapy than women, many of whom are widows when they are diagnosed with disease." Another intriguing difference in treatment applications, which was reported at the expert symposium, concerned oesophageal cancer, where data from one region in England show that radiotherapy is the favoured treatment for women with oesophageal cancer but chemotherapy for men. Marked differences have also been reported in surgery for colon and rectal cancers, and treatments offered for lung cancer. These differences are not easy to explain, although other patterns are, such as more aggressive treatments for younger men.



Targeted message. To catch the attention of an adult male audience, the UK Men's Health Forum published this information and advice on cancer in the form of a 'Haynes manual' – familiar to all car lovers and do-it-yourself enthusiasts

Response to treatment and fundamental differences in biology add further layers of complexity. Trials of new therapies will increasingly look for differences in how men and women respond as knowledge of genetic factors increases. Hormones, notes Coebergh, could also be playing a role in some cancers. Oestrogen, for example, while a risk factor in post-menopausal women for breast cancer, may be protective in sites such as the bowel and stomach where there are also oestrogen receptors. Studies have shown that exposing men to oestrogen can reduce their risk of gastric cancer, for example.

Researchers in the US have recently carried out one of the first studies on mice showing that male animals suffer more skin damage and worse tumours when exposed to harmful ultraviolet radiation.

But it is only relatively recently that a massive gender bias – in men's favour – has started to be addressed in developing therapies. Many cancer drugs were initially tested only on men, and there is continuing bias in clinical trials and research towards men not just for cancer but for most diseases. Safety and comparability with other studies are among the reasons for women's exclusion. In 1994, the US National Institutes of Health issued guidelines that allowed American women to enter phase I, II and III trials, but as Anita Holdcroft, of Imperial College, London, writes, "there has not been a dramatic recruitment of women's data into trial results," and many drugs are withdrawn from the market because of women's health issues (see *J R Soc Med* 2007, vol 100).

There is a good deal more to come in the sex and gender story in cancer, as there is in the development of 'gender medicine' as a specialty in its own right. Just where the biggest impacts are likely to come from – underlying biology, or cultural and treatment factors – and for which cancers, should occupy researchers for some time, provided the will and pressures are there to carry out the studies.

"We need to target men more effectively in the workplace to identify those reluctant to come forward"