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Time to act on trials

KATHY REDMOND EDITOR

Many of the worst economic and bureaucratic burdens that have proved such a deterrent to multi-country clinical trials look set to be addressed with the overhaul of the EU Clinical Trials Directive. There are strong hopes that the new legislation will reverse a trend that has seen the number of clinical trials carried out in the EU drop by 25% between 2007 and 2011.

The new rules will not come into effect, however, until 2016. That is a long time to wait for patients who are hoping to gain access to a trial – and for young oncologists who are keen to gain experience in conducting trials.

The good news is that we can do a lot right now to improve the situation, as has been shown in the UK, where the proportion of cancer patients participating in trials has quadrupled in a decade, from 1 in 26 to about 1 in 6. Setting up a National Cancer Research Network has helped reduce the bureaucracy associated with conducting trials and boosted recruitment by ensuring all NHS hospitals are involved in clinical studies.

There are important lessons here for other European countries, most of which have a pitiful level of enrolment in cancer trials. One is about the importance of ensuring that all patients are told about any opportunities to take part in trials. Without help and guidance, it is very difficult for patients to find out about trials that they might be eligible for, and where they are taking place. Clinical trials registries, such as the new EU register, are an important source of information about ongoing trials (www.clinicaltrialsregister.eu), but even the most informed and motivated patients find registries difficult to navigate. Revamping these key information sources to make them easier to understand will help eligible patients find a trial that is right for them.

There is also a lot we can do to help reduce the burden involved in taking part in a clinical trial. Patients prefer not to have to change to a different healthcare team or a different hospital. Requiring them to travel long distances, or undergo frequent and sometimes painful testing, can also act as a significant deterrent. Trials need to be designed to be as patient friendly as possible. Involving patient organisations at the planning stage can help by ensuring aspects that could act as a deterrent are flagged up and addressed.

Attitudes can also be a block. People who believe trials are all about using patients as "guinea pigs", or think they may get worse than the current standard of care if they end up on the control arm, will be unlikely to sign up. A concerted effort is needed to challenge such unjustified negative assumptions and highlight the potential benefits of taking part in a trial. The media can play a big role here, as is demonstrated in this issue's Best Cancer Reporter article (p 28).

The cancer community – professionals and patients – must work together now to address these barriers and promote the message that clinical trials are good for patients, good for science and good for society. ■

Vincenzo Valentini:

putting knowledge to work

MARC BEISHON

Patients are being let down by a failure to integrate the knowledge we have to get the best possible results for each individual patient and for cancer patients as a whole. Vincenzo Valentini, the ESTRO president with a talent for maths, believes we must do better.

The paradigm of personalised medicine has ushered in a potentially endless stream of new variables that can predict outcomes and response to treatments – far more than any doctor could hope to manage on their own. While high-quality multidisciplinary working among specialists is essential, it is not enough. New tools and approaches are needed that help oncologists integrate all the relevant knowledge and information to guide their decisions.

A European leader who is on top of this agenda is Vincenzo Valentini, current president of the European Society of Therapeutic Radiation Oncology (ESTRO), and chair of radiotherapy at Gemelli hospital in Rome, which sees more cancer patients than any hospital in Italy and is part of Università Cattolica del Sacro Cuore.

Not only has he been designing educational computer tools for many years, he is now at the forefront of a movement to introduce decision-support systems that address the daunting complexity facing oncologists. As ESTRO president, he is also driving the society's ambitious vision introduced in 2012 – with education and multidisciplinarity at its heart – and is reaching out to other parts of the cancer community in an effort to get a more coherent voice for oncology in Europe.

At the centre of his message is what Valentini calls 'knowledge-based oncology', which, as he explains, is not the same as evidence-based medicine. "Evidence-based oncology takes into account prospective studies on defined populations of patients, and doctors try to apply them to individual

patients on the basis of their understanding of patient features and of the study outcomes, taking for granted that they are uniform. Knowledge-based oncology aims to offer a decision model from heterogeneous data – clinical, biologic, imaging, treatment, demographic – to predict the outcome, and can offer a more transparent and reproducible system."

The implications of getting this right for oncology are profound, adds Valentini. By 2020 or so he expects that there will be many thousands of variables that will predict survival, whereas the number of variables that doctors can handle on their own can be counted on the fingers of one hand. "So why not use the databases of information we already have in hospitals – imaging, blood, tissue, clinical records and more – to identify the more important predictors of survival and tailor the treatment?"

Such predictive modelling from large databases is one inevitable and challenging part of the future for personalising treatment for patients, says Valentini. It will integrate data on a patient's clinical features with information derived from continuous monitoring of how the disease is responding to ongoing treatments, which will be adapted accordingly. Data from imaging will be key. "We need to put together variables we are not accustomed to integrating," he says, pointing to the use of mathematical models such as nomograms – graphical calculators – that help make sense of wide sources of data for decision support.

While there is rapid growth in such tools, we are only at the beginning, says Valentini, who notes that the 'big picture' for this could hardly be bigger. The economic challenge of finding more cost-effective ways to deliver high-quality healthcare, as well as the medical challenge of rapidly filling the gaps in translational research and realising the promise of personalised medicine both depend on our ability to integrate large amounts of different types of information. While other branches of medicine are also contributing to the explosion in data, oncology stands out as requiring the data crunching of a wide range of rapidly growing inputs, from cell biology to patient experience.

That there is a long way to go is also evident from the lack of true multidisciplinary teamwork that could make more sense of complex situations, he notes. This is driven partly by what he sees as a lack of ethics in healthcare. "As a profession we need a clear ethical framework that respects the patient, but this can be diluted by focusing too much, for

JORGE NOGUEIRA

"We tend to see things from the perspective of our own tools and not how we can integrate with others"

example, on attracting specialist surgeons." This can lead to cutting costs in other important areas, leading to poorer outcomes overall, he says. For instance, he adds, it is notable that, despite strong evidence, opportunities are being missed to integrate radiotherapy to spare extensive surgery in tumour sites such as head and neck, breast, cervix and prostate.

It was a development in Valentini's own specialist area of rectal cancer that first convinced him of the need to work in a much more integrated way. "When we saw the first rectal and anal cancer patients who showed no more tumour after chemo-radiotherapy, that set us on the course of thinking about how we could work with other disciplines. We had been giving chemotherapy ourselves, like clinical oncologists do in the UK. We could also see that the surgical approach could change with chemo-radiotherapy. Our experience with imaging and data management put us in a good position to support the first multidisciplinary teams and become care drivers for patients at Gemelli at a time when this was not at all usual in Italy or Europe." Valentini's now 17-strong radiotherapy department continues to be the organiser of oncology care, he says.

To promote this more joined-up approach at a wider European level, Valentini is spending a lot of time not just with the top-level networking expected from the president of ESTRO, but also at the front-line of other disciplines, addressing European cancer surgeons and medical oncologists at their respective conferences. He does this, he stresses, in a non-confrontational way, taking a problem-solving learning style he has implemented for ESTRO and his own university hospital, both face-to-face and in particular in computer-based learning.

Understanding the problems faced by other specialists is critical to getting messages across about multidisciplinary working, he believes. "In the 1980s I had the opportunity to do intraoperative radiotherapy, so I could see first hand the difficulties surgeons have in removing tumours and preserving functionality. We tend to see things from the perspective of our own tools and not how we can integrate with others. I find surgeons are much more receptive if you appreciate the challenging problems they have in things like the risks of bleeding when operating in the pelvic area, when putting the case for radiation to reduce recurrence rates. If you just start by saying, 'I do organ-sparing radiotherapy,' you have less chance of being listened to."

Valentini recently put in a long spell as secretary of the International Society of Intraoperative Radiotherapy (ISIORT) and he has certainly been listened to by ESSO (the European Society of Surgical Oncologists), which has given him honorary membership – "I'm the first non-surgeon it has honoured in this way and it is an acknowledgment that I can speak their language," he says.

Patients, he adds, are wanting not only cures now but the best quality of life, given that many will live a long time. "We need to be ready to manage the best combination of treatment for them," he says, noting too that not only is there a mounting challenge of making decisions for so many variables, but there is also little evidence to prove the merits of multidisciplinary working. One paper he cites is on the impact of multidisciplinary team management in head and neck cancer, by a group in Australia. They report that 'robust evidence' that shows improvement in outcomes is lacking, leading to scepticism about the multidisciplinary team approach and its costs. Their own findings show a significant increase in survival when multidisciplinary teams are used – but also that a 'surprisingly high' proportion of patients are still being managed by a variety of disciplines working independently.

One consequence, says Valentini, is that some patients undergo unnecessarily extensive surgery: there is strong evidence, for example, that radiochemotherapy can cure patients without extensive surgery in cancer of the larynx, leaving patients with less damage to their vocal chords.

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At Gemelli there are some 12 tumour board meetings each week and, significantly, in attendance are imaging professionals trained to work on particular cancers as well as the technology, such as PET/CT, MRI and ultrasound. Valentini cannot stress enough how important imaging is becoming, both in molecular imaging within the best laboratory of all – the human body – and with the sophisticated hybrid radiotherapy and imaging set-ups that allow for repositioning of patients day to day and for movements when therapy is delivered.

He is particularly excited about the potential for 'radiomics' – using radiology, including sophisticated CT and MRI scanning, to guide treatment decisions by providing a picture of the cancer's biology and genomic expressions. As he notes, this sort of imaging has two big advantages over molecular testing from biopsies – it can provide information about the whole tumour and, as it is not invasive, it can be repeated to capture changes in tumour biology in response to treatment and progression of the disease (for more on this Valentini suggests recent papers on radiomics by Lambin et al. *EJC* 48: 441–446, and on tumour heterogeneity by Gerlinger et al. *NEJM* 366:883–892).

Again this is about adding more information to address the many variables that cancer has in the body, to both improve the chances of correct decisions for using targeted drug therapy and enable doses of radiotherapy to be targeted to areas of tumours that are, for example, more resistant to treatment. "Understanding tumour behaviour using imaging is the frontier and I trust this much more than what we do in the laboratory," says Valentini, who adds that in a few years' time we will see considerable advances in the contribution of imaging at the molecular level.

What a new approach to decision support needs is validation, and Valentini is leading a project called VATE – 'validation of high technology based on large database analysis by learning machine' – which is using dose distribution data from radiomics along with clinical data and reference databases for outcome prediction. "I refer to this kind of work as

"Conventional controlled trials have not been able to identify those at early risk of an aggressive recurrence"

'reverse angle' because we are coming at problems from an opposite direction," he says.

A typical type of question where more decision support is needed, he says, is in rectal cancer patients, to determine which patients are at high risk and which at low risk of local and metastatic recurrence, so that adjuvant chemotherapy and close follow-up can be given to the right people. Conventional controlled trials have not been able to distinguish those at early risk of an aggressive recurrence from those whose cancer may recur much later. With colleagues he has published just such a model, using nomograms based on data from large European clinical trials. For more on this see *JCO* 29:3163–72 and also www.predict-cancer.org, a project at MASTRO Clinic, a radiotherapy centre in Maastricht, Netherlands, which is one of several organisations developing prediction systems, and with which Valentini and others are collaborating. A paper on multifactorial decision making in radiation oncology has recently been accepted by *Nature Reviews Clinical Oncology*, led by Philippe Lambin at MASTRO.

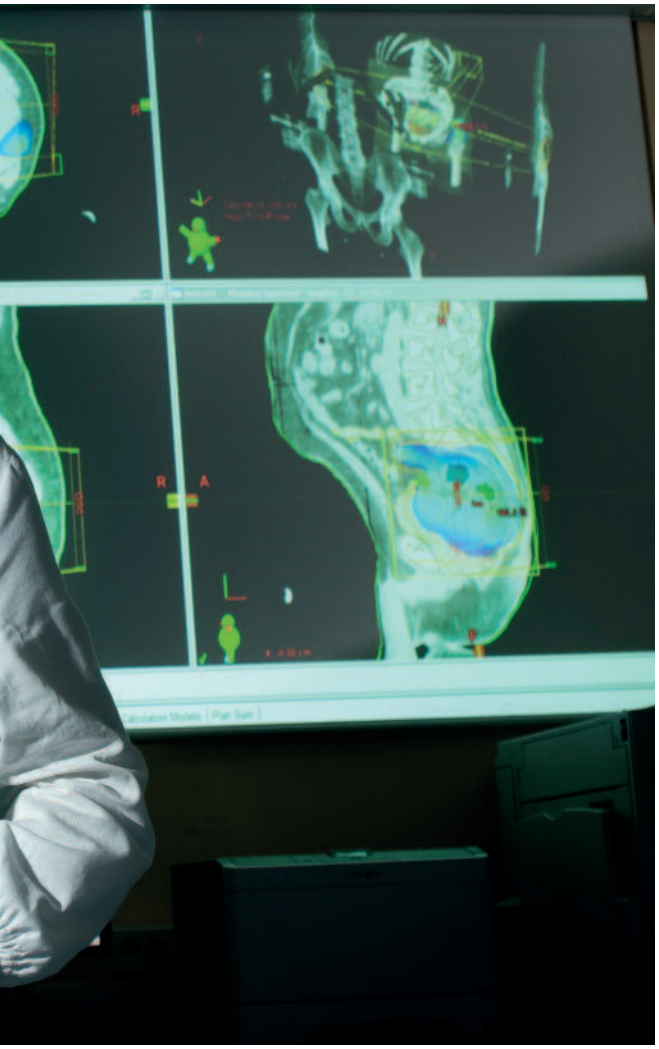
For radiotherapy in early-stage treatment, says Valentini, there is an ongoing process of refining and extending gains that have led to fewer side-effects and better quality of life in rectal, breast, lung, head and neck, and particularly prostate, cancers as newer techniques are able to deliver safer, better-targeted dose volumes. But there is so much more to the field – he picks out a growing interest in treating metastatic disease, including using radiosurgery to consolidate remission after chemotherapy, to remove residual tumour and avoid going to second- and third-line drug treatments.

"We want some patients to avoid always being under treatment and to use a 'stop and go' strategy we see now being applied in colon cancer," he says. An ESTRO forum in April will devote a day-long session to this topic. Giving radiotherapy to older people who cannot tolerate chemotherapy is allied to this, he adds. At Gemelli, there is also provision for people with advanced disease to stay in the hospital with their families for pain treatment with radiation. "We challenged the view of some doctors who thought it was too much trouble to send patients here and who would instead just escalate their opioid drugs," says Valentini.

Valentini has spent his entire career at Gemelli and went into radiotherapy at an early stage.

"I wanted to work in a field with a strong relationship with people, and a good place to do that is where they have troubles. Psychiatry is an obvious choice once you are in medicine, but I had a very good mentor in Numa Cellini [a leading Italian radiotherapist], who suggested cancer, and I've never looked back. If you have a good mentor you have a good chance of being a good doctor, and what's more, he was no English speaker and let me be the 'foreign minister' for the department."

He was in post when the first CT machine arrived, and being mathematically minded – maths could have been an alternative career – he worked on one of the first computerised treatment plans for using CT scans, and also developed a data management system. Out of the computing work also came a strong interest in education, and by the mid-1980s he was instrumental in introducing a computerised learning system for radiotherapy, segmenting knowledge into 'learning objects' for use by department staff and students at his medical school.



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Valentini has a special interest in medical 'e-learning', using problem-solving techniques and tailoring content to specific audiences such as clinicians, technicians and nurses. And it ties in with the large-scale decision-support systems he can see on the horizon, which could use very sophisticated technology such as neural networks.

This e-learning approach is now an important component of the ESTRO educational approach. Valentini is a core member of the education and training committee (chaired by Richard Pötter), and he is chair of Eagle (ESTRO Applications for Global LEarning), which has started online courses for rectal cancer, where more multidisciplinary working is becoming crucial. He has also helped develop Tiger (ESTRO's educational programme on image guidance) and Falcon (on contouring), as well as new core curricula for the three main radiation oncology professionals – clinicians, physicists and technicians – jointly promoted by ESTRO and the European Board of Radiotherapy of the Union of European Medical Societies.

At ESTRO, he admits the vision he has produced with colleagues is very ambitious. "But you won't take any steps unless you set your sights high. I feel that we have achieved a much stronger voice in European oncology, thanks in particular to our past president Michael Baumann, who went on to become president of ECCO. We have set our own house in order with activities such as promoting science with our meetings and our educational programmes. Refining our membership strategy will be a priority this year."

ESTRO's vision remains focused on improving access to radiotherapy and optimising care for patients in Europe and further afield, through international liaison. The lack of a coherent vision within the broader community of cancer societies, however, remains a worry, and Valentini says he is keen to find effective ways for ESTRO "to drive the priorities and activities for the 'village of societies' at the oncopolicy level," which he adds is no easy task. "One way we are doing this was to publish the ESTRO vision

"We are challenging the other societies to set out their visions as we have done"

at our strategy meeting at our 30th anniversary meeting – we are challenging the other societies to set out their visions as we have done."

Of a recent ECCO oncopolicy meeting in Brussels, he comments: "It was light and shadows. It met many different perspectives, but with no clear strategy of what we have to prioritise and ask for from the European Commission on behalf of cancer patients and the scientific community."

He is also keen to invite more people into the ESTRO 'house' by working more with the disciplines that are closely allied to radiation oncology, including the societies that represent radiobiologists, medical physics, nuclear medicine and, of course, radiology. As Valentini says, the separation of European radiotherapy from the more numerous and powerful radiologists may have been a necessity to build the speciality of radiation oncology, but closer cooperation is overdue given that there is now a vital role for both in cancer treatment and research. This lies in what is being termed 'imaging theragnostics' (of which radiomics is a part) – using imaging knowledge (gnosis) to drive therapeutic choices from planning to treatment to follow-up.

He is pleased to report that a first joint course on multidisciplinary cancer imaging was hosted at his own hospital in October 2012, run by ESTRO and the European School of Radiology (the education arm of the European Society of Radiology).

His aims for ESTRO in the near future include cementing the scientific and educational side of the vision, continuing for example with focused 'topics of the day' at meetings. Engaging young professionals is another priority. "We have a taskforce that is setting achievement goals for young people over a year and we also run a school for future leaders," he says. Membership is also an issue for 2013 – "We will introduce block membership for institutions and clarify benefits for the two main classes of members – those who want to buy services and others who want the honour of belonging to a society."

Online education will be extended, but one product looks to need little change: ESTRO's journal, *Radiotherapy and Oncology*, has the highest impact of all journals in the sector – well ahead of the US equivalent – thanks to editor Jens Overgaard, says Valentini. He adds that Europe is also more active in clinical trials and is making more advances in radiotherapy practice, although the US does introduce much new technology.

The US has though provided Valentini's own department with what he considers to be a vital service – quality assurance – thanks to accreditation from the American College of Radiation Oncology (ACRO). "Ten years ago we looked for an external agency to assure our procedures but there were only general industrial bodies in Europe. So we went to ACRO as the first hospital outside of North America for its QA programme. We would of course like to do QA from ESTRO and it has been considered in the past – we may look at it again." Most radiotherapy units in Europe are not externally accredited, he adds, but many do have good internal quality assurance programmes. "But we do need to formalise this more."

While it is easier to measure what goes on in radiotherapy than it is in surgery, for instance, and Europeans tend anyway to be very cautious about implementing technology, Valentini says there are clear pressures now in some countries to compromise on support for expensive units. ESTRO, he adds, is continuing to survey national provision with its HERO (Health Economics in Radiation Oncology) project (see also *Cancer World* September–October 2011 for a report on this and other ESTRO activities at the time of its 30th anniversary).

What will be most difficult for his presidency, Valentini agrees, is building consensus in the 'village' of European oncology for his vision of ethical, multidisciplinary working that best serves the patient. "But we Romans were good at developing a language of values and a moral and political framework for Europe – and that was without the Internet." ■

MARK THOMAS/SCIENCE PHOTO LIBRARY

The reoperation lottery

EMMA MASON

The odds that a woman will be told she needs a reoperation after conservative breast surgery vary between treatment centres, prompting calls for international guidelines – and greater oversight of surgeons.

For many women with early breast cancer, hearing that they can safely be treated with breast-conserving therapy comes as a big relief. What they don't want to hear is that they will have to undergo a second surgery, because the 'margin' of cancer-free tissue cut out from around the tumour is deemed unsafe. Getting it right first time may not always be possible, but growing evidence of big differences in reoperation rates between different centres is raising questions about how many women may be undergoing unnecessary reoperations, and why. Attention is focusing on the need for consensus guidelines on what constitutes a 'safe' margin and how it should be measured.

Ensuring sufficient tissue is excised to minimise the risk of the tumour returning is important, because a local recurrence not only causes the woman extra distress, but is also associated with reduced survival. But reoperating where the margins are judged to have been insufficient also comes at a cost – physical, emotional and financial – so it is important to ensure that women are only referred back for further surgery when there is good evidence to show it is needed.

The need for a greater consensus and more uniform practice regarding when women should be sent back for reoperation was highlighted last July in an article by Ranjeet Jeevan and colleagues in the *British Medical Journal* (vol 345, e4505). The study reported that, on average, around 20% of women who had breast conserving surgery in England had a reoperation, but that the rate of reoperation varied widely from centre to centre. "Some English NHS trusts had adjusted reoperation rates below 10%, whereas for others it was above 30%."

Examining the potential reasons behind such variations, the authors argue that it cannot be explained by patient preference alone. "The variation is sufficiently large to suggest that it reflects differences in clinical practice at various points during the therapeutic pathway, as well as patients' preferences. Practice related causes of variation could include differences in selection protocols for breast conserving surgery, poor surgical technique, and differences in how resection margins are assessed…" They suggest that the "lack of consensus on what constitutes an adequate excision margin" is probably an important factor, and they note that this is not just a UK problem; similar studies have shown reoperation rates of 29% in The Netherlands, 23% in the US, and 21.5% in Germany – again with significant variations in the rates reported by different hospitals.

Bigger 'is not better'

The publication of the *BMJ* article coincided with a 'sounding board' editorial in the *New England Journal of Medicine*, by Monica Morrow, chief of the breast surgery service at the Memorial Sloan-Kettering Cancer Center, New York, that focused on unnecessary reoperations. Under the title "Surgical margins in lumpectomy for breast cancer – bigger is not better" (*NEJM* 2012, 367:79–82), Morrow argues that in many centres women are being reoperated to achieve margins of between 2 and 5 mm, or even more, which cannot be justified by the evidence.

"…20 to 30% of women who undergo breast-conserving surgery require additional breast surgery (re-excision) after the initial lumpectomy, with its associated illness and cost. Approximately half of these procedures are performed in women with negative margins [i.e. no cancer cells at the edge] to obtain a wider clear margin in the belief that a wider margin will further decrease the risk of local recurrence," she writes.

Available data, she argues, do not support the view that wider cancer-free surgical margins reduce the risk of the cancer returning, while there is plenty of evidence that when the cancer is removed with a narrow margin, adjuvant radio- and chemotherapy is effective in controlling local recurrence after surgery.

Among the evidence called on to back up this argument she cites a meta-analysis of 21 studies that showed no statistically significant difference in local recurrence in early-stage invasive breast cancer between margins of 1, 2 or 5 mm after adjusting for the use of radiation and hormone therapy.

The big predictors of recurrence, she argues, have been shown to be tumour biology and the adequacy of systemic therapy. "These data necessitate a shift in thinking regarding the relationship between the width of microscopic margins and the risk of local recurrence." She suggests that such a rethink could see a major reduction in reoperations for women with clear margins, resulting in a decrease in costs and better cosmetic outcomes.

Mike Dixon, professor of breast surgery and consultant surgeon at the Western General Hospital in Edinburgh, was

"These data require a shift in thinking about the relationship between width of margins and risk of local recurrence"

"What we want to do is get the disease out with a little bit, but not too much, normal tissue"

one of the co-authors of the meta-analysis that demonstrated no benefit from margins wider than 1 mm in early-stage invasive breast cancer. He argues that the difference between 1 mm and 5 mm is very significant in terms of the damage done to the way the breast looks.

"You have to leave the breast looking normal," says Dixon. "It's very easy to get all the disease out by taking a wedge out of the breast, but you're going to leave a big dent, a poor cosmetic result, and that is no advantage to the patient. That's why people like me are so obsessed with getting clear but not wide margins, because this allows me to achieve adequate long-term local control, but more importantly it allows the breast to look normal and gives the patient the advantage of a good cosmetic outcome.

"We know that if you do breast conserving surgery and it looks ugly, then the patient is not satisfied, and all the psychological advantages of breast conserving surgery in terms of ability to wear normal clothes, looking good in the mirror, the patient being more confident with good self-esteem and good body image disappear. The benefits of breast conservation are only there if you maintain a good breast shape and a volume that matches your other breast. What we want to do is get the disease out with a little bit, but not too much, normal tissue, and then good radiotherapy and good drug therapy to take care of any remaining disease, and then the patient will have an adequate long-term control and a satisfactory looking breast."

Dixon, whose own centre has been using a 1 mm margin for invasive early breast cancers for more than 10 years, with a five-year local recurrence rate of 1.7%, would like to see a consensus "around a 1 or 2 mm margin", to reduce the number of women who have unnecessary reoperations. "At present, some patients with clear margins of 1 or 2 mm are not only getting a second operation, some are getting a mastectomy!"

Towards a consensus

If the evidence is as strong as Morrow and Dixon claim, the question is why such a consensus is not already in place. One answer may be that leading breast cancer specialists do share a broad consensus – but this is not yet reflected in standard practice. In 2008 a group of opinion leaders from the US and Europe met in Frankfurt to formulate consensus recommendations on the locoregional treatment of primary breast cancer. Convened on the initiative of Manfred Kaufmann, head of gynaecology and obstetrics at the JW Goethe University hospital, Frankfurt, the group included leading oncologic surgeons, radiation oncologists, pathologists, radiologists, plastic surgeons, medical and gynaecologic oncologists, and epidemiologists. Their recommendations, which were published in 2010 (*Cancer* 116:1184–91), were that to minimise the risk of recurrence:

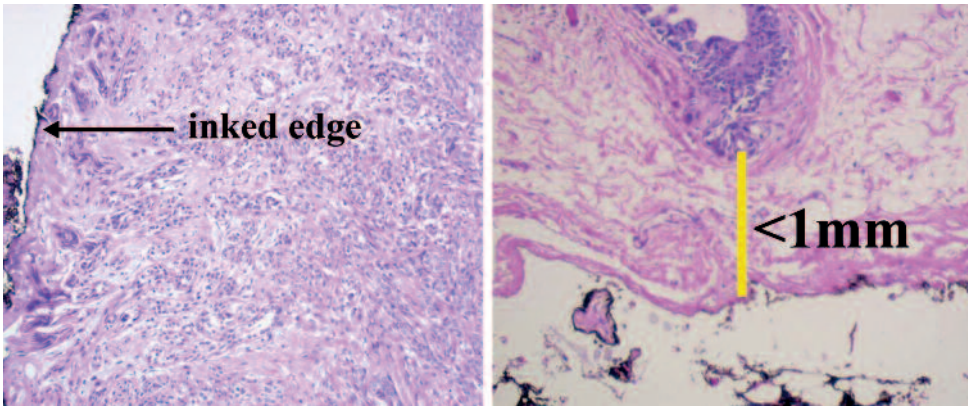
- In general, in cases of positive margins – where cancer cells are visible under the microscope at the surface of the excised tissue – reoperation is required.
- In the case of negative margins – i.e. no cancer cells at the surface of the excised tissue – reoperation is not required in cases of invasive breast cancer, even where the distance between the surface and the closest tumour cells is less than 1 mm.
- In cases of ductal carcinoma *in situ* (DCIS), however, a minimum clear margin of 2 mm is recommended, particularly with low- and intermediate-grade lesions, because DCIS may grow discontinuously within the ducts.
- Anterior and posterior margins of less than 2 mm are not of concern if there is no residual breast tissue.
- All suspicious microcalcifications associated with the DCIS should be removed surgically.
- Lobular carcinoma *in situ* at the margin is not considered an indication for further surgery.

While the wide variations recorded in reoperation rates indicate that many centres are not following these recommendations in practice, neither the recommendations, nor the evidence they have been drawn from, are being fundamentally challenged. The problem, therefore, may lie in how to move from consensus recommendations to effective national guidelines that ensure all women are treated according to the same standards wherever they are.

How good is your pathology?

But there may be other factors that also explain the variability in reoperation rates. Giuseppe Viale, head of pathology at the European Institute of Oncology in Milan, who participated in the expert panel that drew up the recommendations, says the quality of specimen processing and the assessment of surgical margins can vary greatly between different pathology departments. This means

MEASURING THE MARGINS



Following surgery, the excised tissue is 'inked' so that, when thin slices are cut and examined under a microscope, the edge of the tissue is clearly delineated. Pathologists need clear guidelines to ensure their examination of margins is sufficiently thorough and they understand the significance and implications of what they find.

that even if uniform criteria for reoperation are applied, different centres may reach different decisions on a given specimen, because of variations in the way the margins are measured and evaluated.

The standard procedure is to apply ink to the surfaces of the excised tissue. Thin slices are then cut, which are placed under a microscope, where the pathologist can see how close cancer cells come to the inked edge of the excised tissue. But tumour tissue can be tricky to handle, with a tendency to lose its shape and fall apart when sliced thin. And it can be difficult to get a reliable 'all round' view, because samples are taken 'at random', and each slice represents only one cross-section in one particular plane.

Variations in terminology can also give rise to confusion. As Dixon explains, some surgeons define a 'cancer-free margin' as one where there was no ink on a cancer cell. So even if there was a microscopically small distance between a cancer cell and the ink, it would still be a cancer-free margin. "However, most other people use distance. Some studies have used 2 mm, so they would say that if there were cancer cells within 1–2 mm of the edge of the specimen that would be a 'positive margin', and if the distance was more than 2 mm it would be 'negative margin'. But within the 1–2 mm margin distance, a large percentage of those patients would have 'cancer-free margins', because there isn't cancer at the edge."

Pathologists also need to understand the significance of what they are seeing; for instance, if lobular carcinoma *in situ* (atypical cells that are not invasive and are confined to the lobules in the breast) is found at the margins of the tissue, or if margins have only minimal tumour involvement, then further surgery is not necessarily required, says Viale. "This is especially the case for tumour types that have a favourable prognosis, such as luminal tumours and grade 1 tumours. The risk of local recurrence in these cases may be greatly reduced by radiotherapy and proper systemic treatments."

Viale believes there is a need for more guidelines and quality control to ensure patients and doctors can have confidence in the pathology assessments. "Practice in pathology departments should be standardised to allow at least a 'minimal' assessment of the margins; i.e. close examination of the margins nearest to the tumour, and the margin behind the nipple in the case of nipple-sparing mastectomy. Each department may then examine further the margins, but at least those I have mentioned should be evaluated in a standard fashion." Again it comes down to effective guidelines, he says. "National and international guideline recommendations should be strictly followed. Where national guidelines have not been issued, these should be prepared in accordance with the international recommendations."

Getting it right first time

While a more uniform approach to what constitutes an adequate margin, and how that should be measured, should decrease the number of women who are unnecessarily referred for

"Practice in pathology departments should be standardised to allow at least a 'minimal' assessment of the margins"

"The days of individual surgeons getting away with what they think is right are gone"

reoperation, there will still be cases where reoperations are required, because insufficient tissue was removed first time round.

In the *BMJ* study, Jeevan and colleagues noted that reoperation rates were particularly high in women with "a carcinoma *in situ* component recorded at the time of their primary surgery", and suggested that the problem partly relates to difficulties in identifying the extent, rather than just the presence, of carcinoma *in situ*, "because many such tumours are multifocal". They suggest that more thorough use of ultrasound imaging could help decrease reoperation rates.

Some surgeons are experimenting with new tools to help them locate the margins of the tumour while they are operating. Marc Thill, head of the Department of Gynaecology and Obstetrics at the Agaplesion Markus Hospital, in Frankfurt, published a report in *The Breast* in 2011 (vol 20, pp 579–580) on the impact on reoperation rates of using a radiofrequency spectroscopy device while operating on patients with DCIS.

MarginProbe, manufactured by the US company Dune Medical Devices, involves a disposable hand-held probe and a console to detect differences in dielectric properties between normal and malignant breast tissue. Using their historical objective of 5 mm clear margins, in a study of 22 patients, use of the device lowered his department's re-excision rate, from 38.8% to 18%. In line with ongoing discussions about changing to a 2 mm margin, Thill also calculated the re-excision rate using 2 mm clear margins as the threshold, which would have reduced the re-excision rate to 14%. Thill now hopes to extend it to other types of breast cancer, and says he knows of about 11 other centres in Europe that are also using the device.

There are problems associated with the device, however; in particular its cost. The console costs around €28,000, with a further €600 for each probe, which can only be used for a single operation.

There are also questions about its value in younger women who have denser breasts, where the device may have more trouble distinguishing malignant from healthy tissue, leading to false-positive readings. "I think there may be differences in the results when MarginProbe is used in young patients, with a tumour that is right behind the nipple where the most dense tissue is located," says Thill. A further analysis is expected soon, which may shed more light on its usefulness in younger patients.

In Thill's department they calculated that, although the MarginProbe was expensive, it saved money in terms of the length of operations (surgeons' and other staff's time) and avoiding reoperations. Measuring all the margins of the specimen intraoperatively takes only three to five minutes with the MarginProbe, enabling further re-excisions to be performed as part of the same operation. However, the way breast cancer operations and reoperations are funded vary from country to country, and, therefore, the cost-effectiveness will vary too.

How good is your surgeon?

Right now, says Dixon, what is needed are international guidelines on surgical margins that are enforceable, together with systems for checking the performance of departments and individual surgeons.

"There should be national and international guidelines on how breast cancer is managed, and these guidelines should be stricter. Part of the problem with guidelines is that, while it's true that doctors should have the freedom to do what they think is right for an individual patient, they shouldn't have an authority to do something on a regular basis that is outwith guidelines. There should be a lot more emphasis on adherence to guidelines.

"We already collect a lot of data in the UK and we can identify units that fall consistently outwith two and even three standard deviations of everyone else in the UK. The problem is we have no real mechanism to find out why that centre is so different. There may be an explanation. If there is no adequate reason for why they fall outwith what everyone else is doing, then there may be a need for re-education so that these outliers can be brought into the fold. It is what patients expect and deserve.

"There has to be change, because the days of individual surgeons getting away with what they think is right are gone. It's time to follow the evidence and to protect the patient, to make sure that a patient, regardless of where they live, gets the same standard of care in all parts of the country." ■

Stop Cancer Now!

ANNA WAGSTAFF

An appeal for global action against one of the world's greatest and fastest growing health challenges

Cancer poses a rising threat to global health as well as the world economy. International experts have agreed on a strategy that can meet the challenge. They are now calling on world leaders to wake up to their responsibilities and act.

It's official. Non-communicable diseases now account for two out of every three deaths worldwide – a massive turnaround from twenty years ago, when they were outnumbered two to one by deaths from communicable, maternal, neonatal and nutritional causes. This is one of the headline findings of the Global Burden of Disease study, published in *The Lancet*, December 2012. Around eight million people now die of cancer every year, a rise of almost 40% over the past 20 years. This means that cancer is not only one of the biggest global killers alongside cardiovascular diseases, but also one of the fastest growing causes of death. The WHO predicts that by 2030, 22 million men women and children will be diagnosed with cancer every year, and 13 million will die of the disease.

This humanitarian disaster has knock-on effects that extend well beyond those directly affected. A study by the American Cancer Society and the Livestrong foundation has found that, leaving aside the direct costs of treatment, the economic impact of premature death and disability from cancer drains $900 billion a year from the world economy – around 1.5% of global GDP (figures for 2008).

Members of the cancer community are not surprised by these statistics, which confirm trends that have been documented for many years. They are, however, increasingly alarmed at the apparent lack of response among national and global leaders to what is unquestionably an escalating crisis.

Where, they ask, is the sense of urgency that forced the AIDS epidemic on to the agenda of G8 summits? Where is the momentum and drive for the sort of collaborative effort that is providing some of the poorest communities in the world with access to affordable anti-retroviral drugs and developing and strengthening networks of community-based health professionals to deliver care and prevention programmes? Who will take a lead on tackling cancer, and when?

In an effort to build a high-level consensus around such an effort, the European School of Oncology invited leading

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Carrying on business as usual is unthinkable; new strategies are needed

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international experts working on every aspect of cancer, and from all corners of the globe, to a World Oncology Forum in Lugano in October 2012. Their task was to address the question: Are we winning the war on cancer?... and to draw up a battle plan to get the job done.

This unusual and intriguing gathering had experts who straddle clinical and scientific research sitting alongside specialists in cancer epidemiology, prevention, health policy, advocacy and policy implementation, to make a critical assessment of whether their collective efforts are on track – and what needs to happen to turn the tide against cancer.

To ensure that this assessment reflected major regional disparities in the disease burden, and potential solutions, the discussion included experts not just from North America, Europe and Australia, but also from Asia (India, Japan, Korea and China), South and Central America and the Middle East.

A group of health journalists from across the world were invited to play 'devil's advocates' – to subject the whole conversation to the scrutiny of outsiders and ask awkward questions. Two additional outsiders also played a critical role. Rifat Atun, who spent many years working for the Global Fund to Fight AIDS, Tuberculosis and Malaria, led a discussion on what the international efforts against cancer could learn from that experience. Richard Horton, editor of *The Lancet*, was there to ensure that the Forum was more than a talking shop, challenging it to come up with a strategy that works within the context of the wider global health and development agenda, is simple enough to sell to busy people with packed agendas, yet is bold enough to turn the tide on cancer.

Though it was organised with policy makers in mind, the World Oncology Forum was not stage-managed and there was no cheerleading. It was an honest exercise in examining the evidence to ensure that any plan that emerged could command confidence.

Winning or losing?

The evidence on the alarming rate of increase in new cases and deaths tells a clear story: we are failing to control cancer. And this generated the most important message from the Forum: *Current strategies are not working; carrying on business as usual is unthinkable; new strategies are urgently needed*.

Behind the stark headline figures, however, a more complex picture shows important progress in some areas.

Cancer is becoming more common everywhere in the world. In the developed world we are getting fatter, exercising less, eating less healthily and drinking more alcohol – all of which are independent risk factors for cancer. But while the number of new cases is rising, the number of people dying from cancer is slowly falling.

In low- and middle-income countries, the rate of new cancers is increasing even more quickly, as higher living standards enable people to adopt 'western lifestyles' – not least smoking – and fewer people die young from infectious diseases. In these countries the rise in new cases of cancer is leading to a similar rise in the numbers of deaths.

The lessons of falling mortality

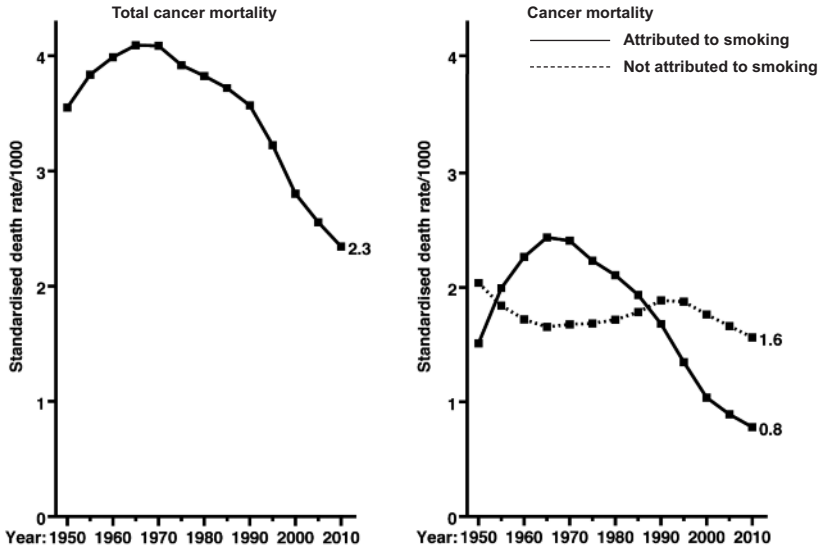
Richard Peto, professor of medical statistics and epidemiology at the University of Oxford, drew the lessons from 60 years of falling mortality trends for the UK, focusing on men in the 35–69 age group. His graphs told a story that came as quite a shock even to this hardened group of cancer professionals. In 1965 smoking-related cancers accounted for

more deaths than all other cancers put together. It is the drop in deaths from smoking-related cancers – from more than 250 per 100,000 in 1965 to around 80 per 100,000 in 2010 – that accounts for almost all the improvement in cancer mortality rates. By contrast, the risk of dying from other types of cancer has changed relatively little in this population – rates in 2010 were similar to the 1960s, though they have been on a slow downward trend over the past 20 years thanks largely to better treatment for colorectal cancer and an unexplained drop in incidence of stomach cancer.

The close link between tobacco and cancer comes as no surprise, given that it plays a role in a wide variety of cancers and causes 90% of lung cancers. However, many participants at the Forum were shocked to see how much of the total burden of cancer is caused by this one industry, and how effective anti-tobacco measures have been in relation to other strategies for cutting cancer deaths. More shocking still were the figures Peto gave for the escalation in rates of smoking across the globe, which accounts for a major part of the explosion in new cancer cases: every year 30 million people are taking up smoking – 50% of young men and 10% of young women. India is already seeing 1 million smoking-related deaths every year. In China smoking-related deaths are expected to triple in the next two decades, killing some 3.5 million people annually by 2030.

Forum participants agreed that any strategy for turning the tide against cancer needs to rapidly reverse this rise in smoking – in the words of one participant, "We need to stop pussyfooting around tobacco." Taxing sales has been shown to be effective up to a point. Experience has shown that tripling the price of tobacco roughly halves consumption and doubles tax revenues – though beyond a certain price the policy is undermined by large-scale smuggling. Far more effective would be to deter investors, through a global agreement to tax the profits of tobacco companies. This single measure could do more to turn the tide on cancer than anything else.

UK CANCER MORTALITY 1950–2010, MEN AGED 35–69



Targeting tobacco has to be at the heart of any strategy to tackle cancer

Source: Courtesy of Richard Peto

Invest in prevention

Paolo Vineis, Chair in Environmental Epidemiology at Imperial College, London, looked at the evidence on what causes cancer and what can be done to prevent it. What is becoming clear, he said, is that cancers are caused by an interaction between hereditary (genetic) and environmental/lifestyle factors. Heredity plays the overwhelming role in

The drop in deaths from smoking-related cancers accounts for almost all the improvement in UK male mortality rates

AN APPEAL TO WORLD LEADERS

The World Oncology Forum agreed a 10-point strategy that it believes is achievable and will significantly stem the rising tide of cancer. The aim is to contribute to the goal of cutting deaths from non-communicable diseases by 25% by 2025, as agreed by governments at the 2011 UN Summit on Non-Communicable Diseases, and to reduce the drain on the world economy by addressing one of the biggest causes of premature death and disability.
On World Cancer Day, Monday, 4 February 2013, an appeal will be published in *The Lancet* and leading national and international newspapers, for policy makers and everyone who can help stop unnecessary deaths from cancer to get behind this strategy.

A 10-POINT STRATEGY TO TURN BACK THE TIDE ON CANCER

Prevent preventable cancers:

1. Wage war on tobacco, by far the biggest cause of cancer death across the globe. Extend to all countries the anti-tobacco measures already found to be effective and tax the profits made from tobacco.
2. Give people the knowledge they need to understand which cancers threaten them most, and how to reduce their risk; develop and implement scientifically sound strategies, including vaccines, to protect against cancers caused by infections.

Treat treatable cancers:

3. Develop early detection programmes tailored to local needs and resources, which target cancers that are the most detectable and treatable and have the greatest social impact.
4. Ensure that every cancer patient has access to a package of diagnostics and curative and palliative care that has been shown to get the best possible results within the local setting and is delivered by trained health professionals.

Support all those who are living with cancer:

5. Give all patients access to optimal pain control by changing attitudes and removing bureaucratic, legal and logistical barriers to the medical use of morphine.
6. Involve patients as partners in decisions about their own care and give them a voice in decision making about policies that affect them.

Accelerate finding cures for cancers that are not yet curable:

7. Replace the current broken business model for developing new therapies with new and more efficient forms of public–private collaboration, geared to accelerating delivery of affordable therapies that are of real benefit to patients across the world.

To achieve all the above:

8. Educate policy makers and the public to counter the entrenched fatalistic myths and misconceptions that undermine efforts to mobilise forces against cancer and deter people who suspect they may have cancer from seeking early medical advice.
9. Promote and strengthen sustainable and universally accessible health systems that are supported by innovative financing mechanisms, and are driven by evidence about cost-effective ways to deliver the best results and not by vested economic interests.
10. Ensure that all countries have a clear cancer control strategy, that evolves in the light of needs and experience, and is built on creative ideas, backed by solid evidence, in order to turn back the tide on cancer.

a few cancers, such as familial adenomatous polyposis – children who inherit the mutated APC gene invariably go on to develop this cancer. In other cancers, environmental exposure is more important, with genetic susceptibility playing a more minor role. Most cancers lie somewhere along this spectrum, with environmental and lifestyle factors interacting with genetic susceptibility.

It is the increase in environmental and, above all, lifestyle risk factors that are the major driver behind the escalation in the number of new cancer cases across the globe (together with increases in life expectancy in the developing world). There is evidence to show that, in richer countries like the UK, up to 45% of cancers in men and 40% in women could have been prevented had risk factors such a tobacco, alcohol, lack of exercise and overweight, been reduced to optimal levels (*Br J Cancer* 105:S77–S81). At a world level, the Global Burden of Disease study shows that eating too much of the wrong stuff has overtaken malnutrition as a risk factor for death, not just from cancer but from a variety of chronic diseases.

While this opens important possibilities for cancer prevention, participants at the Forum cautioned that it is very hard to convince people to change to healthier lifestyles, particularly when 'cancer causing industries' are employing the best brains and huge marketing budgets to encourage them to increase their risky behaviour. Proper funding combined with an evidence-based approach will be needed, drawing on

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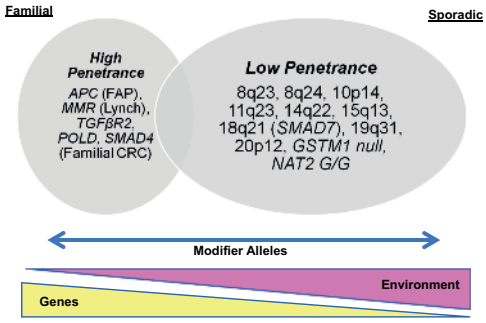
what has been shown to work elsewhere and adapting it to local cultures and demographics. This will require a major shift in government priorities, warned Vineis, who pointed out that in the US, Canada and Europe less than 4% of public funding of cancer research is currently spent on prevention, and that the growing trend towards privatising parts of healthcare systems is likely to impact on preventive activities such as health promotion, which are not appealing for private enterprises.

Cancers caused by infectious diseases, particularly liver and cervical cancer, also offer huge opportunities for prevention, said Vineis. Liver cancer is one of the top three – and fastest rising – causes of cancer death for men in much of the developing world, with a sizeable majority originating in hepatitis B infection, for which vaccines are available that have proved their worth in a variety of developing country settings (other causes include hepatitis C and alcohol). Cervical cancer is one of the top causes of cancer death in women in much of the developing world, and can be controlled though HPV vaccination programmes, or even low-tech screening programmes. Both these cancers are particularly devastating as they have a relatively young age profile, depriving families of mothers and providers. Participants agreed that rolling out prevention programmes, within a short timeframe, to all communities at risk, has to be a key part of any strategy to prevent cancer.

HERITABILITY OF COLORECTAL CANCER



Healthier lifestyles cannot prevent cancer in people with high-penetrance mutations, but they certainly lower risk for the far larger population with low-penetrance mutations

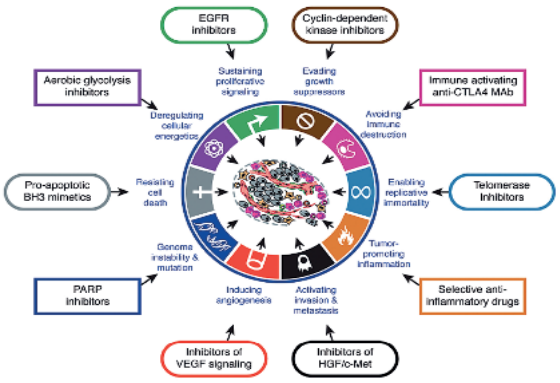
Source: Courtesy of Paolo Vineis

Collaborate for a cure

Prevention is better than a cure – and nowhere is that more true than in cancer. However, even under optimal levels of risk reduction, the majority of cancers are not preventable. We need a cure. Douglas Hanahan of the Swiss Institute for Experimental Cancer Research, in Lausanne, presented the evidence on how well the battle plan to find one is working. "Not very well," was his verdict.

Hanahan is known for characterising the 'acquired functional capabilities' of cancer cells, coining the phrase the 'hallmarks of cancer'. These include the ability to invade tissue and metastasise, evade growth suppressors, resist cell death and avoid immune destruction. The problem with the new generation of targeted drugs, he said, is that while they have been successful at 'taking out' one or maybe two of these functional capabilities, they are not attacking them all. This explains what we have been seeing, for instance, after treatment with angiogenesis inhibitors, or BRAF inhibitors in melanoma: dramatic impact on cancer in a matter of weeks, followed by an aggressive return of the disease. The stream of new cancer therapies are, with few exceptions, failing to deliver the major benefits needed, said Hanahan. He suggested that hitting targets harder and targeting several 'capabilities' at once could be a way forward.

TARGETING THE HALLMARKS OF CANCER



Experience shows that hitting only one or two of the cancer's functional capabilities is not enough to control the disease

Adapted from D Hanahan and RA Weinberg (2011) *Cell* 144:646–674

Courtesy of Douglas Hanahan, Swiss Institute for Experimental Cancer Research, and Swiss Federal Institute of Technology, Lausanne (EPFL)

Not everyone at the Forum was convinced. Doesn't hitting targets harder (with all that implies for accompanying toxicity), and hitting multiple targets, sound a bit like a return to the chemotherapy carpet bombing approach? Given the way tumour cells mutate, shouldn't we expect that if we target and shut down one mutation the cancer will simply find other mutations to exploit to keep going? Before investing billions on drugs targeted at one mutation after another, shouldn't we start by trying to understand some basic principles of cell behaviour that would make it possible to anticipate the cancer cells' evasive strategies, so we can devise rational strategies to cut off their options?

A broad consensus emerged on one point, however: current models for developing new therapies are not working. They are delivering too little benefit at too great a cost. New ways of collaborating will be needed to deliver therapies that can really transform the prospects of cancer patients the world over.

The scale and the breadth of collaboration that is needed was nicely demonstrated by Hanahan in the form of a graphic presentation of his "war room" – a new cancer centre in Lausanne involving a partnership of three institutions, designed to foster "synergistic interactions" between knowledge-driven basic scientists, clinical and surgical oncology researchers, bioengineers, pharmaceutical chemists, and clinical specialists in treating cancer patients.

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As this type of work can only thrive in a publicly funded academic setting, new models of public–private cooperation will be needed, and governments, regulators, reimbursement authorities, independent research foundations and charities, international health agencies – and oncology professionals – must all play a role in making this happen.

Quality care

While progress towards a knock-out blow against cancer has been frustratingly slow, cure rates for some of the most common cancers have been improving through a series of small steps. The best treatments for early breast cancer show almost 90% of people surviving for at least five years. Treatment of colorectal cancer has also been steadily improving, with five-year survival pushing above 60% in some places. Under the best conditions, almost 90% of childhood cancers are now curable. More and better palliative care starting at an earlier point is helping people to live with cancer with a good quality of life; to earn their living; to care for their families – and even to live longer.

These types of results, however, are currently achieved for only a minority of people and in a minority of countries. Michel Coleman, professor of Epidemiology and Vital Statistics at the London School of Hygiene and Tropical Medicine, and Felicity Knaul, director of the Harvard Global Equity Initiative, presented evidence about how many lives could be saved and how much suffering avoided if all health services provided universal access to the best quality of care that can be achieved at a sustainable level.

Coleman presented figures from Kentucky, USA, showing that women with private healthcare insurance have a 20% better chance of surviving three years after a breast cancer diagnosis than those on Medicaid, the 'safety net' insurance for people on low incomes. Even where insurance coverage or co-payments are not an issue, social deprivation can still reduce chances of survival, as was shown in a UK study of survival rates in rectal cancer (*Br J Cancer* 2008, 99:S30–S32). In 1996–1999, relative survival rates for men living in areas of highest deprivation were 15% lower than for men from the most affluent areas – and as treat-

New ways of collaborating will be needed to deliver therapies that really transform the prospects of patients

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ments improve, that gap is getting wider. Understanding and addressing the reasons why people from more deprived backgrounds have poorer survival rates must be a key part of any cancer control strategy.

Important lessons about strategies to beat cancer can also be learnt from looking at differences in survival rates between broadly similar countries. The graph below, which gives five-year survival rates for women diagnosed with breast cancer at two different time points, shows what a difference a well-performing cancer system makes and how concerted efforts to improve results can pay off. In the earlier period, women with breast cancer in Sweden had a 40% better chance of surviving five years than those living in Poland. Over the following decade Poland improved its survival rates by almost 15 percentage points, compared with just over 4 percentage points in Sweden. This graph also shows that there is still plenty of scope for survival rates in the worst performing countries to improve.

This is not all about money – although per capita spend on health does of course play a role. Evidence shows that effective organisation and management are important for getting the best results in cancer. This includes adhering to diagnostic and treatment guidelines, ensuring patients are treated by multidisciplinary teams with expertise in their cancer type, having proper systems in place for monitoring how well different parts of the health system are performing – and of course ensuring that all patients have equal access.

Universal care

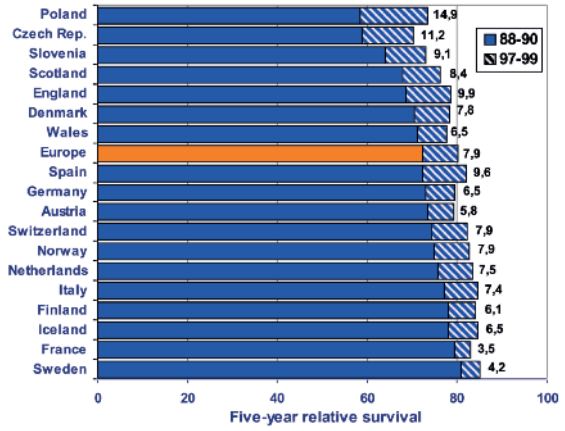
Improving the effectiveness of cancer care delivery across Europe and the US will be important, particularly given the current squeeze on public finances. But it is in low- and middle-income countries that the battle to control cancer will be won or lost. These are the countries that are experiencing the biggest explosion of new cases, and they are currently in a poor position to either detect or treat them.

While breast cancer is still far more common in developed countries, most breast cancer deaths are in developing countries; poorer countries also account for 85% of deaths from cervical cancer. Only around 20% of cancer patients survive for more than five years in the Gambia; in Uganda the figure is 13%, except for breast cancer, where five-year survival is around 45%. In the poorest 25 countries, paediatric cancers are fatal in 90% of cases, while almost 90% of children in the richest countries now survive. Lack of pain control and palliative care means that dying from cancer is a far more terrible experience in precisely those regions of the world where death rates are climbing fastest.

Universal access to treatment is one of the big challenges for a global strategy against cancer. Participants at the Forum spoke of the need to challenge widespread fatalistic attitudes based on misconceptions that cancer is simply too complex and too expensive to treat.

Rifat Atun reminded the Forum that similar attitudes were once prevalent about treating AIDS in poor countries, and it took many years of determined advocacy to turn that fatalism around. Once the international aid effort started, and began to show results, attitudes changed. What initiatives like the Global Fund Against AIDS, Malaria and Tuberculosis have shown is that once you have agreement on international action, and are able to pool resources and use a single platform to interact with donors, suppliers, governments and NGOs, what once seemed

CLOSING THE SURVIVAL GAP IN EUROPE



Concerted efforts by the worst countries to catch up with the best have paid off, as can be seen from these breast cancer survival results, but there is still plenty of scope for improvement

Source: A Verdecchia et al. (2009) *EJC* 45/6:1042–66, reprinted with permission from Elsevier

The goal of ensuring every patient has access to an indispensable package of diagnostics and care is attainable

impossible becomes possible. The prices of essential drugs were slashed – down by as much as 90% in many cases; donations tripled between 2002–2004 and 2008–2010, and many communities are now covered for the first time by primary healthcare networks.

In Ethiopia, more than 30,000 Health Extension Workers were trained and deployed between 2004 and 2009; in Malawi 10,000 Health Surveillance Assistants were deployed by 2009. These people are already acting not just as the frontline for HIV, TB and malaria services, but are also providing community-based maternal and newborn care; family planning advice and disease surveillance. These are the kinds of networks that will be essential for implementing strategies on cancer prevention as well as early detection and some types of palliative care, including pain relief. They will also be important in implementing policies to tackle the stigma and discrimination that can blight the lives of cancer patients and their families. Strengthening and extending these community-based networks, and joining forces with other health and anti-poverty initiatives, will therefore be central to any anti-cancer strategy.

That is not to say that prevention, early detection and palliation is all that people in low- and middle-income countries can expect – indeed early detection is a waste of resources unless the cancers are treated. A key message from the Forum was that many cancers can be treated effectively with basic surgery and radiotherapy facilities, a limited list of essential drugs, and some essential diagnostic equipment, provided the care is planned and carried out by a team of people who specialise in treating those cancers and they have access to evidence-based guidelines on how to deliver the best results with the resources available.

PACT, the International Atomic Energy Authority's Programme of Action for Cancer Radiotherapy, has long been helping some of the world's poorest countries establish a radiotherapy capability, and these efforts could be massively expanded within the context of an international strategy against cancer. The Breast Health Global Initiative has pioneered a set of guidelines for early detection, diagnosis and treatment graded accorded to resources. Funding the research needed to develop and implement these sorts of guidelines for other cancers will be an important part of any global cancer strategy.

Important lessons on sustainability can be learnt from Mexico's universal health insurance programme, Seguro Popular, which started in 2004 and by 2011 had achieved universal coverage for all paediatric cancers, as well as for breast, testicular and prostate cancers and for non-Hodgkin lymphoma. These and other examples indicate that the goal of ensuring that every cancer patient has access to an indispensable package of diagnostics and curative and palliative care is attainable, and this has to be a key element of the international strategy.

An AIDS moment

Opening his presentation on the second day of the conference, Atun commented on a feeling of resignation and lack of ambition he had sensed among participants during the previous day. He had a point. But when Richard Horton introduced the purpose of the Forum – to send an appeal to governments and policy makers to recognise the scale of humanitarian disaster presented by escalating rates of cancer, and to commit to new strategies to meet the challenge – the mood of participants changed from resignation to indignation and determination.

The action plan they came up with (see p 22) is set to be published in *The Lancet* and leading national and international newspapers across the world, to mark World Cancer Day. The question now becomes how to overcome the fragmentation of the cancer community to build the sort of public, and patient-led movement that proved so effective at forcing global action on AIDS. "We need to go back to basics," concluded one patient advocate, "we need to mobilise the cancer community, and engage people into forcing governments to act." ■

Me and my cancer

The power of a well told personal story

SIMON CROMPTON

Journalists who write about their own cancer journeys are able to convey important insights in a language that people understand – and are eager to read.

It is not surprising that a lot of journalists have written about their personal experiences of cancer: cancer is common; writers like writing about themselves; and they also know that real human experience and emotion engage readers like little else. It doesn't get much more real or emotional than having a life-threatening condition.

But some writers stand out from the crowd. In the UK in the late 1990s, John Diamond from *The Times* made a major impact with his weekly columns about throat cancer, and his subsequent book "C: Because cowards get cancer too". Catherine Kalamis of the *Guernsey Press* won an ESO Best Cancer Reporter Award in 2006 for a powerful series of articles based on her personal experiences of neuroendocrine tumour.

And then there is Cassandra Jardine. A popular feature writer and interviewer for the UK's *Daily Telegraph* for the past 20 years, she died of lung cancer in May last year at the age of 57, having spent much of the last two years of her professional life writing about (among other things) her diagnosis of adenocarcinoma of the lung, getting on with life as a mother while having chemotherapy, the impact of her cancer on her family, the itchiness of her wig, the power of a cosmetic makeover, and her highs and lows as she embarked on new treatment regimens.

She also spearheaded a national campaign to raise awareness of cancer symptoms. Just days before she died, she fronted the launch of an early diagnosis campaign 'Be Clear on Cancer', alongside celebrities such as comedian Ricky Gervais and football manager Alex Ferguson, who both lost parents to the disease.

Eulogies from colleagues pointed to Cassandra Jardine's good humour, compassion, lack of self-pity, supportiveness

CLARA MOLDEN

"I don't enjoy being a guinea pig but I want that vaccine." This photo of Cassandra Jardine was used to illustrate one of many articles she wrote for the *Daily Telegraph* that gave her readers insight into the pros and cons of clinical trials and how it feels to be part of them

of others, professionalism and diligence. Readers commented on her warmth as a writer, her wit, her pragmatism – how they felt they had come to know her and became involved in her story.

But for the cancer community, her lasting contribution may be something more specific and unusual. She communicated in an accessible and involving way the reality of clinical trials from a patient perspective – how they work, their positives and negatives, and most of all, how it feels to be part of them. Journalists don't tend to cover this subject: it sounds too dry for editors, and patients themselves can't always be relied upon to provide the emotional insight and clarity about the issues that newspapers and magazines require. Whether for good or ill, it takes a journalist writing about their own experience to bring such difficult issues to the fore.

Just four weeks before she died, Cassandra Jardine submitted three of her cancer articles dealing with her experiences of clinical trials to the ESO Best Reporter Award. In her supporting statement, she said these articles were those of which she was most proud: "I hope they combine clarity on scientific topics with an ability to engage and touch the widest section of the public – whilst still drawing respect from the experts involved," she wrote.

She said she wanted to convey the human experience of cancer not for its own sake, but to get information flowing forwards to patients and public, and backwards from patients like herself to professionals and scientists.

"Patients can be useful sources of subtle information that can be fed back into the research and development pool"

Making science accessible

"I feel we need to find new ways to combine an ability to express medical language so that non-scientists can more readily understand," she wrote. "But I think we need to also remind scientists that these are not just statistics, that there are individuals out there who aren't just passive recipients of therapies but who can be useful sources of subtle information that can be fed back into the research and development pool. It's not a simple case of modern patients deserving to understand fully where they are with their own health (and control it where possible); but of how they can accumulate and utilise that information – together with their consultant – to constantly improve all patient pathways. And, to be frank, outcomes."

In many countries, clinical trials of new cancer treatments are becoming more and more significant in the lives of people with cancer and the clinicians treating them. The UK has seen a five-fold increase in the number of patients being recruited into clinical trials in the past 10 years. Yet public understanding is still poor, with many potential subjects confused about the process – how randomisation works for example – or the potential dangers of new treatments. The need to air such complex areas beyond bedside conversations, formal information sheets and consent forms did not escape Cassandra Jardine.

In her article "I don't enjoy being a guinea pig but I want that vaccine," she charted her emotional highs and lows as she enrolled on a trial of the vaccine Lucanix in an attempt to delay her cancer's return. In the process, the article corrects misconceptions that can deter patients from joining trials (see Editorial). It also addresses concerns that too many trials are now for drugs that are likely to help a lot of patients a little bit, rather than a few patients a lot.

"I found myself in the unusual position of being able to give a rare inside view of that perennial story which dominates headlines – Is X or Y a cure for cancer? It was a good chance to help explain to the public what a trial is, the difference between phases 1, 2 and 3 – and all the time from a personal perspective which I hope helped make it readable." This piece also explained that many trials test a new treatment against a standard treatment, not a placebo. For severely ill patients, worried that they may be merely given a 'sugar pill' if they enter a trial, such knowledge can have real psychological implications. "This is the sort of nugget we cancer patients need to hear – but it's not one the consultant may remember to offer."

Like many others, Cassandra Jardine craved such nuggets. She suspected from the start of the trial that she was on the control arm of the trial because she experienced no side-effects. She knew that standard treatments stood as much chance of helping her as a sugar pill (given the advanced stage of her cancer), but she still wanted to complete the two-year trial: "Helping medical research feels good," she wrote in her article.

Ten months later, in April last year, she wrote the last of her articles she submitted for the Best Cancer Reporter Award. Entitled "Worse? Now that's what I call good news", she presented the paradoxical situation that, as her health deteriorated, so she became eligible to try a promising targeted therapy called crizotinib. She described how, with other drugs failing to control her lung cancer, her oncologist tried to get her the drug on compassionate grounds, or as part of the trial.

"For seven months, he got nowhere," she wrote. "The researchers wanted either a new outbreak of cancer or a minimum 20% increase in the existing sites. And then, in March, we got there. Never has bad news about cancer been more gratefully received."

She described how, in a peculiar euphoria, she invited friends to her house for homemade sausage tortelloni while she took her first dose of a drug that she hoped might not just control but reverse the spread of her cancer. Her hopes had been raised by earlier conversations with the lead researcher into the therapy from Denver, Colorado.

And at the end of the piece, Cassan-

"This is the sort of nugget we cancer patients need to hear – but it's not one the consultant may remember to offer"

dra Jardine described the very human responses to taking a new 'wonder drug' that clinicians rarely glimpse: the initial fear that it was having no effect; the tentative hopes that it was working once she started to experience sickness, the elation of the growing conviction that she was getting well and could consign the rest of her medications to the bin.

"I am on a drug that has a positive effect," she wrote. "It has taken a while to absorb this small miracle, but, four weeks on, I am more energetic, I can walk and work. I am back. It just took me a while to notice."

Cruelly, ironically, the words were published just six weeks before she died. In her submission to ESO's Best Cancer Reporter Award, which was one of the last things she wrote, she said: "I'm sure most doctors and scientists would agree that there is nothing like a human record of how treatment works out of the lab and in the human body. By opening myself up to become that living petri-dish-cum-diary, I hope I have contributed to research and development in oncology. I hope I have also brought comfort to others in my situation."


Health

Health is edited by Cherrill Hicks

Worse? Now that's what I call good news

Only if her lung cancer spread would ***Cassandra Jardine*** *be allowed to join a trial of a radical new gene therapy*

"I can walk and work. I am back": Cassandra Jardine, a month after joining a trial for the drug crizotinib

What the hell, enjoy the moment, even if you do have a face like a hamster

arathon man's life-saving

Mattress Stain Rem

The Daily Telegraph

An ability to engage. This article – one of three Cassandra Jardine submitted to the Best Cancer Reporter Award – described what the opportunity to try out experimental therapies means to patients like her who are running out of options and out of time

She received a Special Merit Award in the ESO Best Cancer Reporter Awards because she succeeded.

A tricky area

This is not to say that her pieces are impervious to criticism. Like all good journalists, Cassandra Jardine was shamelessly accessible, writing to be read. That brings its risks. The judging panel was not unanimous in its praise for Jardine's articles. Were some of her articles likely to raise false hopes about some of the treatments she described? Did they give the impression that clinical trials offered 'miracle drugs'? Did they devote sufficient time and space to weighing the risks against the potentially small benefits provided by many experimental treatments?

These are common concerns with all popular health journalism, indeed in all types of journalism. As Alan Yentob, the controller of BBC1 said, "It's a tricky area, this idea of marrying issues with human interest, human stories, the stories of people's lives... if you do it properly and effectively it makes for good journalism."

The problem is especially acute in the case of personalised, confessional health journalism. By making stories

"By opening myself up to become that living petri-dish-cum-diary, I hope I have contributed to oncology"

"I looked forward to reading her words telling us about her cancer in a very down to earth way"

about life-threatening conditions highly subjective, they can lack rational assessment of the benefits of approaches to populations, and fail to acknowledge the infinite variables of cancer pathology, physical make-up, personality type and environment that inform complex decision-making between patients and oncologists.

There's another problem with journalists writing about their own cancer experiences: it can appear self-indulgently morbid. Brendan O'Neill, editor of the influential online magazine *Spiked*, recently described the glut of journalists writing about their illness as a "sick publishing phenomenon". What turns writers' "rational myopia" into something more macabre, he said, "is a public appetite for details of decay."

But alongside these difficulties, comes the considerable benefit: impact. Well told stories of real people, involving real experiences, are read by millions. Cool, rational assessments of the benefits and risks of cancer treatments are not – in fact, they are rarely published in the mainstream media of many countries such as the UK, simply because editors judge that they will be ignored.

The net effect of the best mainstream, accessible health writers can be, in the end, far more positive than the worthiest of articles that remains unread. In the past, the effect of confessional cancer writers may have been most strongly felt in breaking some of the taboos of discussing cancer in public. Today, their impact lies more often in providing a coherent patient perspective that makes other patients say "Yes, that's what it's like" and prompts clinicians to ask "Is that what it's like?"

PJ PRODUCTIONS

Spreading the message. Shortly before she died, Cassandra Jardine joined other well-known faces to front Be Clear on Cancer, a national campaign that aims to improve public awareness about the early signs of the disease

ESO recognised this complexity when it established the Best Cancer Reporter Award in 2006. It was launched to promote intelligent and critical coverage of cancer, recognising the media's pivotal role in shaping public knowledge and beliefs about cancer. But it has always acknowledged the challenges journalists face – how they must strive for readability while resisting the pressures to sensationalise and distort.

It is the best argued, best written, and most evidence-based journalism that wins the annual prize. But the award scheme also recognises impact, so this year Cassandra Jardine was specially commended by the BCRA judges for the tremendous effort she made to demystify lung cancer.

As Kathy Redmond, editor of *Cancer World* and a member of the judging panel, said, "She demonstrated just how powerful it can be when journalists who are also patients use their skills to convey important messages to the public about issues that have a huge impact on cancer patients."

Perhaps one of Cassandra Jardine's regular readers in the *Daily Telegraph* put it best: "Having read and enjoyed her articles for years and followed her life coping with cancer, I have the most utter respect and praise for her... I felt that I learned so much from all she wrote. I looked forward to reading her words telling us about her cancer in a very down to earth way, making us aware of the importance of early signs. I know that as well as her beautiful family and countless friends, there will be many readers who will miss her." ■

Survivor services: supporting patients living with and beyond cancer

Helping patients make the best of their lives after treatment starts with thinking ahead before treatment and tailoring support for as long as it is needed. A leader in the field talks about key issues and a new European collaborative group.

Who is a cancer survivor? The US National Cancer Institute suggests that an individual diagnosed with cancer is a cancer survivor 'from the time of its discovery and for the balance of life.' Family members, friends, and caregivers are also impacted by the survivorship experience and are therefore included in the definition.

There are essentially three seasons of survival, as first defined by physician and cancer survivor Fitzhugh Mullan, in 1985 (*NEJM* 313: 270–273):

- Acute survival: begins with diagnosis and is dominated by diagnostic and therapeutic efforts
- Extended survival: the period of remission following initial treatment, dominated by concern about recurrence and residual side-effects of disease and treatment
- Permanent survival: roughly equated with 'cure', where the focus is on long-term risks (such as second primaries) and effects (such as chronic fatigue).

European School of Oncology e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the chance to discuss a range of cutting-edge issues with leading European experts. One of these is selected for publication in each issue of *Cancer World*. In this issue Neil Aaronson, from The Netherlands Cancer Institute, Amsterdam, reviews presentations from a recent International Symposium on Cancer Survivorship held last April in Bari, Italy, and organised by the European School of Oncology in conjunction with the Organisation of European Cancer Institutes. Summarised by Susan Mayor.

The recorded version of this and other e-grandrounds is available at www.e-eso.net

I would add a further season:

- Palliative treatment and care/end of life.

The definition of cancer survivorship is important because it defines the target population: does it include only individuals who are 10 years out from their diagnosis of treatment, or also those who are five years – or even one year – out? It also has implications for the focus of care and research: is the emphasis on acute or long-term sequelae, on physical or psychosocial sequelae? It also affects the type of rehabilitation efforts that may be needed.

Growing numbers

Cancer survivors are a growing population, particularly in the developed world, where trends in cancer incidence and mortality in both men and women from 1975 to 2005/10 clearly show increasing incidence and decreasing mortality rates. Cancer incidence is lower in developing countries but mortality is higher. You could argue that cancer is an acute disease with a fatal outcome in developing countries, whereas in developed countries of the world it is becoming more of a chronic disease, increasing the number of survivors. There were around 29 million cancer survivors worldwide in 2008. Twelve million of them were in the US – up from around 3 million in 1971.

About half of people with cancer are diagnosed at the age of 65 or older. This is important because there were 500 million people aged 65 or older worldwide in 2006 and the estimate is this will grow to 1 billion people in 2030. Because so many cancers are diagnosed relatively late in life, many cancer survivors will die of causes other than cancer. Figures show that older survivors of breast cancer are more likely to die of cardiovascular disease than breast cancer (*Breast Cancer Res* 2011, 13:R64) and men who have survived prostate cancer for at least 15 years are more likely to die of causes other than prostate cancer (*Prostate Cancer P D* 2012, 15:106–110). Survivors of testicular cancer diagnosed and treated before the age of 35 have a 1.7-fold higher risk of dying of circulatory disorders compared to their general population peers (*JNCI* 2007, 99:533–544), while an Australian study showed that cancer survivors are 50% more likely to die of non-cancer causes than the general population (*Cancer Cause Control* 2006, 17:287–297).

Successful cancer treatment does not necessarily mean the end of the effect of the disease. Cancer survivors are at risk for late effects, including: disease recurrence/new cancer; cardiovascular disease; endocrine dysregulation; obesity; diabetes; osteoporosis; upper/lower quadrant mobility and functional limitations; and functional decline leading to disability (*Cancer Epidemiol Biomarkers Prev* 2007, 16:566–571).

At the ESO–OECI International Symposium on Cancer Survivorship, held in Bari, Italy, April 2012, Wendy Makin, from the Christie Cancer Centre, in Manchester, UK, pointed out that chronic survivorship conditions are determined by the type and site of cancer, treatment factors, and patient factors. For CNS [central nervous system] cancers, the late effects are largely endocrine and cognitive in nature. Head and neck cancer patients may have dental, speech and swallowing problems. In patients with breast cancer, long-term problems include cardiotoxicity, pain and lymphoedema, while cancers in the pelvic region are associated with bowel, bladder, sexual and fertility issues. These are all in addition to the 'general effects of cancer', which include fatigue, pain, bone loss and changed body image.

Many patients learn to live with, and adjust to, their limitations over time. Some continue to have chronic problems associated with their cancer, some may encounter new problems such as late toxicity, and they may experience a decrease in quality of life over time, which is compounded by the effects of getting older and by comorbidities that may develop. Yet despite all these challenges, many survivors report enjoying a good quality of life.

Fatigue in survival

Fatigue is ranked as one of the most troublesome symptoms in cancer survival, by both patients and professionals, Ollie Minton, from St George's Hospital, London, explained at the symposium. In patients on treatment and in advanced disease, prevalence varies from 60% to 90%, depending on the definition. After successful treatment for cancer, many patients suffer chronic fatigue – i.e. fatigue that lasts at least three months. Assessing fatigue can be tricky, because it is ubiquitous and many people in the general population report tiredness. There are more than 20 tools for assessing fatigue in oncology, but the most frequently used are the functional assessment of cancer therapy (FACT-F) – a scale that is used very widely in the US – and the EORTC QLQ-30 fatigue subscale, which is often used in Europe.

Three modalities are used to treat fatigue in cancer:

- Drugs, including haematopoietic growth stimulants and psychostimulants. Studies show a fairly robust effect of psychostimulants, but many patients do not want to take them and physicians do not want to prescribe them.
- Exercise. There has been a lot of interest in exercise as a way of dealing with fatigue complaints. Cumulative exercise programmes have been shown to be efficacious in

CAROL KALIFF / DANBURY NEWS-TIMES

dealing with fatigue complaints, but the magnitude of the effect is relatively small.

- Complex psychosocial and behavioural interventions. Cognitive behavioural, psycho-educational and supportive therapy can be helpful at group or individual levels.

In a Cochrane review of complex interventions in the treatment of cancer-related fatigue, only seven out of 27 studies reviewed showed an overall reduction in fatigue. There is a clear need to better understand the mechanisms of fatigue in cancer survivors so that more targeted and effective treatments can be developed.

Interventions for psychological wellbeing

Depression is very common in cancer. Susanne Dalton, of the Danish Cancer Society Research Centre in Copenhagen, reported on a population-based investigation of more than 600,000 cancer patients linking cancer registry data to psychiatric hospitalisation records in Denmark for the years 1973–2003. One-year follow-up showed the relative risk of being hospitalised for depression was twice as great among cancer patients as among the general population (*JCO* 2009, 27:1440–45). There continued to be a 40% increase in the risk of hospitalisation for depression from one to four years after diagnosis.

This is just the tip of the iceberg, she suggested, because relatively few patients with cancer develop major depression compared to other psychological problems. A review of 70 studies including more than 10,000 oncology and haematology patients showed depression in 16%, adjustment disorders in 20%, and anxiety disorders in 10%, with 30–40% patients suffering a combination of mood disorders (*Lancet Oncol* 2011, 12:160–174).

The most recent review of psychological support interventions (*CA Cancer J Clin* 2008, 58:214–230) showed that a variety of cognitive-behavioural, relaxation and other types of psycho-educational treatments are effective in reducing anxiety and depression. The benefit appeared similar for all patients, regardless of their type of cancer, but most of the studies were underpowered for subanalysis, and men and patients from ethnic minorities were underrepresented. Few studies have looked at interventions beyond the primary tumour phase, so there is very little evidence base for their efficacy in cancer survivors.

Employment and work-related issues

Anja Mehnert, of the University Medical Centre Hamburg-Eppendorf, in Germany, reported that about two-thirds of people who have had cancer return to work, ranging from 25% to more than 90%. In studies, approximately half of cancer survivors reduced their work schedule, at least temporarily; slightly more than half reported a change in their occupational role; and 25% reported a reduction in their physical or mental work ability or performance levels.

Barriers to returning to work can be work related, including a non-supportive work environment, manual work and physically demanding work, and perceived or actual employer discrimination. Demographic barriers include older age, female gender and lower education levels (*Psycho-Oncol* 2002, 11:124–131; *Acta Oncol* 2007, 46:446–451; *JAMA* 2009, 301:753–762; *Psycho-Oncol* 2010, 19:115–124; *J Cancer Surviv* 2010, 4:415–437; *Crit Rev Oncol Hematol* 2011, 77:109–130). Cancer- and treatment-related barriers include having a poor prognosis or advanced tumour stage. There is

a common misconception that patients with metastatic disease no longer want to work, whereas many of them do want to. Other barriers include extensive surgery, endocrine therapy, poor overall health and disability, persistent fatigue and the presence of comorbid conditions and depression.

As part of rehabilitation, patients should undergo assessment and evaluation of work-related skills and demands. Other helpful interventions include: improvement of physical fitness and psychosocial functioning, skills training, occupational counselling and motivational training. A key element is to ensure that co-workers and employers understand what it is to be a cancer survivor, and that these are normal people returning to their normal jobs who have gone through an episode in their lives (*Cochrane Database Syst Rev* 2011, CD007569).

CAROL KALIFF / DANBURY NEWS-TIMES

Behavioural changes after cancer

Cancer survivors are at greater risk for second cancers and other comorbid conditions. As a healthy lifestyle is associated with better health and reduced risk for a number of health problems, survivors are often encouraged to make healthy lifestyle changes after completing treatment. Kevin Stein, from the American Cancer Society's Behavioral Research Center, outlined guidelines for healthy living, involving diet and physical activity, that have been issued by several organisations. The recommendations are for a diet high in plant foods, focusing on fruit, vegetables and wholegrain, avoiding red and processed meats, and avoiding high-fat and high-calorie foods.

Cancer survivors are now recommended to avoid inactivity, and to return to normal activities as soon as possible after diagnosis. This is a major change from seven or eight years ago, when patients were advised to take it easy when tired. As for the general population, survivors should aim to exercise for at least 150 minutes per week – for half an hour on at least five days a week, preferably seven days a week – and also to include strength exercises for at least two days a week.

Weight gain, overweight and obesity are problems for the general population, and it is no different for cancer patients. The recommendations are similar: to eat less fatty foods and to exercise. But there is a caution here: women who have undergone chemotherapy for breast cancer often gain weight, and the evidence base suggests that weight-loss and exercise protocols will not necessarily lead to actual weight loss in this group.

A significant proportion of cancer survivors continue to smoke after being diagnosed and treated for cancer, with the highest rates among lung cancer and bladder cancer survivors. There have been only about five randomised clinical trials of smoking cessation programmes directed specifically at cancer patients, and all but one (*Cancer Epidemiol Biomarkers Prev* 1993, 2:261–270) found no significant effect on smoking rates. This is an area that obviously needs additional attention and research.

All areas of lifestyle change – diet, exercise and smoking cessation – can have an impact on important health outcomes including depression, fatigue, adverse body composition, functional decline and comorbidity. But there are many challenges to successful behaviour change: persistent symptoms and side-effects can get in the way of people being ready to make changes. The time, cost and access to new lifestyle behaviours are things that affect all of us when we try to change, and it is no different for cancer survivors. Survivors will be in different stages of readiness for change; some will have had a very unhealthy lifestyle, and therefore any recommendations will be taken on relatively slowly, whereas others will already be actively involved in changing their lifestyle and can be supported in doing so. Social support issues, lack of knowledge among providers about what to recommend, and setting unrealistic goals can have a negative effect on the outcomes that we wish to achieve.

Emerging models of cancer survivorship care and rehabilitation

In a paper published in March 2012, Catherine Alfano, deputy director of the Office of Cancer Survivorship at the US National Cancer Institute, outlined a comprehensive rehabilitation model that emphasises a joint focus on optimising functional status and quality of life.

This model addresses pre-existing or treatment-related comorbidities, treats chronic effects of treatment, reduces the risk for late effects, and promotes self-management and healthy behaviour. It aims to prevent future problems,

reduce the risk of recurrence, and prevent the spiral into disability, so survivors can preserve their work and social roles (*JCO* 2012, 30:904–906).

Can we do anything about chronic survivorship conditions? Wendy Makin, from the Christie Cancer Centre, suggested starting at the pre-treatment stage by identifying treatment modalities that are less invasive and less toxic: less invasive surgery, conformal radiotherapy and targeted therapies. Careful patient selection should ensure that patients receive treatments that are going to be effective for them and patients should be prepared by providing them with information about what they can expect. During treatment, and when it ends, survivor programmes should be used to maximise recovery and rehabilitation; patient self-management should be encouraged by drawing up survivor care plans, and patients should be offered after-care and follow-up support services, with capacity for complex case management.

Better screening and identification is needed for patients who have complex problems, with multidisciplinary assessment, including late effects clinics and pathways to support each problem. These should involve a range of specialists and dedicated services in some cases, such as for radiation bowel disease.

The National Cancer Survivorship Initiative

Adam Glaser, clinical director of the UK National Cancer Survivorship Initiative (NCSI), and Jane Maher, chief medical officer of Macmillan Cancer Support, UK, described the approach being taken by the NCSI, a nationwide programme in the UK.

The four emerging principles are:

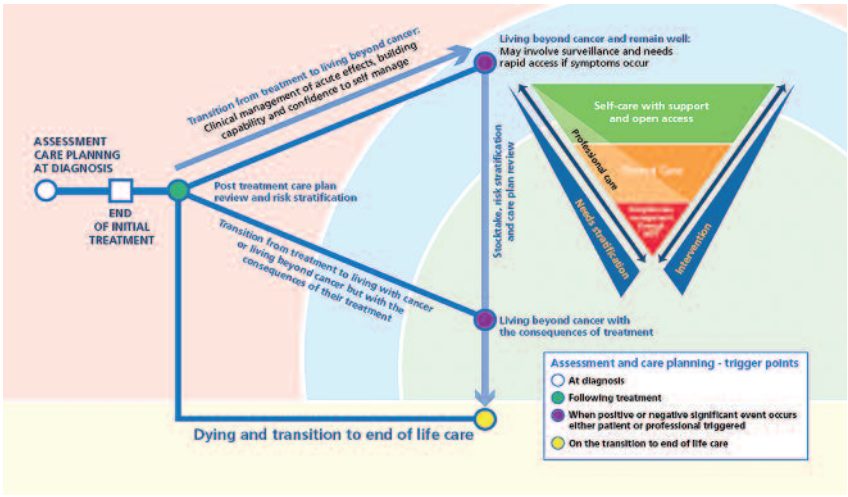
- risk-stratified pathways of care, rather than one size fits all
- a dynamic personal care plan that arises from an assessment of the disease, the treatment, and the individual's personal circumstances
- information provision, which should meet individual needs and should be timely, accessible and promote confidence, choice and control
- encouragement to self-manage with support, and rapid access to appropriate professionals when problems arise.

With regard to risk stratification, the vast majority of patients can self-care, if they have support activity around them that they can call on if needs be. A smaller subgroup of patients has shared care needs, and a much smaller group has complex management problems requiring a multidisciplinary approach.

The NCSI initiative suggests a model of care (see figure) comprising five key elements:

- supporting patients through primary treatment from the point of diagnosis
- promoting their recovery
- sustaining their recovery
- reducing the burden of the consequences of their treatment, and
- supporting patients with active and advanced disease – interfacing with the end-of-life care services.

LIVING WITH AND BEYOND CANCER



The model developed by the UK's National Cancer Survivorship Initiative involves assessment and care planning at multiple points in the patient journey

Source: National Cancer Survivorship Initiative

A European Collaborative Group

Could there be a role for a European collaborative group on cancer survivorship? A discussion at the end of the conference showed strong support. The intent is to involve all the key stakeholders – healthcare professionals, researchers, policy makers and patients – to develop a better understanding of key issues in cancer survivorship research and practice in Europe and to promote high-quality survivorship care and research. A steering committee and international advisory group have been set up.

If you would like to get involved, or if you have any questions about the group, please email Vittorio Mattioli at v.mattioli@oncologico.bari.it, or Neil Aaronson at n.aaronson@nki.nl. ■

Taking the isolation out of isolation

PETER MCINTYRE

The isolation that is essential to the physical health of people undergoing stem cell transplantation can be terrible for their mental health at a time of great stress. Patients are giving the thumbs up to a novel way of staying connected.

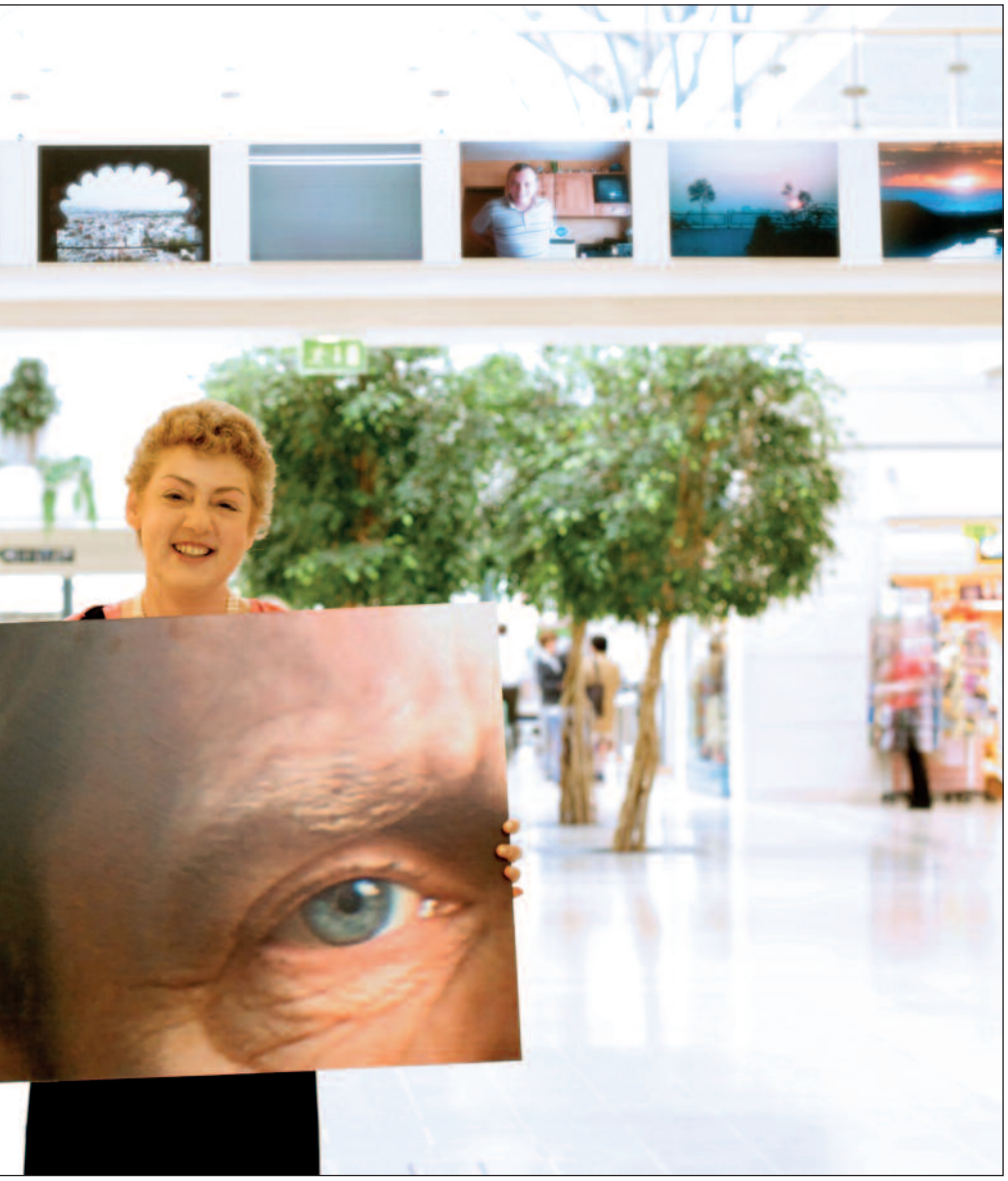
Leukaemia patients who undergo stem cell transplants spend four to six weeks in an air-filtered sterile room, with limited human contact and little stimulation. Facing a life-threatening disease and arduous treatment, they can become isolated and depressed.

St James's Hospital in Dublin hosts Ireland's National Stem Cell Transplant Centre, and when it developed a new 21-suite state-of-the-art unit in the year 2000, Shaun McCann, then professor of haematology, worried about the emotional effect of the environment on patients.

McCann punctures a few Celtic myths about the 'fair city'. "St James's is not in the most salubrious area in Dublin. The transplant unit (then the National Bone Marrow Transplant Centre) is near the Guinness brewery, and the ground floor rooms have a choice of view of air-conditioning pipes, blocks of flats [apartments] or perhaps barbed wire.

"I wrestled for a number of years with how to connect them to the outside world so they would not feel that sense of stress."

In 2001, he met Denis Roche, a musician and artist who was working on a project to do with connectivity through music and art in a unit set up by the Massachusetts Institute of Technology (MIT) in Dublin. During their meetings, Roche came up with the idea of creating a virtual window in patients' rooms and projecting images onto them. McCann recalls, "The idea that we could create a virtual window that would connect them with the outside world, and we could introduce all sorts of different images, seemed to me like a very clever idea."



PAUL O'CONNOR WWW.PAULOCONNOR.ORG

Open Window. Katie Verling in the foyer of the St James's National Stem Cell Transplant centre, with one of the images contributed to the arts project that she says helped save her sanity during five weeks spent in isolation

Roche developed a computer-based system that enabled a projector to throw a large picture onto the blank white wall of a room. Fran Hegerty, a physicist responsible for keeping St James's ITU equipment, and himself an artist, was keen to help. After detailed negotiation with the hospital infection control team and hospital managers, they introduced Open Window into the unit.

Patients control the images themselves from nine channels, which include traditional or classical art (Van Gogh's Sunflowers for example), art works contributed by contemporary Irish artists, and videos with soundscapes, as well as material they could generate by asking for a webcam to be set up at a chosen location or by giving a mobile camera phone (donated by Vodafone) to a friend or relative.

Although there is a centuries-old tradition of art being used in healing, there are precious few trials to test the effect, and those that have been done are small and rarely rigorous. McCann saw a chance to conduct a proper clinical trial to assess whether using images can improve quality of life by reducing patients' anxiety, depression and stress.

Using a psycho-oncology grant from the Irish Cancer Society, McCann recruited Catherine McCabe from the School of Nursing at Trinity College, Dublin, to run a prospective randomised trial.

Between 2006 and 2009, 180 patients with leukaemia completed treatment in the trial, 84 of them being cared for in an Open Window room and the other 96 in rooms with no extra visual stimulation. The severity of their conditions can be judged by the fact that, of the 199 patients originally randomised to the trial, 12 died and seven withdrew after their conditions deteriorated.

One important benefit of Open

"The idea that we could create a virtual window that would connect them with the outside world seemed very clever"

"You are in a room with white walls... you hear no sounds, you get no smells and there is nothing to look at"

Window, notes Shaun McCann, is that it gives patients autonomy. "One patient said it was like having a private art gallery. The image was totally controlled by the individual and they could choose music, pictures, videos, pictures of their families etc. They could go back and look at the same image. They also had a television, but most people who are very ill do not watch television."

Patients in the Open Window group showed significantly lower levels of anxiety on the day before the transplant took place, compared with the control group, and significantly lower levels of depression before the transplant. There were reduced levels of anxiety and depression at other time points, but these were not statistically significant. There were no differences between the two groups in levels of distress.

As well as scoring for depression and anxiety, Catherine McCabe carried out semi-structured interviews to provide additional insight. Notably, patients in the Open Window group were more than twice as likely as patients in the control group to report that the experience of cell transplantation was better or much better than expected (63% against 27%).

In other respects the groups were similar – indeed the study highlighted how patients in both groups undergoing this life-threatening experience had a changed perspective on life and friends, and expressed surprise that they had coped so well.

Finding the images

Curator Denis Roche started by spending time with the patients. "I posed a question: 'If there was any image you wanted to see on the wall, what would it be?' They would mention a location or a person, and we would talk about that. I had to understand the thoughts people were having about what was happening to them, being ill in this room. They spoke about it as a bit of time out of life."

With support from the Arts Council of Ireland, he approached artists who were interested in themes that seemed to fit, resulting in a variety of images, including contemporary and video-based art.

Artist Cathy Fitzgerald had been to visit the ward and understood how isolated patients would feel. "I thought that I would go spare if I had to go through that without being able to look out of the window and see some greenery." She took photos that followed her daily walk. "I had my dog Holly on a lead and one of the high-powered Nokia phone cameras in the other hand, on a walk in a little lane under Mount Leinster in County Carlow. Catherine McCabe told me that many patients thought the pictures were of their own area. It seemed to give them a lot of respite."

Patients in isolation

Katie Verling ran an arts venue in Limerick before she was admitted to St James's five years ago with leukaemia. She contrasts the time she spent in the isolation ward during her chemotherapy treatment with the five weeks she spent in the ward with Open Window during her bone marrow transplantation.

"When I was diagnosed, I was brought to Dublin in an ambulance and was immediately put into one of the rooms in the isolation ward. It is total deprivation without any sensory stimulus. You are in a room with white walls, blue doors and your own bathroom and a kind of ante room with a kind of vacuum system so you hear no sounds, you get no smells and there is nothing to look at.

"You can't put anything on the walls. You have nothing familiar around you. When people come to see you they wear plastic and can't sit on the bed. It is not appropriate for people to hug you – the nurses barely touch you. Your immunity is totally and utterly compromised."

After several spells in isolation over a four-month period she went stir crazy. "For a day or two I was demented from the absence of colour and light and sound."

Later when she was admitted to an Open Window room, she found the experience transforming. Her boyfriend, Tom, took the phone camera through Dublin as he walked to visit her every day. "It was December in Dublin and there were beautiful sunrises and sunsets. I saw the bridge he walked over every day and when he went back to Limerick he took photos in the market of people I know waving at me, and all those lovely things gave me a taste of the outside.

"I loved putting on a video of horses in a field by a river moving around and chewing grass in the dappled sunlight – it was so relaxing. There was another video of a boat going down a river, and I loved that sense of being able to travel

in the countryside in sunshine and wellbeing. It was like being in my own little cinema."

Patient choices often reflected their rural background, and made a vital connection with the outside world. One patient told nurses, "The fact that you look at the wall and you can see horses racing out there with a forest behind them, or lakes and boats – it takes away the feeling of being caged."

Another said, "That video with the cows grazing. I mean being born and reared in the country I felt I was in that field."

Catherine McCabe recalls that one young man asked for the webcam to be put in his local park. "He said that was where he would go when he was recovering, and he imagined himself being able to take walks around the park again. It was like a personal goal."

Not everyone wanted nature. One 18-year-old woman was especially happy when her sister took the mobile phone to her college and sent pictures back to her.

Surprisingly, perhaps, there was limited demand for pictures from home, as for some this could be distressing.

Even if patients did not like what they were seeing, it gave them a talking point. Catherine McCabe said, "I am not an artist and at the beginning I thought this is not working; they don't like it. I came to realise that they were doing what anybody would do in a gallery. They could look at what they liked, when they liked, and they felt they were free to comment because they could control it. There was no hierarchy and nobody judging their opinion.

"One of the images coming in was from Dun Laoghaire, one of the main ports here. That is lovely on a summer's day when the sailing is on, but one day I went into

CATHY FITZGERALD WWW.CATHYFITZGERALD.IE

FRAN HEGERTY

A calming influence. Patients can choose what they see through their 'window', from traditional or classical art, pictures contributed by contemporary Irish artists, or videos with soundscapes; they can also keep in touch with friends and family through pictures sent from a camera phone, and even watch the world go by via a webcam set up in a location of their choice

"You look at the wall and you can see horses racing... it takes away the feeling of being caged"

"I have numerous examples of how the nursing staff got to know things about patients that they wouldn't have"

WWW.PAULOCONNOR.ORG

A window on the world. This image, by Paul O'Connor, is one of many contributed by Irish artists who were approached by Roche because of their interest in themes that seemed to fit

the room and it was miserable and wet and there were splashes of water on the camera. The patient was speaking to the consultant about the image and the three of us stood there for about ten minutes saying how awful it was. That was a conversation that would never have happened without Open Windows. I have numerous examples of how the nursing staff got to know things about patients that they wouldn't have."

Shaun McCann was aware that images can be very potent, especially in Ireland. "One of the mantras I had was that we might not do any good, but we must be very careful not to do any harm." A committee – including an artist, an art historian, a psychologist and some of the nurses – was set up to select pictures, but this did not work too well at first.

McCann recalls, "We used to meet in a seminar room next to the unit and the discussion was extremely sterile because I was still the boss, and everyone kowtowed to me. It didn't go anywhere. Then Denis Roche designed an inflatable tent which we put as far away as possible from the unit. When we showed the images there, the whole hierarchy broke down and everybody started talking about it. I was no longer the professor of haematology – just somebody trying to look at images."

Where next for Open Window?

It is three years since the trial ended, and a year since the results were published in *Psycho-Oncology* (doi: 10.1002/pon.2093). Open Window is now used in St James's transplant centre as part of normal everyday care.

Denis Roche, a Research Fellow of the National College of Art & Design, is promoting Open Window to hospitals, nursing homes and individuals through his Vivartes company (www.openwindow.ie). Though currently focused on Ireland and the UK, Vivartes is also installing the system in another stem-cell transplant unit in Estonia. It currently costs about €600 to install each system into a room, day centre or ward, but Roche hopes that the price can be brought down closer to €250 for the software and hardware. Hospitals and nursing homes pay a site licence to access the artwork, while individuals who buy the system pay a subscription of about €10 a month.

Shaun McCann, who has retired from his clinical posts, now chairs the online training unit for the European Haematology Association, and is promoting the system for other centres in Europe. "The problem is that the hospitals are all broke, even in the most wealthy countries. When you go to the CEO, he says we are buying a new oscilloscope or something, and it is very hard to argue with that."

However, patient advocacy groups recognise the importance of this approach, he says, and he hopes to launch a campaign with the European patient advocacy group network over the coming year.

Catherine McCabe, now an assistant professor at the School of Nursing and Midwifery at Trinity College, Dublin, did her PhD thesis on the project and is putting together a grant application to evaluate its effectiveness with residents in nursing homes. "Recently Ireland published some national standards around residential care for people with dementia. I think Open Window has a role to play in meeting those standards in terms of social contact, maintaining connection with families, and in stimulation and personalised meaningful activities. We are also looking at how it will impact on people with behaviours that challenge." ■

impactfactor

nature REVIEWS CLINICAL ONCOLOGY

Diabetes risk after radiation – not out of the woods

LILLIAN MEACHAM AND KIMBERLEY DILLEY

A retrospective cohort study has shown that pancreatic radiation is a risk factor for diabetes in survivors of paediatric cancer. This validates and refines prior epidemiological observations of diabetes after radiation to the abdomen and total-body irradiation, and will result in modification of surveillance recommendations in national survivor guidelines.

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Survival of paediatric cancer has improved significantly in the past four decades, to the extent that currently 80% of patients will become five-year survivors, and it is estimated that there are now more than 320,000 survivors of paediatric cancer in the USA.[1,2] In light of these statistics, in 2006, the Institute of Medicine called for the expansion of traditional practice in oncology and the development of programmes that included survivorship as a phase of cancer care.[3] The Institute of Medicine emphasised the importance that every survivor be regularly assessed for potential late effects of treatment, and that interventions be put in place to avoid or ameliorate the late effects of cancer therapy.[4] Cooperative groups such as the Children's Oncology Group (COG) in North America, the Scottish Intercollegiate Guidelines Network (SIGN) and the UK Children's Cancer Study Group (UKCCSG) have scoured the literature to develop evidence-based long-term follow-up guidelines that can be used to assist in the early detection of late effects associated with cancer therapy.[5] Concern for cancer-related origins of chronic disease prompted De Vathaire et al.[6] to assess the risk of diabetes among young adult survivors of paediatric cancer. They showed that pancreatic radiation is a risk factor for diabetes in survivors of paediatric cancer.

Through the efforts of the abovementioned cooperative groups and other groups that focused on long-term follow-up, it has been found that most cancer survivors have been living with chronic health conditions.

Diabetes is a serious health condition, with patients having a two-fold to four-fold higher risk of cardiovascular death, which accounts for about 70% of premature death among patients with type 2 diabetes.[7] Oeffinger et al.[8]

reported that the 30-year cumulative incidence for a chronic health condition in cancer survivors was 73%, with 42% of survivors living with a severe disabling or life-threatening condition, or a condition that had resulted in death.[8] It is now standard practice to begin guideline-based surveillance for late effects in all patients who had paediatric cancer once they are two years beyond the completion of cancer therapy. Some late effects begin soon after the cancer therapeutic agent exposure (neuropathy), some worsen as the survivor ages (cardiac disease) and some late effects do not emerge until the survivor is a young or middle-aged adult (second malignancies and infertility). This variable pattern of emergence of health conditions in survivors of paediatric cancer supports the need for lifelong follow-up and ongoing research to continue to identify the late effects of cancer treatment. In addition, the late development of new conditions or progressive worsening of established late effects supports that there is not a window of follow up after which a survivor is 'out of the woods'.

> "This study has led to modifications of the COG Long-Term Follow-Up Guidelines for Survivors"

The concern for cancer-treatment-related diabetes in this population was first reported in 1995 by Teinturier and coauthors, with the observation of a non-autoimmune insulinopenic form of diabetes 20 years after radiation.[9] Further assessment of 121 patients who had received abdominal radiation revealed that 6.6% of them had diabetes. These eight patients were said to have pancreatic diabetes, which was not considered as classic type 1 diabetes or non-insulin-dependent diabetes mellitus. In this Letter to the Editor, Teinturier questions the role of abdominal radiation, specifically left-sided radiation, in the development of diabetes in survivors.[9] In a report from the Childhood Cancer Survivor Study, survivors' self-report of treatment for diabetes was found to be 1.8 times more likely in 8599 survivors compared with 2936 siblings after adjustment for BMI, age, sex, race and ethnicity, household income and insurance. Survivors of neuroblastoma were seven times more likely and survivors of Wilms tumour and Hodgkin lymphoma twice as likely to develop diabetes after treatment if they received abdominal radiation.[10]

De Vathaire et al.[6] have taken this observation and further refined the investigation of risk for diabetes after radiation by verifying the self-report of diabetes in young adult survivors of paediatric cancer, and then calculating the radiation dose to the pancreas through dosimetry. Self-report questionnaires were sent to survivors treated for solid tumours or lymphoma (excluding leukaemia) from eight centres in France and the UK.[6] Of the 3468 survivors, questionnaires were sent to 2923 and returned by 86% of survivors, yielding 95 self-reports of diabetes. Diabetes was confirmed in 65 patients through communication with the healthcare providers for these survivors. Of the confirmed cases, 18% were treated with insulin only, 54% with oral medications, 17% with both insulin and oral medications and 11% had no treatment. Diabetes was associated with radiation to the tail of the pancreas – at the site where the islets of Langerhans are most concentrated – with a relative risk (RR) of diabetes of 11.5 (95%CI 3.9–34.0) in patients who received 10 Gy of radiation to the tail of the pancreas. The effect was dose dependent, with a plateau of risk at 20–29 Gy. Children who were younger than two years at the time of radiation were at higher risk, with a RR of 2.1 (95%CI 1.4–4.3) at 1 Gy compared with 1.4 (95%CI 1.1–2.2) for older patients. These findings were unchanged when adjusting for BMI, and no associations were found with chemotherapeutic exposures or radiation to the head or body of the pancreas.

Key point

Radiation to the tail of the pancreas increases risk of the development of diabetes in survivors of paediatric cancer and thus is a risk factor prompting the Children's Oncology Group to recommend routine screening of at-risk patients using fasting glucose or haemoglobin A1c.

The limitations of this study are the retrospective approach and the dependence on self-report of medical conditions in survivors. The true prevalence of diabetes is difficult to determine without a standardised methodology of screening and a prospective approach to surveillance. With a prospective approach, the time frame for emergence of disease can be better characterised, as well as having the advantage of improved biochemical classification of the impaired glucodynamics. Although associations with chemotherapy were not found, ascertainment of exposure to glucocorticoids was an acknowledged gap in this study, which did not routinely collect steroid exposure data.

The data reported by de Vathaire et al.[6] confirm and further define the risk of abdominal radiation in the development of diabetes as a late effect of cancer treatment. This study has led to modifications of the COG Long-Term Follow-Up Guidelines for Survivors of Pediatric Adolescent and Young Adult Cancers. At the 2012 Fall COG meeting, a new section will be proposed for the COG guidelines recommending prospective

surveillance for diabetes in all patients treated with abdominal radiation.*

Patients who are at risk will be screened with history and physical exam and will be monitored with fasting glucose or haemoglobin A1c prospectively for new development of diabetes. This story of recognition of a new late effect of cancer treatment, confirmation of additional cases in an at-risk population and investigation into potential causal pathways emphasises the need for ongoing research in the field of survivorship. Next steps will include further investigation in the mechanistic role of radiation in beta-cell dysfunction or other possible mediators of impaired glucose metabolism. This understanding could lead to modification in treatment or interventional strategies aimed at minimising risk.

*Update: Since this article was first published, the Children's Oncology Group has added Diabetes mellitus as a potential late effect after radiation to the abdomen and after total body irradiation. Specific recommendations for surveillance are being created and will be implemented with changes to the COG Long Term Follow Up Guidelines for Survivors of Paediatric Adolescent and Young Adult Cancers in 2013.

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Doc, I don't want your poison

FRANCESCA GIORGI AND ROMEO BASCIONI

What can you do when your patient makes an irrational decision to forgo potentially life-saving therapies? Two medical oncologists who faced this challenge tell their story.

Mrs A is a bright and intense 58-year-old woman. She is married and the mother of two sons. She is a Catholic who practices meditation, has trust in natural medicine, and believes that the mind has control over the body's physical well-being. We met her in 2003 when her mother was diagnosed with lung cancer, which eventually led to her mother's death. During this period, although Mrs A clearly trusted our therapeutic approach, she also prepared some homeopathic remedies for her mother, such as Bach flowers. When her mother passed away, Mrs A thanked us for our work. We remained in touch, and every Christmas she sends us handmade presents.

In April 2010, Mrs A found a lump in her left breast. After consultation with a doctor practising complementary and alternative medicine (CAM), Mrs A concluded that the lump was a sign of psychological distress and did not undergo any further diagnostic procedures. However, the lump did not disappear. Six months later, Mrs A finally underwent a mammogram and biopsy; breast carcinoma was diagnosed. In December 2010, Mrs A underwent a quadrantectomy with sentinel node excision. At the follow-up examination a few days later, we discussed the biology of her tumour, which involved a risk recurrence worthy of adjuvant therapy. We proposed a standard chemotherapy regimen including trastuzumab, radiotherapy and hormone therapy. Mrs A calmly but firmly refused all the suggested treatments, saying that she did not want to be poisoned and have her immune system destroyed. We did not make any negative remarks about her decision, but we asked her to consider another meeting to further discuss treatment options. She said, "OK, I'll think about it."

Most patients with cancer accept the treatments proposed by their oncologists, even when the clinical benefit is likely to be modest (*BMJ* 300:1458). Most women who undergo adjuvant chemotherapy for early-stage breast cancer consider its benefits to be worthwhile, whereas only 1%–2% of patients would not repeat chemotherapy regardless of the magnitude of potential benefit (*Lancet Oncol* 2:691–697). Approximately 25% of patients with breast cancer prefer to be the sole decision maker about adjuvant therapy options, with the desire for decisional control increasing after medical consultation (*JCO* 30:857–862).

The widespread availability of web-based medical information and internet forums in which patients share experi-

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

ences and opinions may complicate the oncologist's decision-making approach (*JCO* 21:942–947, *NEJM* 366:581–585). Moreover, CAM is a growing field in oncology, with one study reporting that 80% of patients have used these therapies at least once (*JCO* 18:2505–14). Patients are motivated by the perceived absence of toxicity in these approaches, even though only 37% of patients believed that they could be cured in this way. Of note, almost half of interviewed patients wanted more control over their medical care (*JCO* 18:2505–14). In the setting of adjuvant therapy for breast cancer, most patients use CAM as an additional therapy rather than as an alternative to the established medical practice (*NEJM* 340:1733–39) – a behaviour that is usually harmless. In contrast, there are serious negative consequences in terms of survival rates when the standard oncologic treatment is withheld in favour of CAM (*Am J Surg* 192:471–473).

When an oncologist is faced with a mentally competent patient who makes a medically irrational choice, it is important to separate this irrational preference from the rest of the patient's values and beliefs (*NEJM* 322:1595–99). Although physicians propose therapies based on a set of specific measurable goals (e.g. survival, morbidity), patients' decisions are ultimately based on a complex system of personal values, beliefs, experiences and emotions (*J Med Ethics* 31:131–136, *JAMA* 302:195–197, *Oncologist* 17:91–100). Interestingly, a patient who refuses treatment often seems to assume that this choice terminates the patient's relationship with the oncologist.

Studies on how patients with cancer develop trust-based relationships with their physicians are limited. The few published studies show that professional competence, honesty, and patient-centred

It is important to separate this irrational preference from the rest of the patient's values and beliefs

She did not feel judged for her choices and appreciated our open-minded attitude

behaviour are the main enhancers of trust (*Psychooncology* 20:227–241). Addressing the emotional needs of patients is a fundamental task during the medical encounter. Emotional support from physicians is the most consistent long-term determinant of trust for patients with breast cancer (*J Gen Intern Med* 24:252–255).

At the next visit, Mrs A came alone, although she did state that her husband and sons were "by her side". We talked about her mother's illness and death. She said that it was a difficult time for her because she was the only family caregiver. She remembered feeling hopeful when the first post-chemotherapy computed tomography scan showed complete remission – a feeling that was lost when the cancer returned and was not controlled by either medical treatment or natural remedies. Mrs A believed that the recurrence was triggered by a family crisis that caused serious emotional distress for her mother. Mrs A's mother spent her last days at home. During one visit, we found her mother sleeping quietly, with Mrs A holding her hand and still hoping for recovery – even though it was obvious that this was not going to happen.

The emotional distress that Mrs A experienced during her mother's illness seemed to profoundly influence her decision to refuse the proposed treatment for her own breast cancer. We then discussed her current options and agreed that her decision should not be a mere compilation of advantages and disadvantages. Instead, it should be a process that involved her whole life, her relationships with friends and family, and her ability to deal with the concept of illness.

Mrs A stated that she had not changed her mind, but she seemed less convinced. When asked again about the reasons for this choice, Mrs A said that "conventional medicine destroys the immune system… doesn't have a holistic approach, [and] does not take into account the psychological dimension," which she believed was the key to her illness. We reiterated the difference between "getting better" and "feeling better" (Buckman and Baile, A practical guide to communication skills in cancer care, Medical Audio Visual Communication, Toronto 2001). Although chemotherapy, trastuzumab, and hormone therapy could be transiently detrimental to her quality of life, the long-term benefit is well established. We discussed the evidence for the proposed adjuvant therapy and re-emphasised that CAM therapies have not been shown to have any clinical benefits (*Breast Cancer Res Treat* 95:199–209). We also discussed the key point of contention – treatment toxicity. At the end of our meeting, we asked if all the issues were sufficiently clear and stated that we were available to discuss her concerns again.

Mrs A decided to begin chemotherapy – against the advice of her family and friends. She completed all scheduled treatments, even when she needed granulocyte colony-stimulating factor support for febrile neutropenia after the second cycle of chemotherapy. Upon completion of radiotherapy, trastuzumab and hormone therapy were started after some delay because Mrs A still was not convinced about this therapy; the term 'antibody' frightened her. Trastuzumab was eventually interrupted when a heart ultrasound revealed a 15% drop in the left ejection fraction.

At the next visit, Mrs A stated that she was "depressed" and that "hormone therapy had made her another person." She refused any psychological support and ultimately decided to discontinue the treatment. Although a follow-up ultrasound revealed an improved ejection fraction, Mrs A confirmed her decision to stop any oncologic therapy at that time. However, she did state her intention to continue to be followed at our clinic and expressed her appreciation for our medical care. Despite the difficulties and complexities of this particular patient–doctor relationship, which were mostly related to profound differences in cultural backgrounds and views, Mrs A's trust was not lost due to the emotional support she received during her mother's illness and after her own diagnosis of breast cancer. She did not feel judged for her choices and appreciated our open-minded attitude, which were probably the key elements to maintaining the relationship.

From this experience, we learned that it is important to maintain a trusting relationship with our patients, even when the decisions we suggest are dismissed for reasons with which we do not agree. A compassionate approach is critical to help patients face their disease, now and in the future. ■

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newsround

Selected reports edited by Janet Fricker

Aprepitant for managing pruritus

■ Lancet Oncology

Use of an aprepitant decreased the severity of pruritus induced by biological cancer treatments, an Italian pilot study reports.

Pruritus (itch) is a common symptom among patients taking targeted drugs, especially those targeting the EGFR pathway. Treatment of pruritus is considered important for patients' well-being, not least because untreated side-effects might contribute to poor adherence to oral anticancer treatments.

Aprepitant, an oral neurokinin-1 receptor antagonist that blocks mast-cell degranulation caused by neurokinin-1 receptor, is commonly used for prevention of acute and delayed nausea or vomiting caused by highly emetogenic chemotherapy, and for prevention of postoperative nausea and vomiting.

In 2010, Daniele Santini and colleagues, from the Bio-Medico University of Rome, Italy, reported off-label use of aprepitant for treatment of pruritus in two patients with stage 4 non-small-cell lung cancer receiving erlotinib. On the basis of finding that both patients recovered from pruritus 24 hours after administration, the team designed a pilot study to assess aprepitant in the management of pruritus caused by biological drug treatments.

Between September 2010 and November 2011, 45 patients were enrolled into the single-centre prospective study. Two different populations were studied: patients with severe itch resistant to standard treatment with steroids or antihistamines (the refractory group), and patients who had not received any treatment for severe pruritus (the naïve group).

For the refractory group, aprepitant (125 mg on day 1; 80 mg on day 3; 80 mg on day 5) was given to patients; while for the naïve group, the same schedule for aprepitant was used after the first onset of severe pruritus.

Results show that for patients refractory to standard treatment for pruritis, aprepitant reduced median itch on the visual analogue scale (VAS) from 8.00 (95%CI 7.93–8.57) at baseline to 1.00 (95%CI 0.00–2.00) after one week of treatment ($P<0.0001$). For patients previously treated for pruritis, aprepitant reduced the VAS score from 8.00 (95%CI 7.43–8.37) at baseline to 0.00 (95%CI 0.06–1.08) after one week of treatment ($P<0.0001$).

"To our knowledge, this trial is the first clinical study to show that aprepitant can help management of pruritus caused by biological treatments, both as a first choice treatment and after failure of standard treatments," write the authors.

The results, they add, support the notion that substance P activates dermal mast-cells through neurokinin receptors, inducing release of pruritogens, which causes onset of pruritus. Randomised phase II or III trials should now be undertaken to validate the efficacy of aprepitant treatment.

In an accompanying commentary Olivier Mir, from the Institut Gustave Roussy, Villejuif, France, and Romain Coriat, from Paris Descartes University, France, write, "Particular attention should be given to the risk of drug–drug pharmacokinetic interactions, since aprepitant can alter the activity of cytochrome P450 3A4 isoform (CYP3A4), an enzyme involved in the metabolism of a range of anticancer drugs."

Tyrosine kinase inhibitors metabolised by CYP3A4, they add, include erlotinib, gefitinib, sunitinib, sorafenib, imatinib, pazopanib, axitinib, and regorafenib.

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■ O Mir, R Coriat. Aprepitant for pruritus: drug–drug interactions matter. *ibid*, pp 964–965

Prostate cancer: intermittent androgen suppression non-inferior to continuous treatment

■ New England Journal of Medicine

Intermittent androgen deprivation has been found to be non-inferior to continuous therapy with respect to overall survival for men with prostate specific antigen (PSA) levels rising after initial or salvage radiotherapy. The phase III NCIC Clinical Trials Groups study, funded by the Canadian Cancer Society, also showed some quality-of-life factors improved with intermittent therapy.

The development of reversible non-oestrogenic castrating regimens, along with the availability of PSA assays, laid the foundations for the study. Preclinical studies have shown that intermittent therapy lengthens intervals from initial androgen deprivation therapy to development of hormonal resistance. The adverse effects of androgen therapy on quality of life have been well described and include sexual dysfunction, hot flushes, fatigue, anaemia, decreased bone density and muscle mass, altered blood lipid profiles, depression, cognitive dysfunction and worsening of metabolic syndrome.

Juanita Crook and colleagues, from Columbia Cancer Agency, Kelowna, Canada, investigated

the hypothesis that intermittent androgen deprivation might provide better disease control while at the same time providing relief from castration-associated adverse effects.

Between January 1999 and November 2005, 1386 men with PSA levels greater than 3 ng/ml one year after primary or salvage radiotherapy for localised prostate cancer were randomised in a 1:1 ratio to either intermittent therapy for eight months (n=690) or continuous therapy (n=696). Both groups received luteinising hormone-releasing hormone agonists combined with a non-steroidal antiandrogen. PSA levels were monitored every two months. In the intermittent group, therapy was paused only if there was no evidence of clinical disease progression and the patient's PSA levels were less than 4 ng/ml and not more than 1 ng/ml above previous recorded values.

At a median follow-up of 6.9 years, 268 patients in the intermittent therapy group had died, versus 256 in the continuous therapy group. The median overall survival was 8.8 years in the intermittent group versus 9.1 years in the continuous group. The P-value for non inferiority (HR<1.25) was 0.009, supporting the hypothesis that intermittent therapy was not inferior to continuous therapy.

In terms of adverse events, no significant differences were found between the two groups. Intermittent therapy was associated with significantly better scores for hot flushes (P<0.001), desire for sexual activity (P<0.001) and urinary symptoms (P=0.006), with a trend towards improvements in levels of fatigue (P=0.07).

Although intermittent androgen-deprivation therapy appears to provide overall quality-of-life benefits, write the authors, differences were not as "profound" as expected. "Part of the explanation for this lies in the timing of the quality-of-life assessments, which were performed at regular intervals in both treatment groups without regard to the treatment phase (on or off treatment)," write the authors.

The cost savings from reductions of drug use in the intermittent therapy group (approximately one third that of the continuous therapy group), may be partially offset by the closer follow-up required, write the authors.

In an accompanying commentary, Oliver Sartor, from Tulane University School of Medicine, New Orleans, praised the research as 'the most definitive study to date', comparing intermittent versus continuous androgen-deprivation therapy in non-metastatic cancer. He noted, however, that important questions remain unanswered, such as whether men with rising PSA levels need treatment. "This is a heterogeneous patient group, and only a minority of men might be expected to have clinical consequences from their rise in PSA level," he writes.

■ J Crook, C O'Callaghan, G Duncan et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *NEJM* 6 September 2012, 367:895–905

■ O Sartor. Androgen deprivation – continuous, intermittent or none at all? *ibid*, pp 945–946

Study provides reassurance about cognitive decline following chemotherapy

■ Journal of Clinical Oncology

Cognitive deficits in breast cancer patients treated with chemotherapy six months previously were found to be small in magnitude and limited to verbal and visuospatial ability domains, a meta-analysis has reported.

The terms 'chemofog' and 'chemobrain' are often used by patients to describe an ill-defined impairment of cognitive function following chemotherapy. But evidence is mixed, with several studies reporting deficits and others not. Although four meta-analyses have previously examined cognitive functioning in patients treated with chemotherapy, none has focused exclusively on the post-treatment period.

In the current study, Heather Jim and colleagues, from Lee Moffitt Cancer Center, Tampa, Florida, set out to conduct a meta-analysis of cognitive functioning in breast cancer survivors who had been treated with chemotherapy six months previously. The meta-analysis focused on women with breast cancer, as the vast majority of existing research has been conducted in this population. "If cognitive deficits occur during treatment but resolve thereafter, then studies including patients primarily receiving treatment may negatively influence findings," write the authors. However it is possible, they add, that deficits occurring during treatment may persist.

The meta-analysis identified 17 studies covering a total of 807 breast cancer survivors who had been treated with standard-dose chemotherapy at least six months earlier. For the studies, neuropsychological tests were categorised according to eight cognitive domains: attention, executive functioning, information processing, motor speed, verbal ability, verbal memory, visual memory, and visuospatial ability.

Results showed that deficits in cognitive functioning were found in patients treated with chemotherapy relative to controls or their own pre-chemotherapy baseline in the domains of verbal ability (g=-0.19; P<0.01) and visuospatial ability (g=-0.27; P<0.01). Patients treated with chemotherapy performed worse than non-cancer controls in verbal ability and worse than patients treated without chemotherapy in visuospatial ability (both P<0.01). Age, education, time since treatment, and endocrine therapy did not moderate observed cognitive deficits in verbal ability or visuospatial ability

"Clinically, our findings suggest that patients with breast cancer considering chemotherapy be educated that >6 months after treatment, they can expect normal cognitive functioning with the exception of slight impairments in verbal abilities (e.g., word-finding difficulty) and visuospatial abilities (e.g., getting lost more easily)," write the authors.

However there is likely to be considerable variability in cognitive outcomes, they add, with some patients reporting no impairments and other reporting more severe or pervasive deficits. Patients treated with chemotherapy reporting cognitive difficulties should be referred to a neuropsychologist for evaluation and management of cognitive deficits.

In an accompanying commentary, Gary Rodin from the University of Toronto, Canada, and Tim Ahles from Memorial Sloan-Kettering Cancer Center, New York, write that most studies of cognition and cancer exclude patients with a variety

of conditions that increase vulnerability to post-treatment cognitive decline, including history of head injury, neurologic disorders, depression and learning disabilities. "Consequently, the cognitive changes reported may represent the tip of the iceberg in terms of the cognitive impact of cancer treatments," they write.

■ H Jim, K Phillips, S Chait et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *JCO* 10 October 2012, 30:3578–87

■ G Rodin, T Ahles. Accumulating evidence for the effect of chemotherapy on cognition. *ibid* pp 3568–69

Interventions reduce symptoms in breast-cancer-induced menopause

■ Journal of Clinical Oncology

Women who experience early menopause following treatment for breast cancer who undergo cognitive therapy (CBT) and physical exercise (PE) showed improvements in endocrine symptoms compared to controls who did not receive such interventions, reports a Dutch study.

It is well known that chemotherapy and endocrine therapy in patients with pre-menopausal breast cancer may result in early onset of menopause. Primary symptoms include hot flushes, night sweats and vaginal dryness, and secondary symptoms include weight gain, urinary incontinence and psychological distress.

With growing evidence that cognitive behavioural therapy and physical exercise can have a positive impact on vasomotor symptoms in naturally occurring menopause, Neil Aaronson and colleagues, from the Netherlands Cancer Institute in Amsterdam, set out to explore whether such benefits could also be achieved in breast cancer patients experiencing treatment-induced menopause.

In the study, 422 women with primary breast cancer aged less than 50 years were randomly assigned, between January 2008 and December 2009, to CBT (n=109), PE (n=104), CBT and PE (n=106) or to a waiting-list control group (n=103). Self-report questionnaires were completed at baseline, 12 weeks, and six months. The CBT programme consisted of six weekly group sessions of 90 minutes each, including relaxation exercises; while the PE programme was a 12-week individually tailored home-based programme for 2.5–3 hours per week, where physiotherapists assisted the women in selecting an appropriate form of exercise, from swimming, running and cycling.

Results showed that, in comparison with patients in the control group, those in the intervention groups had significant decreases in levels of endocrine symptoms, measured using the Functional Assessment of Cancer Therapy (P<0.001; effect size 0.31–0.52). Urinary symptoms, measured using the Bristol Female Lower Urinary Tract Symptoms Questionnaire were also decreased (P=0.002; effect size 0.29–0.33). Furthermore, the active groups showed improvements in physical functioning measured using the physical functioning subscale of the 36-Item Short Form Health Survey (P=0.002; effect size 0.37–0.46).

PE, the researchers note, "affects primarily the frequency with which endocrine symptoms are experienced, but not the frequency of hot flashes and night sweats specifically," while CBT, in contrast, "seems to not only affect symptom frequency, but also the perceived burden of hot flashes and night sweats."

"In conclusion, our findings indicate that both CBT and PE can have salutary effects on menopausal symptoms and to a lesser degree on sexuality and HRQoL-related functioning among patients with breast cancer experiencing treatment-induced menopause," write the authors.

The results, they add, tend to support the hypothesis that cognitive and emotional factors can modify the experience of menopausal symptoms, whereas stress reduction techniques and physical exercise may have a more direct effect on menopausal symptoms via the thermoregulatory system and an improvement in overall physical condition. "Future work is needed to improve the design and the planning of these interventions, with an eye toward improving program adherence," write the authors.

In an accompanying commentary, Debra Barton and Charles Loprinzi, from the Mayo Clinic, Rochester, Minnesota, write, "Although the trial... provides helpful information, much more work needs to be completed to best understand the ideal way to clinically apply non-pharmacologic therapies for the treatment of hot flashes, night sweats, and other estrogen deficiency symptoms."

■ S Duijts, M van Beurden, H Oldenburg. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. *JCO* 20 November 2012, 30:4124–33

■ D Barton, C Loprinzi. Using one's head to treat menopausal symptoms. *ibid*, pp 4059–60

Acupuncture relieves symptoms of xerostomia

■ Annals of Oncology

Patients with head and neck cancers randomised to acupuncture were twice as likely to report improved symptoms of xerostomia as patients receiving oral care sessions, the UK ARIX study has found. No significant differences were found in saliva production between the two groups, however.

Patients who have received radiotherapy for head and neck cancer often suffer from the unpleasant and distressing side effect of dry mouth (xerostomia) caused by damage to the salivary glands from radiation. Chronic xerostomia impairs quality of life, interfering with taste, chewing, swallowing, speaking and sleeping. Management options providing short-term help include mouth washes, gels and toothpastes. While the drug pilocarine can offer relief, the side-effects of muscarinic receptor stimulation can cause the unpleasant symptoms of sweating, rhinitis and urinary frequency. Studies have suggested that acupuncture, an increasingly accepted method for controlling pain,

chemotherapy-induced nausea and hot flushes, might also relieve symptoms of xerostomia.

In the ARIX (Acupuncture in the treatment of Radiation-Induced Xerostomia) trial, investigators led by Val Jenkins, from the Brighton and Sussex Medical School, UK, investigated the efficacy of acupuncture in ameliorating patients' self-reported symptoms of dry mouth.

For the study ,145 patients with chronic radiation-induced xerostomia lasting longer than 18 months were randomised to receive group acupuncture sessions for 20 minutes every week for eight weeks (*n*=70), or two oral care educational sessions for one hour, one month apart (*n*=75). Then four weeks after the end of the two different types of care, patients swopped over to receive the other treatment. Patients were recruited from seven cancer centres in the UK.

Patients answered the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQC30), and the Head and Neck subscale. Saliva production was measured using Schirmer strips, both in the stimulated situation (where lemon juice was applied to the tongue) and non-stimulated situation.

Results showed that, in comparison with oral care, acupuncture produced significant reductions in patient reports of severe dry mouth (OR=2.01; *P*=0.031), sticky saliva (OR=1.67; *P*=0.048), needing to sip fluid to swallow food (OR=2.08; *P*=0.011) and in waking up at night to drink (OR=1.71; *P*=0.013). There were no significant changes in either stimulated or unstimulated saliva measurements over time.

"The trial appears to establish the effectiveness of the technique, and group sessions offer a pragmatic and affordable system of delivering the intervention," write the authors.

Future studies, add the authors, may be warranted to refine the technique further, establish the duration of benefit and length of treatment, and whether booster sessions might improve and maintain efficacy.

The mechanisms underpinning the benefits of acupuncture are not clear. "Acupuncture may produce autonomic stimulation of any residual salivary gland tissue directly or by increasing blood supply to it or the multiple minor salivary glands that line the upper aerodigestive tract," suggest the authors.

■ R Simcock, L Fallowfield, K Monson et al. ARIX: a randomised trial of acupuncture v oral care sessions in patients with chronic xerostomia following treatment of head and neck cancer. *Ann Oncol*, published online 25 October 2012, doi:10.1093/annonc/mds515

Asymptomatic VTEs associated with increased risk of death in cancer patients

■ **British Journal of Cancer**

Asymptomatic venous thrombotic events (VTEs) of the lower limbs in ambulatory cancer patients were found to be associated with a 2.4-fold increased risk for death during nine months follow-up despite anticoagulation medications.

VTEs are a common complication associated with malignancy, with increased microparticle tissue factor activity described in cancer patients with VTE, in addition to increases in circulating tumour cells and high platelet counts. In a recent study, symptomatic and asymptomatic VTEs were found to occur in more than one third of pancreatic cancer patients.

In the current prospective cohort study, Thomas Gary and colleagues, from the Medical University Graz, Austria, evaluated the occurrence of VTEs of the lower limbs in 150 consecutive ambulatory cancer patients seen at their outpatient clinic. The team explored the association with survival during nine months of follow-up. To evaluate the occurrence of VTEs, compression ultrasound (CUS) was performed by two experienced vascular specialists in all patients at baseline, with venous thrombosis in the pelvic veins examined by duplex Doppler sonography of the common femoral vein performed after a Valsalva manoeuvre.

Results show that the most frequently included tumour entities were colorectal and anal cancer (32.7%), breast (22.7%), pancreatic (21.3%), lung (4.7%), gastro-oesophageal (4.7%) and prostate (3.3%). Chemotherapy was being used by 82.7% of patients in the study.

Altogether asymptomatic VTEs were identified in 27 patients (18%), with 13 asymptomatic SVT (superficial venous thrombotic) events in the saphenous system and 16 asymptomatic DVT (deep venous thrombotic) events – two patients had both a SVT and DVT event. In the nine-month follow-up period, 9 out of 27 patients with asymptomatic VTEs at baseline died, compared with 14 out of 123 patients without VTEs at baseline (*P*=0.001). Even after adjustment for age, sex, stage of cancer, tumour entity, chemotherapy, surgery and radiotherapy, an asymptomatic VTE of the lower limbs was associated with a 2.4-fold increased risk for death (HR 2.4, 95%CI 1.2–5.3; *P*=0.03).

In patients with asymptomatic VTEs, the main tumour entities were pancreatic cancer (29.6%), colorectal and anal cancer (25.9%), and breast cancer (18.5%). Chemotherapy was applied in 88.9% of these patients.

"Our study shows for the first time in a prospective manner that ambulatory cancer patients are at high risk to suffer a completely asymptomatic VTE of the lower limbs. These patients are at higher risk to die in the following 9 months," write the authors.

Most interesting, they add, was the finding that death occurred despite low-molecular-weight heparin therapy, making a fatal pulmonary embolism (PE) as a reason for death in these patients unlikely. "We therefore hypothesise that the occurrence of an asymptomatic VTE seems to be an expression of an advanced stage or associated with a more aggressive biologic behaviour of the malignant disease," they write. The aetiology of these completely asymptomatic VTEs requires further investigation.

Limitations of the study include small sample sizes and the fact that only one compression ultrasound was performed at baseline. There is a need for larger prospective studies, add the authors, powered to detect differences in short-term survival between superficial, distal and proximal deep venous thrombosis.

■ T Gary, K Belaj, K Steidl et al. Asymptomatic deep vein thrombosis and superficial vein thrombosis in ambulatory cancer patients: impact on short term survival. *Br J Cancer* 9 October 2012, 107:1244–48

My World

Ramon Salazar is head of translational research at the Institut Català d'Oncologia near Barcelona. He leads the Early Clinical Research Unit and is in charge of the colorectal and neuroendocrine tumour clinics. He is a leading figure in national and European groups on GI cancers and NETs.

Why I chose to work in cancer

I was attracted by the scientific challenge and I wanted to help patients live longer with a better quality of life.

What I love most about my job

Studying cancer and how to defeat it. I hate the disease for its consequences on my patients, but I am fascinated scientifically by the biology, and I take pleasure in reading science and medicine related to the disease.

The hardest thing about my job

When the disease takes away my patients too early. I will never learn to cope with this. You make yourself strong and try to help the families, but there is no way to help them with the terrible feeling of loss.

What I've learnt about myself

I am compassionate and intuitive. When you are young you think nothing will prevent you from a successful career curing cancer. But after a while you look back and see how many of your patients you have lost, and you realise that maybe spending time on palliation and consolation is at least as important as healing. We can do so much for people we do not cure.

I'll never forget...

My clinical and translational ESMO fellowship at the Beatson Oncology Centre in Glasgow, under the direction of Stanley Kaye and Chris Twelves. I discovered all the faces of the speciality – the biological background and preclinical and clinical pharmacology.

A high point in my career

Being part of successful research that can improve the life of my patients, such as the discovery of new resistance mechanisms in BRAF-mutant colorectal cancer or the validation of a prognostic genomic classifier in stage II colon cancer.

I wish I were better at...

Understanding the economics related to my job, and my sleep habits (going to bed earlier).

What I value most in a colleague

Team work and dedication to improve both knowledge and patient care.

The most significant advance in my specialty in recent years

ErbB2 [HER2] in breast cancer. Amongst all the molecular targets that seem to offer significant progress, it is the only one that has shown a real relevance in the adjuvant setting.

My advice to someone entering my specialty today would be...

Do formal training in both communication skills and molecular technology. People are looking for empathy and want to feel there is a human being taking care of them who really cares for them. This can be trained. Oncologists also need to learn about the molecular technologies behind biomarker validation and testing, because there is so much bias and noise in the literature, and we are the ones who have to interpret and apply it.

What I wish I'd learnt at medical school

How to budget and organise teams, and provide leadership. We now find ourselves facing a huge challenge because of the economic situation, where we have limited budgets and have to lead teams that provide cancer care to patients and also do research. Skills in how to control expenses and deliver within budget, along with the interpersonal and leadership skills needed to run a team, are even more important than technical, medical or research skills.