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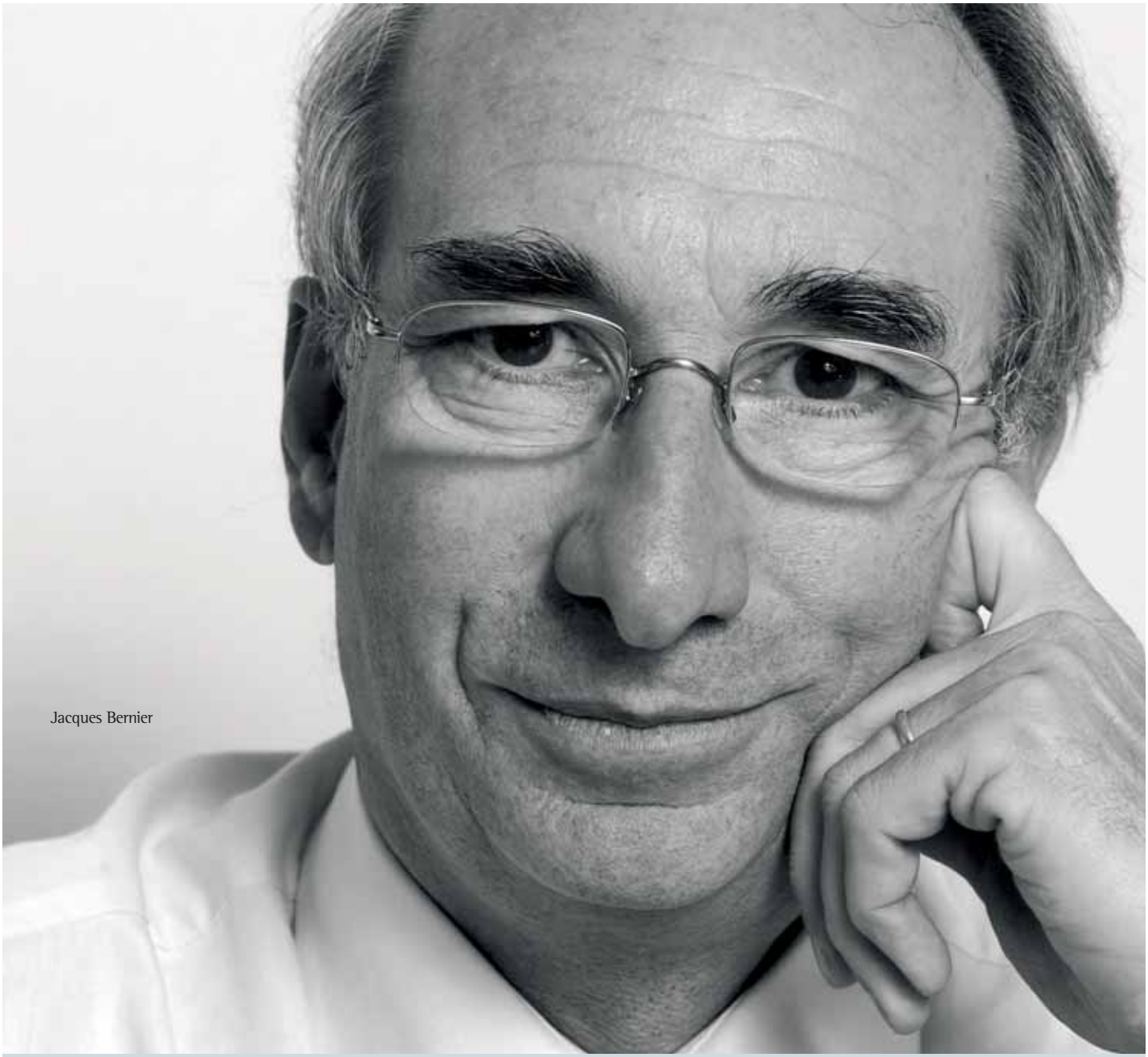
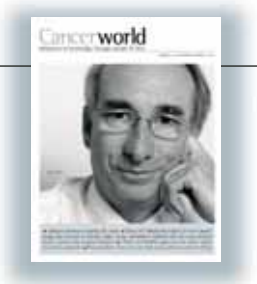


Jacques Bernier

➜ Jacques Bernier: keeping the faith ➜ New cancer drugs and survival in Europe: does the Karolinska report make sense? ➜ Roland Holland tells the story behind breast-conserving surgery margins ➜ ASCO and ESMO spell out ten basic rights for cancer patients ➜ Prescriptions: how you can help your patients stick to theirs



Contents

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Making rights a reality

Kathy Redmond ■ EDITOR

That all cancer patients should have the right to quality care is something we can all agree on. But there have been few attempts to define exactly what this means. After a lengthy consultation exercise, two influential oncology organisations, the American Society of Clinical Oncology and the European Society for Medical Oncology, have now issued a consensus statement on what constitutes quality care in cancer (p48).

This document spells out the rights that should be guaranteed to every cancer patient, such as the right to be treated with dignity, the right to a second opinion, the right to receive care from a multidisciplinary team, and rights to palliative care and rehabilitation services. The statement offers an authoritative marker against which every cancer service can be judged, and it raises questions about why rights that are considered fundamental are still being flouted by so many health systems, hospitals and doctors, and what we can do to turn this around.

The right to a second opinion is a case in point. Access to a second opinion is important because doctors can make mistakes. A second doctor could see something that the first has missed, or know something the first did not. Second opinions are particularly important in rare cancers, borderline cases, and cancers of unknown origin. They can help ensure that the cancer is diagnosed and staged correctly and the patient receives optimal treatment and follow-up.

However, a poll of patients at the 2005 masterclass of the European Cancer Patient Coalition showed that few European cancer patients have easy access to a second opinion paid for by their public health-care system – 50% indicated that in theory there is access, but in practice bureaucracy hinders the process. In some countries, patients find it almost impossible to get hold of their pathology reports and imaging studies, which they need if they are to get a second opinion. Many health-care systems are set up in a way that makes it very hard to see a second doctor on a reimbursed basis.

Personal issues also play a role. Where second opinions are not actively encouraged, it can be very difficult to ask for one. Some patients worry about offending their doctor; others are concerned about having to build up a relationship with a new team of carers if they change health-care institution.

Why are cancer patients still being denied rights that most of us believe to be fundamental? What can be done to narrow the gap between our aspirations and reality? *CancerWorld* will be seeking answers to these questions through an e-survey sent to all our readers in September. We welcome all contributions. If you would like to take part in this survey, please write to me at editor@esoncology.org.

Jacques Bernier: keeping the faith

Marc Beishon

As a young medical school graduate in the '70s, Jacques Bernier ignored warnings that drugs were about to replace radiotherapy. He believed that new technology would make it safer and more effective. Today, he has faith that synergies between radiotherapy and targeted drugs can bring further benefits – and he is determined to see Europe play a full part in the research effort.

Jacques Bernier must have one of the most glorious vistas of any oncologist – from his office balcony in Genolier, Switzerland, he has a panoramic view of Lake Geneva and the mountains beyond. He's recently moved to co-head radiation oncology at the private Genolier Swiss Medical Network, having spent a long spell in Bellinzona in southern Switzerland in a similar capacity. While these centres may not be the biggest cancer operations around, Bernier has proved that this is no obstacle to scaling the heights of oncology – on more than one front.

His core work in clinical radiation oncology, in particular on head and neck cancers, has led to pioneering work on radiation dose fractionation, quality assurance and new technology, and, more recently, synergistically combining radiotherapy with chemotherapy, molecular targeted drugs or surgery. In 2000, he started the International Conference on Translational Research and Pre-Clinical Strategies in Radiation Oncology (ICTR). The third meeting, held this year in Lugano, looks to have cemented this critical discussion on translational research in the packed oncology calendar.

And what better place than the traditionally neutral Switzerland for a senior, multilingual oncologist to play a part in bridging the divide between northern and southern Europe, through numerous committee and training positions, especially in the European School of Oncology (ESO) and the European Organisation for the Research and Treatment of Cancer (EORTC), where he has designed and supervised many clinical trials.

He has some good news – and not so good – about bridging the gaps in oncology and in the wider research and development community. In his own field he says the growing synergies between radiation oncology and targeted drug therapies, and the emergence of new technologies, has led to exciting progress. "Over the last decade or so radiation oncology is again in the game, which wasn't the case back in the 1980s." The traditional isolation of radiation oncology centres has been breaking down in recent years, he adds, noting the appearance of

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Growing synergies between radiation oncology and targeted drug therapies has led to exciting progress

more collaborative papers at his own ICTR meetings.

But in a wider context, he feels strongly that Europe has missed the boat in terms of competing with North America on the research front, in oncology and indeed in most medical and scientific disciplines. "In oncology we should have done something five to ten years ago when we saw that ASCO [the American Society of Clinical Oncology] was prevailing," he says. "Top level papers go to ASCO now for scientific and financial impact; we should have tried harder to keep them here."

That's a view shared by many, of course, but Bernier feels it's symptomatic of a fairly serious brain drain among the current generation of younger researchers, too many of whom are working in the US and not returning to Europe. It has prompted him to look closely at an issue he says is affecting much of European science. "There is no European market for research – it simply doesn't exist," he says, noting how sad it has been for him to see so many bright young researchers leave for the States. But he is not one to sound off from the sidelines. He's put pen to paper on the issue, researching and

suggesting action points – applying similar rigour to his 'big picture' interests as he's known for in his clinical work.

That work currently involves rather too much administration for his liking, as he helps build the oncology department at the Genolier Swiss Medical Network, which will include a new centre in Geneva. Having spent 18 years at Bellinzona, he says he was ready for new challenges in the last part of his professional life, with the opportunity to add state-of-the-art radio-oncology equipment, which will be in place by the end of this year.

Admin is a necessary evil, he adds, to maintain a proper integration of oncology disciplines and to plan for the medium term at least. "But it's now very difficult to have a long-term vision as things are changing so fast," he says. "I'm not sure I can say now what radiation oncology will look like even by 2011."

This certainly poses a challenge for radiation oncologists as they push for investment in expensive machinery and resources to staff facilities. They also face competition for resources with other departments. "Medical oncology is usually much bigger, which is not favourable to integration – there's an imbalance of people and financial resources. Radiation oncology has been the poor relation."

Bernier is a Belgium national and went to medical school in his own country, following in his grandfather's footsteps. He became interested in oncology as he felt, like many in the early 1970s, that 'something had to be done'. Taking his time over a specialism, he wasn't put off by people telling him that radiation oncology would be finished in 10 years' time thanks to new drug treatments. For certain, the machinery of the day could have severe side-effects, "But I was sure that new technology would improve treatment efficiency, and once the modern linac [linear accelerator] was in widespread use, we've seen a steady progression."

He went on to achieve distinctions in both radiation oncology and nuclear medicine in Liège, with training also at MD Anderson and the Curie Institute, and spent his formative clinical days in hospitals in Eupen and Charleroi. Here he carried out lab research, developing in-vitro assays for interferon, interleukin and the tumour necrosing factor – his path crossing that of Paul Franchimont, a 'visionary' Belgian doctor and scientist – and received awards for both his clinical and research work.

While his specialty may have taken a back seat to the rush to chemotherapy in the 1980s, he says the presence of powerful and forceful figures in radiation oncology helped him and others keep the faith. They include Jean-Pierre Bataini, from the Curie Institute in Paris, Emmanuel van der Schueren, a Belgium oncologist who died too young and who Bernier says was a great loss to European oncology, and, in the US, well-known names such as Herman Suit and Gilbert Fletcher (the latter Bernier worked with at MD Anderson). "They were either pioneering or reinforcing things, and I never had the impression that we'd reached a plateau in radiation oncology," he says.

The history of his specialty is of more than just passing interest for Bernier. Over the last few years he has written several times on the historical context, including a paper published in 2004 in *Nature Reviews Cancer*, entitled 'Radiation oncology: a century of achievements', on which he was lead author. "We have to understand the lessons of the past to develop treatments that are most fruitful for the future," he says. "For example, we have followed paths such as neutron technology that, while efficient, had severe side-effects and were too niche to be worthwhile. History has a habit of repeating itself."

Naturally, he has a modern day example in mind – although reluctant to single out any professional colleagues, he wonders whether the interest at European level in boron-neutron capture therapy might be subject to rather too much hype. But given the huge development costs and timescales involved in creating new machinery, open debate – and patience – is surely needed. As Bernier also points out, there have been periods in the 100 plus years of radio-oncology where little outward progress was made, and much persistence and trialling with the right approaches is essential.

What is striking about his historical article is that, although the timeline for techniques such as positron-emission tomography (PET) and

ELIGIO PAONI / CONTRASTO

Man and machine. The precise images obtained through modern CT–PET scanners like this one enable Bernier to tailor the radiation dose precisely to the contours and density of each tumour, using intensity-modulated radiotherapy techniques

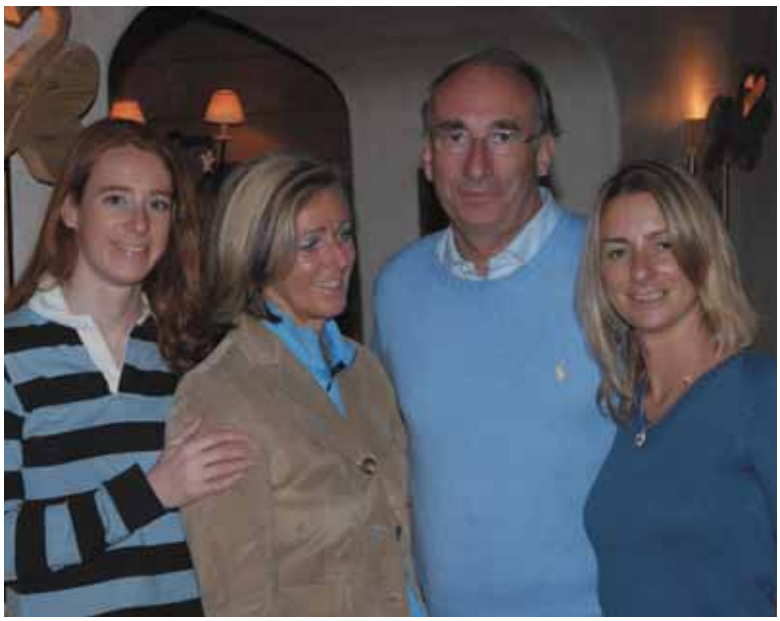
intensity-modulated radiotherapy (IMRT) shows that they were first developed some years ago, widespread access to affordable machinery, and new clinical techniques, are much more recent. The old cobalt-60 units, he notes, are still in use, especially in the developing world, thanks to their relatively simple operation. Meanwhile in Europe he reckons that the average age of machinery in use has not changed much since he carried out some surveys over 15 years ago.

In his own history, Bernier reached deputy department head in Charleroi before, in 1988, taking a step up to be director of the radiotherapy and nuclear medicine department at the Italian Swiss Institute of Oncology, based at the San Giovanni hospital in Bellinzona, Switzerland. He took with him his earliest and most important specialism, head and neck cancer, which he'd worked on at his various placements and with his main mentors. "Head and neck is a good model for clinical investigation, which is probably why I started there," he says. "Later, I have also specialised in breast irradiation – that's a key topic in my training activities with the European School of Oncology – and also lymphomas, as there are significant numbers treated at Bellinzona. But clearly head and neck is my main field."

His most significant contribution to date has been pioneering the combined use of radio- and chemotherapy in head and neck oncology. When the emphasis in the field was largely on altered fractionation techniques, which he also contributed to, Bernier was working in the early 1990s on radio/chemo combination, culminating in a paper showing the advantages of concomitant cisplatin and irradiation as an adjuvant treatment for stage III or IV head and neck cancer.

"This was based on clinical trials and

"It's very difficult to have a long-term vision as things are changing so fast"



Taking a break in the French Alps with wife Anne and daughters Caroline *(left)* and Géraldine *(right)*. Bernier's love of skiing has also led him to take breaks in a more radiological sense

published side by side in the *New England Journal of Medicine* with American work that reached more or less the same conclusions. It is a good example of evidence-based medicine."

Bernier is described by one close collaborator as a "model clinical researcher – innovative and lateral thinking with a solid grasp of clinical reality," and he's been a highly valuable research coordinator at the EORTC, standing down from chairing the head and neck group only recently.

"My EORTC work was extremely time consuming, but it offers an excellent platform to conduct trials and there are many top-quality people involved. But it will have to evolve to meet several challenges."

Chief among these, he says, are the increasing administrative burdens placed on trials thanks to the "negative impact of the EU Clinical Trials Directive", and the advent of translational research and the need to have a companion trial, say on biomarkers, alongside the main clinical trial. "We will have to change the format of trials and it will also be important to obtain quality of life data – to calculate the therapeutic index and increase efficacy without increasing toxicity. Otherwise there is no point to the treatment."

Another factor is a need to reverse to some extent the role of smaller centres in Europe-wide trials, as they simply will not have the resources to participate to a meaningful degree. As Bernier says of his own contribution at Bellinzona, his focus was on quality not quantity of trials – "It is better to participate with a lot of patients in 10 trials than one or two in 50, which is a nonsense," he says.

At Bellinzona, Bernier contributed to the establishment, in 1999, of the Oncology Institute of Southern Switzerland, which marked the shift to multidisciplinary integration of specialisms, away from a general hospital model, and was one of the first such moves in the country. He notes that the geography of the region posed problems for integrating services, but modern communications such as e-mail are a great aid.

"Interdisciplinary tumour boards have the great advantage that you don't take decisions by yourself, and they can improve the quality of treatment especially where you have many cases of one cancer type." His model for the ideal oncology department involves what he terms the 'magnificent five' – training, organisation, specialism, networking and funding.

As for the status of radiation oncology in Europe, he broadly agrees with Michael Baumann, current president of the radiation oncologist body ESTRO (who was profiled in the January 2006 issue of *CancerWorld*) that radiotherapy suffers from a lack of visibility; it is dwarfed by the drugs lobby, with the result that too little money is allocated to replacing worn out and out-of-date equipment. Bernier also highlights the problem of isolation, which while

"Radiotherapy is not Herceptin, interleukin or cetuximab – it's much cheaper"

starting to break down, still remains. "Some centres are persisting with old institutional policies, and do not integrate enough lessons from the past into their daily practice."

He also mentions the abiding, old-fashioned image of radiotherapy in the public mind, and the shortage of professionals entering the specialty in some countries. "In Switzerland, there are few radiotherapy centres, so potential radio-oncologists and medical physicists could be concerned about their careers. Our mission is to make the case that radiotherapy is cost effective," he adds.

"While the effectiveness arguments are well rehearsed, Bernier also notes that, as cancer patients are living longer, the number of patients needing radiotherapy is rising – quite markedly so in some countries such as the Netherlands. "It is less so in Switzerland, but the trend is still upwards.

"Radiotherapy is not Herceptin, interleukin or cetuximab – it's much cheaper. But the message is still difficult to get across, as the magnitude of investment for new machinery and the multidisciplinary team needed to operate it is high at the start."

The economic argument won the day at Genolier, where the latest adaptive technology will be installed at the new site in Geneva. Genolier will no doubt be a rising force in European oncology, having both Bernier and a high-profile director of the multidisciplinary team on board – the latter being Matti Aapro, another multitasking international operator.

"We are now in position to mine a rich seam of contributions from radiation oncology," says Bernier. "I would class these essentially into technical improvement of the equipment, concomitant therapies, big-dose fractionation, and of course we can't ignore the relationship between genomics and radio-oncology" – meaning, for instance, that a better knowledge of the tumour radiosensitivity level prior to any treatment is bound to help oncologists tailor more accurately the patient management.

He has concerns that, while satisfactory for the present, the R&D of new equipment is vested in a small handful of manufacturers, and that in any case radiation oncology is but small compared with the radiology diagnostics field. New technology will certainly be needed to investigate big-dose fractionation, an area Bernier feels has not been fully explored. "We don't know enough about the biology of large doses – we can deliver them with new techniques at higher precision without an increase in toxicity, but it will require more sophisticated machinery than we have now."

Translational research is one of Bernier's main interests now – in particular efforts to optimise dose distribution according to variations not just in the physical dimensions of the tumour but also biological parameters such as the metabolism or hypoxia of the tumour tissue. "One of the main breakthroughs was presented by James Bonner at ASCO in 2004 on a trial using the anti-EGFR [epidermal growth factor receptor] drug cetuximab [Erbitux] in head and neck cancer, which paves the way for any cytotoxic or non-cytotoxic drug to be used in combination with radiotherapy – it is one of the main contributions in a new field."

Bernier would like to see more attention paid to non-cytotoxic drugs, most of which are currently directed towards cell membrane receptors – either monoclonal antibodies for the outer domain of the cell membrane, or small molecules for the inner domain that trigger the signaling pathways in the cytoplasm.

"I have a mind that is rather mechanistic – I feel close to this membrane receptor, signaling pathway research field. The clinical model is not important – it's the use of targeted therapies with radiation that appeals."

It is the testing of drug therapies with radiotherapy that for Bernier has brought radiation oncology 'into the game' and into the world of clinical oncology and systemic treatment. After promoting various translational studies, into areas such as radio-resistance mechanisms and modulation, and organising several courses for the European School of Oncology, Bernier felt it was time to do things on a bigger scale, and set up in 2000 the first conference devoted to translational research strategies in radio-oncology, the ICTR. For this conference, he drew principally on his ESO, EORTC and US contacts, and as a result it initially received a somewhat cool

A drastic reduction in permanent positions and low salaries are still driving young researchers to the US

reception from the radiation oncologist body ESTRO. However, Bernier has since invited several ESTRO people in as contributors, and the proceedings of the third meeting were published in ESTRO's journal, *Radiotherapy and Oncology*.

It's a good example of his ability to act as a bridge builder – although he points out that there is some ongoing discontentment with the 'north–south divide' in oncology in Europe, with northern countries having more senior positions in societies, and also having most of the major cancer centres. "There are clearly very large variations in the quality and quantity of centres between north and south," he says. "And I know that, despite a somewhat better balance observed recently, some colleagues in southern Europe feel frustrated about the representation on society boards – language plays a role of course."

A poverty of ambition and funds in most countries feeds into his view that Europe as whole should be worried about its overall R&D picture. "It has been a shock to me to find so many of the next generation leaving to go to the US." He has noted for example, that there has been perceivable unrest in a number of European research laboratories, especially in France and Italy, commenting that France has spent just $3 a head on cancer research – compared with $14 in the US.

"Overall, Europe is investing 40% less in R&D than the US and the gap is still widening. In the medium term the European Union needs to recruit 700,000 scientists to meet its needs – and what's alarming is that out of 400,000 European science and technology graduates who now work in the US, only a third intend to return home."

A toxic mix of factors is contributing to this situation, according to Bernier. Chief among them are a drastic reduction in permanent positions, low salaries – a differential of three to one between the US and the UK, for example – and "rapidly deteriorating working conditions in laboratories", with "scores of dysfunctions resulting from staff shortages". Research programme fragmentation has reduced labs to 'science hotels', where each group is independent and responsible for its own funding and survival.

Bluntly: "Billions of euros and tens of thousands of jobs are at stake."

Bernier has a three-pronged prescription to reverse this decline. For researchers, more clusters of excellence for academic training should be established, he says, with a better balance of temporary and permanent posts. Further, the bureaucracy associated with applying for posts and grants should be greatly reduced. "Decision times are far too long." As a contribution, Bernier has himself set up the Foundation for the Advancement of Radiation Oncology (FARO), based in Geneva, which offers a number of training grants, and also raises funds for equipment.

For the scientific leadership, he advocates more mobility for scientists – an issue often raised in *CancerWorld* – and less fragmentation of research. The UK's National Cancer Research Institute and France's new 'canceropoles' are steps in the right direction. "The formation of a European equivalent of the US National Cancer Institute could help exchange between these centres," he adds. For policy makers, he is backing the idea of a European research area and the concerted take up of a plan to allocate 3% of GDP to research.

While active on many bodies over the years, Bernier does not aspire to head an oncology society – and says that it is perhaps easier to communicate these big picture issues from the background. However, on the brain drain issue he is not overly pessimistic in the long run. "The problem is not as extreme as the rush to the US in the 1950s/60s, and there is excellent research and clinical work being carried out in Europe – the issue is how to develop the work and make it more visible."

Bernier has only been at Genolier a few months, so his work programme away from routine clinical work has yet to be decided. He does not feel that the switch to a private institute will affect his networking ability – he is also a professor at the University of Geneva, for example, and will continue with teaching duties there and at ESO. He adds that Genolier is not an exclusive set-up, although inevitably a lot of patients come from well-off, overseas backgrounds. Genolier also has a special relationship with Memorial Sloan-Kettering in New York for knowledge exchange, he says.

While at Bellinzona, he also became president of the Tessin League, a cancer patient organisation that interfaces with professionals, and notes that this canton in Switzerland has been a leader in such support bodies. "We developed an approach first used in France where patients could express their frustrations to medics," he says. "It is very helpful for patients who have not so far vented their feelings and also for doctors to realise it is not a perfect world."

With his mind back on trials – which it often is – Bernier notes that patient power could render the gold standard randomised controlled trial rather less than academic. "Patients and families are accessing a lot of information on the Internet that even insiders find difficult to interpret," he says. "One consequence is that we are finding it harder to randomise patients into different treatment arms as they are increasingly reluctant to accept our proposals. I'm not a statistician, but methods other than randomisation may need to be found for evidence-based medicine."

Away from work, Bernier enjoys jogging and skiing. His wife Anne, a physiotherapist, probably came in more than handy after several broken bones on the slopes. His two daughters both work in Italy, one a lawyer, the other in tourism.

On his reading list are books on geopolitics, not surprisingly, while a favourite author is Umberto Eco, whose 'translational' literary works no doubt appeal to Bernier's mechanistic mind. Another Umberto, the Italian cancer leader Veronesi, is a close contact and Bernier is on the scientific committee of this year's Future of Science conference in Venice, set up by Veronesi, where luminaries such as the experimental psychologist Stephen Pinker and the evolutionary biologist Richard Dawkins will be holding court.

No doubt evolution is yet another core interest for Bernier – even though he still won't be taking bets on what his own field will look like in five years time.

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"There is excellent work being carried on in Europe – the question is how to make it more visible"

Targeted drug development by trial or error?

Anna Wagstaff

Bringing the new wave of targeted cancer drugs to the market poses new challenges for researchers and clinicians. It is not enough to design a smart drug to hit a molecular target. Researchers need to know how to test and develop the drug. The potential prizes are enormous – so is the price of failure.

The discovery of the first human oncogene in April 1982 marked an explosion of knowledge about the molecular biology of cancer. It delivered scientists their first molecular target, which had profound implications for the development of anti-cancer drugs. If patients are to reap the huge potential benefits offered by molecular targeted therapies as quickly and cheaply as possible, industry and academia alike will need to adapt their drug development strategies accordingly.

Mariano Barbacid, now head of the Centro Nacional de Investigaciones Oncológicas (CNIO) in Madrid, led one of three teams that separately, and simultaneously, isolated the mutant gene. In the same year, dubbed by *Nature* the Year of the Oncogene, he went on to show the gene was from the *ras* family, that it differed from the normal gene only in a single point mutation and that it could be found in the tissue of lung adenocarcinoma, but not in the patient's normal tissue.

What happened next is a cautionary tale that Barbacid makes a point of telling young researchers. Pharmaceutical companies rushed to find a way to inhibit the activity of the mutant *ras* gene. They identified as a likely target the farnesyltransferase enzyme, without which the *ras* gene would be unable to send its pathogenic signals. A billion dollars was sunk into the race to find the first effective farnesyltransferase inhibitors. None of them worked. Too late, it was discovered that the *ras* gene has a contingency plan. In the absence of the farnesyltransferase enzyme, a related enzyme, geranylgeranyltransferase I, is called into action, and the gene is back in business.

The researchers had identified their target correctly and had found a way to inhibit their target, but they had failed to check that hitting their target had the desired effect on the tumour. (Attempts to resolve the problem by inhibiting both enzymes at once have so far failed due to unacceptable toxicity.)

This lesson has been reinforced by subsequent history. New targets discovered in labs offer vital pointers for the development of effective anti-cancer drugs. But unless researchers explore, as early as possible, what happens in real tumours when the target is hit, they risk committing themselves to an expensive development of a drug that will not work. Worse, there is a possibility of overlooking a potentially effective drug because it was tried on the wrong patients, at the wrong dose or schedule, or without recognising its efficacy in combination with other therapies.

Development has replaced discovery as the key to getting new drugs to the market, says Jean-Pierre Armand, who set up the phase I clinical trials unit at the Gustave Roussy in Villejuif, Paris, almost 25 years ago, and was a founder of the Flims Clinical Trials Workshops. "Ten years ago there were very few drugs, but now we have many drugs that are very similar. The difference now is not in the discovery but in how you develop them."

The good news is that the possibilities for finding out what is going on at a molecular level are expanding at an impressive speed. The pathological/diagnostic imaging industry is working overtime to find improved, easier and more accurate ways to demonstrate and interpret what is happening in tissue at a genomic and proteomic level, enabling researchers to track the biological impact of their drug on the tumour and adapt their development according to what they find. The new mantra for the academic drug development community, coined by José Baselga of Vall d'Hebron University Hospital in Barcelona, is "no tissue no trial". In the words of Lex Eggermont, past President of the European Organisation for Research and Treatment of Cancer (EORTC), "The patient should guide the process," and "a properly designed clinical trial is a tool to better understand cancer biology."

It is taking a while for the message to get through. Armand tells of a more recent rerun of the farnesyltransferase inhibitor saga, this time with metalloproteinase inhibitors – a type of antiangiogenic compound. "There were five or six big companies in the game, including Schering and Bristol Myers Squibb. They had shown preclinical activity, they had a nice target, and nice concept of activity and they showed biological modifications in phase I and II. People said the clinical results will follow. They were wrong."

Armand is not at all surprised that none of these drugs turned out to be clinically active in phase III, as none had shown evidence of clinical activity in phase I or II. "We used to go into a randomised phase III trial only when we had very strong data from phase II. But now companies are so rich that they already have the money for phase I, II and III, and they believe that the phase III will tell them that the drug is active, even when they have not seen anything in phase II."

This approach, he adds, partly explains the exorbitant price of the new anticancer drugs. "It is because there are such stupid phase III trials launched, because of some minimal activity, in the hope that they will get fantastic results, when the clinical data on phase II are not encouraging. They are relying too much on serendipity."

He accepts, however, that lessons are being learnt, and that pharmaceutical companies are far more cautious about committing themselves than they were five years ago, "sometimes too cautious". Surprisingly, perhaps, it is the smaller 'biotechs', for so long hailed as the creative engines of the drug industry, who are now branded as the main culprits – and their problem is too little money, rather than too much.

Eggermont says "The culture in biotechs is to try to hit a home run. They have a budget that depends on very quick decisions and offers the chance for only a very limited amount of study, and one phase III trial. If they don't score on the phase III, they usually are dead. So you see a lot of wishful thinking and jumping into phase III trials, where you take the whole population into your study, hoping you are going to be lucky, rather than working with more selected patient populations where your chances of being successful may be enhanced, because at least you have proved that the patients have the target, and that you have reached the target. Some biotechs may be simply too small to have the time and money to go through all these steps, and they make a tremendous push to try to make the home run without having done all these studies."

There has also been a failure among clinicians and statisticians involved in designing trials to appreciate just how unlikely it is that the traditional trial protocols used for the old-style cytotoxics would work for a drug designed in the laboratory to hit a very specific molecular target.

Traditional trials do not work

Clinical trials have traditionally been designed to answer only minimal

Too late, it was discovered that the *ras* gene has a contingency plan

questions, the key one being: does this drug work better (prolong survival, prolong disease-free progression, etc) than a given alternative or placebo, with secondary questions about side-effects. Phase III, usually a large randomised controlled trial, was designed to answer this question, while phases II and I were merely designed to clear the way. Phase I tested for toxicity in humans and tried to identify the maximum tolerated dose; phase II looked for signs of efficacy – usually tumour shrinkage – and was used to judge whether it would be worth investing in a phase III.

The whole point about the new targeted agents, however, is that they are targeted. Some are precisely targeted against a particular molecule such as the epidermal growth factor (EGF) or HER-2 receptor, others, notably the kinase inhibitors, often hit a number of proteins similar to their intended target, but they are nonetheless highly selective compared to the blanket bombing approach of traditional cytotoxics. They can therefore be expected to work only in patients in whom the target is a significant driving force behind their cancer.

Sadly, with an experimental drug, it is rarely possible to identify in advance who the responders will be. Though targeted drugs by definition aim at a target believed to be involved in driving the cancer in question, only in the more 'simple' cancers such as chronic myeloid leukaemia, has shutting down that target proved sufficient to get a response in the vast majority of patients. Even Herceptin, hailed as a huge step forward, is only effective in half the breast cancer patients with HER-2 overexpression. A key part of developing a targeted drug therefore has to be finding predictive 'markers' that differentiate responders from the non-responders. Rushing into phase III trials without doing the necessary work to identify the patients likely to respond is therefore likely to be a recipe for failure.

In addition, there is also the 'old' problem that experimental drugs are usually tested first for use in advanced disease. In early disease the molecular mutations are likely to be implicated in driving the cancer, and are therefore potential targets. Over time, however, the tumour will usually mutate further as a result both of the natural history of the disease and the effect of treatments given earlier in the disease, making it very hard to interpret what is going on.

For this reason it is becoming common, before going into phase III trials, especially with less toxic drugs, to explore how they function in a small group of patients with earlier disease, if a 'window of opportunity' can be found. Typically this will be in a neoadjuvant setting, for instance in women with locally advanced breast cancer in the run up to surgery, or perhaps prostate cancer patients who have undergone surgery or radiotherapy with curative intent, who still show rising levels of prostate specific antigen, but are without sufficient symptoms to warrant hormonal therapy.

Neoadjuvant/adjuvant studies also have the advantage that pre- and post-treatment tissue is readily available from preoperative biopsies and later from the excised tumour. In studies of metastatic cancer, by contrast, it can be difficult to harvest tissue, for instance when the lesions are in the bone, liver or lung.

These trials may be designed as non-randomised single-arm studies, but very often they will move on to a randomised controlled phase II trial. They may be stratified to refine understanding of the best dosing schedule, or to check whether a potential marker of response really can differentiate patients who are likely to respond from those who are not, or even to look at the effect of using the drug in combination (each combination must of course have been tested preclinically and in a phase I to establish toxicity). Phase I/II trials now often comprise a series of studies, each step adapted to the findings of the previous one.

A third problem with relying exclusively on traditional phase III trials is that many targeted drugs are expected to be effective mainly through halting disease progression (cytostatics) rather than by killing tumour cells (cytotoxics). For example, anti-angiogenesis agents choke tumours by inhibiting their ability to grow new blood vessels.

Though angiogenesis inhibitors are now proving effective in what had hitherto been some of the hardest cancers to treat, such as renal cell cancer and metastatic colon cancer,

"They had a nice target and nice concept of activity. People said the clinical results will follow..."

SCIENCE PHOTO LIBRARY

Genetically destined to develop cancer. By engineering genetic changes in mice that mimic mutations known to cause specific cancers in humans, researchers can now breed strains of mice that will, for instance, develop a particular type of breast cancer 'like a clock', 6 months from birth, and whose offspring will do the same

Mouse models can tell you if a drug is hitting its target, and if the target is indeed driving the cancer

they are not natural performers in clinical trials. The tumour shrinkage shown with cytotoxics is a strong indicator of activity; it is harder to prove activity where the aim is non-progression. However studies that show the scientific concept of the drug works in live tumour tissue – in this case, that vascular growth is inhibited – increase its medical plausibility, and can help to convince regulators that a cytostatic drug is clinically effective.

Doing the science preclinically and in phases I and II is crucial to success at phase III. It is also essential to the early identification of those early drugs that are enticing in their scientific concept but do not actually work in human tumours.

The return of the mouse

Clinical trials are costly, they take time to accrue patients and they are heavily restricted by ethical consideration safeguarding the best interests of the patients. One way to avoid wasting time on inactive drugs and quickly to find out as much as possible about active drugs is to subject them to a thorough examination before allowing them into the clinic. The era of molecular medicine has opened up new possibilities in this area that are often not fully exploited.

The mouse model, criticised for its shortcomings in predicting human responses to drugs, is making a comeback in mutant form. Instead of injecting mice with carcinogenic agents, 'transgenic mice' are genetically engineered to model specific mutations known to be driving particular cancers. These 'transgenic mice' can be used to examine the pathogenic mechanisms involved, to try out the efficacy of targeted drugs and to look for surrogate markers for anti-tumour activity.

Pier Paolo Pandolfi, of the Sloan Kettering in New York, sits on the US National Cancer Institute's Mouse Model of Human Cancer Consortium, which is dedicated to extending the range of mouse models and making them available for research. He stresses that when it comes to predicting toxicity or even efficacy in humans, mice models are not much help. However, they can tell you whether a drug is actually hitting its target, and whether the target

is indeed a driving force for the cancer in question.

The story of the farnesylase inhibitors, he says, is a case in point. Researchers used a mouse model engineered with a mutant *ras* gene, and then inactivated the farnesylase enzyme. "They proved that knocking out this enzyme, which was what the farnesylase inhibitors were designed to do, did not affect the tumorigenesis driven by *ras* at all, and they even came up with an explanation, which is that *ras* uses another enzyme to be activated." Sadly, this was only done after millions had been wasted on the drug.

Pandolfi says that such tests are essential before jumping into the clinical arena and testing for efficacy and toxicity in labour-intensive, expensive and long-term experiments in humans. "You cannot quote me a single example where a drug that should work in a mouse and does not, has been shown to work in humans. If they would first assess whether the target, once inhibited or taken out from a mouse, would impact at all on the tumour, they could save an enormous amount of money."

The transgenic mouse is a far more powerful investigation tool than its predecessors. "Technologically speaking we are in a position to literally recreate a tumour with the genetic makeup that we want, because we are able to inactivate genes, activate genes, mutate genes in a specific tissue at a specific given time."

Of course models can only be made after the genetic make up of the equivalent human tumours have been profiled – and scientists have only just scratched the surface of that work. But as Pandolfi points out, the benefits increase as more profiles are defined. The more that genetic subtypes of a given cancer are identified, the smaller the patient population for each becomes, which makes it more difficult to accrue patients in trials. Genetic subtypes are not a problem with mice, which can be bred for each strain of the relevant mutation. In this way, a potential breast cancer drug can quickly be screened across a variety of genetic subtypes, while a drug aimed at a particular mutation can be screened across a variety of tumour sites. The information can be used as a guide to stratify patients in early clinical trials to help refine the target patient group.

Eggermont from EORTC also believes that mouse models enhance understanding of targeted drugs. "With all the technology we can now knock out and knock in genes, which greatly enhances your biologic understanding of what a certain target means. It would be a failure of understanding of how biology moves forward to say that mouse models are not important. Mouse models can be very important, but they are part of a much bigger picture."

He cites work by Craig Jordan, of the Fox Chase Cancer Center in Philadelphia, into tamoxifen resistance in mouse models. "The tumours were originally sensitive, then after treatment with tamoxifen become insensitive. Then you give second-line and third-line hormonal therapies and you can end up with tumours that are tamoxifen sensitive again. Those mouse models give great insight into what actually may be happening in the subset of patients with hormonal sensitive tumours who 'live on for ever' despite having metastatic disease. It's a new thing to even conceive that you could go back to tamoxifen after a number of lines of hormonal therapy."

Phase 1 trials

Although a lot can be learnt from preclinical trials about a target, its role in driving a cancer and the ability of the drug to hit that target, it is only by trialling it in patients that it is possible to discover its toxicity, activity, and optimal dosage and to identify in which

THE MUTANT MICE MARKET

Mice models of human cancer have only recently been liberated from a highly controversial all-encompassing 'oncomouse' patent held by Harvard University. Patents are still in force covering the use of these mice or cell lines derived from them for testing drugs. However, Pier Paolo Pandolfi, who sits on the US National Cancer Institute's Mouse Model of Human Cancer Consortium (MMHCC), says that in his experience there is a lot of scope for academic exploratory studies without running foul of the patent.

So far, mouse models are available from the MMHCC for around 64 genetic mutations, with types of leukaemia, lymphoma, skin, breast, lung, gastrointestinal, prostate and brain tumours being the most frequently modeled. They can be purchased over the Internet, as live mice or in frozen embryo form at http://mouse.ncifcrf.gov/. Though Europe does have a consortium, the European Mutant Mouse Archive (www.emmanet.org) dedicated to archiving and distributing 'relevant mutant strains essential for basic biomedical research', it does not have the same focus on generating engineered models of human cancers. There are individual institutions, such as the CNIO in Madrid, that are heavily involved in this sort of work.

SCIENCE PHOTO LIBRARY

The ultimate investigative tool. The diagnositic imaging industry is working flat out to develop sophisticated techniques that show what is happening to a tumour at a molecular level. But feedback from patients may still offer the most reliable – and most speedy – indication of whether a drug is active or not

"Tell me a blood test that can predict activity quicker than the clinic. I don't have one"

patients it works best. Phase I trials were traditionally limited to establishing maximum tolerated dose, but Armand from the Gustave Roussy, who did the phase I trials on sunitinib [Sutent], says this has all changed. Phase I trials are where you begin to learn about how the drug impacts on the tumour, and how best to measure that impact to find out the most effective dose and schedule, and maybe tease out some pointers to what differentiates responders from non-responders, which can be tested in phase II.

"I believe this phase I moment is very critical. You should do more than one phase I trial and you should explore more than 40 patients, maybe 60 or 80 at this level, because that is the moment you do the fine tuning to optimise the dose and recognise a few signals of activity."

Armand uses a variety of techniques to see what the drug is doing, including expensive high-tech methods like genomic profiling, cheaper quicker functional imaging techniques and, above all, his clinical experience as a doctor.

His advice to clinicians involved in clinical trials is not to get blinded by the technology. "When you are a clinician, you should remain a strong clinician. You cannot see your patients through a chart. You should see your patients every week during development, because the patients have tools which tell you, before you can read it anywhere, that there is some activity. So see the patient and measure what they say."

Everyone, he says, is rushing around desperate to find 'surrogate markers' of activity that can quickly and reliably predict whether a treatment will be clinically effective, in order to speed up the phase I and II studies. "The real activity, and this is one of my latest discoveries, is the clinical benefit," says Armand. "When I have patients telling me, 'Dr

"When there is no change in the genes, most of the time I have no responders"

Armand, I am happy with this drug,' even if the surrogate markers are not significant, for me it is a real drug.

"We are back to the old story: let the patient tell you whether they are happy or not with the treatment, and then you have something in your hands. On the other side, you have people who would prefer to say: 'We don't need the patients. We only need a sample of blood to say this is a good drug for the patient'."

Most phase I trials are conducted with patients reaching the end of their disease, when they are getting worse by the week. Armand cites the example of Glivec (imatinib) in gastrointestinal stromal tumour [GIST]. "You just give the patient the drug, and one week later they are playing tennis, when before they spent all day in bed. Tell me a blood test that can predict activity quicker than the clinic. I don't have one."

Patients can also give vital information about dosage. "I treated the first 15 patients in the world with Sutent, and I can tell you data about the activity even the company doesn't know. Some of my patients have enough drug for one month, and they take it in one week. And they say, 'You know your dosage is not enough, so I increased it and I feel a lot better.' There is critical clinical information available when, as a good clinician, you know how to listen to a patient."

That is not to say that biological markers of activity and predictors of response are not essential, but merely that highly relevant information from patients is too often ignored in favour of charts of assay results and tumour genomic profiles.

Surrogate markers

Surrogate markers, the indicators of anti-tumour response, can give an idea, in a relatively short time, about a drug's anti-tumour activity. Good markers are key to exploring the most effective dosing schedule and whether a drug will work better in combination or alone. Crucially, they can also be used to sort patients into responders and non-responders (sometimes more of a continuum than a 'yes/no' variable). This information is then used to look for 'predictive markers' that can prospectively identify the target patient group.

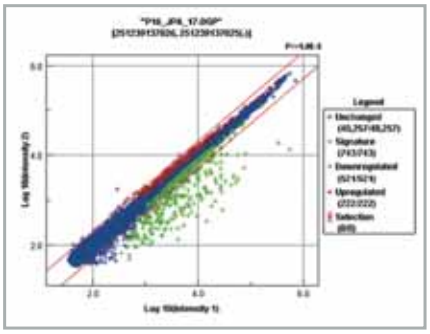
As individualised therapy is increasingly tailored to the exact phenotype of a cancer, the ideal is to find biological markers (biomarkers) of response based on key changes in the tumour's genetic expression profile, or even better, changes at the proteomic level, as demonstrated in biopsies taken before, during and after treatment. This can be difficult and expensive, and is by no means a requirement for getting a drug through to approval.

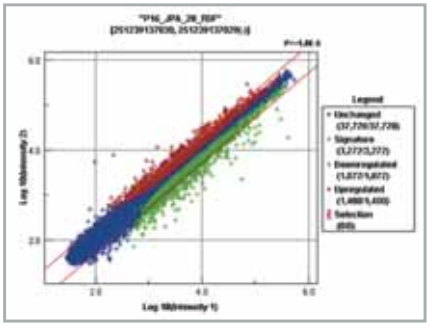
The key to an effective surrogate marker is simply that it reliably indicates anti-tumour activity (evidence of biological changes is not enough), that it reveals itself within weeks, days or hours of initiation of treatment, and that it can be easily and reliably measured. There is a huge international research effort underway to find and validate new biomarkers that can be used in this sort of research. Currently prostate specific antigen (PSA) for prostate cancer and CA125 for ovarian cancer are the only strong candidates, and neither of these have yet been fully validated.

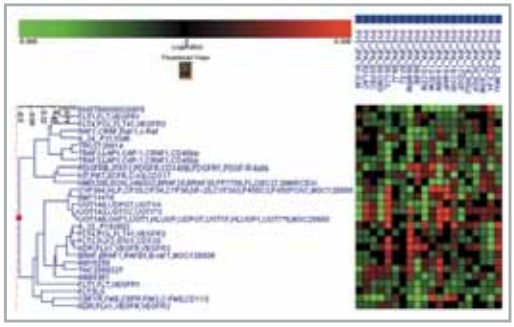
THE SEARCH FOR BIOMARKERS

Hopes that the new molecular imaging techniques would quickly deliver reliable surrogate 'biomarkers' that correlate with anti-tumour activity and predict clinical response have so far not been realised – prostate specific antigen (PSA) for prostate cancer and CA125 for ovarian cancer are the closest so far, and neither have yet been validated.

This is not for lack of effort. The US National Cancer Institute is allocating millions of dollars to teams looking for protein biomarkers using transgenic mice. In Europe there are proposals to set aside funding for research into biomarkers as part of the initiative to promote a European Technology Platform proposed for the European Union research programme, FP7, set to run from the beginning of next year. Eggermont of the EORTC is confident that finding biomarkers is only a matter of time, and says – in a reversal of the advice given to people investing in uncertain financial activities – "Failure in the past is no guarantee of failure in the future."







Doing the science. In his phase I exploratory work, Armand of the Gustave Roussy Institute in Paris, is looking at how an exploratory combination of two drugs changes the signalling pattern of 40,000 genes in a variety of cancers. He compares patterns of change in responders (e.g. patient DGP *top left*) with non-responders (e.g. patient RDF *bottom left*) and tries to identify the genes of relevance *(bottom right)*. With proper analysis, this exercise can reveal a wealth of information about the disease and the drug. Armand hopes to be able to identify a genomic signature that will predict who is likely to respond and who is likely to be resistant to the combined therapy. Source: Jean-Pierre Armand, Gustave Roussy Institute, Paris. Reproduced with permission

However, while evidence-based validation will probably be required if the regulators are ever to licence a new drug on the basis of such a surrogate biomarker, the level of validation for surrogate markers used in exploratory phase I and II trials can be a lot less robust. As Eggermont points out: "Most surrogate markers are not able to have a direct 100% outcome correlation, certainly not with survival. But you need target validation and some surrogate marker in order to make rational decisions about the next step in your drug development plan. Without that the chance of failure is greater."

The most commonly used markers remain changes in the size or rate of growth of lesions, which have been codified into a set of 'rules' with the acronym RECIST (Response Evaluation Criteria In Solid Tumors, see www.eortc.be). These define when cancer patients 'respond', remain 'stable', or 'progress' during treatments. Others include markers derived from functional imaging measuring changes in metabolism or blood perfusion in the tumour, and measures of apoptosis or proliferation.

Armand believes in keeping things as simple as possible for both the patient and the technician, and he is very proud of the novel technique of dynamic contrast-enhanced Doppler ultrasound, invented and validated at the Gustave Roussy Institute, which shows changes in perfusion of the tumour tissue (*Ann Oncol* 16:995–996; 1054–60).

"It is a fantastic predictor of activity or resistance. In GIST for instance it shows the effect of Glivec [imatinib] three months before a CAT scan can tell you what is going on. I use this tool in phase I trials, because it helps me to optimise the schedule and the dose. We need to have a tumour where we can inject bubbles, for instance the liver, but not the lung. We see the angiogenesis by injecting bubbles and exploring the ultrasound. We see how it is before treatment, and we see it seven hours later. It is a dynamic exploration of the new vessels, which showed, for instance, that the perfusion of the tumour had decreased by 30% or 40%. And if there is a change, this predicts clinical activity later on.

"It is very cheap, because you need minimal software, and you don't need to schedule a scan weeks in advance as you do with CT. We are very strong believers in this type of tool."

One of the key goals of phase II trials is to identify which patients are likely to respond

He also works with expensive high-tech micro-array techniques for genetic profiling, which can profile the expression of 40,000 genes in tumour tissue. This has to be done off site at the cost of around US $2000 a throw.

"I do a tumour biopsy before the treatment, and I do the same tumour biopsy one day, one week or a little longer after. And I see the change in the tumour as it is manifest in 40,000 genes. When there is no change in the genes, most of the time I have no responders. When there is massive change, very quickly, then I have some clinical activity. This is not yet validated. I just use it in a very experimental way."

At this stage, Armand is using the before and after data, simply to identify the changing patterns that correlate with clinical response, to help him "fight for the drug".

"Then we will move to phase II and confirm what we have seen, and *maybe* try to see if we can select the responding patients with the special profile, and identify from the 40,000 genes, the 50 or so that can be applicable in a microchip in any type of patient.

Phase II trials

Well-designed phase II trials ensure that a potentially valuable drug is given the best chance to show its worth and so be included in a phase III trial, and that complete duds are rejected as early as possible.

Traditionally, phase II trials checked for activity, usually by estimating the proportion of tumours that shrink by 50% or more when the drug is administered (singly or in

DOING THE SCIENCE

Susie Stanway of Imperial College, London, has spent the last two and a half years researching STX64, the first in a new class of drug, sulfatase inhibitors, which may help patients with hormone-responsive breast cancer.

The scientific concept

More than three-quarters of breast cancers are oestrogen-receptor positive (ER+) and it is known that suppressing oestrogen is an effective treatment. Current treatments include drugs such as tamoxifen and Fulvestrant, which block the activity of oestrogen at the receptor level, and aromatase inhibitors, which inhibit the conversion of androgens to oestrogens. However, another pathway exists, the steroid sulfatase (STS) pathway, which is responsible for the conversion of sulphated steroids, such as oestrone sulphate and dehydroepiandrosterone sulphate to biologically active oestrogenic steroids. This pathway may account for resistance to aromatase inhibitors. STX64 is a potent non-steroid-based irreversible inhibitor of the STS enzyme.

Preclinical trials

Was it likely to work? STX64 was tested in rats in which breast cancer had been induced by nitrosomethylurea, and whose ovaries had been removed. The tumour was stimulated with oestrone sulphate and the drug was then given orally, resulting in regression of the tumour.

Surrogate markers? Taking successive biopsies to measure levels of STS activity in the tumour tissue would not be feasible. Studies were done to see whether STS activity in blood correlated with that in tumour tissue, and the correlation was seen to be very strong. STS activity in peripheral blood lymphocytes (PBL) was therefore accepted as a valid surrogate marker, and its validity was later checked in human tissue.

Phase I translational research

A two-centre (London and Belfast) single-arm, dose-escalation design was used. Fourteen post-menopausal patients with metastatic ER+ breast cancer who had undergone at least one form of systemic (endocrine or chemotherapy) treatment were recruited over a period of two years.

Each patient was studied for seven weeks, using an intermittent dosing schedule – one week on, one week off.

Stanway saw her patients every day during the weeks they were on the drug, and one day in each of the intermittent weeks. Every two weeks she did a formal examination, including clinical measurement of the lesions where possible. Tumour response

combination) to patients with advanced-stage tumours of a specific primary site. Only if the proportion was high enough – and in most cases it was not – would the drug continue to a full-scale randomised phase III trial.

Under the new paradigm, the idea is that by the time a drug moves into phase II, a lot is already known from translational work in phase I about its activity in humans. Surrogate markers of activity will have been established and validated, allowing more nuanced studies into dosing schedules and to find ways to identify patients most likely to respond.

Randomisation is being increasingly used in early trials to tease out relevant information to guide the development process. As cytostatic drugs find it hard to impress over a short time-scale, and would never pass the traditional 50% tumour shrinkage criteria, randomised controlled studies can be used to provide the confidence needed to proceed to a phase III, or provide the evidence of lack of activity needed to condemn the drug. Such studies can use significance levels set far below the requirement for approval, say $p<0.1$, thus requiring far fewer patients.

Randomised controlled phase IIs were used in the development of both sorafenib and sunitinib – two of the first multi-kinase inhibitors to reach the market. In a "randomised discontinuation phase II trial" patients were given the drug, and those whose disease stabilised were then randomised to either continue or stop taking it.

Randomising to different doses or schedules (including sequential or combined administration with other

was measured according to the RECIST criteria using pre- and post-treatment bone scans and plain films, CT or MRI scans, depending on the nature of the lesion and where it was.

Every week she took a blood sample. At the end of the seven weeks, all blood samples were assayed at the same time.

Was the drug safe? Patients spent the night under observation in hospital the night after taking their first dose. They were assessed for side-effects using the US National Cancer Institute Common Toxicity Criteria version 2 at every visit and in a formal examination every two weeks. The only adverse events that were thought to be drug related were mild – grade 1 or 2.

Did the drug hit its target? Stanway measured changes in the level of STS activity in PBLs and in selected patients' tumour samples. Median STS inhibition in PBLs was 98% and in tumour samples 99% of baseline activity. This confirmed that the target was being hit, and also that STS activity in PBL is indeed a reliable surrogate marker for STS activity in the tumour.

Did inhibiting the target have the desired biological effect? The study aimed to cut down the concentration of oestrogenic steroids, oestrone, oestradiol and androstenediol, which are substrates for the aromatase enzyme. Stanway compared the concentrations pre- and post-treatment and found a significant decrease. Unexpectedly a decrease was also found in androstenedione and testosterone concentrations.

Did inhibiting the target have evidence of anti-tumour activity? She compared pre- and post-treatment scans using the RECIST criteria for disease response, stabilisation or progression. Four patients, all of whom had previously progressed on aromatase inhibitors, showed evidence of stable disease for 2.75-7 months, with a further patient showing stable disease in target lesions only.

The future

Dose. Stanway now intends to explore optimal biological dose using a continuous daily oral dosing schedule.

Target population. She also wants to identify which patients are most likely to benefit from this new therapy. To do this, an 'enrichment strategy' will be employed (which restricts recruitment to those deemed most likely to respond), exploring the use of potentially predictive biomarkers. Over-expression of STS is known to correlate with a poorer survival, and Stanway is particularly interested to see whether this predicts a stronger response to STX64. She also wants to find out about the clinical benefit rate in a homogenous enriched population of patients who have previously been treated with aromatase inhibitors.

Other indications. Ultimately, she hopes STX64 will show a significant clinical benefit rate and a favourable risk/benefit ratio in metastatic disease. If it does, the next step may be to seek approval for it to be used in the adjuvant setting. Because the drug shuts down a pathway that is common to the production of many hormonal agents, she also thinks it would make sense to test it in other hormone-dependent tumours, such as prostate and endometrial cancers.

drugs) can also yield important information about the most effective way to use the drug, which could be used to further develop a promising drug that might have failed a traditional approach using a single protocol.

One of the key goals of phase II trials is to identify which patients are likely to respond, so that the phase III trial can exclude patients known not to respond to the drug (this is known as patient 'enrichment'). Stratified phase II trials test for differences in response between patients stratified according to potentially relevant criteria – be they genomic/proteomic criteria, age, ethnicity, history of smoking, or even history of previous cancer therapies.

Very often phase II trials involve a number of different studies, some of them in patients with early-stage and some with advanced disease, looking to refine knowledge about the drug and its use. In what is known as an 'adaptive trial', as more is found out about dosing schedules and target patient groups, the patient selection in the relevant trial arms can be progressively enriched and ultimately can form the basis for a larger phase III trial, thus minimising the number of new patients who have to be accrued at this stage.

Discourse on appropriate designs for phase I/II trials of targeted drugs is still at a very early stage. A good introduction to the subject can be found in papers by Marc Buyse, Elizabeth Eisenhauer and Karen Gelmon, and Richard Simon, which can be found under the clinical trials heading of the ASCO 2006 educational book. The US Food and Drug Administration also recently conducted a workshop on this issue – Accelerating Anti-cancer Agent Development and Validation – slides from which can be found at www.fda.gov/cder/genomics/presentations/anticancer.pdf.

Approval: the final hurdle

At the end of the science, there is still phase III, where every drug has to show clinical effect in a large randomised trial – if not on survival, then at least improved disease-free survival, time to progression, or possibly decreased side-effects compared to existing therapies. The dream is that progress in validating surrogate endpoints will allow this cumbersome procedure to be dispensed with. We're not there yet, but being able to show medical plausibility can still clinch it for a drug that can only show marginal benefit in a phase III trial.

It is therefore essential not just to get the science right, but to keep the regulators on board throughout the development process. They need to be convinced that the chosen biomarkers and the assays for those biomarkers are valid, and researchers are well advised to discuss these issues, as well as the phase I/II trial design, with the regulators as they go along, to avoid spending years going down one particular path, only to be told at the end of it to go back to the drawing board. Storing tissue according to accepted standards is also vital, as regulators may well ask the researchers to go back and do further tests before their application can proceed.

Undoubtedly, developing drugs in the era of molecular biology is a complex process. The upside is that with every new anti-cancer drug developed, we learn a great deal more about the disease itself. Eggermont talks of moving from one level of complexity to the next, and is confident that Europe has the resources to meet the challenge. "The infrastructure, the institutes, the basic science and translational research labs are there and we perform very well in the translational research field. In terms of tissue legislation we are on a footing that actually has more opportunities and is simpler than in the US, where exchange of tissue between institutes is almost impossible because of the HIPAA [Health Insurance Portability and Accountability] Act."

He warns, however, that for a successful trial, researchers must take the time and money to do the necessary science. He offers the following advice: "Make sure that you have done sufficient early phase II studies with translational research components to be convinced of the potential efficacy of your drug, that you reach your target and that you can narrow down the patient population you want to study in a phase III trial. If you don't raise enough funds to take those steps, the likelihood is that you will fail in phase III. In the process you may actually kill your own drug."

With every new anti-cancer drug developed, we learn a great deal more about the disease itself

New drugs and survival: does the Karolinska report make sense?

Michel Coleman

Is it possible to demonstrate that access to new drugs impacts on a country's survival rates? Last September, the Karolinska report claimed to have done just that. Here, **Michel Coleman** argues that its conclusions were misleading and unsupported by the data and analysis. In the Debate that follows, the authors respond and health economists and policy advisors offer their views.

IN a recent cancer debate in the British House of Commons, the opening statement by John Baron MP included the following: "The Opposition recognise that there have been improvements in outcomes, but they have not outstripped comparable improvements in continental survival rates. **According to last year's report from the Karolinska Institute, the UK still lags behind other European countries** when it comes to survival rates over periods of one year and five years. In fact, Britain has one of the worst survival rates in all of western Europe: whereas 81 per cent of cancer patients in France survive for one year, the equivalent UK figure is only 67 per cent. Even Albania and Lithuania have better one-year and five-year survival rates than we do." (Bold text throughout indicates emphasis added.)

These remarks are seriously misleading, but Mr Baron is not to blame. The report from the Karolinska Institute has gained wide currency since its publication in September 2005. But the report is seriously flawed: the cancer survival data in the report, the statistical models of survival as a function of the availability of chemotherapy drugs, the authors' conclusions from those models – they are all wrong. It seems important to set the record straight, since the faulty data and conclusions may lead to inappropriate decisions by politicians, or undue frustration among cancer patients.

The efficacy of many cancer drugs in improving survival and reducing mortality is supported by solid evidence from high-quality randomised trials, and it is no part of my intention here to challenge that evidence.

But I do challenge the nature and scope of the cancer survival data presented in the Karolinska report, and the way in which those data have been modelled with data on the national availability of cancer drugs. If my critique of the Karolinska report is correct, those analyses cannot be used to support its policy-related conclusions about the impact of the availability of cancer drugs in a given country on cancer survival rates in that country.

*Michel Coleman is Professor of Epidemiology and Vital Statistics in the Non-Communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine. He was one of the authors of the EUROCARE-3 report into the survival of cancer patients in Europe, which was the original source of the survival data used in the Karolinska report

"It is important to set the record straight, as faulty data and conclusions may lead to faulty decisions"

What the report says

The executive summary and the conclusion show that the potential policy i mpact of linking cancer survival with the availability of drugs in Europe is clearly understood. The report says: "These results [on the speed of uptake of drugs throughout Europe] underscore the reality that cancer patients in Europe do not have equal or rapid access to cancer drug therapies, but what is the real-life impact of this imbalance? Dr Frank Lichtenberg of Columbia University highlights that **access to more cancer drugs means improved survival rates for patients.** His analysis of the situation in the US demonstrated that the increase in the stock of cancer drugs accounted for 50–60% of the increase in survival rates in the first 6 years post diagnosis.

"In addition, his examination of the USA and selected European countries indicates that an increase in the number of available drugs is associated with an increase in both the one-year and five-year survival rates. Therefore, with the importance of new drug therapies in the battle against cancer, it is clearly in the best interest of cancer patients that new, innovative drug therapies are made available to them as soon as possible. **Reduced or delayed access to cancer drugs has a very real impact on patient survival."**

The evidence for this assertion is based on chapter 7 of the report, "Pharmaceutical innovation and cancer survival", which is described as a 'commentary' prepared by Frank Lichtenberg at Columbia in August 2005. He examines cancer survival trends in the US in relation to drug availability, and carries out a similar exercise with European data. This is described as an investigation of "the effect of availability of new drugs on survival from 17 types of cancer in more than 35 countries." The data sources and the description of the methods are reprinted here in the box on p 28. No other detail is provided on either data sources or methods. No reference for the method is given.

Results are shown for 38 European countries (Table 7.2, p89 of the report) in the form of one-year and five-year survival rates (%), for all cancers combined in both sexes, along with the annual number of cases and the number of new drugs launched since 1982. No survival data are shown for 17 different cancers. No results are given from the modelling of cancer survival as a function of the availability of drugs. Instead, these results are summarised as follows:

"The estimates indicated that an increase in the number of available drugs is associated with an increase in both the 1-year and the 5-year survival rates. The sample includes both European and non-European countries. Two additional analyses related to this distinction have been performed:

1. We estimated survival models using the full sample of countries but allowed the ln(N_DRUG) coefficient to be different in the European and non-European sectors. We saw no evidence of a difference. Availability of drugs seems to have the same effect on cancer survival within Europe as it does in the rest of the world.
2. We tried estimating survival models using data for European countries only. This reduces the sample size by

THE KAROLINSKA REPORT

A pan-European Comparison Regarding Patient Access to Cancer Drugs, generally known as 'the Karolinska report', was written by Nils Wilking of the Karolinska Institute in Stockholm, Sweden, and Bengt Jönsson of the Stockholm School of Economics. The data modelling and analysis was carried out by Frank Lichtenberg of Columbia University in the US. The report was funded by Roche and was published by the Karolinska Institute in collaboration with the Stockholm School of Economics in September 2005. It can be accessed at http://ki.se/content/1/c4/33/52/Cancer_Report.pdf.

60%. We did not obtain statistically significant results. However, one might well obtain statistically significant results based on European data only using time-series incidence, mortality and drug utilisation data."

Interpretation

Several serious problems complicate the interpretation of this material.

First, the report says of the GLOBOCAN data (used for survival, see box below): "These incidence data are collated from national cancer registries". This is not so. The GLOBOCAN website (http://www-dep.iarc.fr/globocan/database.htm) makes it clear that "Incidence data are available from cancer registries. They cover entire national populations, **or samples of such populations from selected regions.**" This leads the authors into modelling what are often regional cancer survival rates with national drug marketing data.

Second, the International Agency for Research on Cancer (IARC), which compiles the GLOBOCAN database, does not itself collect or produce cancer survival data. As the website clearly states, survival data in GLOBOCAN 2002 were taken directly from the EU-sponsored EUROCARE study into cancer survival in Europe, in this case EUROCARE-3 (Berrino et al. *Ann Oncol* 14:v1–v155). They relate to patients who were diagnosed during 1990–94 and followed up to 1999. Yet those survival data have been deployed in the model in the Karolinska report in relation to the number of drugs available in 2000, as if they were for patients who had been diagnosed in the year 2000 or later.

Third, five-year survival data for cancer patients diagnosed in 2000 could not have been published at the time of these analyses (August 2005). Only so-called 'period estimates' (Brenner et al. *Int J Epidemiol* 31:456–462) could have been used to 'predict' such survival rates, but period survival estimates were not included in the GLOBOCAN database that was the source of the data.

Fourth, in 12 of the 38 countries (Albania, Bosnia-Herzegovina, Bulgaria, Cyprus, Greece, Hungary, Luxembourg, Macedonia, Moldova,

KAROLINSKA REPORT: DATA SOURCES AND METHODS

The data used to model drug availability against survival in the Karolinska report came from three different sources.

- The *survival* data were taken from the GLOBOCAN 2002 database (though in the Karolinska report this was given as GLOBOCAN 2000)
- Data on drugs approved by tumour type were taken from the Cancer Care Ontario (CCO) Formulary
- Data on *drug availability* were taken from the IMS Lifecycle New Product Focus

The model to which these data were applied is described in the report as follows:

"These data are used for estimating a model that included both fixed cancer-type effects and fixed country effects, which control for all determinants of cancer survival that are invariant across cancer types within a given country and that are invariant across countries for a given cancer type.

$$SURVij = , \ln(N\_DRUGij) + \bullet i + \%_{o}j + \hat{A}ij\ 1$$

Where:

SURVij = the (1-year or 5-year) survival rate for cancer type i in country j

N_DRUGij = the number of drugs for cancer type i available in country j

ai = a fixed effect for cancer type i

dj = a fixed effect for country j

eij = a disturbance

"Due to inclusion of fixed cancer-type and country effects in the model, , [sic: i.e. the comma ","] represents the effect of relative drug availability within a country on relative survival rates within the country. Suppose that, on average (across all countries), the survival rate of cancer type A is 25% higher than the survival rate of cancer type B, and the number of drugs for cancer type A is 35% higher than the number of drugs for cancer type B.

"Then one would expect that if, in a particular country, the number of drugs for cancer type A is only 20% higher than the number of drugs for cancer type B, the survival rate of cancer type A is less than 25% higher than the survival rate of cancer type B. Indeed, estimation of the model requires that the relative availability of drugs for different cancer types varies across countries."

"It treats the number of drugs on the market as the sole explanation for differences in cancer survival"

Romania, Serbia-Montenegro, Ukraine) for which the authors purport to give national survival rates for patients diagnosed in 2000, no cancer registry was in operation in those countries in that year, and in most cases there is still no such registry. In fact, the 'survival rates' for those countries, reproduced in the Karolinska report, were taken in GLOBOCAN to be a weighted average of survival rates in other countries in the same region of Europe for which national or pooled multi-registry estimates of survival *were* available from EUROCARE-3. For example, for Albania, in Southern Europe, survival rates in GLOBOCAN were taken to be a weighted average of the cancer-specific survival rates reported from EUROCARE-3 for Italy, Malta, Portugal, Slovenia and Spain, weighted by the cancer-specific mortality rates in Albania. Equivalent procedures were adopted for other countries from which no survival data were available. This was done in order to estimate cancer prevalence[1], *not* as the basis for an international comparison of survival, and *certainly not* as the basis for modelling international variation in survival as a function of the availability of cancer drugs.

Fifth, almost no information is given on the methods or the results of the modelling. The results are simply summarised in the form of the conclusion "that an **increase** in the number of available drugs is associated with an **increase** in both the 1-year and the 1-year survival rates. The sample includes both European and non-European countries."

Sixth, the survival data from Europe that are used in the model represent a single time point (supposedly in the year 2000). No data on survival trends are presented that could support a conclusion of any *increase* in survival over time as a function of drug availability.

Lastly, the model is extremely simplistic. It treats the number of drugs available on the market, regardless of their availability to patients, or their actual use in individual patients included in the survival analyses, as the sole explanatory factor for international differences in cancer survival. Most of the Karolinska report deals in detail with the marketing of cancer drugs in Europe over the last 20 years. I have no comment on the analysis of the availability of cancer drugs per se, except that the report seems to be pervaded by an assumption that the market availability of a licensed cancer drug is the chief factor influencing the national survival rate for that cancer, whereas surgery and radiotherapy remain the mainstay of treatment for most of the common malignancies.

Conclusion

The analysis of cancer survival in relation to the availability of cancer drugs in the Karolinska report is very misleading. It purports to show cancer survival data from several countries for which no such data are available: those incorrect data have already been cited in a parliamentary debate in the UK, and quite possibly elsewhere. The report provides no data on cancer survival beyond those published in 2003 for EUROCARE-3. Real survival data from some countries are then used alongside imaginary data for other countries in a crude statistical model designed to estimate the 'effect' of the number of cancer drugs on the market in 2000 on cancer survival (all cancers, both sexes combined). Worse, the survival data used to model the impact of cancer drugs available in 2000 are for patients who were diagnosed in 1990–1994 – some *six to ten years before the currency of the drug data*. For 12 of the 38 countries, the 'survival data' are actually the average survival rates from four or five completely different countries from the same broad geographic region of Europe. The conclusion that an *increase* in the availability of cancer drugs is associated with an *increase* in cancer survival rates is also completely unsupported by the data presented in the report.

Neither the cancer survival data nor the analyses of them can support the policy conclusions in the Karolinska report.

1. Methods of estimating prevalence: "Partial prevalence (1-, 3- and 5-year prevalent cases) were obtained by combining the annual number of new cases and the corresponding probability of survival by time. ... Several sources of site-specific survival were used. ... Europe: The EUROCARE-3 project provid[ed] figures from several European cancer registries for [patients diagnosed during] the period 1990–1994. Where possible, country-specific survival estimates were used, based on regional cancer registries, and **four regional estimates were prepared for countries where no local survival data were available.**" (Ferlay J et al. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5, version 2.0. IARC 1 May 2006; http://www-dep.iarc.fr).

THE DEBATE

CancerWorld asked the authors of the Karolinska report to respond to the points raised in Coleman's critique, and European health economists and policy advisors were asked to comment on the report, and more generally on whether it is possible to draw out the impact one particular aspect of cancer therapy has on survival rates, and if so, how this can be done in the most meaningful way.

In their response, the authors said that the report's findings show significant differences in access to new drugs and the implications of these differences merit discussion. "The Karolinska report provides for the first time comprehensive information on the use of new cancer drugs in different countries, and it documents substantial variation in the uptake of new drugs, and systematic differences between countries. The UK, for example, is slower than other European countries in the uptake and use of new cancer drugs." The report goes further, they said, and investigated different reasons for the observed differences. While it concluded that economic factors play a role, "countries with lower GDP and health-care expenditures per capita, such as Poland, the Czech Republic and Hungary, tend to have slower uptake of new cancer drugs," most of the variation, said the authors, "seems to be explained by factors related to how cancer care is funded and paid for, and by attitudes towards innovation."

"We think that it is important to point out these differences and to discuss the factors behind them, and to consider what can be done to achieve a more rational allocation of resources to cancer care in Europe. This is of interest not only for oncologists and other health-care professionals, but for patients and the general public as well."

Coleman's criticisms related both to the quality of the data and to the methodology used to model survival data against access to new drugs. On the question of the data, the authors agreed that Coleman's criticisms regarding the use of drug availability rather than actual use in the models was fair comment. "The point is well taken, and in the follow-up report to be published later this year, we will have a new set of estimates based on the vintage of drugs actually used. This may strengthen the relation, but probably not lead to a different conclusion since availability and use are correlated."

However, they rejected the other charges relating to the quality of data, arguing that, though "the data available for assessing the relation across countries between actual use of new cancer drugs and improvements in survival over time are far from perfect", the limitations are by no means sufficiently serious to invalidate the findings of the report.

Taking Coleman's points in turn, they stated, "First, we do not see any problem modelling regional cancer survival rates with national data on drug availability. If a drug has not been launched in a given country, then it is not available for use in any region of the country. So regional drug availability = national drug availability.

"Second, the estimated survival rates were obtained by dividing one-year or five-year prevalence by incidence. The results of this procedure appear to be consistent with other estimates of survival rates. For example, the method used implies that the five-year survival rate for all sites other than non-melanoma skin for males in the US is 63.8% [=2431746/ (5*762399)]. According to the US National Cancer Institute, the five-year survival rate for all sites for males in the US during 1995–2000 was 64.0%.

"Third, the fact that the incidence and prevalence data may refer to different time periods would, of course, introduce errors of measurement in the estimates of survival rates. However, these errors are likely to be random, i.e., uncorrelated with the drug availability measure. Random errors of measurement in the dependent variable do not cause any statistical bias."

Regarding Coleman's point about

the GLOBOCAN/EUROCARE 3 data having been compiled to estimate cancer prevalence and not as a basis for modelling survival as a function of the availability of cancer drugs, the authors said "The argument that [these data] can only be used for the specific purpose for which they were collected is absurd."

As for the criticism that changes in survival as a function of access to new drugs cannot be explored using survival data from a single time point, the authors commented, "We did not use international data on survival trends since such data are not available. The analysis on changes in survival over time is done for the US survival alone."

CancerWorld asked European experts from a variety of fields to what extent they felt that Coleman's criticisms of the quality of the data were valid.

Renée Otter is a director and medical oncologist at the Comprehensive Cancer Centre North-Netherlands, who sits on the board of the Netherlands' National Comprehensive Cancer Plan and is involved in many European projects relating to registries, benchmarking of cancer care and guidelines.

She agreed with Coleman's analysis and said the flaws he pointed to effectively invalidated the claim of the Karolinksa report to demonstrate an impact of drug availability on survival.

"If you don't have other data, the only report you can make is about two different things. One part is the survival analysis, the other one is the availability of drugs." These results, she said, could be used as the basis to propose a project that could use both data but in a different way. "You should try to get these data over the same period, and only use data that are not an expectation, but are actually observed in the different countries."

Isabelle Durant-Zaleski is a health economist based at the Hôpital Henri Mondor in Paris, and has a long history of working with epidemiological data to investigate disparities in health outcomes. She says that international comparisons in healthcare are difficult, but can be useful. "What these very large macro-economic comparisons do is draw your attention to something strange. And to me that is exactly what the Karolinska report does.

"It is very good academic practice to challenge the methods and challenge the results, and this is what Michel Coleman is doing, but it is also useful to do some perhaps imperfect comparisons and difficult comparisons, as the authors of the Karolinska report do, because it puts access to cancer care on the political agenda."

Her views are echoed to an extent by Mattias Neyt, a pharmaco-economist who works for the Belgian health technology assessment agency, the KCE, and has recently been involved in assessing the cost-benefits of Herceptin [trastuzumab] in an adjuvant setting. He argues that you have to work with the data you have. "What is best? To do no research or to research with the best available data? I would choose the second. You can find interesting results. How robust they are is another question, but if they don't have more recent figures, that doesn't mean they shouldn't do research at all."

Mike Richards, the UK's National Cancer Director, in contrast, thinks that modeling survival rates from one period against the number of drugs available in another is very likely to come up with misleading results. "The only accurate measure we have of survival rates between countries come from EUROCARE 3, and they relate to patients diagnosed between 1990 and 1994. None of the new drugs we are now talking about, except for Taxol [paclitaxel], had even been licensed at that point. Everything people are talking about now, like Herceptin or Glivec [imatinib] or Rituximab [mabthera], weren't even available so they could not possibly have affected survival rates for people diagnosed in 1990–1994."

The authors counter that they could have chosen to use drug availability for 1995 or 1997 instead of 2000. "But since availability (and vintage) in different years is strongly correlated that will not make the results misleading."

Methodology

In addition to the issues relating to the data used, Coleman also criticised the methodology of the Karolinska report. He argued that the methods used to analyse access to drugs as a function of survival did not provide any basis for the assertion made in the executive summary that "Reduced or delayed access to cancer drugs has a very real impact on patient survival." Firstly, says Coleman, no information was given on the methods or results of the modelling, and secondly, the number of drugs available on the market was treated as the sole explanatory factor for differences in survival.

The authors say they were surprised by these criticisms, particularly as Coleman himself acknowledges that "The efficacy of many cancer drugs in improving survival and reducing mortality is supported by solid evidence from high-quality randomised trials." Information from clinical trials needs to be supplemented with studies based on drug availability and use in actual clinical

"How can our results be misleading if they support the results from clinical studies?"

practice, said the authors, particularly given the fact that of the 57 cancer drugs approved by the US Food and Drug Administration through the regular process since 1994, only 18 were approved on the basis of a survival endpoint, and in none of the 14 granted accelerated approval was a survival endpoint used (see *J Clin Oncol* 21:1404–11).

"Observational studies enable investigation of the impact of innovation in cancer management on costs as well as outcomes… How can our conclusions be misleading if they support the results from the clinical studies?"

While welcoming serious discussion and comments on the methods and data used for these sorts of observational studies, the authors argued that it would have been better if Coleman had read the original research papers before concluding that the models were all wrong. "A number of misunderstandings could have been avoided." The full paper to the similar study conducted by Lichtenberg in the US can be accessed at www.nber.org/papers/w10328, and a revised version taking into account the European data will be posted there soon, say the authors.

They also point out that Coleman fails to provide any alternative explanation or interpretation of the results, and merely implies that the results obtained should not have been obtained.

On the question of the methodology, Zaleski said, "In my view the method is not appropriate for the causal relationship, but it is appropriate to attract attention to discrepancies. It showed there might be a correlation, but establishing causal relationships between a treatment and an outcome – in this case new drugs and survival – is very difficult outside of randomised controlled trials."

She mentions, however, a similar piece of research carried out by the OECD health policy unit, which looked at the use of mammography and survival of breast cancer. "It is not quite the same exercise, but it is not very different. In the case of the OECD report, they identified the fact that, for example, France has 10 times as many mammographs as Canada, standardised by women over the age of 40, yet the survival in Canada from breast cancer is exactly the same as in France. So this means that for people who are interested in public health, you have to look more in-depth."

The Karolinska report, she says, "is a good attempt to have comparisons that would enable you to go further. It is very much what the OECD is doing, but it is more far-fetched in the case of the Karolinska report. The OECD is extremely prudent."

Zaleski suggests one possible explanation for the correlation found between survival and access to new drugs could be that the latter is a "surrogate marker" for something else. "Countries which have speedy access to new drugs may also have better coordination of care and better access to specialised oncologists. It also means access to research protocols, possibly access to multidisciplinary teams, or even access to other innovative or state-of-the-art cancer treatments." This, she stresses, can only be conjecture, which can only be validated by more detailed research, "which is what the Karolinska report and Michel Coleman's piece urge us to do."

Otter also questions whether the methodology used could ever demonstrate a causal relationship between new drugs and survival. "I don't think that in the way they have put their project together you can make any relationship – even if it was in the same time period. It sounds like the story I was told in my first course on epidemiology about there being an increasing number of births because we have an increasing number of storks."

The issue, she suggests, should be whether patients are getting the drugs recommended in evidence-based guidelines. "The drugs you give are dependent on the stage of the tumour. So in some countries you routinely give adjuvant chemotherapy, and in others you will rarely give adjuvant chemotherapy, because there are no stage I patients in these countries. They come too late to the doctor."

She also argues that the role of drugs in cancer management makes it unlikely that they are a big factor in explaining differences in survival. "Very good surgery and very good radiotherapy are more relevant for survival than drugs. The exceptions are all haematological diseases, children's cancer and testicular cancer. For all the others we know that the

additional drugs influence your survival chances less than surgery with or without radiotherapy. Drugs have more influence on survival in the palliative phase of the tumour than in the curative setting."

More fundamental still, says Otter, is getting the diagnosis right so you can plan the most appropriate treatment. "Everything starts with a very accurate diagnosis and staging. Then you need people who are very specialised for the surgery, people who are very specialised for the radiotherapy with access to state-of-the-art radiotherapy equipment. Third comes the medical oncology."

Back in 2000, Richards called in a team of international experts to look at exactly the same survival data as was used in the Karolinska report, with the brief that they were to establish whether the data that showed the UK bumping along the bottom of the European cancer survival league table were an actual reflection of reality, and if so, what could explain the poor results.

"The overwhelming view from that meeting was that we did have to accept the UK had worse survival rates than comparable Western countries. But we also found that the main reason for that was due to patients presenting with more advanced disease in the UK than in those other countries. What that tells me is that it matters as much what goes on before diagnosis as what goes on after diagnosis, if not more."

This finding was reached by looking at the patient data on stage of diagnosis that was available from a number of high-resolution studies that were included in EUROCARE-3. "But that's all the registry studies can tell us – they can't tell us more because they have insufficient data on treatment."

Richards speculates that drug expenditure may be a proxy for overall cancer expenditure.

Future studies

As a policy maker whose job is to use the resources available in the most effective way to improve Britain's cancer services, Richards warmly welcomes studies that throw light on the relative contribution of different aspects of cancer care to the overall outcome. He says, however, that to be of practical value they need to look at a range of input variables. He points to the growing body of evidence that in certain cancers, such as colorectal cancer, the quality of surgery is decisive in reducing local recurrence rates, and is therefore likely to be important in explaining differential survival rates.

"You would need data on stage at presentation, then compare that with a whole load of different things like what treatments are actually being given, what training is being given, what is the quality of surgery and the radiotherapy."

He accepts that such studies are not easy, because it is difficult to get comparable measurements across countries. The best way, he suggests, would be to get countries that are prepared to do this well to work together. "I think you need to engage with people from the individual countries who know what is going on and can advise as to what the data might mean and what is a realistic and reasonable comparison to make."

Zaleski points to a study recently carried out by Stanford University, which posed the question: Has the introduction of new technologies for heart treatment changed the outcome in heart attack? It also looked at how variations in the speed at which these new technologies were introduced into routine practice impacted on survival. "Heart attacks is a much easier topic, because people die quickly, so survival data are easy to get. They have been able to show correlations between the introduction of new technology, the use of health care, and survival. But that is a multicountry endeavour with a very large database and a lot of work to have comparable data."

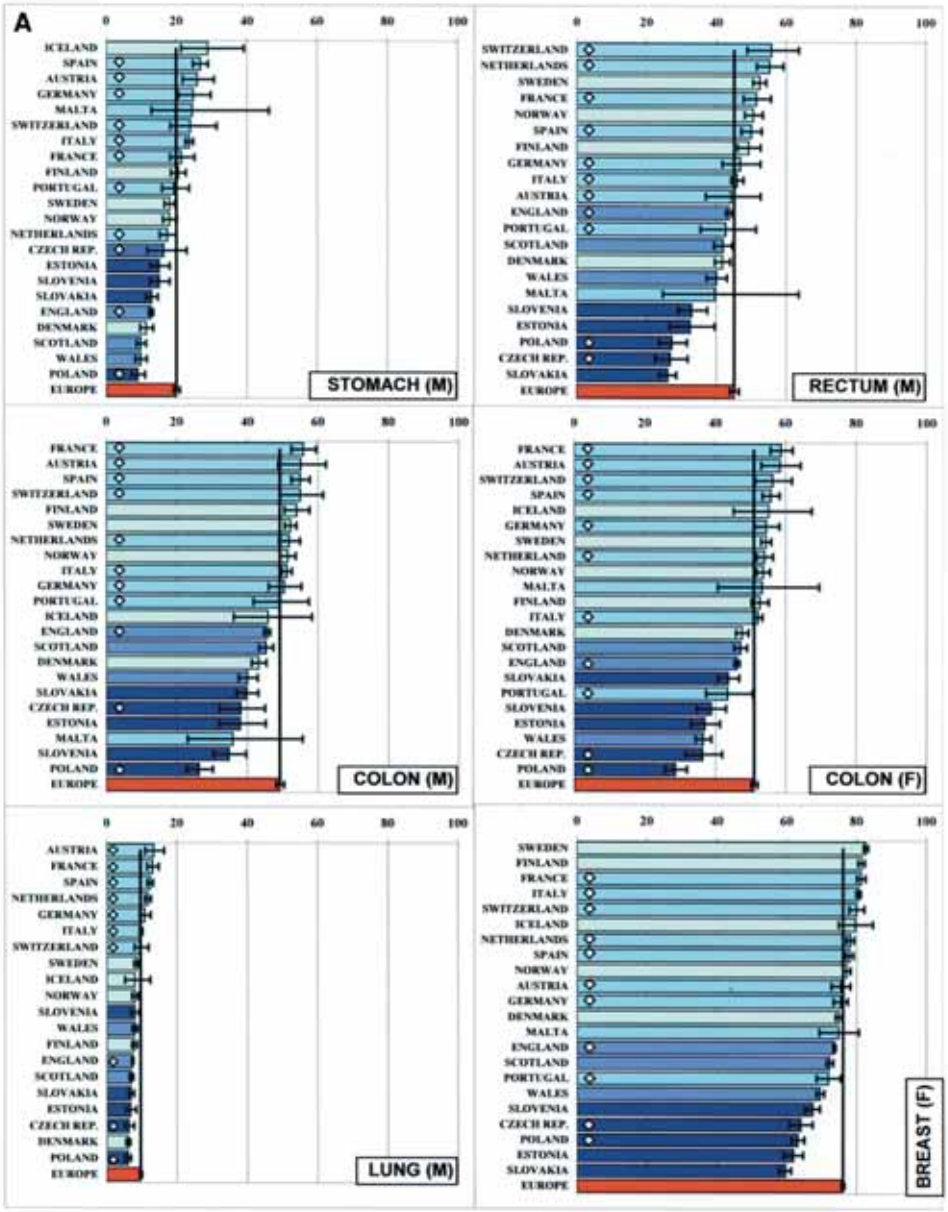
It should in principle be feasible to apply a similar methodology to cancer, says Zaleski. "The idea there would probably be to look at one type of cancer and begin with a case study. This would have to be done with multicountry comparisons. You would need to have a large number of countries, because there are so many treatment variables. You want to have more countries than variables, and you need longitudinal data of good quality."

Longitudinal data are needed to track the treatments a single patient has throughout their cancer journey. Getting hold of this data, says Zaleski,

"It is very much what the OECD is doing, but it is more far-fetched in the case of the Karolinska report"

Why the disparity? The EUROCARE results showed that in some countries cancer patients stand a better chance of survival than in others. The reasons will vary from cancer to cancer. In colorectal cancers, good quality surgery is known to be critical in avoiding recurrences. In breast cancer, expert surgery, radiotherapy and appropriate drugs all play a role. Catching the cancer early and getting the diagnostic work-up right are enormously important. Evidence showing the relative contribution made by each factor on survival rates would be very helpful for policy makers deciding where to concentrate their resources

CANCER SURVIVAL ACROSS EUROPE



Source: MP Coleman et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. *Ann Oncol* 14 (Suppl 5):v137. Reprinted with permission from Oxford University Press

"It would be worth looking in detail at what accounts for survival differences"

Access to drugs may be a proxy for general expenditure on cancer or state-of-the-art innovations

could prove a problem. "In many countries, like France, you do not have linkage of discharge data. When a patient has had several treatments, there is no national database where those treatments can be linked to the same patient. That is why they looked at heart attacks, because most of the treatments are done on the first admission."

She also mentions the need to look at how reimbursement systems determine which patients actually have access to drugs that are on the market – something also highlighted in the Karolinska report.

Otter suggests that it would be worthwhile comparing some regions in Eastern Europe with some in Western Europe and looking in detail at what accounts for survival differences. Incidence and survival data would have to come from well-documented regional-based cancer registries, but the study would have to be hospital-based, using 'cancer centres of excellence', to get good data on diagnosis and treatment. It should look at one cancer at a time, focusing on high-incidence cancers in order to have enough patients to be able to identify small differences. The variables she would like examined include the use of good diagnostic procedures and good staging procedures, the education of surgeons, the volume of surgeons, multidisciplinary discussions, radiotherapy equipment and the availability of drugs.

"First we should identify some countries which are able to get drugs or not able to get drugs, able to give adequate radiotherapy or not, and high-quality surgery or not. And this is what we should try to compare between countries."

She feels there is potential for making better use of existing networks and data. She mentions in particular the EUROCHIP project – a Europe-wide study to compare different indicators of diagnostics and treatment in different countries.

"I think by combining high-resolution studies, EUROCHIP and some additional data, at least we can try a pilot study. It won't be easy, but I think it should be possible, and it is a much better approach than the Karolinska one.

Otter believes that working to coordinate European guidelines and find ways to ensure that guidelines are followed is the way forward, not just for drugs, but also for diagnostics, radiotherapy, surgical procedures and so on. The availability of a given therapy is not the issue, she says, because if that therapy is not in the guidelines, it won't be paid for and it won't be used.

She mentions the European project CoCanCPG, which is bringing together all the bodies responsible for drawing up guidelines in countries and institutions. It aims firstly to identify the level of evidence in relevant publications to reach conclusions for international guidelines, and, secondly, to gain insight into the problems and processes of translating the evidence into national guidelines that are regularly revised and applied in practice.

Better research needed

The Karolinska report flagged up some significant differences in the rate at which cancer drugs hit the market across Europe. There seems to be general agreement that the suggested correlation with survival merits further examination. Though the experts *CancerWorld* spoke to do not believe the evidence in the report substantiates the claim that "Reduced or delayed access to cancer drugs has a very real impact on patient survival," they do believe access to drugs may be a proxy for general expenditure on cancer, or access to research protocols or state-of-the-art innovations in general – a point also made in the report.

The authors themselves are committed to further refining the findings of the report, "We are well aware of limitations of methods and data, and will continue to work to improve on both, because questions about the relation between innovation, costs and outcome in cancer deserve answers."

The contributors to this discussion, however, clearly believe that modelling drug availability alone against survival cannot guide policy makers in deciding where to concentrate resources and efforts to get the best impact on survival.

This can only be done through more in-depth studies that can look at the contribution of a variety of aspects of stage of detection, diagnostics and treatments.

The Debate was compiled by Anna Wagstaff

The man behind the margins

Peter McIntyre

Roland Holland started investigating mammograms and their relation to pathological findings as part of the first European pilot of breast screening. His findings were later used by Umberto Veronesi as key evidence in support of breast-conserving surgery. More than 20 years on, his data are again being called into service, this time by America's brachytherapists.

Roland Holland started a new life at the age of 40 as a paediatric pathologist in Nijmegen, the Netherlands, after escaping with his family from Hungary, via Nigeria, sort of disguised as a Dutch airline pilot.

It was 1976, and although he was not immediately aware of it, Nijmegen and Utrecht had just become the second region in the world to set up a pilot mammographic breast screening programme.

Sooner or later, this inquisitive pathologist was bound to start poking his nose into the pilot programme, and this led to a confrontation in the corridor with one of the young radiologists pioneering mammography reading. They settled their differences to strike up a lifelong friendship and teamwork that helped make the Dutch screening programme the most respected in Europe.

Holland's work on the clustering of tumour foci in the breast was used by Umberto Veronesi in Milan and by others to develop procedures for breast-conserving surgery. Today this 1985 paper is making renewed ripples, as radiotherapists consider how to narrow the range of radiotherapy dosage after surgery.

Before getting into the science, or even the adventure story, we have to deal with this coincidence of name between person and the country, that we shall call the Netherlands. Did he change his name from something more obviously Hungarian, or choose the country because of his name? In fact, neither is the case. The name Holland goes back a long way in Hungary, apparently.

"My Dutch friends say: 'Your ancestors were probably slaves on our ships, and they did a good job so we gave them the name Holland,'" he says.

He has certainly done a good job for his adopted country and some might say he is still shackled to his work at Nijmegen, even after his formal 'retirement', but it does not seem likely that Holland would have made a good slave. He would probably have escaped.

Holland did his medical training in Budapest, specialising in pathology, because his (doctor) father advised him that this was the foundation of good medicine. He took part in

PETER MCINTYRE

the Hungarian uprising of 1956 as a student. "Half of us got a gun and the other half who had a bicycle were messengers. I was in the bicycle group. Afterwards, I was not in direct danger, because I had no gun. I wanted to escape but my father and family were very depressed about that and asked me not to."

As an out of favour non-Communist Party member, his career was blighted. By the early 1970s, he was married, with a young daughter, and deputy head of pathology at Peterffy Hospital, Budapest.

He wanted out. In 1973, Hungary was recruiting a pathologist to complete a Hungarian medical aid team in Nigeria. The rest of the team were trusted Party members. Holland, and his family, were included because none of the Party pathologists agreed to go.

"This was a wonderful opportunity. We spent three years in Nigeria. My duty was to set up and run the first pathology laboratory in Port Harcourt (the coastal 'Garden City'). My greatest reward was that when I left, the surgeons said we can never work without a pathologist again."

Under the terms of his contract, someone arrived regularly from the Hungarian Embassy to take away half of his salary. To make up the shortfall, the whole Hungarian team worked in private practice. Holland became company doctor to a number of large international companies and their staff, despite warning them that as a pathologist "I am only really an expert after you have already died." Studying at night he taught himself to be a family doctor.

Senior staff at the Dutch multinational Interbeton heard that he was thinking of trying to gain admittance to the US, and urged him to try the Netherlands instead. When he was sent on a two-week course to England, his contacts arranged for him to visit Nijmegen on the way.

"My greatest reward was that when I left, the surgeons said we can never work without a pathologist again"

"Holland's job was to compare the biopsy specimen with the microcalcifications on the mammogram"

The Professor of Pathology Peter Vooijs promised him a job, once he had completed his tour in Nigeria.

There were troubled sounds out of the Dutch Embassy in Lagos, but Holland was backed by powerful friends in industry who ensured that the Hungarian Embassy heard no hint of his departure. A Dutch-American helicopter company flew him to Lagos and walked him around the back of immigration control wearing a Dutch pilot's tie.

There he joined his family on a KLM flight for Amsterdam. "They sent a note from the plane, to my Dutch friends saying 'your doctor is safe'. I am still very emotional when I think about this."

Holland arrived at the University Medical Centre at Radboud University in 1976 as pathologist for the new paediatric oncology centre. Aged 40 he was both student and expert, travelling to the Netherlands Cancer Institute in Amsterdam every weekend to study paediatric cases, and working in Nijmegen during the week, while at the same time learning Dutch.

What he found most enjoyable was being included in ward visits to see the children – and the fantastic cure rate. "I loved this job and we were very effective with children. This was 30 years ago and this was my first encounter with a multidisciplinary approach. It was an innovation here; you saw the patient first and later examined the specimen."

Even a University Centre like Nijmegen did not see enough child cancer cases to keep a hard-working pathologist busy, and Holland began also to work in general surgery, examining breast cancers uncovered during screening.

Inspired by the New York breast screening programme, William Penn, head of the Radiology Department, set up the Nijmegen pilot to test the potential for national screening in the Netherlands.

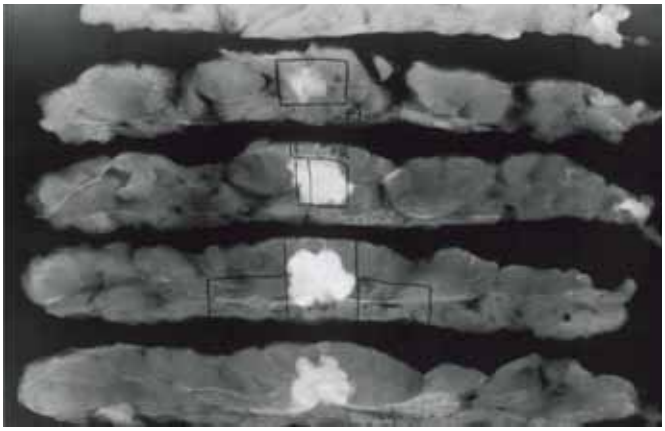
X-RAYS AND BIOPSIES

Many of Holland's studies deal with the detection of the precursor lesion of breast cancers, so-called ductal carcinoma in situ (DCIS). Mammography does not detect DCIS directly, but detects the microcalcification that occurs as a cancer progresses. Holland's job was to compare the biopsy specimen with the suspicious microcalcifications on the mammogram. In one of his first examinations he reported that there was no calcification in a biopsy taken on the strength of a radiologist's report. The young radiologist, Jan Hendriks, came to visit this junior 'idiot' who was questioning his expertise. They met in the corridor and after a healthy exchange of views, decided that they liked what they saw and that it was probably the surgeon's fault for sending the wrong bit for testing.

Holland, Hendriks and a young radiographer Henny Rijken started working together to understand the relationship between the mammogram and the pathological findings, learning about each other's jobs on the way. Holland became personally skilled at reading the mammograms, while Jan Hendriks and Henny Rijken became familiar with the pathology of breast tumours. "They called us the troika. We did courses, scientific projects and publications together. We came back here at 9 o'clock in the evening and worked two to three hours without anyone disturbing us. We never called what we did work."

After the screening programme had been running for its first four-year cycle, it became apparent that screening was not finding all the cancers. "I was starting to work on this. I saw the so-called 'missed' interval cancers. They were categorised as negative from the mammogram, and women come back with a palpable mass. This was disappointing."

Holland produced the first international paper on interval cancers in the 1980s, and in



Hidden tumours. By comparing breast cancer biopsy sections against their corresponding X-ray images, Holland and his team were able to show that tumour foci did not always have microcalcifications, which explained why some cancers were not being picked up at mammography screening

1984 defended his thesis on "New aspects and pitfalls in the diagnosis of breast cancer" 'cum laude'. "Invasive cancers start always as in situ intraductal (DCIS) or intra-lobular (LCIS). At a certain point they break through the basement membrane and they become invasive, forming a tumour mass.

"So long as they are in the ducts or lobules, limited to the basement membrane, there is no possibility of spreading to the lymph nodes or to other parts of the breast. They are theoretically 100% curable if you take them out. If it is already invasive, then you have always a certain percentage chance that it has already spread when detected.

"If we could find all breast cancers in their in situ intraductal phase, nobody would die of the disease. Unfortunately, not all intraductal cancers have microcalcifications. In others the process of becoming invasive is rapid and the two-year screening interval is most likely too long."

In almost two-thirds of invasive cancers, there are multiple foci in the breast, even if they do not show up on the screening mammogram.

Holland did a study with the Joint Centre of Radiotherapy at Harvard together with Jay Harris, Jim Connolly and Stu Schnitt. "We showed that if you have a recurrence of cancer after breast-conserving therapy it is usually based on residual intraductal foci. If you leave this behind, even if you irradiate the breast, the intraductal tumour will grow out and recur.

"The question was: How far do these other foci exist around the detected lump? That was the study that nobody had done. If you take out a lump and irradiate the breast you don't know any more what you have left behind. You could only do that on mastectomy specimens."

Margins of safety

That is what Holland set out to do, slicing and examining 314 breasts that had been removed by mastectomy, but could have been candidates for breast-conserving surgery. Of these, 282 breasts had invasive cancers, and of these, only 105 (37%) did not show other foci. By measuring the distance from the 'reference' tumour, Holland estimated what percentage of tumours would be left behind after each extra centimetre of breast was excised.

Holland, Hendriks and two colleagues (Veling and Mravunac), calculated that if invasive cancers that were 4 cm or less were removed along with 3–4 cm of surrounding tissue, invasive cancer would be left behind in 7%–9% of women, with non-invasive cancer left behind in a further 4%–9%.

Their paper was published in *Cancer* in September 1985. Holland says he had no idea of the significance of this work until it was finished. "The world discovered it after three or four years when they started doing breast-conserving surgery."

Veronesi in Milan pioneered the route from

"The question was: how far do these other foci exist around the detected lump?"

mastectomy to breast conservation. He argued that if the cancer had already spread, mastectomy would not help, while if it had not spread, taking the whole breast was unnecessary. Why not just take the tumour? Holland's work was just what he needed to support his practice.

"In my studies in Nijmegen, working with many hundreds of mastectomy specimens, I came always to the same answer – a 5% chance that there was a tumour in a remote quadrant, other than the one where the primary tumour was found. Veronesi put my figures on the wall of the operating theatre and said, 'Look, he says we have to excise this area.'"

Holland's work was based on the morphology of the tumour. A few years later, clinical statistics began to tell the same story. Just as Holland predicted, there was a 90%–95% chance that any recurrence appears in the same area of the breast and not in a remote quadrant.

Research over the past 20 years has revealed a more complex picture, without shaking the underlying arithmetic. In 1996 a study by JS Vaidya and others at the Tata Memorial Hospital in Bombay used three-dimensional techniques to visualise the breast. They came to a different answer – finding remote multicentric foci in 15 out of 19 breasts. However, studies continue to show that more than 90% of early recurrence is in the same quadrant as the primary tumour.

The key question is why some foci of DCIS develop into invasive cancers, while others do not. Holland believes that the answer lies in the differentiation of the cells. "Poorly differentiated cancer with many mitoses can go crazy in a short time and in one to one-and-a-half years become an invasive cancer. A well-differentiated tumour is quiet, the nuclei are evenly distributed and approximately the same size. It may become invasive in 10 to 15 years. Maybe these foci are biologically less important, but we never see a DCIS disappear."

Holland was recently approached by radiotherapists at the Annual Congress of the American Brachytherapy Society, who dusted off his 1985 paper and asked him to revisit his figures applying current criteria about tumour size and type, the extent of microcalcification and the age of the patient. They hope to use the results to guide them in reducing the area of the breast they need to irradiate. Holland has promised to help them to estimate a 'safe zone'.

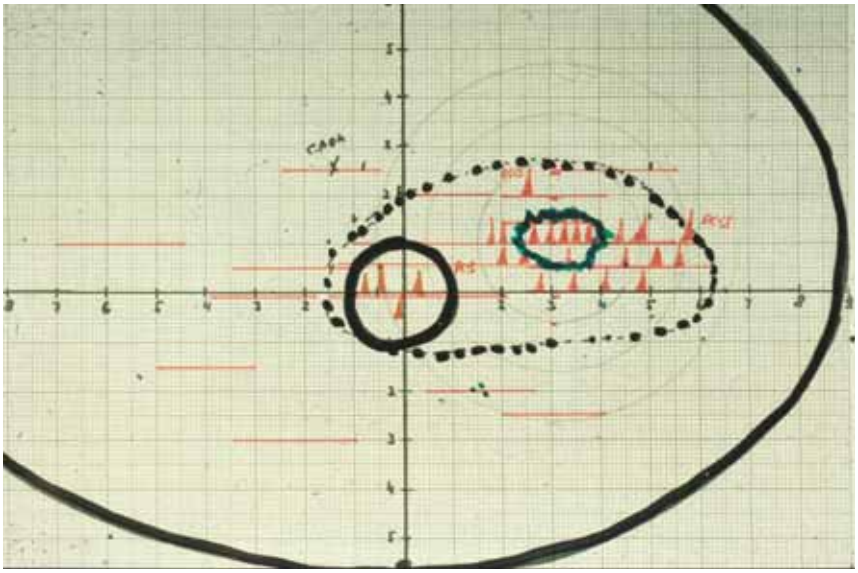
In 1989, on the basis of the mortality decrease shown in Nijmegen and Utrecht, the Netherlands approved a national breast screening programme for women aged 50–69, at two-year intervals, although it took until 1996 to extend this to the whole country. In 1998 the upper age band was increased to 75.

Mammography is done by radiographer technicians in 68 mobile buses, who send the mammograms to 28 radiology reading centres in the nine screening regions of the country.

In 1988 Holland was appointed director of the National Expert and Training Centre for Breast Cancer Screening (LRCB) at Radboud University Hospital, responsible for training and for quality assurance of the nation-wide population-based screening project. Every radiographer and radiologist in the country must train here before being allowed to work in the national screening programme.

For many years the Netherlands had the lowest referral rate of any screening programme in the world – until 1999 it was under 1%. One of the last papers that Holland and Hendriks worked on together with the support of epidemiologists in Nijmegen and Rotterdam – Hendriks died from melanoma in 2004 – was to look at the likely extent of missed cancers and calculate how many more would be detected if the referral rate increased.

Holland felt that the low referral rate was connected with the Netherlands being the



Surgical margins. Original drawing showing tumour distribution in a mastectomy specimen with the nipple in the centre, the invasive tumour in the upper outer quadrant and the DCIS foci surrounding the invasive tumour (triangles). The circles imitate various sizes of surgical excision, showing the amount of potential residual DCIS

European pioneer of mammography. "At that time there were no pre-operative minimally invasive procedures like core biopsies or vacuum-assisted biopsy. We were afraid that if we sent too many women for unnecessary examination and surgical biopsies they would not come back. They would say 'they operated on me when there was nothing wrong'."

As some of the cancers have only less obvious, subtle signs on the mammogram and only 20 to 30 mammograms of 1000 may show a suspicious sign, of which 5 to 6 are cancers, there is always the possibility of missing something. For this reason, each mammogram is read by two radiologists. If they do not concur, they talk to each other and come to a consensus.

Holland and his team visited the screening centres and urged them to change their practice. "I feel that the most logical thing is not to talk to each other, because consensus usually lowers the recall rate. If one of you feels she should be recalled, then recall her."

Quality control

By 2002, the recall rate had risen from below 1% to 1.3%, and is now around 1.4%. Above 3%, says Holland, there is a law of heavily diminishing returns.

As part of quality control, a team from LRCB visits each mammography reading centre every three years. They review data on the number, size and tumour stage of cancers detected. They also review the cases of 120 women who had interval cancers that had not been detected by screening. "We look at the previous mammograms and assess whether the cancer could have been detected early. Many interval cancers are very fast growing so you don't see anything on the previous screening mammograms. In some cases there is a minimal sign. And some you just miss," says Holland bluntly.

A weakness in the Dutch system is that once the recall has been issued, the national screening programme loses control of the subsequent assessment. The woman's doctor sends her to any one of 100 or more general hospitals in the Netherlands, where mammography is repeated with extra views, magnification and ultrasound if necessary. In about 20% of cases, they decide there is nothing wrong. The other 80% of woman are referred for histological examination.

Holland says this was a mistake – again a result of being early in the field – that they are now trying to correct. "There is not enough contact between a radiological department of a hospital and the screening radiologists, and the radiologists at the radiologist department are not trained here. Assessment must be incorporated in the screening process.

"In every visit we do, there are two or three cases where the screening radiologist had said it was suspicious, the radiologist in the hospital said it was nothing and the cancer came in half a year or one-and-a-half years. That is what we call doctor's delay. We are happy to know that EUSOMA [the European Society of Mastology] and EUREF [the European Reference

"There is not enough contact between radiology departments of hospitals and screening radiologists"

Organisation for Quality Assured Breast Screening and Diagnostic Services] are urging countries to form specialist breast centres. We are trying to change now. We could have 20 to 30 breast centres in the Netherlands with good cooperation with the screening."

When Holland planned to make his journey to the Netherlands 30 years ago, his Dutch business contacts in Port Harcourt told him he would be fine there so long as he learned to drink Dutch gin (jenever) and smoke Dutch cigars. As a cancer specialist he could not accept this definition of Dutchness. However, when he was appointed Professor of Pathology at St Radboud in 1998 he reached for another Dutch tradition to draw a lesson for screening.

"The Dutch herring is very delicious and there is always a test for the quality of the Dutch herring in May each year when the first catch of new herring start to be sold in the fish shops. I say if we can have quality control for the Dutch herring, why can't we have a comparative quality control of the management of breast cancer patients in our hospitals?"

With an award from the Queen of the Netherlands and a professorship, Holland is well accepted by the country whose name he bears. Despite being retired – radiologist Dr G den Heeten has now taken over as director of the LRCB – he works almost every day and is in demand on scientific groups and at international conferences. He also keeps a friendly eye on the progress of the breast screening programme in Hungary, where he is, today, welcomed.

He promotes multidisciplinary working where specialists tread over boundaries. "I teach people the relationship between what you see on the mammogram and the histology. I always tell radiologists to find a pathologist who is interested, and to look at everything together. Look at the mammogram and then look in the microscope."

The future of breast screening is digital. Ultimately, computers will help to highlight changes in consecutive scans for the specialist to review. "Tomosynthesis, a kind of CT scanning, can section the breast into hundreds and thousands of sections and then you will have a much better three dimensional image. You can manipulate the image and probably have a better chance of finding cancers in dense breasts of women under 50 years of age. Whether you can also reduce the number of missed cancers, we don't have yet data on that."

And that is the key question.

"Usually in medicine we tolerate 5% errors, whether it is a false-negative rate of sentinel node technique, recurrence after breast-conserving treatment, or whatever. But you cannot tolerate 25% or 30% errors. I don't think mammography will survive more than 15 or 20 years. A method must come that can detect at least 95% of breast cancers.

"I always say we are working with statistics and science, but statistics cannot tell you anything about an individual patient. We must give women the best information and tell them that we find 70%–75% of cancers, not all of them. You should not absolutely rely on screening but still palpate your breast between screening examinations."

"You cannot tolerate 25% or 30% errors. I don't think mammography will survive more than 15 or 20 years"

Quality cancer care

Ten rights that should be guaranteed to every cancer patient

➜ Elizabeth DeVita-Raeburn

If equal access to quality cancer care is to be more than an aspiration, we need to define minimum standards. ASCO and ESMO have now taken a lead with a consensus statement.

There are parts of Europe where newly diagnosed cancer patients are not given access to their diagnostic reports. They have to trek to their general practitioner to find out what the reports say. In other regions, it tends to be the patient's family that is told the diagnosis. They then decide what, if anything, to tell the patient. In many places, the notion of a second opinion is laughable. In some countries, patients diagnosed with cancer stand to lose their job; they're either summarily sacked or their working lives are made so difficult they are forced to quit. And, despite scientific advances that should produce good outcomes, cancer survival rates vary dramatically from country to country, because patients do not all have access to the same standards of care.

"The progress that's been made in the basic science of cancer and treatments for a variety of tumours faces tremendous obstacles in much of the world in terms of application," says Gabriel Hortobagyi, president of the American Society of Clinical Oncology (ASCO), and Professor of Medicine and chairman of the Department of Breast Medical Oncology at the M.D. Anderson Cancer Center in Houston, Texas.

Many parts of the world, he says, have not even begun to think about the broader issues pertinent to the lives of those struggling with a cancer diagnosis – such as discrimination on the job, rehabilitative needs after treatment, and even problems with such basic tasks as getting a mortgage, because of the cultural misapprehension that a cancer diagnosis inevitably means a death sentence.

In response to the enormous challenges faced by cancer patients around the globe, ASCO and the European Society for Medical Oncology (ESMO), the two largest associations of clinical oncologists, recently issued a joint statement on quality cancer care (see p 48). Announced in June at ASCO's annual meeting in Atlanta, Georgia, it calls for, among other things, privacy, confidentiality and dignity for patients, access to medical records, non-discrimination and the right to innovative treatment.

The decision to make it a joint statement was an easy one. "We felt it was critical for us as organisations that cover much of the Western world, and influence, to a large extent, what happens in the oncology world, to provide the road map about the principles on which we should base our clinical approach to cancer patients," says Hortobagyi. "It gives it more power and value," agrees Håkan Mellstedt, president of ESMO and Professor of Oncologic Biotherapy and managing director of the Department of Oncology at the Karolinska University Hospital in Stockholm, Sweden.

But agreeing on the principles that should be the standard of care is one thing; putting those standards into operation will be something else again. The statement, which is aimed largely at the national political machineries that control health-care systems, isn't enforceable by law. Neither society can force countries

and their oncologists to adopt it. "A statement," agrees Hortobagyi, "does not mean implementation."

"It's easy to say everybody should have access to high-quality care, but if the infrastructure and resources don't exist, it's very hard to implement," says Hortobagyi. "And it's easy to say everyone should have access to preventive services, but if it's not in the budget, it's much more complicated. We hope, over the next several years, to cause gradual alterations and change, first in the cultural acceptance of these issues, and secondly in the rearrangement of resources to fully implement the plan," he says.

Some critics say the statement is not as strong as it could have been, partly because of concerns that by raising the bar too high, developing countries with limited resources would be unable to meet the standards. But neither the ASCO nor the ESMO president felt the statement had been watered down.

"We are critically aware that, in many parts of the world, the limitation of resources will make this extremely difficult to implement fully," says Hortobagyi, "but that's no justification for setting the bar any lower."

Mellstedt agrees. "I think it's time for them to start to see whether it's possible to reallocate money from other areas to address the priorities within their society. Clearly there are problems with the health-care system that need to be revised."

Both societies have made a commitment to continue to work together to promote the right to quality care via an ASCO–ESMO Task Force. The statement was published in the July 20 issue of ASCO's *Journal of Clinical Oncology*, and the July issue of ESMO's *Annals of Oncology*, and is also available online at each organisation's website.

ESMO has given staff in its Brussels office, and ESMO national representatives in each country, the task of distributing the statement among members of the European parliament, along with documentation showing the difference in survival rates between countries.

Heinz Ludwig, chairman of the ESMO Cancer Patient Working Group, says he hopes that ASCO and ESMO members – there are more than 30,000 in all – "will act as a multiplier of this idea, and use this statement in their interactions with their policy makers and society in general."

Mellstedt adds that they are also counting heavily on the cooperation of patient advocacy groups, whom they see as critical to the cause. "We have to have all the patients on board. They are often the most effective at distributing the message. They are a very powerful pressure group. Previously," he says, "we have forgotten the patients."

ASCO expects to invest several million dollars in the coming years on, among other things, a task force on quality affairs to address issues of quality measurements; an online quality assessment tool that physicians can use to evaluate their performance in the care of cancer patients; and a task force to push through initiatives related to issues of survivorship.

But both societies say it's just a start. What the document really does, for now, is set a standard, much as both organisations once did by collaborating on a global core curriculum for medical oncologists. "It sets a bar where the application of certain principles should get to as a minimum," says Hortobagyi. "It provides a goal to national organisations, and to patient survivor and advocacy movements. And it provides guidelines for individuals in politics who make decisions that influence quality of care.

"And that will make it much easier to get into a discussion with those who need to provide improved quality of care, regardless of where they are, as to where they should be heading and put pressure on them to come in line. ESMO and ASCO have taken a very courageous first step," he says. "We hope it's contagious."

But the proof will come in what actually happens on the ground, in hospitals, clinics and doctors' offices. Five to ten years from now, for instance, will all cancer patients leave the hospital with a copy of their diagnostic report in their hand? Or will there still be some who have to persuade their GP to reveal what it says?

"It provides guidelines for individuals in politics who make decisions that influence quality of care"

ASCO-ESMO consensus statement on quality cancer care

The American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) are both dedicated to the provision of quality cancer care to patients worldwide. Recognising that resources, financial and otherwise, vary greatly from country to country and that systems for providing medical care are similarly varied, ASCO and ESMO nevertheless believe that health care plans should aspire to meet certain common goals to ensure access to, and continuity of, quality cancer care.

1 **Access to Information.** Patients should receive adequate information about their illness, possible interventions, and the known benefits and risks of specific treatment options. These matters should be discussed with qualified health care personnel who are committed to responding forthrightly to patient inquiries. Patients should have the ability to ascertain names, roles and qualifications of those who are treating them.

2 **Privacy, Confidentiality and Dignity.** Patients should have the benefit of privacy with respect to their diagnosis and treatment. Medical records and other patient-specific information, including genetic information, should be regarded as private, except to the extent that they are required to be shared for treatment or payment purposes. If access to patient-specific information is necessary for research efforts, including clinical trials, epidemiological research, translational research or other clinical investigations, patients should be given the opportunity to agree to such uses of their information for the benefit of cancer patients in general. Patients should be treated with dignity at all times.

3 **Access to Medical Records.** Patients should be permitted to review their medical records and obtain copies for free or for a reasonable fee. Health care providers should be available to explain the contents of medical records to patients.

4 **Prevention Services.** Individuals should be advised with respect to prevention of cancer and provided any preventive interventions that are evidence-based and available.

5 **Non-discrimination.** Access to health services should be provided without discrimination as to race, religion, gender, national origin, or disability. Patients should also be free of discrimination on the basis of their disease with respect to both employment and health insurance.

6 **Consent to Treatment and Choice.** Patients should be empowered to participate in decision-making about their treatment and care to the degree they desire, and the health care team should respect those decisions. Patients should have access to a second opinion and the ability to choose among different treatments and providers.

7 **Multidisciplinary Cancer Care.** Optimal treatment of cancer should be provided by a team that includes, where appropriate, multidisciplinary medical expertise composed of medical oncologists, surgical oncologists, radiation oncologists, and palliative care experts, as well as oncology nurses, and social workers. Patients should also have access to counseling for their psychosocial, nutritional and other needs.

8 **Innovative Cancer Care.** Patients should be offered the opportunity to participate in relevant clinical trials and should have access to innovative therapies, which may improve their disease outcome.

9 **Survivorship Care Planning.** Cancer survivors should be provided a comprehensive care summary and follow-up plan at the completion of primary therapy and systematically monitored for long-term and late effects of treatment. The need for rehabilitation services should be evaluated as part of the long-term follow-up plan.

10 **Pain Management, Supportive and Palliative Care.** Quality cancer care requires pain management, including the use of opioid analgesics, and other supportive care for conditions induced by cancer treatment or by the disease itself. When effective cancer therapy is no longer available, patients should have access to optimal palliative care and counseling.

Does trastuzumab increase the risk of isolated CNS metastases in patients with breast cancer?

Robert J Weil*

Research shows that brain metastasis of breast cancer may occur more often in women with HER2 overexpression. These patients require more aggressive surveillance to identify disease earlier, and new therapies are needed that can overcome barriers to effective CNS drug delivery.

Metastatic central nervous system (CNS) tumours represent an important health burden and portend a poor prognosis. Clinically, 10–16% of patients with breast cancer – up to 200,000 cases yearly in the US – have symptomatic brain metastases; up to 30% of autopsies in these patients show evidence of intracranial metastases.[1,2] Survival in patients with breast cancer and metastatic CNS tumours ranges from 2 to 16 months, depending on CNS involvement, the extracranial (systemic) metastatic disease present, and the treatment used; the mean 1-year survival rate is approximately 20%.[2] Traditionally, inability to control systemic disease is the limiting factor for survival.[2] As systemic therapies improve, extracranial disease control could become less influential, a point strengthened by studies of HER2-positive patients with breast cancer treated with trastuzumab.[2,3] Nearly half the patients in one study [4] died of progressive CNS disease, with a median survival of 13 months in patients treated with trastuzumab. Other studies have shown that HER2 overexpression increases the risk of developing CNS metastasis, whether symptomatic or occult, and most of the women with this type of breast cancer had controlled extracranial disease.[2]

To explore the prevalence of and predictors for CNS metastasis among women with HER2-overexpressing metastatic breast cancer receiving trastuzumab, Burstein et al. re-examined two clinical trials of first-line trastuzumab-based therapy (see opposite). In one phase III trial of 464 patients,[3] chemotherapy was used alone or with trastuzumab, while in a phase II trial of 54 patients, chemotherapy and trastuzumab were administered. In both trials, 9–10% of patients had isolated CNS metastasis as the first sign of progressive metastatic disease, accounting for 14–16% of all disease progression. CNS metastasis occurred later than progression at other sites in both treatment arms. Overall risk of initial progression within the CNS was not lowered by addition of trastuzumab to chemotherapy. *HER2* amplification was associated with a trend toward greater risk of initial CNS progression. Simultaneous CNS and other metastases were not investigated. Additionally, follow-up was limited (<8 months in both studies) and probably led to underestimation of the true incidence of CNS metastasis. These findings have been seen with other successful chemotherapeutics for systemic breast cancer.

This study highlights important pathophysiological questions. Several molecular mechanisms have been suggested to mediate the aggressive behaviour of HER2-positive breast cancers. First, increased activation of HER2 signalling enhances cell proliferation, survival, apoptosis resistance, migration and invasion.[2] Second,

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doi:10.1038/ncponc0487,

HER2 overexpression might endow tumour cells with increased metastatic aggressiveness, and increase spread to visceral sites such as the lungs and CNS.[2] Third, by enhancing patient survival, trastuzumab might permit brain metastases to develop or become symptomatic.[4] Finally, trastuzumab is likely to be ineffective against CNS metastases because of poor penetration of the blood–brain and blood–tumour barriers.[2,4,5] The Burstein paper supports this final hypothesis, since CNS metastases continue to overexpress HER2.[2,4,5]

The clinical challenges are to define new strategies for surveillance and therapy. We need to recognise occult or minimally symptomatic disease at an earlier stage – when the CNS tumour can be more easily controlled with focused radiation and surgery – and to develop preventive or novel therapeutic biologic or chemotherapeutic agents that take advantage of molecular and biological factors to overcome the critical, innate barriers to effective CNS drug delivery, such as the blood–brain and blood–tumour barriers.

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

Synopsis

HJ Burstein, G Lieberman, DJ Slamon, et al. (2005) **Isolated central nervous system metastases in patients with HER2-overexpressing advanced breast cancer treated with first-line trastuzumab-based therapy.** *Ann Oncol* 16:1772–1777

Background. The predictors for central nervous system (CNS) metastases in women with advanced breast cancer have not been well established. It has been suggested that HER2 overexpression and therapy involving trastuzumab might be associated with a high rate of CNS metastases.

Objective. To study the prevalence and timing of occurrence of isolated CNS metastases in women with HER2-positive breast cancer receiving trastuzumab in combination with chemotherapy, and to assess the contributing effects of HER2 status and trastuzumab treatment.

Design and intervention. Two clinical trials of chemotherapy in conjunction with trastuzumab as first-line treatment for HER2-positive metastatic breast cancer were reviewed for timing and sites of first progression. Sites of progression were classified as 'isolated CNS disease' (brain or leptomeningeal metastases) or 'other'. One trial was a multicentre, randomised phase III study of chemotherapy (paclitaxel or doxorubicin plus cyclophosphamide) with or without trastuzumab. The other trial was a multicentre phase II study of vinorelbine in combination with trastuzumab.

Outcome measures. A competing risks analysis using the Cox proportional hazards model, with isolated CNS disease and progression at any other sites as the two competing risks, was used to establish time to disease progression resulting from isolated brain metastases.

Results. The initial site of tumour progression was identified in all 518 patients; isolated tumour progression occurred in the CNS in 9–10% of patients receiving first-line treatment with trastuzumab and chemotherapy. Median follow-up times in the phase III study were 7 months for women receiving trastuzumab-based therapy and 4.6 months for those receiving chemotherapy alone. Risk of isolated CNS progression was similar in women receiving trastuzumab-based therapy and those receiving chemotherapy alone (hazard ratio 0.83, 95% CI 0.45–1.54), but CNS progression was a later event than progression at other sites ($P<0.0001$). Analysing outcomes according to follow-up time available, the incidence rate of isolated CNS progression was 16.1 per 100 person-years in patients receiving trastuzumab-based treatment versus 15.7 per 100 person-years in those receiving chemotherapy alone. The incidence rate of progression at other peripheral sites was 96 per 100 person-years in the trastuzumab-based arm and 188 per 100 person-years in the chemotherapy-alone arm. The effect of *HER2* gene amplification measured by fluorescence *in situ* hybridisation (FISH) was analysed for patients in the phase III study by estimating the CNS progression-free survival from the time of primary breast cancer diagnosis. Patients with FISH-positive tumours had a greater likelihood of CNS recurrence than patients with FISH-negative tumours, but the trend was of borderline statistical significance ($P=0.09$; hazard ratio 2.14, 95% CI 0.89–5.18).

Conclusions. Isolated CNS metastases can develop in patients receiving trastuzumab-based therapy for reasons such as improved peripheral tumour control, longer survival time and the lack of penetration of trastuzumab through the blood–brain barrier.

Acknowledgement: The synopsis was written by Petra Roberts, Associate Editor, *Nature Clinical Practice*

Radiation dose for prostate cancer: is more better?

Frank Vicini*, Larry Kestin, Michel Ghilezan and Alvaro Martinez

In prostate cancer, a trial comparing conventional- versus high-dose conformal radiotherapy has shown that increasing the dose can improve outcome, with only slight increases in toxicity.

Major technological improvements in the treatment of prostate cancer with radiation therapy have allowed dramatically higher doses to be delivered with minimal or no additional normal-tissue toxicity. Three-dimensional treatment-planning software used in conjunction with sophisticated, computer-controlled treatment accelerators and intensity-modulated radiation therapy with or without newer radiotherapy modalities (e.g. protons, neutrons or brachytherapy) has produced unprecedented dose-delivery capabilities. These technologies have been developed according to the premise that treatment outcome can be improved as the dose of radiation to the prostate gland is escalated. A dose–response relationship in the treatment of prostate cancer is now generally accepted by most clinicians and physicists involved in the management of this malignancy. Until recently, few well-designed prospective randomised trials with large patient numbers specifically addressing this critical issue have been published. As a result, this dose–response relationship has been extrapolated from data originating primarily from retrospective and prospective nonrandomised studies.[1,2]

The study by Zietman et al. (see opposite), using a combination of conventional photon radiation with protons, clarifies this point by documenting that a higher dose is objectively better than a lower dose in achieving an improved 'biochemical outcome' in well-defined subsets of patients. Although the trial was optimally designed, efficiently executed and has sufficient follow-up, several critical issues related to the 'dose–response question' in particular, and to prostate cancer treatment in general, remain unresolved.

Firstly, the absolute minimum dose needed to eradicate cancer for each stage of disease is still not established. Although dose–response data such as these suggest that more is generally better, it is difficult to determine how much of the improvement in biochemical control noted in many older dose escalation trials is simply related to better patient selection or the more optimal delivery of the radiotherapy dose (through better targeting, dose specification, and patient immobilisation or tracking). If, using modern three-dimensional techniques, a portion of the target is occasionally found to be outside the intended high-dose region, it is possible that lower doses could be sufficient with the superior targeting of off-line adaptive or on-line image-guided radiotherapy approaches.[3]

Secondly, it remains uncertain if the appropriate biochemical endpoint – that acts as an early surrogate for cure – to measure treatment success with all forms of radiotherapy is being used. Debate on the best biochemical definition continues.[4]

Thirdly, although protons were used very effectively in the study by Zietman et al. (some increased grade

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2 or greater morbidity was noted), the best method of radiotherapy to provide safe and economic delivery of these higher doses is debatable. While it is clear that higher energy particles and modern brachytherapy (i.e. high-dose-rate brachytherapy) can be targeted more precisely, it is uncertain whether more-expensive and more-labour-intensive technologies are any more efficacious than conventional methods applied with more recent advances in imaging, planning software and treatment-delivery techniques.

Finally, even if higher radiotherapy doses are superior to lower doses in eradicating cancer, these new radiotherapy technologies must be directly compared with other forms of treatment (e.g. surgery) in terms of cost, quality of life, ease of administration, availability and reproducibility. Unprecedented capabilities for radiotherapy techniques to efficiently eradicate cancer and surgical techniques to comprehensively remove cancer have been achieved. What will prove just as critical will be the long-term effects of these treatment strategies on patients' quality of life and the cost of their administration.

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

Synopsis

AL Zietman, ML DeSilvio, JD Slater, et al. (2005) **Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial.** *JAMA* 294:1233–1239

Background. Conventional-dose radiotherapy is unable to eradicate prostate cancer in a substantial proportion of cases. Increasing the radiotherapy dose might achieve better local tumour control, but there is a risk of higher morbidity unless the radiotherapy can be targeted accurately to avoid damage to normal tissue.

Objective. To establish whether local control of prostate cancer could be improved by the use of higher doses of radiotherapy using conformal techniques.

Design and intervention. In this randomised controlled trial, patients with localised prostate cancer received external radiotherapy at a conventional dose of 70.2 Gy or an increased dose of 79.2 Gy. All patients received the same dose of conformal photon therapy (50.4 Gy), but boost dose differed between the groups (19.8 or 28.8 Gy) and was delivered using proton-beam therapy. Men with stage T1b–T2b tumours (using the American Joint Committee on Cancer criteria), serum prostate-specific antigen (PSA) levels below 15 ng/ml and no metastatic disease according to whole-body bone scan and abdominopelvic CT scan were included. Patients were stratified according to nodal status and serum PSA levels.

Outcome measures. Biochemical failure, local control and morbidity were the endpoints for this study. Biochemical failure was assessed using the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria (i.e. 3 successive increases in PSA level), local control was estimated using a surrogate measure in lieu of biopsy (PSA levels <1 ng/ml) and morbidity was graded using the Radiation Therapy Oncology Group (RTOG) criteria.

Results. Median follow-up was 5.5 years (range 1.2–8.2 years) for all 392 patients. Five-year freedom from biochemical recurrence was 61.4% (95% CI 54.6–68.3%) in the conventional-dose group, and 80.4% (95% CI 74.7–86.1%) in the high-dose group ($P<0.001$), a 49% decrease in the risk of failure. High-dose therapy was advantageous in both low-risk disease, defined as PSA level <10 ng/ml, Gleason score of ≤ 6, tumour stage ≤ T2a (51% risk reduction; $P<0.001$) and higher-risk disease (44% risk reduction; $P=0.03$). Local control at 5 years was 47.6% (95% CI 40.4–54.8%) in the conventional-dose group vs 67.2% (95% CI 60.4–74%) in the high-dose group ($P<0.01$). The overall survival rate did not differ significantly between the groups (97% vs 96%; $P=0.8$). Acute genitourinary or gastrointestinal (rectal) morbidity ≥ grade 3 developed in 1% of patients in the conventional-dose group and 2% in the high-dose group, and late genitourinary or gastrointestinal morbidity of grade 3 or higher developed in 2% and 1% of patients, respectively. High-dose treatment increased acute and late genitourinary morbidity ≥ grade 2, however.

Conclusion. Men who have localised prostate cancer are more likely to be free from biochemical recurrence at 5 years, and have a lower risk of locally persistent disease, if they are treated with high-dose as opposed to conventional-dose radiotherapy.

Acknowledgement: The synopsis was written by Petra Roberts, Associate Editor, *Nature Clinical Practice*

NEWSROUND

Selected press reports compiled by the ESO Cancer Media Centre

Women diagnosed with metastatic breast cancer should have primary tumour totally removed

→ Journal of Clinical Oncology

Surgery to remove the primary tumour is generally not advised for patients whose breast cancer has already spread at the point of diagnosis. This is because the disease is considered incurable. However, a recently published study has revealed that women who have a complete removal of the primary tumour have a 40% lower chance of dying of breast cancer. The population-based study carried out in Switzerland between 1977 and 1996 evaluated the impact of surgery on the original area of the cancer, and the survival of patients whose cancer had already spread when they were diagnosed with breast cancer. The study looked at all 300 metastatic breast cancer patients recorded at the Geneva Cancer Registry between 1977 and 1996. It compared mortality risks from breast cancer between patients who had surgery of the primary breast tumour and those who had not, and adjusted these risks for other prognostic factors. Women who had had their primary tumour totally removed and checked for healthy tissue all around had a 40% reduced risk of dying from breast cancer compared with women who did not have the same surgery. This prolonged survival did not differ significantly according to the location of the metastases , but in the stratified analysis the benefit was particularly evident for women in whom the cancer had only spread to the bone. In an accompanying editorial, Monica Marrow and Lori Goldstein, from the Fox Chase Cancer Center, Philadelphia, suggest that the relative benefit of aggressive multimodality therapy for women with stage IV breast cancer and a low disease burden should now be assessed.

■ Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. E Rapiti, HM Verkooijen, G Vlastos, et al. *J Clin Oncol* 20 June, 24:2743–2749; Surgery of the primary tumor in metastatic breast cancer: closing the barn door after the horse has bolted? (editorial) M Morrow, L Goldstein, *ibid* pp 2694–2696

Adult survivors of childhood cancer are more likely to face unemployment

→ Cancer

Adults who survived cancer as a child are twice as likely to be unemployed than the general population, according to a new study. The report showed that employment problems differed by cancer type, with survivors of some cancers being up to five times more likely to be out of work. Among other factors associated with increased risk of unemployment were: living in the US, younger age, and female gender. As part of the study, which was conducted by the Coronel Institute for Occupational Health, at the Academic Medical Center in Amsterdam, researchers systematically summarised and analysed data from 40 studies that investigated the questions of whether childhood cancer survivors have a greater risk of unemployment than the general population, and what factors may identify individuals and groups at risk.

Analysis of the data showed that adults treated for brain or other central nervous system tumours were five times more likely to be unemployed. Blood-cell and bone marrow cancer survivors had an elevated unemployment risk, but the difference did not reach statistical significance. Similarly, survivors of other cancers had no elevated risk.

Analysis of other factors indicated that nationality, gender, age at diagnosis, and physical and mental impairments were all linked to higher unemployment rates. For example, survivors in the US were three times more likely to be unemployed, while European survivors had no elevated unemployment risk. Female gender and younger age at diagnosis also predicted higher risk of failing to find work.

The prognosis for children diagnosed with cancer is excellent. More than seven in ten paediatric cancer patients now survive more than five years and most of those survive to adulthood. Survival is not without secondary problems, such as other cancers, heart disease hormone abnormalities, infertility, chronic fatigue and depression. These complaints can act as lifelong impairments to social development and well-being. Employment, and a professional career in particular, can be important to an individual's self-image and confidence.

Cancer can rob survivors of that and many other social experiences.

The authors conclude that "interventions aimed at obtaining and maintaining employment are needed, especially for the vulnerable subgroups." Such interventions, they argue, "could mitigate the economic impact of surviving cancer and improve the quality of life of survivors."

■ Adult survivors of childhood cancer and unemployment: a metaanalysis. AGEM de Boer, JHAM Verbeek, FJH van Dijk. *Cancer,* published online 22 May, doi: 10.1002/cncr.21974

Personality traits do not influence risk of developing or dying from cancer

➜ British Medical Journal

A new study has found no major impact of obvious personality traits on the chances of developing cancer or dying from the disease. The population-based study looked at around 5,000 German men and women aged between 40 and 65. The participants completed an extensive personality test and questionnaire on lifestyle factors and health. During the follow-up period of 8.5 years, 257 participants died and 240 were diagnosed with cancer.

The study examined five broad independent dimensions of personality – symptoms of depression; anger control; time urgency (those frequently concerned with the passage of time and how they can most efficiently fill it with productive activity); internal locus of control over the disease (the patient's belief that the onset and process of an illness is the result of their behaviour) and psychoticism.

Participants in whom these qualities were only weakly displayed were rated low on the personality scale, and those who demonstrated the characteristics more obviously were rated high. The study found that people who were rated higher on time urgency appeared to have a reduced risk of cancer. The risk of cancer did not increase for those who were rated lower on time urgency. The other major personality traits – anger control, psychoticism, internal locus of control and symptoms of depression – were not consistently associated with cancer. Even when family history, smoking, body weight, alcohol consumption and other factors were taken into account, personality did not appear to be a risk factor for cancer.

■ Personality, lifestyle, and risk of cardiovascular disease and cancer: follow-up of population based cohort. T Stürmer, P Hasselbach, M Amelang. *BMJ*, 10 June, 332:1359

Weight training not linked to lymphoedema in breast cancer survivors

➜ Journal of Clinical Oncology

A new study published in the *Journal of Clinical Oncology* suggests that there is no reason why breast cancer patients who have had lymph nodes removed should not take part in resistance exercise such as weight training. The randomised trial found that a six-month programme of resistance exercise did not increase the risk of lymphoedema, or worsen existing symptoms.

Breast cancer patients often have the lymph nodes under the arms removed to prevent the cancer spreading through the lymphatic system. This can lead to excess fluid building up in the body's tissues, causing long-term swelling of the arms. Doctors usually advise women to refrain from physical activity, for fear that this might trigger the onset of lymphoedema, or make an existing condition worse.

This latest study followed 45 breast cancer survivors who participated in an upper- and lower-body weight-training programme. The participants had an average age of 52 years, and their treatment, which included the removal of the main lymph node (axillary dissection), had finished between 4 and 36 months earlier. Thirteen of the women had lymphoedema at the start of the exercise programme.

The study participants underwent supervised weight-training sessions twice a week for six months. The circumference of their arms was measured at the beginning and at the end of the programme. The study found that none of the group involved in the exercise programme experienced a change in arm circumference and none showed clinical or self-reported signs of lymphoedema.

The study's authors call for a re-evaluation of common clinical guidelines that advise breast cancer survivors to avoid upper-body resistance activity for fear of increasing the risk of lymphoedema.

■ Randomized controlled trial of weight training and lymphedema in breast cancer survivors. RL Ahmed, W Thomas, D Yee, et al. *J Clin Oncol*, published online 15 May, doi:10.1200/JCO.2005.03.6749

Younger men with prostate cancer may benefit from radiation therapy

➜ Cancer

Men under the age of 55 with localised prostate cancer may benefit from radiation therapy as an alternative to invasive surgery according to a new study. The research is the first to investigate the outcome of radiation therapy in men under 55 years of age. The study reveals that external beam radiation therapy is as effective in younger prostate cancer patients as it is in older patients with same-stage, localised disease.

Prostate cancer is usually diagnosed in older men; however, younger men can also be affected. There is a strong perception

that younger age may be associated with a more aggressive disease and poorer prognosis. Consequently, doctors tend to recommend more aggressive treatments, such as radical prostatectomy, to younger patients – even to patients with local disease that has not spread. However, older patients diagnosed with a similar localised cancer are offered more choices, including external beam radiation therapy.

Andre Konski and colleagues from the Fox Chase Cancer Center in Philadelphia compared how men aged 55 and under performed five years after diagnosis compared to men aged between 60 and 69, and men aged 70 and over – looking at survival, disease progression, and whether blood tests (PSA) showed signs of disease recurrence. All the men had localised prostate cancer and were treated with external beam radiation.

They found no statistically significant differences in the outcomes of these three age groups after five years: 94%, 95% and 87% of patients in each respective age category were alive five years after diagnosis; 96%, 97% and 98% of patients in each respective age category were without metastatic disease; and 82%, 76%, and 70% of patients in each respective age category had no evidence of disease recurrence according to blood tests.

While this study did not compare radiation to other therapies, the authors concluded that "External beam radiation at appropriate dose levels has been shown to be equivalent to permanent prostate seed implant [brachytherapy] and radical prostatectomy in the treatment of patients with stage T1-2 prostate cancer." Because younger men with localised disease respond as well as older men to radiation therapy, the authors suggest that this less invasive treatment option should be considered for this patient population.

■ Does age matter in selection of treatment for men with early-stage prostate cancer? A Konski, D Eisenberg, E Horwitz, et al. *Cancer*, published online 8 May, doi:10.1002/cncr.21923

Biomarker predicts spread of kidney tumours

➜ Lancet Oncology

A biomarker whose presence can be identified through a simple, inexpensive and reliable test has been found to identify kidney tumours that are most likely to spread to the rest of the body.

As part of a programme to develop biomarkers for clinical use, Zhong Jiang and colleagues, of the University of Massachusetts, Worcester, USA, studied the expression of the protein IMP3 in 501 patients with primary and metastatic renal-cell tumours. They then further studied 371 of these patients who had localised primary tumours to see whether their cancer had spread. The researchers found that the presence of IMP3 was significantly increased not only in metastatic renal cell tumours but also in primary tumours that later developed metastases: patients with IMP3-positive primary tumours were almost six times more likely to subsequently develop metastasis and four times more likely to die than were those with IMP3-negative tumours, even after adjustment for other well-known clinical variables.

"Tumour metastasis, the spread of cancerous cells from an original site to elsewhere in the body, is almost always deadly news," said Jiang, "early detection and treatment of these patients with a high potential to develop metastasis is crucial for the survival of cancer patients."

At present, 'watchful waiting' is the standard of care for patients with localised kidney cancers that have been removed by surgery. The authors suggest that, with the use of the IMP3 test, patients with early-stage disease and a high potential to develop metastasis after surgery can now be identified and offered additional treatment.

■ Analysis of RNA-binding protein IMP3 to predict metastasis and prognosis of renal-cell carcinoma: a retrospective study. Z Jiang, PG Chu, BA Woda, et al. *Lancet Oncology*, July, 7:556–564

Two follow-up CT scans are adequate for some testicular tumours

➜ Journal of Clinical Oncology

Computed tomography (CT) scans are an important part of surveillance for men after surgery (orchiectomy) for stage I non-seminomatous germ cell tumours (NSGCT) of the testis. Because CT scans are costly and deliver a substantial amount of radiation to the body, researchers have been interested in determining the minimum number of post-operative CT scans needed to safely follow patients.

New data from a study presented at ASCO 2006 suggest that two post-operative CT scans are as safe for detecting relapse as five scans. Investigators from the UK's Medical Research Council randomly assigned 414 patients who elected to have only surveillance after surgery to follow-up routines containing either two CT scans (247 patients at 3 and 12 months after surgery) or five CT scans (167 patients at 3, 6, 9, 12 and 24 months after surgery). All other surveillance tests were performed with equal frequency between groups during monthly follow-up visits during the first year, every other month during the second year, and every 3 to 6 months thereafter. At a median follow-up of 40 months, the investigators had detected 37 relapses (15%) in the two-CT group and 33 (20%) in the five-CT group. Recurrent tumours were approximately the same size at detection in both groups. "There is no clear advantage to more frequent CT scans in follow-up" of these patients, stated GM Mead, of the Mount Vernon Cancer Centre in Middlesex, England. "The two-CT-scan schedule can be considered a new standard."

■ Medical Research Council trial of 2 versus 5 CT scans in the surveillance of patients with stage I non-seminomatous germ cell tumours of the testis. GM Mead, GJ Rustin, SP Stenning, et al. *J Clin Oncol* 20 June, 24(18 Suppl):4519

New research may help identify individuals at risk of skin cancer

➜ Journal of Clinical Oncology

US researchers have developed a new scientific model to help identify individuals who have an increased risk of developing melanoma.

The number of people developing the disease is rising, and it is most prevalent in young adults. The risk factors are complex and include family history, skin type, the use of sun lamps and exposure to sunlight. Monitoring those with an increased risk of the disease could help to identify cases earlier and reduce the number of deaths.

The study analysed data from more than 700 white non-Hispanic patients with invasive melanoma recruited from melanoma clinics in Philadelphia and San Fransicso and more than 900 control subjects from similar catchment areas.

All participants were interviewed and given thorough skin examinations. This information was combined with incidence and mortality rates in the US and used to determine the risk of developing melanoma within five years.

The relative risk models showed an attributable risk of 86% for men and 89% for women, using at most seven variables. Attributable risks did not vary by age, exposure to ultraviolet B or the amount of time spent outdoors. Absolute individual risk varied widely, depending on age and geographic area. The study suggests that the risk factors can be put into two broader categories: individual interaction with sunlight and the number of moles present at a particular time in the participant's life.

This new predictor for skin cancer is based on a successful model used to calculate the risk of breast cancer. The new information can help identify those at risk of developing melanoma so that they can undergo skin examinations and counselling and be made aware of the increased importance of avoiding sun exposure. It will also be valuable in designing clinical trials in order to select participants who are more likely to develop melanoma.

The accompanying editorial comments, "Overall, this article represents an important and seminal contribution to the field of cancer control."

■ Identifying individuals at high risk of melanoma: a practical predictor of absolute risk. TR Fears, D Guerry IV, RM Pfeiffer, et al. *J Clin Oncol*, published online 25 May, doi: 10.1200/JCO.2005.04.1277

Type of Hodgkin disease can influence prognosis

➜ Cancer

Regional differences in the survival of Hodgkin disease (HD) can be partially explained by the type of the disease, according to a new population study. The study showed that a type of HD known as nodular sclerosis was much more common in the US than in Europe, and that there is significantly more variability in the types of HD found across Europe. Differences in type of HD accounted for differences in survival between the US and most of Europe, with Eastern Europe being the exception.

HD is a malignancy of the lymphatic system of the body, which includes lymph nodes and the spleen. Like many cancers, there are different types of HD, and studies have shown that certain types have worse prognoses. However, treatment regimens, particularly the newer generation of chemotherapy and radiotherapy, are generally successful at curing the disease. Despite this, a recent study of European cancer registries showed significant geographic differences in the survival of blood-borne cancers, such as HD.

In order to understand the causes of these regional differences, Claudia Allemani from the Istituto Nazionale per lo Studio e la Cura dei Tumori in Milan, and the EUROCARE Working Group compared 6,726 cases from 37 cancer registries in Europe (EUROCARE-UK, EUROCARE-West, and EUROCARE-East) and 3,442 cases from 9 US (SEER – Surveillance, Epidemiology, and End Results) registries diagnosed between 1990 and 1994 and followed for at least five years.

Analysis showed that the distribution of HD types in a region was a major factor in determining regional differences in HD five-year survival and risk of death. In the model that was adjusted by age, gender and years since diagnosis, the relative excess risk (RER) of death (relative to the SEER data) was 0.93 in EUROCARE-West, 1.15 in EUROCARE-UK, and 1.39 in EUROCARE-East. When the model was also adjusted for type of HD, EUROCARE-UK and SEER no longer differed (RER 1.06). However, the type of HD did account for the differences in mortality risk between cases in the EUROCARE-UK and EUROCARE-East regions.

Even after the type of HD was adjusted for, mortality risk remained significantly increased in EUROCARE-East compared to EUROCARE-UK, suggesting factors other than HD morphology, such as stage of disease at diagnosis and treatment, influenced outcome.

The study also confirmed the conclusions of previous research that HD tumours with lymphocytic predominance have an excellent prognosis and HD tumours with lymphocytic depletion are associated with significantly worse outcomes.

Allemani and her colleagues conclude, "Differences in excess risk of death between the geographic regions diminished when corrected for morphology, indicating that differences in morphologic case mix are an important determinant of regional survival differences for HD."

■ Hodgkin disease survival in Europe and the US. Prognostic significance of morphologic groups. C Allemani, M Sant, R De Angelis, et al. and the EUROCARE Working Group. *Cancer*, published online 12 June, doi: 10.1002/cncr.21995

Guardian journalist named Best Cancer Reporter

The Best Cancer Reporter Award 2006, sponsored by the European School of Oncology, has gone to **Sarah Boseley**, health reporter for the UK's *Guardian* newspaper. She was commended for her 'thorough, balanced, informed and articulate' approach to covering cancer from a wide variety of angles. Below we reprint one of her articles, entitled: *Can you catch cancer?*

Within a few years, girls will be vaccinated against cancer. Not every cancer – at least, not yet. But the cervical cancer jab is well on its way. There are currently 3,000 new cases of cervical cancer a year in the UK. A couple of shots in the arm, perhaps, and young women may never have to think about it again.

That is possible because cervical cancer is spread by a virus called HPV, or human papilloma virus. You can catch it by sleeping with somebody who has it, so women with more sexual partners are more likely to get it. The vaccine does not act against cancer per se, but protects against the virus which causes it. Which makes cervical cancer, effectively, an infectious disease.

Can you really catch cancer? And if cervical cancer is caused by an infection, is it remotely possible that we might also catch breast cancer, or prostate cancer, or bowel cancer? The answer is yes and no. Certainly, catching cancers is not the same as catching a cold. Human papilloma virus may trigger cervical cancer, but many women infected with it will never develop the disease. There must also be other factors.

Where a virus is involved in cancer, it appears, it is one of many causes – a trigger in a chain of triggers. Along with the virus, there may have to be something in your genes that tips your chances of getting this particular cancer the unlucky way. Diet affects some cancers, alcohol others, smoking is an important risk factor and air pollution is under suspicion. But the remarkable and exciting thing about the involvement of viruses in cancer is that they are a switch that can potentially be turned off. This is not a bad news story; quite the opposite. If an infection is involved in the onset of some cancers, then there is a way to stop them developing. Potentially, we could invent a vaccine. That is exactly what has happened in cervical cancer


Can you catch

In the early 1980s, US doctors began to notice a strange phenomenon. A rare form of cancer, once confined to elderly Jewish men in Europe, was suddenly cropping up among young gay men. The explanation? By catching a new virus, called HIV, they were also developing cancer. Now doctors believe that other infections, even simple coughs and colds, can trigger everything from childhood leukaemia to cervical cancer. Should we be worried? **Sarah Boseley** investigates

theguardian

A good read. In her article *Can you catch cancer?* Boseley doesn't dodge the difficult science, but she also takes a balanced look at the hope vaccines can offer and explores the wider issues – such as parents who take a dim view of being asked to vaccinate their 10-year-old girls against a sexually transmitted disease and environmental campaigners who are unwilling to consider the possibility that cancer clusters may not always be caused by local radiation levels

and there is every reason to think that, one day, it may be possible in other cancers too.

We do not know to what extent viruses are implicated yet, nor in which cancers, but the estimate is that they may play a part in up to 20% of cases. The evidence is slowly accumulating. Just before Christmas, a paper appeared from Newcastle University that offered new evidence that minor viral infections such as colds, respiratory problems and mild flu might trigger childhood cancer. Richard McNally, an epidemiologist, had mapped outbreaks of two cancers – forms of leukaemia and brain tumours – in children under 15 over a period of 45 years from a tumour database in Manchester. He discovered clusters of children who were born around the same time and in the same place – and went on to develop cancer.

Whenever clusters of childhood cancers have been spotted, parents have understandably ascribed them to the man-made environment, assuming that fallout from a power station or radiation from a phone mast must be to blame. But McNally and colleagues have identified a pattern which is exactly like what you would see in infectious diseases.

"We found that place of birth was particularly significant, which suggests that an infection in the mother while she is carrying her baby, or in a child's early years, could be a trigger factor for the cancer," says McNally. "These could be minor common illnesses that are not even reported to the GP, such as a cold, mild flu or a respiratory virus." But no, he hastens to say, you cannot catch cancer. His research suggests that infection is one of the factors in its onset, but it is not the only cause.

Instead, the hypothesis that his research helps to support is a double-whammy theory. Firstly, babies are born with a propensity to leukaemia. Mel Greaves, a professor at the Institute of Cancer Research in London, analysed the blood taken by midwives from the heel-pricks of newborns and found that many already have cell damage that could lead to the disease. But it is now clear that a second thing has to go wrong before a possibility becomes a likelihood. And that could be a viral infection.

This fits with the work of Leo Kinlen at Oxford University, who has been lambasted by anti-nuclear campaigners for his theory, first mooted in 1988, that childhood leukaemia is not the result of radioactive fallout and waste but caused by 'population mixing'. Cancer clusters occur where whole groups from towns and cities have arrived to live and work in a remotish rural setting, he observed. Look at the oil fields, military installations, the building of new towns

Where a virus is involved in cancer, it appears, it is one of many causes – a trigger in a chain of triggers

– and nuclear plants too. The incomers bring with them new viral infections, which could spark cancers among the native local population.

In fact, infections associated with cancer have been known for some time. There is a cat virus which causes leukaemia and a vaccine against it, causing people to wonder if there could be a parallel in human leukaemia. But the neatest example of infection as a significant cause is in stomach cancer. This is not triggered by a virus, but by a bacterium called *Helicobacter pylori*. That discovery netted a recent Nobel prize. "Fifteen to 20 years ago," says Heather Dickenson, principal research associate at Newcastle University's centre for health services research, "nobody would have taken seriously the theory that stomach cancer was the result of infection."

Helicobacter pylori is a bacterium that enters the stomach in food and drink, but does not get destroyed by the acid there. Around 30%–40% of us are thought to be infected with it, and it can cause inflammation of the stomach lining, known as gastritis. In a small number of cases (about 3%, which means that other triggers such as diet or smoking have to be involved) that progresses to stomach cancer. But now we know that *H. pylori* is one of the guilty parties, many of these cancers (though not all) can be prevented. Give patients the right antibiotics, and *H. pylori* goes away.

Research into the links between cancer and viruses began around the start of the last century. In 1908, two Danes, Wilhelm Ellermann and Oluf Bang, identified a virus which they found spread leukaemia between chickens. In 1911, Peyton Rous in the United States found another chicken virus which caused sarcoma. The work was ignored for decades, but eventually won Rous a Nobel prize in the 1960s.

In that same decade, the first definitive link between infection and a human cancer was established. A British scientist called Anthony Epstein, based at the Middlesex hospital, went to listen to a British surgeon called Denis Burkitt, who had identified what is now known to be the commonest childhood cancer in Africa. This was a tumour of the jaw that became known as Burkitt's lymphoma.

In a remarkable piece of scientific detective work, Epstein mapped the incidence of the tumour across the wet, lowland areas of central Africa and realised he was looking at the malarial belt. He hypothesised that the cancer was caused by an infectious agent, spread by the malarial mosquito, and spent two years staring down an electron microscope attempting to find it.

He and his team had no luck until one tumour biopsy arrived from Uganda in an unfit state for microscopic examination. So Epstein cultured the cells instead. To everyone's surprise, it grew a previously unknown form of herpes virus, which became known as Epstein-Barr. Epstein-Barr was later found in almost all samples of Burkitt's lymphoma from Africa.

Almost everyone has this virus. "Ninety-five per cent of us are infected by Epstein-Barr," says Lawrence Young, professor of cancer biology at the institute of cancer research in Birmingham. "It doesn't cause us any effect at all. But with certain co-factors it could cause problems." Malaria was a co-factor in Africa, which is why the pattern of incidence of Burkitt's lymphoma matched the malarial regions.

The ultimate proof that a virus is a contributory cause of cancer is if you remove it, says Young. "Hepatitis B virus is associated with primary liver cancer. It's very common in Africa and the Far East. About 25 years ago they introduced a vaccine for Hepatitis B in Taiwan where it had been a very common infection and you would see liver cancer in young adults. The incidence of liver cancer in the population has been significantly reduced."


The selling of a wonder drug

There is a risk that patient groups could be influenced by drug firms with turnovers as large as the GDPs of small nations

Public watchdog. In *The selling of a wonder drug*, also submitted to the award panel, Boseley takes a critical look at drug company marketing techniques. Over the years, she has helped readers build up an understanding of cancer from a medical, social, political and economic standpoint. More than 400 of her articles touching on cancer can be accessed on Guardian Unlimited, the *Guardian*'s free Internet site, which is visited by more than 9 million readers

If you have Epstein-Barr and you catch malaria while on holiday, it does not mean you will develop Burkitt's lymphoma. None of this is quite that simple. You would have two of the risk factors – two possible triggers – but because this is mostly an African cancer, there is probably a genetic component involved too. Too little is known about the causes of cancer, for all the noise made about diagnosis and treatment. But if scientists can nail down a particular virus as a risk, they can interrupt the process that can cause disease and death. Young calls the virus "a link in the chain of events. This is not like catching a cold. You can't catch cancer as an acute disease. But if it is a vital link, you can break the chain."

Epstein-Barr is also implicated in about half of Hodgkin's lymphomas, but not the other half. In China, Epstein-Barr is in nasopharyngeal carcinoma – but fascinatingly, the extra link in the chain is the salted fish in the Cantonese diet (and probably some genetic propensity as well). "We know because if populations from China move to the west coast of America, in one generation they lose it," says Young. "It's the changes in their diet." Breast cancer, too, appears to have dietary links. The incidence in Japanese women who move to the US soars. "Diet is a major contributory factor to cancer," acknowledges Young.

Diet we can change. Viruses and bacteria we live with, for the most part harmoniously as long as our bodies' infection-fighting systems are in good order. Epstein-Barr does most of us no harm unless our immune system is suppressed. In the early days of heart transplants, for instance, most patients died not because the heart gave out or was rejected, but of Epstein-Barr-associated lymphomas. They were being given massive doses of immuno-suppressant drugs, which meant that the virus was no longer kept in check, allowing the cancer to develop.

And in the early 80s, the first sign that we were in trouble from a new virus that would wreak havoc across the planet was the arrival of a new cancer in America called Kaposi's sarcoma. It

If scientists can nail down a particular virus as a risk, they can interrupt the process that can cause disease

had once been a very rare disease in elderly Jewish men from the Mediterranean. Suddenly, young gay men had it, as the HIV virus knocked out their immune systems, allowing the Kaposi's sarcoma herpes virus to flourish.

Viruses are now thought to be implicated in up to one in five cancers. As time goes on, we may find it is more. There are some controversial theories around. Papers have been written that suggest a monkey virus called SV40 is a trigger, with asbestos, for mesothelioma – a cancer of the lining of the chest wall, the abdominal cavity or the lining of the heart. Some have speculated that the monkey virus may have passed to humans through contaminated stocks of polio vaccine. Others are looking for a virus in lung cancer. In Australia, researchers are studying a human virus similar to one called MMTV which is responsible for mammary tumours in mice. They want to know if it could be implicated in breast cancer.

Finding any cause of cancer – even one that plays a small part – is very good news because it means prevention is possible. If a virus is involved, it opens up the possibility of a vaccine to disrupt the chain of events that leads to cancer. That is, in short, a holy grail. The revelations of the excellent results in trials of the cervical cancer vaccine were greeted with euphoria. Gardasil, manufactured by Merck, was 100% effective among the 12,000, mostly young, women who took part. It knocked out the two strains of HPV, 16 and 18, that are implicated in 70% of cervical cancers.

And the vaccine could prove even more useful. The trials showed that some of the other HPV types which are involved in a minority of cervical cancers were also stopped in their tracks. "Because there are beginning to be signs of cross-protection against other HPV types, [the proportion of cancers affected] could go up," says Anne Szarewski, a clinical consultant for Cancer Research UK who has been involved in the trial. She thinks the proportion of cancers affected could eventually be as high as 80%. At that point, the vaccine becomes more effective as a prevention tool than the cervical screening programme. As newer vaccines are developed, it is assumed they may hit the rest of the troublesome HPV types too.

So cervical cancer could, in theory, be wiped out, just as smallpox was. This is unlikely to happen, however, since it is only achievable if every girl and boy in the country has the jab. The vaccine is expected to be offered to sexually inexperienced girls who will not have HPV, aged around 10 to 13, but suggesting a vaccination for a young girl that will protect her from a sexually transmitted disease has not gone down well with parents. The Merck vaccine, unlike its GlaxoSmithKline rival, protects also against two types of HPV that cause genital warts. "It has proved a nightmare to promote in the States," observed Szarewski. Trials in women over 25 who will have the virus – for most pick it up at some point – are only just beginning.

Cancer is the scourge of our times, the most feared disease of the 21st century. It appears to come from nowhere and kill at random. The more we know of the causes, the better we will be able to protect ourselves. At the moment, the best advice we have is generally to live well – to eat a lot of fruit and vegetables, drink in moderation, stop smoking and take exercise. But there are plenty of people who have lived unimpeachably healthy lives and died of cancer. Finding a silent trigger such as a virus that scientists may be able to knock out of the equation with a vaccine is not a reason to panic, but a cause for hope.

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Take one at bedtime and you'll soon feel worse

Are your patients following the regimen you prescribed?

➜ Claire Laurent

Many cancer patients, intentionally or by mistake, fail to take their medication as prescribed. Understanding why can help doctors encourage their patients to stick with the treatment.

Most patients, when faced with a diagnosis of a life-threatening disease, feel they would 'do anything' to survive. It would therefore seem reasonable to expect that if you offer a treatment protocol that promises additional survival, if not a cure, this would be grasped by patients and closely followed.

But that doesn't account for human nature. For all kinds of reasons many patients, including cancer patients, fail to take their medication. For many, the drugs make them feel worse than their cancer, others forget – perhaps because they are in denial about their illness or maybe they feel so well on the treatment that they forget they are ill.

If these reasons appear trivial, it is because they are often symptoms of more fundamental underlying problems to do with how the patient understands their disease and the proposed treatment, and how the patient and doctor work together. In recent years, increasing attention has been paid to this issue, and it is now known that the whole nature of patient adherence to treatment is very complicated and requires understanding and negotiation by health-care professionals if their patients are to fully benefit from the treatment they prescribe. This can only happen if doctors become more aware that there may be a problem.

In an editorial in the *British Medical Journal* (326:348–349), Marinker Marshall and Joanne Shaw say that doctors tend to think non-adherence is a problem for other doctors, so when a prescribed drug fails to produce the benefit they expect they often respond by varying the dose or choosing another medicine rather than by talking to their patient about how closely they are following the prescribed drug regimen. This can lead to serious consequences – not just for the individual patient but also for understanding therapeutic benefit as well as on financial costs.

A growing awareness of the need for greater communication between doctor and patient on this issue has been accompanied by a change in the language used. The World Health Organization, in a report entitled *Adherence to Long Term Therapies: Evidence for Action*, recommends the term 'adherence' rather than the more traditional term 'compliance', arguing that 'compliance' implies an imbalance in the doctor/patient relationship: the doctor is in charge and the patient must do as they are told.

CORBIS

" 'Compliance' implies the doctor is in charge and the patient must do as they are told"

'Adherence', in contrast, is a more neutral term, simply designating "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health-care provider."

The word promoted by many health practitioners today is 'concordance'. This goes further than 'adherence'. According to Giselle Jones (*BMJ* 327:189), the concordant model is one of shared understanding. It's about shared decision making and an agreement that respects the wishes and beliefs of the patient. What it should not be, she stresses, is a gift-wrapped version of compliance.

In the UK, the Department of Health has given its backing to the Medicines Partnership (www.medicines-partnership.org), an initiative set up to encourage a move from 'compliance' to 'concordance'. It is calling for more appropriate

"Patients' own beliefs about what works for them may be at odds with those of the medical profession"

prescribing and a different approach to patient adherence. Patients comply with treatment, says the Medicines Partnership, when they understand and accept the diagnosis, agree with the treatment proposed and have had their concerns about the medicines specifically and seriously addressed. Part of the cultural shift for doctors entails a recognition that the patients' own beliefs about their illness, their treatment and what works for them might be at odds with those of the medical profession.

Size of the problem

Research shows that about half of the medicines prescribed for people with chronic conditions are not taken (*Lancet* 348:383–386). Lesley Fallowfield, professor of psychosocial oncology at the Brighton and Sussex Medical School, in the UK, who co-authored a study on non-adherence in breast cancer (*Eur J Cancer* doi:10.1016/j.ejca.2006.03.004), says, "We know from our research that around 40% of women with breast cancer, be that in a chemoprevention, adjuvant or more advanced setting, do not take their oral drugs as prescribed."

According to Michael Mauro of the Center for Hematologic Malignancies at the Oregon Cancer Institute, Canada, the overall average compliance amongst all CML patients prescribed Glivec (imatinib) was 75%. Speaking on a telephone educational programme organised by the Leukaemia and Lymphoma Society this February, Mauro said that 50- to 70-year-old men were the most compliant, whilst younger men were the least compliant, with up to 20% of them failing to take their medication properly. He suggested the difference might be that the older men were more likely to have wives who supported them through the treatment.

Benjamin Gesundheit is a paediatric oncologist at the Hadassah Hospital in Jerusalem. He argues that for young people, the discipline of adhering to a drug regimen can be particularly difficult. Speaking at the 4th International conference on Teenage and Young Adult Cancer Medicine earlier this year, he said that young people don't want to be told what to do at an age when they just are beginning to make their own decisions. Young people are also more likely to be risk takers than older people.

The evidence shows that the reasons for non-adherence are many and varied. The WHO says adherence is simultaneously affected by several factors. These include: social and economic factors, the health-care team/system, the nature of the disease and its therapies as well as what it calls 'patient-related' factors.

In the study of adherence amongst breast cancer patients, the authors found that the issue was not necessarily related to sociodemographic factors such as level of education or race. The key factors were whether the therapy had adverse side-effects, and whether it was complex and/or lasted longer.

According to Fallowfield, the most common reason for non-adherence in breast cancer is quality of life. Women may take 'drug holidays' if they are experiencing side-effects such as hot flushes, which might not be life-threatening but

"In behavioural terms it makes sense to stop taking something that makes you feel sick"

can make life miserable. In one study of adherence to treatment amongst breast cancer patients, she found that women aged between 40 and 49 years were less likely to adhere to medication than both younger and older patients. While this could simply be an 'artefact' of the numbers in the study, she thinks "it's more to do with that age group experiencing an early menopause and being blown over by that along with everything else going on in their lives."

With many long-term conditions such as diabetes, hypertension, schizophrenia and epilepsy, if the patient stops taking their medication they quickly begin to notice symptoms. Cancer patients don't necessarily have this tangible and immediate connection between medication and relief from the disease. "Rather," says Fallowfield, "they just experience noxious side-effects, so in behavioural terms it makes sense to stop taking something that makes you feel sick or gives you vasomotor problems."

Bridging the gap

Understanding this behaviour is essential if health-care professionals are to help their patients stick to their treatment. Doctors may be confident that a particular therapy works and not taking it will result in a poor health outcome, but patients will, understandably, want to take account of their own experience of how the drug works for them, which may be telling them something very different. Bridging this gap is the transition towards concordance.

Jan G, a patient with chronic myeloid leukaemia who runs Leukaemie-online (www.leukamie-online.de) for German-speaking patients, agrees that side-effects can be important when you are on a medication for any length of time. He says, "For those drugs that have strong side-effects, adherence depends on whether patients feel the drug might save their life, but take away all quality of life. Some might decide to stop taking the medication/chemotherapy and resume 'normal' life, taking the risk that it might reduce how much time they have left."

One study of adherence to tamoxifen over five years (Lash et al. *Breast Can Res Treat*, doi:10.1007/s10549-006-9193-0) found that 31% of women who started tamoxifen failed to complete the five-year recommended course, despite the fact that five years of treatment confers a significant benefit beyond one to two years of tamoxifen. Reasons given included severe side-effects and having an additional prescription added to their treatment. Interestingly, patients with more prescription medications at baseline were *less* likely to discontinue, as were patients who had a positive view of the drug and an improving view over follow-up.

Other evidence has shown that patients may not adhere to their treatment if they don't know enough about the advantages or disadvantages of taking it, when they don't feel unwell (so don't feel in need of treatment), or when they do feel unwell but find the therapy makes no perceptible difference or makes them feel worse.

Not all non-adherence comes down to a deliberate decision by the patient, however. Sometimes patients just get it wrong – they either don't understand the regimen or they forget to follow it. Again, there are a variety of reasons why this might happen. They may have been told one thing by the doctor, another by a nurse and something else again by the pharmacist. Consistent, clear and accurate information is therefore essential.

Research shows that patients forget up to 80% of what they hear in a clinical consultation, and almost half of what they do remember is incorrect, so health professionals have to think hard about how to ensure that medication regimens are understood and likely to be followed.

"It is important to gain the support of other family members or friends in the management of treatment"

An hour's investment

Gesundheit says it is important to explain the treatment thoroughly. "I dedicate an hour to explaining everything to them: each drug, what it is for and how long they have to take it. This hour is a good long-term investment, because I see much less non-compliance and misunderstanding."

He says this explanation has to be repeated at intervals and emphasises that clinicians must always remember that the early part of the discussion will be forgotten as the patient may be in shock from hearing their diagnosis. Gesundheit advises that it is important to gain the support of other family members or friends in the management of treatment. He adds that talking to patients about their treatment regimen can often encourage them to open up about themselves and their illness. "It's a very good opportunity to understand the patient."

He also suggests a number of techniques that might help patients remember their regimen. A written contract between clinician and patient or a home diary where the patient records that they have taken their medication can help. More consultations or a home support person to clarify the responsibility of drug administration can improve adherence. At the high-tech end of the market is the Medication Event Monitoring System (MEMS). These are microprocessors in the cap of standard medicine bottles. Every time the bottle is opened it is regarded as a presumptive dose. Any patterns in non-adherence will become apparent over time – but this is an expensive way to monitor compliance and does not address the reasons why a patient is not taking their medication.

Doctors can routinely address the issue of adherence at patient consultations. One way to do this is simply asking the question: "How are you managing with your medication?" – patients are often more accurate about non-adherence than adherence. Doctors also routinely run blood tests to monitor the disease and treatment effects. These can be checked for inconsistencies with the drug regimen.

It is also important not to assume that the patient has the literacy skills to follow the information on medicine bottles or on the literature that comes with them. It is estimated that between one-quarter and three-quarters of adults do not have the minimum reading skills needed for coping with the demands of modern life. A report by the OECD, *Literacy in the Information Age*, (OECD 2000) found at least 15% of adults had only the most rudimentary of reading skills in 14 of the 20 countries studied: Australia, Belgium (Flanders), Canada, Chile, Czech Republic, Hungary Ireland, New Zealand, Poland, Portugal, Slovenia, Switzerland, the UK and the US.

Doctors need to be aware that patients who cannot read are likely to have developed all sorts of coping mechanisms to cover up their poor literacy skills. It is important to go through everything very thoroughly with every patient, and make sure that they have understood.

Some simple strategies that can help doctors communicate clearly are detailed at www.askme3.org, a project of the Partnership for Clear Health Communication in the US. The project title refers to the three questions they advise patients always to ask:

1. What is my main problem?
2. What do I need to do?
3. Why is it important for me to do this?

Ensuring adherence or concordance with treatment is about involving the patient, one way or another, in a dialogue that tackles these three issues, so that the doctor can be sure the patient understands what is wrong with them, what they need to take/do and when, and how the treatment can help.

A quarter to three-quarters of adults don't have the minimum reading skills needed in modern life

Reefer madness

Marijuana is medically useful, whether politicians like it or not.

IF cannabis were unknown, and bioprospectors were suddenly to find it in some remote mountain crevice, its discovery would no doubt be hailed as a medical breakthrough. Scientists would praise its potential for treating everything from pain to cancer, and marvel at its rich pharmacopoeia – many of whose chemicals mimic vital molecules in the human body. In reality, cannabis has been with humanity for thousands of years and is considered by many governments (notably America's) to be a dangerous drug without utility. Any suggestion that the plant might be medically useful is politically controversial, whatever the science says. It is in this context that, on April 20th, America's Food and Drug Administration (FDA) issued a statement saying that smoked marijuana has no accepted medical use in treatment in the United States.

The statement is curious in a number of ways. For one thing, it overlooks a report made in 1999 by the Institute of Medicine (IOM), part of the National Academy of Sciences, which came to a different conclusion. John Benson, a professor of medicine at the University of Nebraska who co-chaired the committee that drew up the report, found some sound scientific information that supports the medical use of marijuana for certain patients for short periods – even for smoked marijuana. This is important, because one of the objections to marijuana is that, when burned, its smoke contains many of the harmful things found in tobacco smoke, such as carcinogenic tar, cyanide and carbon monoxide. Yet the IOM report supports what some patients suffering from multiple sclerosis, AIDS and cancer – and their doctors – have known for a long time. This is that the drug gives them medicinal benefits over and above the medications they are already receiving, and despite the fact that the smoke has risks. That is probably why several studies show that many doctors recommend smoking cannabis to their patients, even though they are unable to prescribe it. Patients then turn to the black market for their supply.

Another reason the FDA statement is odd is that it seems to lack common sense. Cannabis has been used as a medicinal plant for millennia. In fact, the American government actually supplied cannabis as a medicine for some time, before the scheme was shut down in the early 1990s. Today, cannabis is used all over the world, despite its illegality, to relieve pain and anxiety, to aid sleep, and to prevent seizures and muscle spasms. For example, two of its long-advocated benefits are that it suppresses vomiting and enhances appetite – qualities that AIDS patients and those on anticancer chemotherapy find useful. So useful, in fact, that the FDA has licensed a drug called Marinol, a synthetic version of one of the active ingredients of marijuana – delta-9-tetrahydrocannabinol (THC). Unfortunately, many users of Marinol complain that it gets them high (which isn't what they actually want) and is not nearly as effective, nor cheap, as the real weed itself.

This may be because Marinol is ingested into the stomach, meaning that it is metabolised before being absorbed. Or it may be because the medicinal benefits of cannabis come from the synergistic effect of the multiplicity of chemicals it contains.

Just what have you been smoking?

THC is the best known active ingredient of cannabis, but by no means the only one. At the last count, marijuana was known to contain nearly 70

It suppresses vomiting and enhances appetite – qualities that those on chemotherapy find useful

SCIENCE PHOTO LIBRARY

The first wonderdrug? Marijuana can help control nausea, appetite loss, pain and anxiety, without serious side-effects. Many cancer patients could benefit from it, but only a tiny minority can get it on prescription

different cannabinoids, as THC and its cousins are collectively known. These chemicals activate receptor molecules in the human body, particularly the cannabinoid receptors on the surfaces of some nerve cells in the brain, and stimulate changes in biochemical activity. But the details often remain vague – in particular, the details of which molecules are having which clinical effects.

More clinical research would help. In particular, the breeding of different varieties of cannabis, with different mixtures of cannabinoids, would enable researchers to find out whether one variety works better for, say, multiple sclerosis-related spasticity while another works for AIDS-related nerve pain. However, in the United States, this kind of work has been inhibited by marijuana's illegality and the unwillingness of the Drug Enforcement Administration (DEA) to license researchers to grow it for research.

Since 2001, for example, Lyle Craker, a researcher at the University of Massachusetts, has been trying to obtain a licence from the DEA to grow cannabis for use in clinical research. After years of prevarication, and pressure on the DEA to make a decision, Craker's application was turned down in 2004. Today, the saga continues and a DEA judge (who

"This has no medical benefit because no tests have been done, and we refuse to let you do any tests"

No one would argue for chewing willow bark when aspirin is available

presides over a quasi-judicial process within the agency) is hearing an appeal, which could come to a close this summer. Dr Craker says that his situation is like that described in Joseph Heller's novel, *Catch 22*. "We can say that this has no medical benefit because no tests have been done, and then we refuse to let you do any tests. The US has gotten into a bind, it has made cannabis out to be such a villain that people blindly say 'no'."

Anjuli Verma, the advocacy director of the American Civil Liberties Union (ACLU), a group helping Craker fight his appeal, says that even if the DEA judge rules in their favour, the agency's chief administrator can still decide whether to allow the application. And, as she points out, the DEA is a political organisation charged with enforcing the drug laws. So, she says, the ACLU is in this for the long haul, and is already prepared for another appeal – one that would be heard in a federal court in the normal judicial system.

Verma's view of the FDA's statement is that other arms of government are putting pressure on the agency to make a public pronouncement that conforms with drug ideology as promulgated by the White House, the DEA and a number of vocal anti-cannabis congressmen. In particular, the federal government has been rattled in recent years by the fact that 11 states have passed laws allowing the medical use of marijuana. In this context it is notable that the FDA's statement emphasises that it is smoked marijuana which has not gone through the process necessary to make it a prescription drug. (Nor would it be likely to, with all of the harmful things in the smoke.) The statement's emphasis on smoked marijuana is important because it leaves the door open for the agency to approve other methods of delivery.

High hopes

Donald Abrams, a professor of clinical medicine at the University of California, San Francisco, has been working on one such option. He is allowed by the National Institute on Drug Abuse (the only legal supplier of cannabis in the United States) to do research on a German nebuliser that heats cannabis to the point of vaporisation, where it releases its cannabinoids without any of the smoke of a spliff, and with fewer carcinogens.

That is encouraging. But it does not address the wider question of which cannabinoids are doing what. For that, researchers need to be able to do their own plant-breeding programmes.

In America, this is impossible. But it is happening in other countries. In 1997, for example, the British government asked Geoffrey Guy, the executive chairman and founder of GW Pharmaceuticals, to come up with a programme to develop cannabis into a pharmaceutical product.

In the intervening years, GW has assembled a 'library' of more than 300 varieties of cannabis, and obtained plant-breeder's rights on between 30 and 40 of these. It has found the genes that control cannabinoid production and can specify within strict limits the seven or eight cannabinoids it is most interested in. And it knows how to crossbreed its strains to get the mixtures it wants.

Nor is this knowledge merely academic. Last year, GW gained approval in Canada for the use of its first drug, Sativex, which is an extract of cannabis sprayed under the tongue that is designed for the relief of neuropathic pain in multiple sclerosis. Sativex is also available to a more limited degree in Spain and Britain, and is in clinical trials for other uses, such as relieving the pain of rheumatoid arthritis.

At the start of this year, the company made the first step towards gaining regulatory approval for Sativex in America when the FDA accepted it as a legitimate candidate for clinical trials. But there is still a long way to go.

And that delay raises an important point. Once available, a well-formulated and scientifically tested drug should knock a herbal medicine into a cocked hat. No one would argue for chewing willow bark when aspirin is available. But, in the meantime, there is unmet medical need that, as the IOM report pointed out, could easily and cheaply be met – if the American government cared more about suffering and less about posturing.

Holistic oncology
a new paradigm?

➜ Raphaël Brenner

Like it or not, health-care professionals are having to come to terms with the growing demand for complementary therapies in the treatment of cancer – a phenomenon reflected in the array of new books on the subject.

Physicians in the West have long viewed the various non-allopathic methods of treatment with suspicion, considering them at best ineffective and at worst harmful. However, except for cancers such as lymphoma and testicular tumours, standard tumour-destructive therapies can severely impair the quality of life of patients, while not significantly lowering cancer mortality, and a growing number of patients have been turning to complementary and alternative medicine (CAM). CAM has become very popular among cancer patients for a variety of reasons: it can offer better symptom management and quality of life; patients often feel more involved with their treatment; it can stimulate the patient's immune system; alternative therapists can be more empathetic, better listeners, and can impart new hope. In 1993, in response to the overwhelming demand by patients and health-care practitioners, the US National Institutes of Health established the Office of Alternative Medicine (later renamed the National Center for Complementary and Alternative Medicine), an organisation dedicated to scientific research into CAM. In addition to promoting research the initiative boosted recognition of CAM as a popular therapeutic option. Academic publishers have now followed suit with new textbooks on the subject.

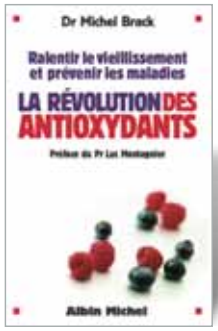
Patients are often the groundbreakers. Some oncologists persist in referring to CAM as quackery, but the fact is that many patients credit CAM with making them feel better. In both *Complementary Oncology* and *Integrative Oncology*, the authors stress, however, that complementary therapies are not intended to replace approved standard therapies and should be integrated on the basis of sound scientific principles. This is what differentiates complementary medicine from 'alternative therapies' (although the acronym CAM is used throughout *Integrative Oncology*): complementary oncology simply claims to be an important addition to conventional therapies.

Complementary Oncology
Adjunctive Methods in the Treatment of Cancer
Edited by Josef Beuth and Ralph W. Moss
Thieme, 312 pp, euro 79.95 *(hardback)*

Integrative Oncology: Principles and Practice
Edited by Matthew P. Mumber
Taylor & Francis, 538 pp, £85 *(hardback)*

Ralentir le vieillissement et prévenir les maladies
La révolution des antioxydants
by Michel Brack
Albin Michel, 176 pp, euro 13.90

In view of the fact that CAM is most popular in Germany and the US, it is not surprising to discover that the first textbooks on CAM are the work of German and American teams. *Complementary Oncology*, written by an almost all-German team, was first published in German in 2002: the current edition is a completely revised translation of that first edition. Beautifully presented, rigorously researched and clearly written, the book is divided into two main parts. The first part of the book offers a critical analysis of the current situation in oncology and introduces readers to tumour immunology. There are also chapters analysing study designs and problems



related to the evaluation of oncological studies. This part ends with the presentation of the QoL-Recorder, a tool designed to determine patient quality of life.

The rationale of complementary therapies is then described in Part Two, which consists of 13 chapters. Nutrition, exercise, psycho-oncology (excellent chapter), antioxidants, selenium, proteolytic enzymes, mistletoe extracts, thymic peptides, probiotic therapy and hyperthermia are among the main topics discussed. There is also a very useful chapter, consisting of tables, in which the authors note the accompanying complementary measures (including dosage and duration of treatment) for each stage of standard therapeutic treatment for most solid tumours.

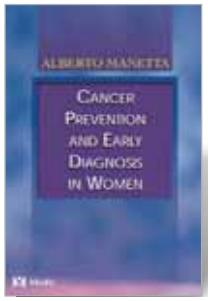
Written by an American team, *Integrative Oncology* emphasises the importance of integrating complementary therapies into conventional cancer treatment. Patients should now be able to ask their oncologists questions such as: "What can I do in addition to conventional care to improve my chances of living longer and better?" The first part of this textbook is devoted to the principles of integrative oncology and the second to its practice. While some chapters are highly US-oriented (costs, legal issues), others such as the "Introduction to Integrative Oncology" and the "Health of the Healer" are quite instructive.

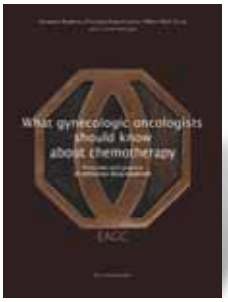
Integrative Oncology overall offers greater scope regarding the modalities of integrative oncology than the German book. In addition to physical activity, nutrition, botanicals and manual therapy, *Integrative Oncology* also discusses methods such as body–mind interventions (meditation, yoga, psychology), energy medicine (chakra system), spirituality and alternative medical systems (traditional Chinese medicine, Ayurvedic medicine…), which are not mentioned in the German book. While all these methods are clearly worthy of interest, they are not supported by much evidence-based research, as the authors point out.

The book is badly-structured, leading to much redundancy and lack of clarity. The reader's task would have been facilitated, had the modalities of each method been presented separately: physical activity, for instance, is discussed in several chapters – prevention, supportive and antineoplastic care, and in each chapter on interventions for specific malignant diseases.

The scarcity of data for most modalities in integrative oncology hardly justifies such a disease-specific approach. Since both the above books cater to a general readership of health professionals, some chapters are too basic for physicians but, this said, these two books offer a helpful introduction to the world of integrative oncology and will hopefully encourage oncologists to be more open to the diverse resources offered by these new disciplines. Armed with greater knowledge, they will also be able to communicate more freely with their patients on the subject. As Matthew P. Mumber writes, integrative oncology has not only the potential to improve outcomes, but also to transform individuals and the system of cancer care. Is it not time for physicians to do away with the absurd barriers erected by allopathy, and view their patients in their entirety – physically and intellectually, emotionally and spiritually? Patients can but benefit from a holistic approach that blends conventional with unconventional therapies.

Finally, French readers desiring to know more about antioxidants and oxidative damage (an important issue in cancer treatment and prevention) can turn to Michel Brack's book *Slowing the aging process and preventing diseases – the antioxidant revolution* – which caters to specialists and lay people alike. The second part of the book is particularly good. It includes numerous tables on the antioxidant power of fruits and vegetables and practical advice on dietary antioxidants (recipes, ways of cooking, menu suggestions, etc.).





Cancer Prevention and Early Diagnosis in Women
Edited by Alberto Manetta
Mosby, 366 pp, euro 72.95

What Gynecologic Oncologists Should Know About Chemotherapy
Principles and Practice of Anticancer Drug Treatment
Edited by Péter Bősze and Maurie Markman
European Academy of Gynaecological Cancer, 264 pp, euro 85
(for online order: *www.eagc.hu*)

Alberto Manetta, Professor of Obstetrics and Gynecology at the University of California, Irvine, views women's health "as a new discipline that transcends and blends the boundaries of traditional clinical disciplines" relating to women, such as obstetrics and gynaecology, internal medicine, family medicine, geriatrics and paediatrics. He clearly wants gynaecology to return to its etymological origin, i.e. the study of woman. The book he has compiled addresses assessment of risk, prevention and early diagnosis of cancer in women, for cancers that occur most frequently and are responsible for the highest mortality in Western countries. It thus covers nine specific cancers: lung, breast, colorectal, skin, cervical, vagina, vulva, ovarian and uterine corpus. There are also chapters on the principles of cancer screening, the ethical and legal implications of genetic testing in preventive health, and a lengthy final chapter on the role of complementary therapies in cancer prevention.

Even if the inclusion of non-gynaecologic tumours is surprising in this context, one must acknowledge that the authors have succeeded in gathering together a wide range of information on risk factors, screening and prevention. The discussion on cancer screening is particularly comprehensive and covers the benefits and the risks involved, as well as the potential for bias and error in evaluation. The book offers a systematic approach for evaluating the effectiveness of screening programmes and the analyses of clinical trials for the chemoprevention of lung, breast or colorectal cancer, to name a few, are sound, while not too long. There is also an evidence-based analysis of the potential anticarcinogenic effects of complementary therapies, both in general and in relation to specific cancers. Manetta thus provides health-care professionals involved in women's health with a good overall picture of cancer prevention.

Péter Bősze and Maurie Markman's book, published by the European Academy of Gynaecological Cancer, a non-profit, independent organisation, describes the cytotoxic drugs used in gynaecologic oncology and the cytotoxic treatment of each cancer. It offers a comprehensive analysis of the various aspects of chemotherapy in the treatment of gynaecological malignancies – from the mechanisms of action of cytotoxic drugs and the clinical pharmacologic principles of their administration, to the clinical trial methodology for gynaecologic cancers and the molecular biology underlying the discovery of new treatment approaches. Readers will find in this book a wealth of up-to-date, practical, clearly presented information. The use of tables in the chapter on dosing, schedule and route of chemotherapy is particularly helpful.

Without obfuscating the complexity of the issues, the authors manage to give an intelligent overview of the current status of cytotoxic treatment of gynaecologic tumours. Breast cancer, especially systemic adjuvant therapy of early-stage tumours, where many shades of grey remain, is dealt with particularly well. The chapter on chemoprevention of breast cancer sums up the major chemoprevention trials for breast cancer published so far. Maybe here, the authors do not sufficiently stress the fact that, until we have surrogate markers that identify those who are at high risk of breast cancer, clinical cancer prevention research will remain in limbo, with the danger that we end up treating risk as a medical condition and thus substituting one disease for another.

For such a technical book, it is unusual and praiseworthy to see that it includes a chapter on the psychological aspects of chemotherapy. Curiously, most of the side-effects of chemotherapy are discussed in this chapter. Psychological care is indeed important for patients suffering from side-effects, but readers would expect to find here a more detailed analysis of the pharmacological management of the main side-effects caused by cytotoxic drugs. This aside, the book is an excellent aid for all those interested in learning more about the chemotherapy of gynaecologic cancers.

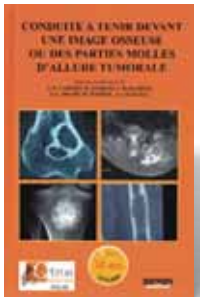
Why Mum? A Small Child Dealing with a Big Problem
Catherine Thornton, with illustrations by Robert Thornton
Veritas, 20 pp, euro 5.95
(for online order: www.veritas.ie)

When she was fighting breast cancer, Catherine Thornton, a mother of three, tried to find a children's book that would help her talk about her illness with her youngest son, but there was none. So, when she got better, she decided to write the book herself.

Told through the eyes of Matthew, a seven-year-old child, *Why Mum*? is a picture book, beautifully illustrated by one of the author's sons, which describes with moving simplicity the anguish experienced by the child of a cancer patient: Mum crying in the kitchen, the strange atmosphere of a hospital room, having to go to a friend's home after school, Mum wearing a wig, and so on. Far more informative than a psychological manual, Thornton's book graphically depicts, through the little things of life, the fears and frustrations experienced by small children when their mother has to go away for treatment or is at home, but so weak she is unable to take care of them. Matthew's Mum explains to him, in words he can understand, complicated procedures such as chemotherapy and radiotherapy. As Françoise Dolto, the celebrated French child psychotherapist, noted, talking with children and putting the right words to what they feel helps alleviate their suffering and enables them to cope with frightening situations. Matthew acknowledges this when he remarks that he feels a bit better after his Mum took time to talk and listen to him. "She promised to talk to me and tell me what was happening as it went along, and that I could ask her any questions I wanted to." Through her heart-wrenching but optimistic story, Thornton has produced a valuable tool for helping parents and children deal with cancer in the family. The book was recently awarded the Nathwani prize for improving the relationship between science and the arts by the European Breast Cancer Conference committee.

New Technologies in Radiation Oncology
Edited by Wolfgang Schlegel, Thomas Bortfeld and Anca-Ligia Grosu
Springer, 478 pp, euro 210.95

Radiation therapy is a fast-moving discipline that is based on a multitude of sciences: physics, mathematics, computer science, radiation biology as well as electrical and mechanical engineering. *New Technologies in Radiation Oncology* provides an excellent overview of recent advances in the field, such as 3D treatment planning for conformal radiotherapy, stereotactic radiotherapy, proton therapy and image-guided, time-adapted radiotherapy systems. More clinically orientated chapters discuss the use of brachytherapy on patients with prostate and breast cancer, while the last section of the book deals with quality management in radiotherapy. Though the subject may seem obscure to non-specialists, the clarity of the explanations together with the many excellent photos and illustrations make the book accessible not only to radiation oncologists and medical physicists but also to any physician interested in the subject.



Conduite à tenir devant une image osseuse ou des parties molles d'allure tumorale
Coordinated by Jean-Denis Laredo, Bernard Tomeno, Jacques Malghem, Jean-Luc Drapé, Marc Wybier and Jean-Jacques Railhac
Sauramps médical, 470 pp, euro 99

This book fully reflects the amazing advances achieved in medical imaging – especially with 3D imaging of bones – for the management of bone and soft tissue tumours and pseudo-tumoral lesions. This is an exhaustive work, which covers, with a plethora of illustrations, a wide range of conditions, from Paget's disease and cartilage tumours to lipoma variants and osteosarcoma. It also analyses various possible lesions, difficult cases and diagnostic pitfalls, and provides a useful discussion of the differential diagnoses. A highly recommended guide for French-speaking specialists.