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Learning to care

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EUREKA!

A five-point plan to promote innovation in cancer care

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HIGHLY IRREGULAR

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Editor
Kathy Redmond
editor@eso.net

Managing Editor
Anna Wagstaff

Editorial Coordinator
Corinne Hall

Editorial Advisors
Matti Aapro
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Contributing Writers
Marc Beishon, Barrie Cassileth
Simon Crompton, Gary Deng
Janet Fricker, Susan Mayor
Peter McIntyre, Anna Wagstaff

Publishing Advisor
Gillian Griffith

Art Editor
Jason Harris

Production
HarrisDPI
www.harrisdpi.com

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Cover photograph
Jorge Nogueira

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Direttore responsabile
Alberto Costa

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All enquiries about Cancer World should be made to:
ESO Editorial Office
Via Turati 29
20121 Milano, Italy
e-mail: magazine@eso.net
Tel: +39 02 8546 4522
Fax: +39 02 8546 4545
All correspondence should be sent to the Editor at editor@eso.net

Cancerworld
Shaping the future of cancer care

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Learning to care

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'Why me?' Helping patients find answers

ROGER WILSON GUEST EDITOR

People with cancer have time to think. Not every patient will think about spiritual matters, but most of us probably do, either alone, or when talking with close family or friends. This spiritual questioning may never have a satisfactory conclusion. Loved ones aware of the struggle can be left questioning why important support was absent during the last weeks of life.

The need for spiritual support is readily identified in palliative care. It represents a problem for clinical and care professionals – they can be asked the questions but are not trained to help find answers. Handing the problem over to ministers of religion is not a solution. Many patients reject a particular brand, or any brand, of faith. Spirituality is not an issue of religion.

The questions often start with the simple "why me?" The answer of course is "why not you?" – cancer does not discriminate between the good and the bad, and it does not spare someone just because there are people who depend on them. Such answers will challenge those who believe in an all-powerful god.

The search for a miraculous cure can be based on religious belief. What does "successful prayer" depend on? The quantity of faith built up over a lifetime? The earnestness of those praying? Feelings of inadequacy and personal guilt about having cancer are quite common.

Then there is the journey to heaven. In some faiths heaven seems to be a promotable destination. For someone with cancer, doubts can cause the 'brochure' to look less glossy. There is no website to consult and heaven is a bit short of bloggers.

Those who belong to no faith may ask the same questions but in a different way. Is there such a thing as god? Where do I go when I die?

The question for the cancer community is how we put support in place. It must help people identify the questions they need to address and find their personal answers. Ministers of religion may help someone from their own tradition. A psychologist may provide counselling in a dispassionate manner, but if the counsellor has little relevant life experience it will be shallow. This is not an area for earnest young people. Perhaps we should seek older people to train as spiritual counsellors.

However, whether old or young, we have no training resources, no curriculum, no assessment criteria and no practice guidance to ensure counsellors work within boundaries, which themselves have yet to be defined. What we do have is a lot of words in a lot of reports about the need for spiritual support. There is certainly a body of work to be undertaken. ■

Roger Wilson is the President of the advocacy group Sarcoma Patients Euronet

Roger Stupp: What's so ethical about strangling research?

SIMON CROMPTON

Patients are losing out because the rules governing research are designed to restrain rather than facilitate. It's got to change, says Roger Stupp, who is frustrated that 10 years after helping set a new standard of care for glioblastoma, patients are still waiting for something better.

Until ten years ago, the average life expectancy for someone diagnosed with the most common brain tumour, glioblastoma, was one year. The route for patients was radiation therapy to hospice. But the discovery in Switzerland of a new therapy combining radiotherapy and chemotherapy changed all that.

The new treatment increased survival rates at two years from 10.9% to 27.2%, and has become the international standard. For people with primary brain tumours – often younger men and women with young families for whom every extra day is precious – the impact has been enormous. Around 5% of cancer diagnoses are primary brain tumours, and they are still usually fatal: but they are no longer seen as hopeless cases.

The story behind the breakthrough is one of luck, people coming together at the right place at the right time, professional commitment, and a young oncologist prepared to make the most of what seemed the most unpromising opportunity.

He was Roger Stupp, today the President of the European Organisation for Research and Treatment of Cancer (EORTC), Professor at the University of Zurich, and Director of both the Department of Oncology and the Zurich Cancer Centre at the University Hospital Zurich. This year Stupp won both ESMO's distinguished Hamilton Fairley Award for lifetime achievements in cancer science and clinical/laboratory research, and the US Society for NeuroOncology's Victor Levin award.

The implications of his discovery continue to

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reverberate. Stupp has presided over the development of molecular characterisation in brain tumours, which helps target the right treatment to the right patient, with all the benefits that can bring for quality of life. He has seen neuro-oncology develop from an unpopular speciality defined by a sense of hopelessness to one which now holds its own in the programme of international cancer conferences.

But today, as one of cancer's leading opinion-formers, he looks back at how the leaps in research and treatment have happened in the past, and wonders if they could ever occur now. Regulation is obstructing advance at every turning, Stupp believes, and he is angry about it. "We have this world of mistrust, no one wanting to take responsibility any more, everyone being defensive."

"The effort required to make progress has increased exponentially," he says. "I know that many clinical trials that need to be done are not done because regulation systems make them too complex and too expensive," he says.

What amazes him is how, less than 20 years ago, so much was achieved in very little time, with almost no money.

Born, bred and medically trained in Switzerland, Stupp arrived at the multidisciplinary oncology centre at the University of Lausanne in 1996. He had just qualified in haematology/oncology after spending three years at the Department of Medicine at the University of Chicago in the United States, where he gained experience in haematological malignancy, head and neck cancer and lung cancer. "But in Lausanne, I was put on what other people didn't want to do, and that included brain tumours."

It wasn't long before the head of the oncology department asked him to look into a new pre-market chemotherapy drug called temozolomide. The hospital had stocks of it, available on a compassionate use basis – they had trialled it for melanoma, and trials had also been planned for brain tumours, but patients had never been recruited.

Early research into the drug in the UK, reported in 1997, had indicated that it brought some benefit to those with brain tumours. "It was simply for me to evaluate. Here I was, I had the drug, I used it and had been lucky enough to

"In those days there were no unnecessary checks to be done, and we had the leeway we needed"

see a couple of patients respond well to it – and when you've seen that for yourself, that makes a lot of difference. When you see young patients dying within a year or less, you have to try to do something more.

"It was a group of patients that had been neglected. There was nothing to offer them, so they were hardly even sent to medical oncologists. They normally went from the radiation oncologist to hospice care."

When deciding what to do next, his American experience of combining different cancer treatment modalities came into play – it was a practice rarely considered in Switzerland. So he and his colleagues put together a protocol investigating an early and aggressive combination of temozolomide chemotherapy with radiotherapy.

He was criticised. Hadn't he considered the effects of late toxicity? "My answer was, if you get late toxicity, then it's a success. With other treatments you would never see late toxicity because the patient died before effects would show."

He collaborated with colleagues in radiation oncology and neurosurgery in Geneva and Lausanne to ensure he could recruit enough patients for his phase II pilot trial, Schering-Plough provided the drug free, and the whole project was funded from the department's own resources. "Of course, everything was done according to the rules, and we made sure we did the pharmacovigilance, reported serious adverse effects, and we were very careful that patients took the correct doses. But in those days there were no unnecessary checks to be done, and we had the leeway we needed. My team and I did the data management, the research nurse put in the extra time to treat patients, we made the blister packs of the drugs ourselves to ensure that patients got the right doses."

The result of the long hours was something unexpected. Stupp saw from the reaction of radiation oncologists that patient outcomes were changing significantly. Double checking the data for the first time, he became aware of its significance. "It was a very special feeling, no question," he says. A phase III trial, in collaboration with EORTC and NCIC (National Cancer Institute of Canada Clinical Trials Group), recruited 573 patients in 15 months – an indication of the demand for a new treatment. After the results were presented at ASCO in 2004, the treatment became the international standard.

But this original breakthrough led to another, which was equally significant. Looking at the trial data, Stupp wanted to know why some patients benefited from the chemotherapy/radiation combination and some did not. So the laboratory research team, led by Monika Hegi, looked at what might be leading to temozolomide resistance on a molecular level. They discovered that survival was best in those patients who carried an inactivated MGMT gene, which meant that testing tumours for methylation of the gene would allow patients to be selected for this aggressive treatment. For the remainder, who were unlikely to benefit, supportive care could be made the priority.

"I remember when we did the first analysis of this data – it was in my crampy little office about 15% the size of this one" – he waves his arm around his current airy room in the University Hospital Zurich, its large windows opening onto parkland – "so it shows you don't need big offices to do big work. Monika Hegi and I were looking at the computer, and I remember saying, do you know what this means? Coming from the lab side she didn't immediately realise why I was jumping up and down."

The finding had an impact on all glioblastoma patients, not just those who responded, because better molecular understanding not only allowed better targeting, but has raised the prospect of finding new targets.

What is more, the speciality has taken off, as more researchers and oncologists have become interested in brain tumours. Up until the late

1990s, there had been a few small collaborative groups interested in neuro-oncology, and ASCO meetings did not have a track devoted to the central nervous system. Today neuro-oncology conferences attract 1000 people or more.

But it's not all good news. Stupp's description of past triumphs is tinged with regret. "The sad part is that here we are in 2014 almost, and radiotherapy with temozolomide is still the standard of care. I would have loved that this protocol could have been replaced by something better."

Currently the mood is again depressed when it comes to brain tumours. For the past decade, trials into new agents – chemotherapy, anti-angiogenics, EGFR inhibitors – have failed to fulfill early promise. Stupp, true to his America-induced enthusiasm for combination therapies, believes that part of the problem is that all these approaches are being looked at as single agents.

"We have competing companies developing molecules that probably inhibit one pathway in a clinical trial," he says. "But of course, when you look at the complexity of the biology, it's logical there will be escape mechanisms. That doesn't mean that the agent isn't good, or that the target isn't good, but as a sole target it won't work."

"What we need is better predictive pre-clinical models, we need to learn more from early clinical trials before moving on to large trials. For example, using molecular imaging to show that an agent inhibits a target, finding ways to repeat biopsies of brain tissue to see what has been happening, being allowed to do early combinations of therapies. While still paying utmost respect to ethics, we need innovative designs which can tell us much more than we are learning at the moment. This is true of all oncology, not just brain tumours."

A strong belief in translational medicine, a propensity for challenging orthodoxy, and the ability to find reward in virtually any field of activity lie at the heart of Stupp's story, taking him from office clerk at the age of 15 to head of one of cancer's most influential research bodies today.

There was medicine in his family – his uncle was a doctor, his father worked in the pharmaceutical industry – but it held no interest for Stupp when he left school early in the 1970s and qualified as a commercial clerk. He started work for a big Swiss food supplier, stacked shelves and quickly progressed into the company's public relations office. He learned a valuable lesson from his boss, who refused to sign letters that Stupp had composed on his behalf. "You wrote the letter, you sign: you are responsible," the

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boss said. The belief in empowering people with responsibility has stayed with Stupp, and it is a lesson that he passes on to the students and junior doctors he supervises today.

He also edited a youth page in a weekly newspaper and considered a move into journalism. At age 18, despite plenty of job offers, he decided that university would give him more career options later in life, so went back to school to get his qualifications and took a medical degree at Zurich's Medical Faculty. Medicine, he says, simply seemed interesting. And, since he found it hard to learn facts by rote, he discovered he progressed fastest if he completely understood things: "There was no end purpose apart from curiosity, and a refusal to accept that I couldn't do some things just because I didn't have a degree. I need my freedom."

He wanted to go to the US so his mentor in Zurich pulled in contacts and found Stupp a placement in haemo-oncology at the University of Chicago. That was his introduction to cancer: "Up until then I'd been interested in the sexy things like cardiology and gastroenterology. But I thought, 'Okay, you take the opportunities when they come.' And I discovered a new world. Everything was research-driven, everything was protocol-driven, you questioned everything, you read original research not textbooks, the professor's door was always open. This was not at all like germanic Switzerland. I thought haemo-oncology was great – being a doctor paired with research, biology and innovation, interaction with lots of people. I knew it was for me." Every day he started work at 7.30, left at 7.30pm to enjoy the nightlife of Chicago, returned at 11pm and worked until 2am.

He returned to Zurich to finish medical school, went back to Chicago to complete his oncology training, came to the University of Lausanne Medical Centre in 1996, and stayed there for 17 years working in lung and head and neck tumours as well as brain tumours.

"At the beginning I had very low expectations of neuro-oncology. It wasn't popular because it was considered difficult. People like to go into something that is advancing, but this was not the case. It's very difficult when you have nothing to offer to the patient. But I take the challenges as they come and very quickly things

"As long as we are treating patients outside clinical trials when there are trials to be run, that is what is unethical"

changed. I found it gratifying because I learned by collaborating with neurologists just how much you have to take care of toxicity, cognitive function and patient factors that perhaps were becoming neglected in the 1990s as we were giving higher and higher doses of therapy. So it opened my mind."

He rose through the ranks, from head of the oncology clinic at Lausanne University Hospital to head of clinical research in oncology in 2001, then on to master of teaching and research at the university's biology and medicine faculty in 2006. In 2008 he became head of the Department of Oncology-Hematology at the hospitals of Vevey and Monthey, and head of neuro-oncology at the Department of Neurosurgery at Lausanne University Hospital.

After 17 years in Lausanne, he needed to energise himself with a new environment, and last August he returned to University Hospital Zurich, where he had received his medical training, to take up the positions of Director of the Department of Oncology, Director of the Zurich Cancer Centre and Professor at the University of Zurich. There's considerably more management for him here, as he tries to build a truly multidisciplinary cancer centre with patients at the heart of structures. Making sure that the young people around him can thrive is a priority: Stupp is keen to build strong teams, and pass on all those lessons about taking responsibility and asking questions that he learned in his medical education.

He also wants junior doctors to have the freedom to inquire that he has had. This is why one of his main priorities, in the midst of his three-year term as President of EORTC, is to speak out against the regulation that he believes is choking innovation and investigation at its very source. He is not just talking about the EU's Clinical Trials Directive – he wants to see an end to the complex mesh of inconsistent rules and protocols that entangle collaboration and progress in Europe.

"I'm not against regulation," he says, "but it has to serve a purpose and currently regulation is just for the sake of regulation." An overwhelming burden of paperwork prevents doctors from spending time on the business that makes them good doctors – interacting with patients, being curious, translating clinical practice into research.

"Apparently in clinical research we are all crooks, we all don't want the best for our patients and we all have conflicts of interest. That is the assumption. Of course I have potential conflicts of interest, but that doesn't mean that my work is influenced. If you think about it, as a doctor I'm making a living out of treating patients – so that's already a potential conflict of interest. So shall we have civil servants as doctors?

"You need people who are responsible, but in this world of mistrust you take away people's responsibility: everything that is not explicitly allowed is forbidden. Stupid. It should be the other way around – you regulate as much as is needed but as little as possible.

"Do you really think that researchers don't want the best for their patients? How do you think it feels when ethics committees tell us that something we are doing is unethical, when we have a protocol which we haven't just discussed in my office, but in a collaborative group according to EORTC protocols involving up to 30 people, over many days? How do outside regulators know better what is ethical? To me, as long as we don't cure this disease, as long as we are treating patients outside clinical trials when there are clinical trials to be run, that is what is unethical. We need to learn and make progress on every patient we treat."

Stupp acknowledges that the subject makes him angry. It's borne as much out of contact with patients as professional pride. Many patients, he says, are prepared to take risks, to further scientific progress for their children's sake, if not for their own. Some patients have a different

"There are too many egos, who ask 'What do I get out of it?' when you come to them with a new idea"

approach, and that also has to be honoured.

He urges academics to get back into control, so that opportunities are not lost and new funding models are found. It is ridiculous, he says, that if he wanted to conduct a randomised controlled trial of a drug already on the market to see whether a lower dose worked as well as the current standard of a high dose, he would suddenly need new infrastructure, expensive trial insurance, stringent pharmacovigilance monitoring – even though patients would be exposed to lower toxicities. What's more, he would have to find ways of getting the drug free, because health insurance companies would no longer reimburse it. "Something is not right," he says.

His other main worry as EORTC President is the fragmentary nature of the EU: every country has its own healthcare system, its own systems of funding, reimbursement and regulation. This affects not only research – the administrative enormity of organising multicentre trials – but also the flow of knowledge in the cancer community. A universal health system is too big a project, he acknowledges, but EU support for the EORTC research structure, which can function effectively in most EU countries, would go a long way.

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"Instead, you currently have all these national groups. There are too many presidents, too many clubs. The endeavour has become so complex that things are only going to move forward if we all pull on the same rope together – molecular biologists, pathologists, imaging, researchers, clinicians, computer technology, statistics, informatics..."

Stupp is restless for progress and the biggest frustration of his career has been the way that laws and people get in the way of new ideas: "There are too many egos, who ask 'What do I get out of it?' when you come to them with a new idea. That's not the question: the question is, what does it bring to the patient, to science?"

Throughout our interview, Stupp returns to the image of the patient sitting in front of him. What can he tell the patient with a brain tumour? What messages of hope? What quality of life? What expectation of cure or control? From the moment he was reluctantly pushed into neuro-oncology nearly 20 years ago, the politics, the research, the pursuit of academic and clinical freedom, have centred on that.

The number of patients with brain tumours may be small compared with other cancers, he says, but that does not make the need to pursue new options for treatment and quality of life, the need to overcome all those unnecessary obstacles, any less urgent.

"We treat patients, not numbers," he says. "Maybe when pharmaceutical companies are looking at the marketing potential for a new drug, the incidence is important. But when you are sitting in front of me, all that matters is you, a patient." ■

Approval rating: how do the EMA and FDA compare?

MARC BEISHON

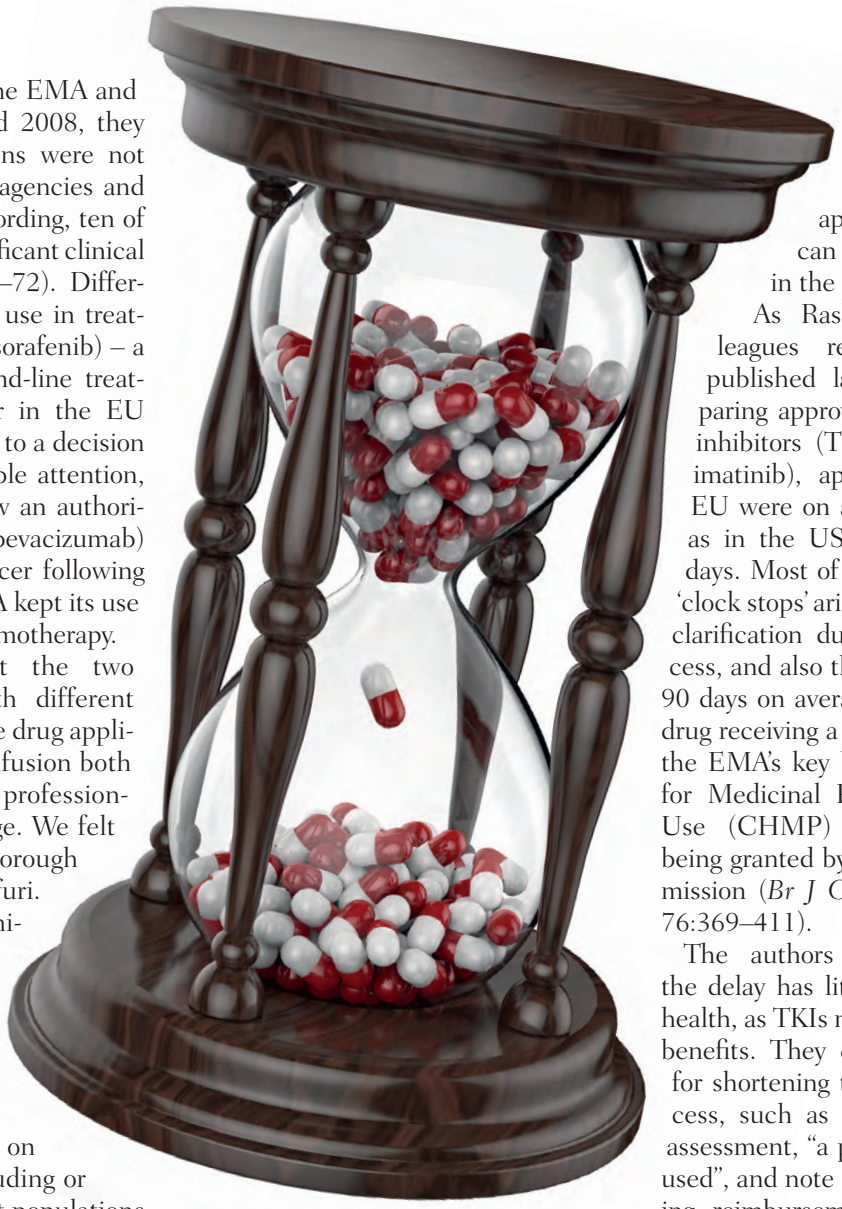
When new cancer therapies regularly become available more than half a year earlier in the US than in Europe, or get regulatory approval on one side of the Atlantic but not on the other, patients and clinicians want to know why.

Few issues in healthcare are as emotive as access to new cancer drugs, as they are often seen by patient advocates, politicians and the wider public as lifesaving treatments. In Europe, the agencies in the frontline of recommending drugs for use in national healthcare systems, such as NICE for England and Wales, bear the brunt of criticism for turning down drugs on cost-effectiveness grounds, and for slowness in considering new agents. But in the European Union, no oncology drug can even make it to this stage without marketing authorisation from the European Medicines Agency (EMA).

Since November 2005, all new cancer agents have to be approved centrally for the EU by the EMA, and there has been a growing interest from various players – national medicines agencies, the pharmaceutical industry and patient groups – in its decision-making processes and how they compare with what many consider to be the 'gold standard' approval body, the Food and Drug Administration (FDA) in the US.

While new drugs are often available in clinical trials, and existing drugs are sometimes used 'off label' in indications for which they have not been approved, widespread use and potentially massive financial returns to drug companies depend on precious marketing authorisations in Europe and North America, and increasingly in Asia. But despite the submission of identical drugs and supporting data from the same clinical trials to both the EMA and FDA, the two regulators can arrive at different authorisation decisions, both initially and when reviewing new data for an already authorised agent. In the past few years, a number of papers and editorials in oncology journals have looked at the reasons for the different decisions, as the answers are not immediately apparent – and even when subject to close scrutiny, authors have not been able to find clear predictors of regulatory outcomes.

But they have detailed differences that can affect clinical practice. When in 2011 Francesco Trotta and Giovanni Tafuri at the Italian Medicines Agency, and colleagues elsewhere in Europe, looked at 100 indications for 42 can-



cer drugs evaluated by the EMA and FDA between 1995 and 2008, they found that 19 indications were not approved by one of the agencies and 28 had different label wording, ten of which they said had significant clinical meaning (*JCO* 29:2266–72). Differences noted range from use in treatment, as with Nexavar (sorafenib) – a drug approved for second-line treatment for kidney cancer in the EU but first-line in the US – to a decision that attracted considerable attention, when the FDA withdrew an authorisation for using Avastin (bevacizumab) for advanced breast cancer following new data, while the EMA kept its use in combination with chemotherapy.

"The possibility that the two agencies come up with different decisions about the same drug application may generate confusion both at the level of health professionals and in society at large. We felt this topic deserved a thorough investigation," says Tafuri. "In particular, the definition of a therapeutic indication is a critical step in regulating medicinal products, and differences in the wording of indications can have a huge impact on clinical practice by including or excluding certain patient populations from the available therapies."

Most if not all of the differences in authorisations in oncology are not about drugs with clear efficacy benefits compared with risk, but concern agents where there is highly complex detail about narrow therapeutic margins between benefit and harm, so it may not be surprising that different committees of scientific advisors can in turn influence decision makers at the EMA and FDA to come down narrowly on one side or another.

Differences can also arise because of timing and the options open to the regulator, in particular the FDA, which is often the first to receive an application for a drug, and also tends to implement more fast-track and conditional procedures than the EMA (in 2012 the FDA was mandated that it could apply a 'breakthrough therapy' designation for serious or life-threatening disease). So new data can also appear during the gap between decisions by the two agencies, and certainly approvals in the EU can take a lot longer than in the US.

As Rashmi Shah and colleagues report in a review published last September comparing approval of tyrosine kinase inhibitors (TKIs, such as Glivec/imatinib), approval times in the EU were on average twice as long as in the US – 205 days vs 410 days. Most of the delay was due to 'clock stops' arising from requests for clarification during the review process, and also the time lapse – about 90 days on average – between a new drug receiving a positive opinion from the EMA's key body, the Committee for Medicinal Products for Human Use (CHMP) and final approval being granted by the European Commission (*Br J Clin Pharmacol* 2013, 76:369–411).

The authors also consider that the delay has little impact on public health, as TKIs mostly have only small benefits. They do make suggestions for shortening the EU approval process, such as by using accelerated assessment, "a procedure hardly ever used", and note too that actually gaining reimbursement for these often very costly drugs at national level is often a source of much longer delay.

Clinical relevance

This is not a static field. The EMA, FDA and others need to develop new processes to cope with a pipeline of new agents, such as immunotherapies, taking into account new science and different ways of quantifying and qualifying the benefit–risk balance. Relations with patient groups, as

"We try to communicate more transparently the data and justifications for the Agency's opinions"

well as health technology assessment (HTA) agencies are evolving – and the 'goalposts' for approving agents with only minor benefit may also be changing. As Markus Hartmann, of European Consulting and Contracting in Oncology, comments, it is just as important to be aware of how each regulatory agency is changing its own approach, rather than focusing purely on how their outcomes compare with those of their main counterparts.

"There is a big discussion about statistical significance versus clinical relevance, and it is now the case that, despite positive clinical trial outcomes, a drug company may not get marketing approval," he says. "A good example at the EMA is with Tarceva (erlotinib), which was finally approved by the agency for pancreatic cancer after a controversy about its very small but statistically significant gain of 0.3 months in overall survival. But then in 2009 the agency turned down Merck's Erbitux [cetuximab] for first-line metastatic non-small-cell lung cancer although there was similar significant survival data, from a phase III study including more than 1100 patients, demonstrating an overall survival gain of 1.2 months."

Hartmann, and colleagues from Merck, have since looked in detail at underlying parameters such as hazard ratios that could be a guide to when the EMA is likely to approve or not approve a new drug, and also when it could gain accelerated approval (*Crit Rev Oncology/Hematol* 2013, 87:112–121).

Francesco Pignatti, head of the EMA's section that coordinates marketing authorisations for oncology products, says: "A number of things have changed over the past 18 years or so since I came to the EMA. For example, the first assessment report produced by the Agency in 1999, for docetaxel, was only a few pages long. Now they typically run to hundreds of pages. I don't think the criteria for assessing oncology products have fundamentally changed, but we try to communicate more transparently the data and justifications for the Agency's opinions. This is continuing – we now have a proposal for making public, under certain conditions, the clinical trial data on which authorisations are based."

Transatlantic differences

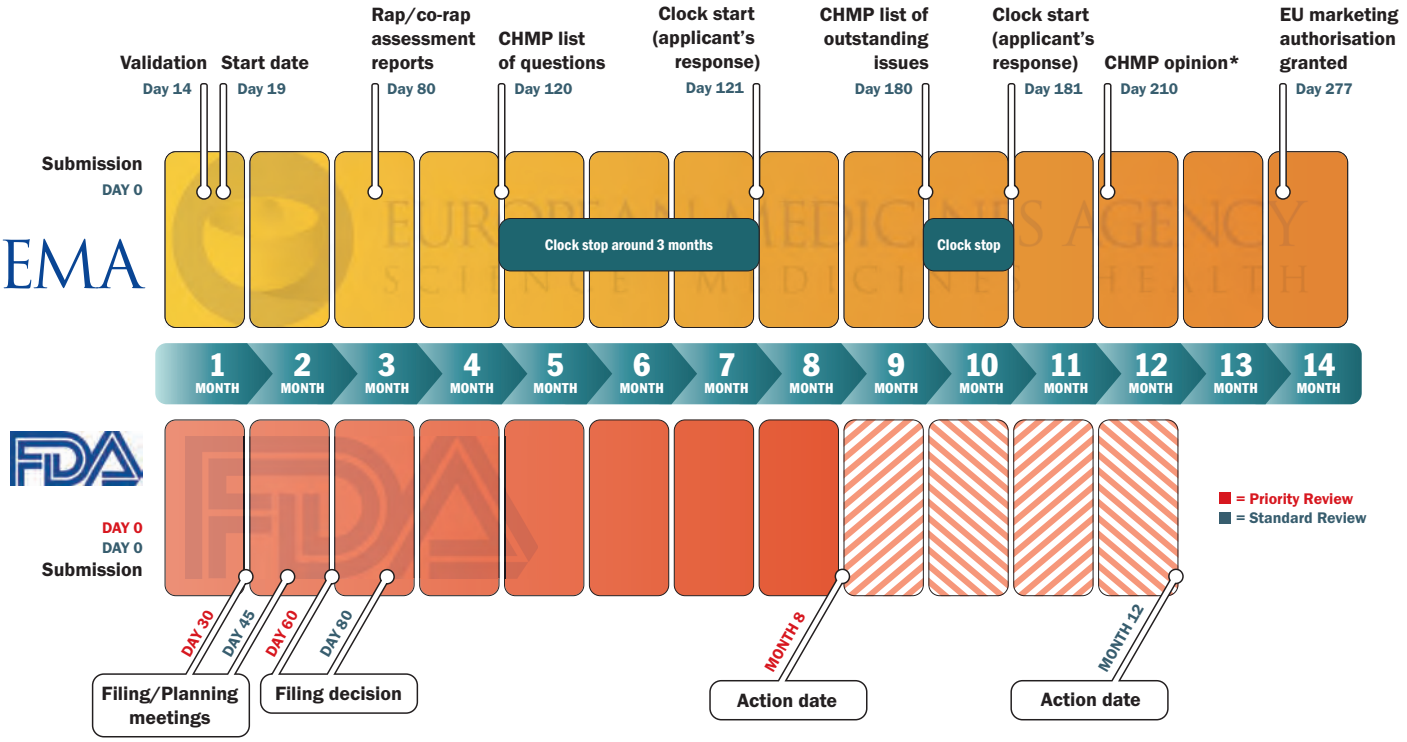
There are important differences to note with the FDA, he says. One is that it issues investigational status (IND) for new drugs in clinical trials – this is managed by member states in the EU. "A company can do all its development up until seeking authorisation without the EMA being actively involved," says Pignatti, who adds though that companies do ask for scientific advice during development, such as about clinical studies that have to be submitted, and about requirements for paediatric indications and orphan drugs. The EMA also manages a database of clinical trials.

"Another fundamental difference is after submission for authorisation – the FDA carries out its own analysis of patient-level data to replicate main analyses or to explore possible bias, sensitivity to assumptions and so on. We don't do that systematically – if we need to explore something, we generally ask the company to submit more details. Some have criticised us, saying that we should do similar in-depth analysis ourselves, but I can't say that is necessarily better – and if we receive an application after the FDA has done this, the process is partly redundant anyway, at least when replicating analyses. But it is possible we will do more of such analyses in the future, as we do of course receive some drugs for authorisation first."

There is a lot of collaboration between the agencies under a confidentiality arrangement. The EMA and FDA will give joint advice if requested by a company, and there are monthly teleconferences (also with Health Canada) in a so-called 'oncology cluster'. "We discuss issues such as ongoing drug application reviews, advice on clinical trial design, and when early approval mechanisms are being considered," says Pignatti.

One big difference between the EMA and the FDA is that the former is itself an exercise in collaboration. EMA's CHMP has members from all EU countries and is informed by statutory scientific advisory groups (made up of academic experts and patient representatives). With the expansion of the EU, inevitably it has a much more complex structure than the equivalent review group at the FDA.

As Tafuri explains: "The EMA is based on a network of national regulatory agencies, which has certainly



On average the EMA takes around six months more than the FDA to approve a new drug or new indication for a drug. This is mainly due to time lost to clock stop and the delay between getting a positive CHMP opinion and approval from the European Commission. Furthermore, in the US almost all cancer drugs are approved under priority review, whereas accelerated assessment is rarely used by the EMA

Source: CDER 21st Century Review Process (www.fda.gov); User Guide for Micro, Small and Medium-sized Enterprises (www.ema.europa.eu)
*Day 150 for accelerated assessment; Rap – Rapporteur

contributed to increasing the level of communication and harmonisation across national agencies. However, even between the EU member states, achieving harmonisation has often proved to be an onerous process, requiring legal referral and arbitration procedures for resolving disharmony." Tafuri and colleagues have also recently conducted a qualitative interview study concerning the assessment of cancer drugs as well as the reasons for regulatory divergence between the EMA and FDA, which he says will be published soon in *Annals of Oncology*. "Interestingly, we found that although factors related to the data package of the drug application are the main drivers for regulatory decisions, the influence of factors unrelated to the data, such as the level of interaction with external stakeholders (e.g. pharmaceutical companies or patients), as well as sociocultural and behavioural aspects, play an important role in the drug evaluation process."

EMA's Pignatti feels that, while cultural and political factors undoubtedly do play a part, given the diversity in Europe, "just small changes in clinical judgement can make the difference in approving drugs that have very narrow benefit–risk balance." As he says, weighing up multiple factors such as survival, symptom improvement, response, quality of life, toxicity and more is difficult, and expert judgment still comes into play.

When opinions diverge

Having said that, differences between the EMA and FDA, when they occur, can have a big impact and also result in heated debate. The decision on Avastin in breast cancer is one with major implications, given the prevalence of the disease. Pignatti says that, in his view, although both agencies consider progression-free survival (PFS) as a reasonably likely surrogate endpoint, "we considered that PFS could be a relevant clinical endpoint in its own right – this has been clear in our anticancer guideline for many years. It won't have the same weight as overall survival, but still some weight." The FDA, in contrast, when sufficient benefit in overall survival did not

"It may be time to take a hard look at whether PFS can be used as a primary efficacy endpoint in a specific setting"

materialise in further trials, and given the toxicity profile, took the view that Avastin should be withdrawn for the combination indication (with paclitaxel) for metastatic breast cancer.

But in another case the EMA did not approve Avastin, this time in recurrent glioblastoma, as it was not convinced by phase II trials and the efficacy data that led the FDA to grant accelerated approval. There have been outspoken views on this, with one US proponent having said the data is "unchallengeable", while European experts said there were too many unanswered questions and that accelerated assessment on uncontrolled trials could set bad examples for drug development.

Both Pignatti and Hartmann comment that there is little evidence that one agency is more conservative than the other, given the diversity in judgements where there is a difference, and that in most cases the decisions reached are the same. Everyone in oncology is grappling with how to assess clinical relevance, says Hartmann, and there will be increasing pressure to introduce new drugs earlier in treatment lines for ethical reasons, but this will make overall survival harder to assess for a certain agent and puts more emphasis on wider quality-of-life benefits and surrogate measures of possible success.

At present, Pignatti says, the FDA does tend to look at PFS as a likely surrogate for overall survival and requires confirmation of this, as in the Avastin breast cancer case, unless the effect on PFS is very large. The EMA, however, takes a slightly different approach. "Our scientific advisory groups, oncologists and patients have said that it is valuable for a patient to delay disease progression and likely worsening of symptoms, and not to have the anxiety of a doctor telling them the tumour is progressing and maybe then having to switch to a less effective therapy. We don't put a limit in terms of minimum clinically relevant effect size for PFS, as this depends on the balance with the risks."

Tafuri adds: "It may be time for the oncology community and regulatory agencies to take a hard look at PFS and reflect on whether this can be used as a primary efficacy endpoint in a specific oncology setting."

As Hartmann says, this can also be seen as part of a move to incorporate patient groups much more in evaluating what factors are important in the benefit–risk assessment of drugs. The EMA will be adding an appendix on quality of life and patient-reported outcomes to its main guideline, 'Evaluation of anticancer medicinal products in man', and last summer the FDA started a series of public workshops on understanding patient needs.

In September, the EMA also held a workshop that explored ways to further involve patients in the benefit–risk assessment of medicines. Currently there are no patient representatives on the main committee (the CHMP), but Pignatti stresses they are on scientific advisory groups and on some committees, such as for pharmacovigilance risk assessment and orphan medicines.

Engaging with HTAs

And all patients and oncologists are concerned about the health technology assessments and cost–benefit evaluations of drugs – because they are often approved only to be turned down by reimbursement and HTA agencies on the grounds of cost-effectiveness. As Olli Tenhunen, an oncology specialist at the Finnish Medicines Agency, comments: "There is more to be done in terms of reimbursement procedures and HTAs. These are not harmonised in Europe, and there seems to be a significant gap between the marketing authorisation and national reimbursement."

While it is not part of a medicine regulator's remit to consider cost-effectiveness, the EMA does engage HTA organisations in so-called parallel scientific advice for drug development, and there is ongoing work, including pilots with the European Network for Health Technology Assessment (EUnetHTA), to address concerns that "sponsors are not sufficiently addressing the varying evidence needs of payers and healthcare-guidance and HTA bodies in their medicine-development programmes".

Hartmann says that the need for them to do so is increasing following legal initiatives such as the Cross-Border Healthcare Directive (which came into force in October 2013, and has an HTA component informed by the EUnetHTA). There is also now a need, he adds, to include a relative effectiveness assessment in risk management plans for drugs, which also

also points to such assessments being explained more fully in submissions to the EMA. He notes too that in the US there is now a legal basis for comparative effectiveness research, and the FDA is empowered to enforce the conduct of post-marketing studies and to assess effectiveness data after approval.

Transparency and trust

If the greater emphasis on HTA is one big point, another major move on both sides of the Atlantic is indeed to upgrade the frameworks for benefit–risk assessment for qualitative as well as quantitative approaches. Pignatti confirms this is the case for the EMA. "We are piloting a new template on benefit–risk so that the CHMP can be more explicit about the reasons that matter for the evaluation, and about where there are value judgements," he says.

Most important, says Pignatti, is the need for trust and transparency to be at the heart of regulation, which is why the EMA is pressing ahead with a draft policy on publishing the clinical study reports on which it bases its assessments. "At present these are either not released or only with big redactions, and we feel we can address concerns about commercial confidentiality, inappropriate analysis and data protection. We think the release of these data can be managed so that it adequately addresses these concerns while allowing secondary analysis to scrutinise the regulatory process but, more importantly, to generate discovery about other factors such as prognostics, which will move forward the development of new drugs. Industry will have a lot to benefit from this as well."

Tenhunen, who has commented on 'how to assess assessments' in *Annals of Oncology* (2013, 24:1138–40), says that regulators will have difficulties achieving "a delicate balance between transparency, legislation, interests of patients and healthcare professionals as well as those of the industry". A 'one size fits all' regulatory approach will not work, he adds, especially with complicated new products such as Glybera (alipogene tiparvovec), the first gene therapy approved in the EU.

Tafuri's prescription for better communication of processes and opinions includes the attendance of EMA regulators at FDA public hearings or of FDA staff at CHMP meetings. "This would certainly help mutual understanding of different regulatory systems and improve harmonisation."

"With regard to transparency," he adds, "all agencies should provide public access to the data and results from clinical trials on which regulatory decisions are based, and to committee minutes and public reports about the reasons why certain procedures for the approval of new active substances and indications result in either a successful or a failed application. Communicating the rationale of benefit–risk decisions to the public is crucial to promote trust in the regulatory system." ■

TIME TO APPROVAL (DAYS) FOR TKIs IN THE EU AND US

	EMA[a]	FDA
Axitinib	503 (401)	288
Bosutinib	n/a [b]	292
Crizotinib	453 (357)	149 [c]
Dasatinib	312 (252)	182 [c]
Erlotinib	389 (301)	111 [c]
Gefitinib	414 (352)	273 [c]
Imatinib	255 (147)	72 [c]
Lapatinib	614 (434)	181 [c]
Nilotinib	410 (350)	396
Pazopanib	472 (356)	304
Regorafenib	n/a [b]	153 [c]
Ruxolitinib	449 (323)	166 [c]
Sorafenib	315 (232)	166 [c]
Sunitinib	323 (240)	168 [c]
Vandetanib	535 (443)	273 [c]
Vemurafenib	290 (226)	111 [c]
Mean (range)	409.6	205.3 (167.1[c])

[a] Numbers indicate time to final approval from the European Commission, with time to positive opinion from EMA's Committee for Medicinal Products for Human Use given in parentheses; [b] under review at time of publication; [c] Priority review procedure used

Source: Adapted from RR Shah, SA Roberts and DR Shah. (2013) *Br J Clin Pharmacol* 76:369–411

Challenging the sceptics with stories of hope

PETER MCINTYRE

It was stumbling across a poster for a meeting about cancer in the developing world that turned journalist Joanne Silberner from a sceptic into a believer, and prompted her to do her bit to change fatalistic attitudes about tackling the disease in poorer countries.

Outside a cancer outpatient centre in Kampala, Uganda, the sound of women sweeping paths with brushes made of twigs; inside the Fred Hutchinson Cancer Research Center in Seattle, the hum of a centrifuge. Journalist Joanne Silberner hears the soundscape as a metaphor for the technological gap between a state of the art centre and the basic service in a developing country, available only to the most fortunate of patients.

But the story that Silberner tells is not only about contrasts. She has highlighted collaboration and a sense of optimism as the world starts to address cancer in low- and middle-income countries, where it causes more deaths than AIDS, malaria and TB combined, but receives a fraction of their funding.

For her series entitled "Cancer's New Battleground – the Developing World", on Public Radio International, and for supporting pieces in the *Seattle Times* and on KUOWradio,

Joanne Silberner

Silberner was named one of the two joint winners of the European School of Oncology's Best Cancer Reporter Award for 2013. Silberner receives €5000 for the award that recognises the focus she brought to the growing crisis of cancer in developing countries, the neglect that surrounds this issue and the need for urgent action.

However, this prize-winning series nearly did not happen. Silberner, who reported for National Public Radio in Washington DC for 18 years, now freelances in Seattle and sees her mission as exploring neglected health topics. She has covered tropical diseases and mental health, but cancer almost got away.

"I saw a poster for a meeting at the Fred Hutchinson Cancer Institute about cancer in the developing world. Seattle is very globally orientated; people think they can save the world. But when I saw this poster I thought this is crazy – nobody lives long enough in the developing world to get cancer, and even if they did, there is no way you can get the technology to treat them. So I went to this symposium thinking they will have nothing to say.

"I was absolutely stunned to hear how many cases of cancer there are, and the lack of treatment, but also the possibility and ease of treatment.

I heard that the success rate is not zero – there is a real difference you can make even in a developing country."

She looked to see who was reporting this and found some pieces in the *New York Times* which seemed only to emphasise the awfulness, "five anecdotes in a row of people dying in front of the reporter's eyes." She knew she wanted to do something different, "to show that at least there is something that can be done if people get interested."

With financial support from the Pulitzer Center on Crisis Reporting, Silberner visited Uganda. She met Jackson Orem, who had studied in the United States but returned to pioneer cancer treatment and, for a while, was the only practising oncologist in this country of more than 30 million people. Even today, 20,000 of the 22,000 patients attending the Uganda Cancer Institute each year die within a year. Orem and his five new oncologist colleagues have been able to offer mainly pain relief and care.

An increasing priority

That is changing through a link with the Hutchinson Center, which includes exchange visits, research and training, and with a higher priority from the Ugandan government, which commissioned a 200-bed specialist hospital. Although some Ugandan languages still have no word for cancer, awareness is growing and so are treatment options. "The truth of the matter is that cancer is a disease of the African person just like any other person elsewhere in the world," Orem told her. "People are much more receptive to our messages than before."

JACQUELINE KOCH/FRED HUTCHINSON CANCER RESEARCH CENTER

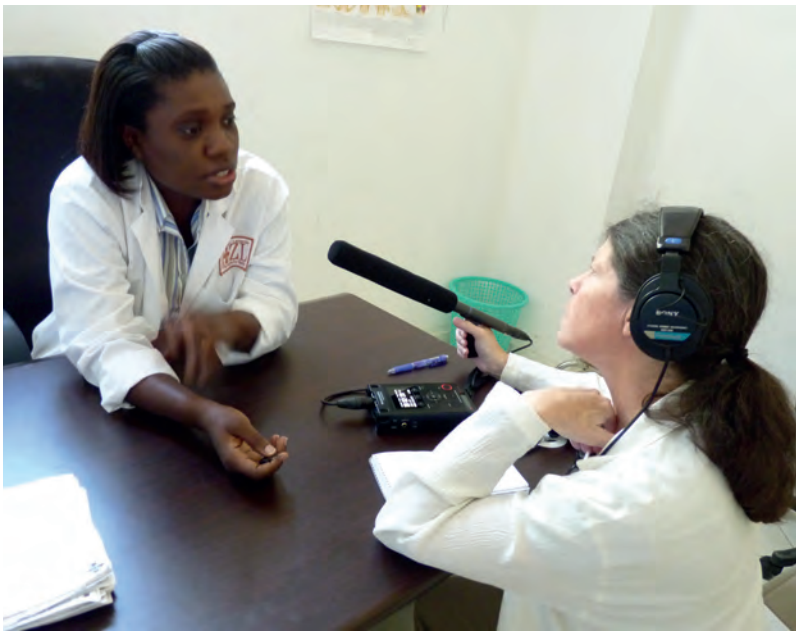
Wanted: a vaccine. Silberner's coverage of cancers with infectious causes spotlighted Burkitt's lymphoma, the most common childhood cancer in sub-Saharan Africa, caused by the Epstein-Barr virus

Silberner's visit provided the basis for the first of her PRI broadcasts in December 2012, entitled "Cancer's Lonely Soldier". She followed this up with a piece focused on viral cancers, including Burkitt's lymphoma – the most common childhood cancer in sub-Saharan Africa – and Kaposi's sarcoma, which is often found in people with HIV infection. She also highlighted the difficulty in accessing morphine, although the drug is a cheap and effective way of controlling pain. Silberner cited the chilling World Health Organization statistic that more than five million people with cancer die in pain each year.

She wanted to do something different to show that something can be done if people get interested

Some Ugandan languages still have no word for cancer, but awareness is growing and so are treatment options

STORIES FROM THE FRONTLINE



ANSEL HERZ

Silberner interviews oncologist Ruth Damuse about the breast cancer service she and her colleagues provide in a small town in Haiti

Silberner's series on Cancer's New Battleground gave doctors and patients the chance to tell the story of the suffering that cancer causes in developing countries and the low-tech cost-effective ways they are finding to help tackle it.

Cancer World, published by the European School of Oncology, promotes the need to address cancer in low- and middle-income countries, as this is where almost two-thirds of cancer deaths occur. In a further recognition of the role of the media in making this health challenge a priority, ESO judges gave special merit awards to two African journalists: Esther Nakkazi from Uganda, who reported on innovative ways to communicate health information, and Busani Bufana from Zimbabwe, who also highlighted the desperate need for pain relief.

In Haiti, Silberner accompanied oncologist Ruth Damuse from the local group Zanmi Lasante on International Women's Day as she spoke to women about the need to report symptoms in a country where 50% of women diagnosed with breast cancer present too late for their lives to be saved. We hear medical staff in Haiti consult colleagues at the Dana Farber Cancer Institute in Boston on a speaker phone, receiving advice that is tailored to available technology and chemotherapy. This link was established by the US charity Partners in Health, and the head of their cancer programme, Sara Stulac, insists that treatment can save lives as well as reduce suffering. She points out that AIDS drugs were once considered too costly and difficult to deliver in developing countries, yet millions of people with HIV in Africa and Haiti are now routinely treated.

In India, Silberner saw the use of acetic acid (vinegar) to test women for the early signs of cervical cancer, and heard how teams from the Tata Memorial Hospital in Mumbai and Walawalkar Hospital in Maharashtra have worked patiently with women and men in rural communities to overcome cultural obstacles to testing, setting up all-female teams and offering a range of other health tests as well as vaginal examination. After eight years, they are succeeding in finding early-stage pre-cancers that can be easily treated.

In pieces for radio, newspapers and the Internet, Silberner found the positive as well as the negative and focused on the role of the local health teams in leading the bid to diagnose and treat cancer, with support from partners in the US.

Hundreds of public service radio stations broadcast *The World* from PRI, and Silberner's reports also ran on the BBC World Service website, where they received an enormous number of hits. Silberner has been very encouraged to see how much interest they have aroused. "The way

that cancer is explored in the media here in the US is in terms of new high-tech treatments, the cost of treatment, and people who cannot afford treatment or drugs. It is not the developing world issue.

"Just talking about the issues is really important to people working on cancer in developing countries, because it is tough trying to get a programme going if nobody seems to care. The series told people in the field that this is a subject people are learning about."

Shining a light on unreported suffering

For Silberner, the Best Cancer Reporter Award was one of a clutch of prizes related to her work. Together with her producer and editor David Baron, she received the TV and radio award from the US National Academy of Sciences, "for shining a light on the hidden toll cancer takes in impoverished nations". Silberner also shared the 2013 Victor Cohn Prize for Excellence in Medical Science Reporting from the Council for the Advancement of Science Writing for her consistent record in "recognising new angles in important stories rather than offering stories that everyone else covers". *The World* pieces were a major factor, cited for "sparkling storytelling and the human dimensions".

Silberner came to journalism late and reluctantly. Her ambition was to be an endocrinologist and study the beauty of hormones. She studied at Johns Hopkins and was delighted that she did not have to write essays to get in. "I had no intention of writing ever," she says firmly. In her final year, she had to add one extra module and "completely by accident" added a course in scientific writing. Despite praise and support from her professor, her professional experience was limited to writing the labels on fish tanks during an internship at the Scripps aquarium in San Diego! After a spell analysing health and scientific bills for the California state government, she accepted her destiny and went to journalism school. After graduation, she reported on science for magazines before joining National Public Radio.

Silberner is still committed to neglected health topics, recently researching stories about diabetes and high blood pressure in Cambodia. So will she write further about cancer? "I would love to. I just have to figure out a way to do it and for somewhere to publish my stories."

The good news is that Silberner does not just write and broadcast. She also now teaches journalism at the University of Washington – inspiring others to find and tell neglected stories. ■

Joanne Silberner's series was broadcast over five programmes in December 2012 on Public Radio International's *The World*. Hosted by Marco Werman and heard on more than 300 stations across North America, *The World* is a co-production of WGBH/Boston, PRI, and the BBC World Service.

JACQUELINE KOCH/FRED HUTCHINSON CANCER RESEARCH CENTER

We can help. The Uganda Cancer Institute in Kampala cares for hundreds of young leukaemia patients like four-year-old Swabura Namiiro; the opportunity to meet other patients with the same disease gave the family "a sense of support and strength"

Five steps to putting innovation at the heart of cancer care

ANNA WAGSTAFF

With health budgets flat-lining and demand for healthcare rising, the only way Europe can improve patient outcomes is by finding new ways to do things better. But who will champion innovation in cancer care and how? The European School of Oncology convened a Task Force to come up with some solutions.

If reimbursement authorities in Europe decline to invest in innovative treatments, they not only deny patients access to treatments that could benefit them, but risk seriously slowing the pace of progress in the fight against cancer. So claims the pharmaceutical industry, increasingly frustrated at obstacles in the way of getting new products accepted for reimbursement and adopted into clinical practice.

Cancer is not the only serious or widespread health problem that requires innovative solutions, retort the payers, and medical therapies are not the only way to improve outcomes. The cost of new cancer therapies is rising faster than any other class of medicine, without a commensurate increase in benefit. We cannot justify putting money into new cancer drugs if the money can be spent to greater effect elsewhere.

Both make valid points. In a future when health budgets will struggle to keep pace with rising demand, investing in new and better ways to care for patients – and decommissioning interventions of poor value – is the only hope of improving outcomes. But ensuring that limited funds are put to best possible use requires making good choices about innovations and evaluating their true worth as they are developed and rolled out across health services.

There is an important discussion to be had about how health systems can best combine value for money with the flexibility to foster innovations and evaluate what they can contribute. However, the pharmaceutical industry cannot have that dialogue alone. Everyone involved from early detection and diagnosis, through planning and implementing treatment and care, to rehabilitation should be involved.

To broaden this discussion, the European School of Oncology (ESO) initiated an Innovation Task Force, where experts in health economics and health technology assessment sit with patient advocates, clinical researchers, cancer nurses, and representatives from companies involved in developing cancer drugs and diagnostics to learn from one another about how innovation is promoted, funded, evaluated and brought into clinical use and to find points of consensus about how to improve the process.

Towards an innovation-friendly cancer care system

When the ESO Task Force met for the first time in full in October 2013, it started by defining what they were talking about. Innovations in cancer care, they agreed, must address real unmet need in a measurable and sustainable way, or offer a cheaper

or faster way of providing equivalent benefit to a currently available alternative, thereby freeing up resources that can be reinvested. Products can be innovative, but so can techniques and ways of organising and delivering care. Their value is measured in terms of the overall benefit they bring to the lives of patients and the overall cost/savings to the health system and society.

Understanding the priority needs of different groups of cancer patients must be the starting point for any health system looking to improve outcomes through innovation, they agreed.

Step 1: Research unmet needs

Cancer patients need treatments that are accessible, effective, safe and give good quality of life. How well those needs are met, and where patients' priorities lie, vary between cancers and change over time as successful innovation meets the most pressing needs.

Three decades ago, for instance, the priority in childhood cancer was improving survival. Today, when four out of five children with access to high-quality treatment survive, the priority is to reduce toxicity and particularly the long-term effects. This was not fully appreciated until a group of researchers at a US children's hospital asked the right questions. Their study of more than 1700 survivors of childhood cancers, published in *JAMA* this year (vol 309, pp 2371–81), revealed that 98% had at least one chronic health condition, and that by age 45 about 80% had at least one life-threatening, serious, or disabling condition.

In breast cancer, by contrast, 25 years ago patients reported nausea and vomiting as their biggest problem. Today, research done by the New South Wales Cancer Council in Australia, for instance, records access to car parking as the most frequently mentioned issue.

This is not as silly as it may sound, says Paul Cornes, a clinical oncologist at the UK's Bristol Oncology Centre, with a special interest in health economics. "You have a treatment [radiotherapy] that takes five or ten minutes, and needs to be done daily for many weeks, and it's an imposition on people's lives." He points to a number of studies that have correlated acceptance of radiotherapy for breast cancer with the time it takes to commute to and from that treatment (e.g. *Cancer Causes Control* 17:851–856).

"It's been done in different countries, and we know that the effect is also higher in winter, when travel is harder. So you can demonstrate that something people may laughingly dismiss, like car parks, has a real impact on patients."

Health systems aspiring to get the best possible outcomes must do more to encourage systematic research into patients' priorities across all cancer types, says Cornes, and use those findings to inform their decisions. When evaluating the option of delivering radiotherapy over a shorter period or using medical therapies that can be delivered orally, for instance, the impact on convenience to patients should be taken into account.

Trials must seek to show clinically relevant benefit not just statistical significance

Giampaolo Tortora

Chair of ESMO's Translational Research Working Group

Step 2: Support an innovation culture

Encouraging all professions in the patient pathway to look for better ways to do things as a standard part of their work, was seen as the next step for building innovation into the system. Avoiding regulations that load unnecessary cost and bureaucracy onto even the most simple clinical studies was an obvious point here. As Matti Aapro, chair of the Task Force and Dean of the Multidisciplinary Oncology Institute in Genolier, Switzerland, commented, teams that want to try out potentially better ways of doing things, however innocuous, can quickly fall foul of the rules. "If you call it a study, regulators make your life a misery," he said.

Improving the coordination and planning of trials was identified as important to reduce duplication, improve trial design and make it easier for patients to enrol. This is an issue that some European countries are already tack-

Patients can advise on whether the innovation you are developing corresponds to real need

Kathy Oliver

Co-Director of the International Brain Tumour Alliance

ling, with national trials structures and networks. Giampaolo Tortora, chair of ESMO's Translational Research Working Group commented that trials don't always take into account the latest biological information and are often more concerned with showing statistical significance than meaningful clinical benefit. Kathy Oliver, a patient advocate who is Co-Director of the International Brain Tumour Alliance, said the latter problem could be avoided if trialists consulted patient groups at the design stage. "So often people consult patients when it's already too late," she said. "If you ask their views at the start, they can advise on whether what you are proposing corresponds to real need and how best to show that."

Taking a broad view of where innovation can come from was seen as an important element of developing an innovation culture. Few people anticipated that adding early palliative care to standard treatment in patients newly diagnosed with metastatic non-small-cell lung cancer would extend patients' lives by more than two months, until the Temel study asked the question (*NEJM* 2010, 363:733–742).

This unexpected finding raises questions about whether other opportunities are being missed to improve patient outcomes because of assumptions about the relative value contributed by the different professionals involved in caring for patients, including those working in a largely supportive role. As Birgitte Grube, past president of the European Oncology Nursing Society, pointed out, this in turn raises questions of whether the cuts in nursing posts that are happening across Europe might be based on assumptions rather than real evidence about the value nurses contribute to patient outcomes.

Innovatory concepts and processes can also make a huge difference to patient outcomes, as multidisciplinary teams have shown

Peter Naredi

Former President of the European Society of Surgical Oncology

Peter Naredi, past president of the European Society of Surgical Oncology, pointed to another aspect of cancer care whose potential for improving outcomes is often overlooked: namely the way care is organised and delivered. Naredi knows about innovation: he pioneered new techniques in liver and pancreatic surgery and promoted the systematic uptake of new techniques in treating rectal cancer in his home country of Sweden. But at the Task Force, he singled out tumour boards and multidisciplinary teams as having the greatest potential to improve outcomes, because they ensure that treatment decisions are not made by the first specialist who sees the patient, without input from other professionals.

Working in multidisciplinary teams, it was noted, can also facilitate a patient-centred team approach to improving patient outcomes. Though as Grube, speaking from the cancer nursing perspective, pointed out, for this to work well, each profession in the multidisciplinary team must have knowledge and respect for others' roles and responsibilities.

Cancer plans – which take a system-wide joined-up approach to assessing needs and delivering services – and registries – which provide information on outcomes – can be added to the list of concepts that have potential to yield substantial benefits for patients, as can guidelines to document and spread best practice, benchmarking, performance monitoring and audit.

Step 3: Introduce early and evaluate effectively

Intuitively, it might make sense to evaluate first and introduce later, but the Task Force concluded that this is impractical in cancer because of the complex interplay between different contributions to patient care and the variety of costs and benefits to be taken into account. Innovations also typically evolve rather than emerging fully fledged, so deciding at what point in their evolution they should be evaluated is a matter of judgement.

Each profession in the multidisciplinary team must have knowledge and respect for the others' professions, roles and responsibilities

Birgitte Grube

Former president of the European Oncology Nursing Society

That is not to say that innovations should be introduced before they have been shown to be safe and effective – something that the Task Force noted is currently mandatory only for medical therapies. However, the overall value can only become apparent when the new product, technique or process becomes fully integrated within the patient pathway, used in a non-selected patient population in a real-life setting, where the benefits and costs to patients and the health system can be measured against the alternative it may replace.

As Aapro, chair of the Task Force, put it: "Something potentially innovative is introduced into a whole pathway, from diagnosis through decision making and all the different modalities of treatment through to palliative care, or rehabilitation and so on. Whether or not it actually turns out to be innovative depends on how it plays out within that whole context."

How is the evidence gathered?

Evidence to show how innovative therapies do "play out" in real-life settings is increasingly being demanded by payers in addition to data required by the regulators for marketing approval. Pharmaceutical companies have accordingly started to invest in registries to gather the required information from centres where their new product is in use.

They are also trying to integrate the gathering of 'value' data into the development process to ensure it is available as soon as possible after a product gets regulatory approval. Joerg Adamczewski, Project Head for Oncology Development at Sanofi, said that an increasing willingness by payers to interact with manufacturers early in development to provide guidance is very welcome. "We hope this engagement will allow us to work with payers to develop a definition of value that incorporates unmet need, the level of scientific innovation, and the impact that the drug has on the lives of patients and caregivers," he said.

The problem is that getting Europe's various decision makers to agree on similar measures of costs and benefits is turning out to be a major challenge.

We welcome greater dialogue with payers and want to work with them to develop a shared definition of value

Joerg Adamczewski

Project Head for Oncology Development at Sanofi

This has big implications for the practicalities of demonstrating to payers the value of an innovation, because every country – and sometimes each region or even individual hospitals – demand different sets of data relevant to their own needs.

Agreeing on the seriousness of toxic side-effects from a medical perspective is more straightforward than assessing the cost to a patient of diarrhoea, bloating, anxiety, or disruption to daily life. Though progress towards a common evaluation has been made, for instance with a variety of quality of life 'instruments' validated across many European countries, these are too blunt to capture the level of detail for assessing the added value of most innovations.

One innovative approach to gathering quality of life information, which is about to be piloted in conjunction with the UK national brain tumour registry, was mentioned by Kathy Oliver. It involves an online Brain Tumour Patient Information Portal, where patients can access their own clinical and pathological records, but can also contribute information (www.nbtr.nhs.uk/patientportal.html). "Patients can feed in information about side-effects and give feedback on what they think has been innovative about treatments. This is hopefully something that will be rolled out to other site-specific cancers in the future," she said.

The impact on cost/savings of introducing an innovation will also play out differently, for instance, according to whether care is primarily delivered by doctors in a hospital setting, or greater use is made of specialist nurses in an outpatient or community setting, and according to the levels of sickness ben-

Systems are already in place to coordinate certain aspects of health technology assessment, it is up to Member States to make better use of them

Finn Kristensen

Chair of EUnetHTA

efit, rights to social care and so on.

One suggested solution to reduce the proliferating demands for different types of data lies with greater coordination in the analysis of new health technologies across Europe.

A more strategic approach to developing registries is needed to facilitate gathering evidence on value in a real-life setting

Yolande Lievens

Head of radiation oncology, Ghent University Hospital

The foundations for this have already been laid through EUnetHTA, a network of European health technology assessment (HTA) bodies, set up in 2009 with a mission to develop reliable, timely, transparent and transferable information to contribute to health technology assessments in European countries. Finn Kristensen, chair of EUnetHTA, freely admitted that it will never be to HTA what the centralised procedures of EMA are to drug regulation, as there are obstacles even at the level of national legislation to getting countries to work together in HTA as closely as in drug licensing. However, he felt that EUnetHTA is an underused resource that could play an important role in improving the way Europe evaluates innovation in health. "There is a lot more that we can still agree on about how we assess quality of evidence from a scientific point of view. It is now up to the cancer community to say to Member States: we have a problem, and you need to use this HTA network more!"

Greater investment in registries to gather real-life outcome data was also suggested as essential to improve capacity for evaluating the impact of innovations. There could be potential, for instance, for companies to collaborate more in running multi-sponsor registries for particular disease groups.

This is not just an issue for pharmaceutical companies, however, as Yolande Lievens, head of radiation oncology at Ghent University Hospital in Belgium, pointed out. She and her colleagues are currently running a registry to evaluate which patients benefit from being treated with stereotactic body radiotherapy, which uses advanced image guidance to pinpoint beams on the tumour. As this is more about techniques than equipment, manufacturers don't have an incentive to cover the cost of gathering evidence. To avoid delaying patient access to these promising techniques until they are included in formal reimbursement schemes, the Belgian government has therefore agreed on provisional financing of the treatment and the registries for four years while further evidence is gathered and analysed. This programme is being run in collaboration with the Belgian health insurance and cancer registry.

Lievens suggests a more strategic approach to developing registries – involving collaboration between industry, the academic world and professional societies – will be key to developing Europe's ability to evaluate and promote innovation.

When is the evidence gathered?

Given that innovation is a process that can take decades to mature, the question arises of when decisions are made. A decision made too early, before clinical researchers have time to learn how an innovation can best be integrated with other treatments and which patients derive the greatest value, could kill off something that would yield beneficial results. Wait too long and patients will be deprived of access to something that could benefit them.

Lievens said that this was a problem with the stereotactic radiotherapy techniques she is now evaluating in Belgium, because progress was incremental. "If you look back you can say that from cobalt to linacs was a very important change. Or when we started to use CT scans to plan conformal treatment, that marked an enormous change. But at the time it was insidious. It wasn't obvious. It's only years afterwards that you can look back and say that was really an innovation."

One consequence, said Lievens, is that there is often a serious delay from the time the technology is developed at research centres to the point at which it is introduced and reimbursed in daily care. To ensure quicker patient access to new technologies, she suggests greater use of "coverage with evidence development" programmes like the one she is involved in for stereotactic body radiotherapy. Funding could come from government, industry or other sources, and should be made available to introduce the innovation into clinical practice – perhaps at selected cancer centres – at an early stage of technology development. "In return, providers to whom the new technology is made available, should commit themselves to generating cost and outcome data, necessary for well-timed economic evaluation and health technology assessment."

These sorts of approaches are

beginning to be used more widely in some European countries. In Germany, for instance, under the 2011 Reform of the Market for Medicinal Products law (AMNOG), reimbursement of a new medical therapy is guaranteed at the manufacturer's price for 12 months from the day it gets approved by the EMA. A cost-benefit evaluation of the therapy is then done by an umbrella body of health insurance funds, in collaboration with the HTA body IQWiG. The final reimbursement price is negotiated at the end of the 12 months, according to the evidence on whether or not the therapy adds value in some way (and for which patients) compared to the currently used alternative.

The UK, meanwhile, has launched a Commissioning through Evaluation programme, that will allow certain treatments that show "significant promise in terms of improving quality of life or potentially survival, but [are] not accessible through a formal research trial," to be funded in a small number of participating centres, and within an explicit evaluation programme.

Who decides, and how?

Promoting innovation that benefits patients – and cutting spending on things that add no value – is about making informed judgements from a system-wide perspective. In practice, as the Task Force heard from many participants, this is not always the way decisions are taken.

Lack of understanding of the real issues was seen as a big problem, particularly when decisions are made by doctors with no background in health technology assessment and health economics. "Typically decisions are often made on budget impact rather than clinical effectiveness or cost-benefit," said Daniel Schneider, Senior Director EMEA [Europe Middle East and Africa] Sales and Marketing at the diagnostics company, Genomic Health. This is a particular issue for innovation in diagnostics, he added, because "it is the physicians who drive the process, so in many countries we are reliant on the physicians to apply [for reimbursement] for us."

Typically decisions are made on budget impact rather than cost–benefit

Daniel Schneider

Director, EMEA Sales and Marketing, at Genomic Health

Statistics from France, on the cost–benefit of screening lung cancer patients for the EGFR mutation illustrate the dangers of focusing on costs alone – studies have shown that while the health system spends around €1.7 million a year on the diagnostic procedure, €69 million is saved by ensuring that patients without mutated EGFR are not treated with a tyrosine kinase inhibitor.

The Task Force also heard how sometimes even the more established HTA bodies fail to grasp, for instance, the way statistical significance works. "They say 'We will look at the 25% of patients who interest us from this trial.' But when it is only 25%, the effect is no longer statistically significant, as the number of events becomes too small! So they conclude 'You have not demonstrated anything relevant from the trial.'"

Lack of understanding about cancer among many decision makers was felt to be an equally serious problem. Progress over past decades has tended to result from incremental advances in every part of the treatment pathway, as clinicians learn to combine them to greatest effect and in the right patients. People who are not familiar with this may be less inclined to give new products and processes the chance to prove themselves. People who are not familiar with cancer can also underestimate the difference seemingly "little things" can make to quality of life and/or adherence, or what a difference a few additional weeks of life can make to some people. They may adopt a more defeatist attitude; a greater tendency to assume that cancer is a 'hopeless case' and that investing in things that are not clearly 'breakthroughs' is a waste of resources.

We are asked to show evidence of overall survival benefit, but is the same demand being made in other areas of health spending?

Matti Aapro

Chair of the Innovation Task Force

Greater consistency and streamlining of decision making was also seen as an issue. Task Force chair Matti Aapro questioned whether treatments for other diseases have to fulfil the same stringent criteria as new drugs for cancer.

20 STEPS TO PROMOTE INNOVATION

FOCUS ON UNMET NEED

- Invest in researching patient needs, in different cancers, with a view to developing a broad picture of patient priorities. Focus the research along the whole pathway of care, including how the care is organised, delivered and evaluated, looking at issues during diagnosis/treatment/care, but also after treatment.
- Seek patient input as early as possible in the innovation process.

PROMOTE AN INNOVATION CULTURE

- Develop a system-wide strategy for investment in innovation that fits needs. This requires a joined-up approach involving people responsible for developing and implementing cancer strategies/plans, those involved in developing innovation, and the payers who take decisions on reimbursement.
- Implement patient-centred multidisciplinary teams, where all professionals are treated with equal respect, and teams are expected to continuously pose the question: how can we do things better?
- Invest in the development and evaluation of innovation – costs should not be borne by individual hospitals or departments.
- Provide training for clinicians in cost-effectiveness evaluation.
- Provide strategic oversight of studies and trials to avoid duplication or unnecessary, poorly designed trials.
- Ensure regulations governing trials at EU, national and hospital level are fit for purpose.

EVALUATE EFFECTIVELY

- Institute clear and transparent processes for reimbursement decisions on innovations, and subject all innovations to cost-effectiveness analysis using consistent criteria.
- Allow more flexibility in reimbursement procedures so patients can get early access to innovation that might benefit them and evidence on value can be gathered in a real-life setting.
- Use the broadest criteria for measuring cost and value to the patient and society, use instruments that capture those costs and benefits effectively, and ensure that decision makers understand cancer issues as well as health economics.
- Make greater use of EUnetHTA to promote a coordinated approach to evaluating innovations.
- Centralise evaluations and decisions on reimbursement as far as possible – replicating processes at regional or hospital level wastes resources, leads to poorer quality decision making, and allows local interests to trump wider social interest.
- Invest in registries for gathering evidence in real-life settings. Aim for greater conformity in data gathering to enable fewer, larger studies.
- Incentivise data collection: clinical researchers/departments need funding to generate evidence on the cost-effectiveness of new techniques and procedures.

OUT WITH THE OLD, IN WITH THE NEW

- Invest in spreading innovation throughout clinical practice and monitor uptake.
- Scrutinise every aspect of clinical practice – stop wasting resources on things that have no value.
- Facilitate access to information by patient advocates – they are very effective at driving innovation uptake.

A VISION AND A WILL

- Expand the EU cancer research agenda to include exploring systems issues in how to foster and evaluate health innovation and promote speedy and widespread take up.
- Unite cancer agencies across Europe behind a pro-innovation agenda, and build political will to balance the safety agenda with actively championing innovation in cancer.

"We need to remember that cancer is part of wider health spending. We face demands to show increased survival which we can't always meet. But are the evaluators using the same criteria for other areas?" Even within cancer, there are anomalies in the way decisions are taken, as Bengt Jönsson, a health economist from the Stockholm School of Economics, pointed out. "In Sweden we have one system for deciding on oral cancer drugs and another for deciding on infused drugs. We need more consistency in how we make decisions," he said.

Centralising evaluation and decision making was strongly felt to result in a better quality of analysis, with decisions more likely to reflect the best interests of the health system or society as a whole, rather than being driven by a local perspective. Pere Gascón, head of the medical oncology department at the Hospital Clínic of Barcelona, gave as an example the way hospitals in Spain tend to weigh up the pros and cons of epoietin, used as an alternative to transfusion to treat anaemia. "Epoietin is expensive, but it's about half the price of transfusion. However the government pays for transfusions, so it costs the hospital nothing. By comparison, any drug

Hospitals are on a fixed budget and they don't want to think about the broader picture

Pere Gascón

Head of the medical oncology department at the Hospital Clínic of Barcelona

that can be used as an alternative is expensive," he said. "Hospitals are on a fixed budget and they don't want to think about the broader picture."

Sectoral agendas can also trump broader health economic considerations when it comes to buying expensive high-tech equipment like DaVinci robotic surgery machines, said Naredi. There is no clear evidence to show that robotic surgery improves outcomes, he argued, "It's probably just more fun for surgeons, or good for hospitals from a recruitment perspective."

Step 4: Out with the old, in with the new

Innovation won't pay off until patients get access, so the next step is ensuring that all health professionals who care for cancer patients incorporate innovative products and practices into their daily practice quickly and effectively. This can be a challenge, the Task Force participants agreed, as health systems can be resistant to change. Changing the practice you were brought up to believe was the gold standard can feel tantamount to "being a traitor to ones training," was one comment. Another phrase that came up was "ritualistic practice" – we do it this way because that's how it's always been done.

Implementing change is an area that the European Oncology Nursing Society pays great attention to in its own training courses, said Birgitte Grube. "It is important to choose an implementation strategy and acceptance at every level of the process, to make sure that innovative thinking is valid and has a real chance for success."

At a national level, systems based on networks of specialist multidisciplinary teams, working to regularly updated national guidelines, were recognised as having an advantage when it comes to promoting rapid uptake of innovation. The ability to monitor uptake was also seen as important, but would require practitioners to co-operate with clinical registries – which record interventions as well as outcomes – or some other form of performance monitoring.

Although NICE might slow down the initial assessment, once they say 'yes', it does get taken up everywhere within 12 weeks

Paul Cornes

Clinical oncologist at the Bristol Oncology Centre, and health economist

The role of patients in driving uptake should not be overlooked, said Kathy Oliver, who made a plea for advocates to be given support and encouragement, including access to relevant information, to facilitate lobbying for the latest improvements. "Patients often know about innovations before health professionals," she said.

Paul Cornes, from the Bristol Oncology Centre, suggested that promoting uptake may be less of an issue where innovations are subject to more systematic and robust evaluation. "The argument for NICE [the UK's HTA body] is that, although it might slow down the initial assessment, once they say 'yes', it does get taken up everywhere within 12 weeks." Patients might benefit if surgery and radiotherapy were to come under the NICE remit, he argued, "because approval comes with budget and speedy uptake".

He cited total mesorectal excision, which has been shown to cut recurrence in rectal cancer from 25% to 10%, as an example. Much of the work to spread the technique, nationally as well as internationally, was done by one surgeon, Bill Heald, from a district hospital in Basingstoke, England. He earned the nickname "Saint Bill" for the personal effort he put in, over many years, often having to scrabble around for money. Might the uptake have been quicker if the procedure had gone through NICE for formal evaluation, Cornes asked?

Conducting thorough evaluations also has the advantage of forcing a reassessment of existing practices, which could free up resources currently being wasted. Jönsson of the Stockholm School of Economics gave the example of a new drug for benign prostate hyperplasia, which the German payers initially argued was too

expensive. "Then they noticed they spent millions of euros a year on herbal medicines which had no effect. So they were paying for undocumented herbal medicine, but didn't want to pay for a drug with documented effectiveness."

One question was whether European health systems would benefit from a more systematic approach to cutting wasteful spending, along the lines of ASCO's Choosing Wisely Campaign, which annually highlights five categories of procedures or treatments that are not supported by available evidence.

Something similar is currently under consideration in Italy, where the health ministry is exploring ways to introduce a requirement on clinicians to actively screen what they do to identify obsolescence.

Conducting thorough evaluations of innovations forces you to reassess the value of what you are doing

Bengt Jönsson

Health economist at the Stockholm School of Economics

Step 5: A vision and a will

Step 5 is the step needed to translate steps 1 to 4 from a paper exercise and well-intentioned words into action that can make Europe's health systems work better for patients. This is the hard part, said Agnès Buzyn, who heads up France's national cancer institute, and participated in the Task Force. Appointed by former President Nicolas Sarkozy, Buzyn has strategic responsibility for both research and delivery of care, which makes her uniquely well placed to promote innovation and foster its uptake. But while there is much France can teach other countries about integrating research and care agendas, Buzyn insists that no single country can sort out this problem alone.

"You need vision at a European level to champion innovation as a goal," she said. The reason why pharmaceutical companies are dominating the innovation agenda is because of the complete absence of a strong vision and leadership championing a broad perspective of innovation on behalf of patients and citizens. "On the one side you have industry, on the other we are split into agencies, regulators and countries. We need to pull the agencies together, not at a national but at a European level."

This, she adds, requires political will that is painfully lacking at present. "The problem with politicians now is the only contact they have with health is over scandals. Health systems are mostly geared against innovation, because their only interest is the safety agenda."

Finn Kristensen of EUnetHTA, suggested that a good start could be to expand the EU's cancer research agenda to incorporate some of the system-level issues raised at the Task Force, by assembling a European consortium involving scientists from relevant research disciplines to put in for funding from the Horizon 2020 EU research budget. "Cancer people probably think traditionally about what kind of research you can make proposals on, which would be clinical research, which is of course important. But you can also look at an area, say cancer, and say we have some problems across Europe in getting systems to work better for patients and maybe encourage researchers to make a consortium to do research on that." This was supported by Jönsson, the health economist, who pointed out that focusing on developing a more consistent approach to the way investment and spending decisions are taken would link to the EU agenda on transparency and accountability.

"The message that came out of the Innovation Task Force meeting," said Cornes, "is that we spot innovation in treatment badly, we delay it coming through, we don't fund it and we must learn how to do better." Will oncologists be willing to step beyond their clinical responsibilities and get involved? We have to, said Cornes, who now spends half his time teaching health economics to oncologists. "We have more people to treat with more treatments but potentially less resources in the future. If we abrogate the responsibility to lead on that, inevitably we will be led by economists, administrators and politicians, and that would be a bad thing." ■

You need vision at a European level to champion innovation as a goal

Agnès Buzyn

Head of INCa, the French national cancer institute

Imaging in oncology – over a century of advances

Imaging techniques used in staging and evaluation of response to treatment have improved dramatically over the past 120 years. The issue going forward will be learning to combine anatomical and functional imaging modalities to get a picture that is as close to the truth as possible.

This e-grandround charts the evolution of pioneering imaging techniques. It describes their clinical applications in two tumour types – breast cancer and lymphoma – and the impact they have had on the management of patients with these cancers, and looks ahead to cancer imaging aspects of the future.

The timeline showing the development of different imaging techniques over the last 120 years is shown overleaf, together with information on the key individuals involved in their design. A recurring theme is that the work leading to the development of most imaging modalities took place over many years, even decades, before the eventual invention. In addition, a large number of people from a wide range of disciplines, including chemists, physicists, mathematicians, biologists and electrical engineers as well as physicians, were involved in these inventions.

European School of Oncology e-grandround

The European School of Oncology presents weekly e-grandrounds that allow participants to discuss a range of cutting-edge issues with leading European experts. One of these is selected for publication in each issue of *Cancer World.*

In this issue Bhuey Sharma, Consultant Radiologist at the Royal Marsden in London, traces the evolution of oncological imaging from the invention of the X-ray in 1895 through to the hybrid anatomolecular imaging techniques used today. The presentation is based on a paper published in *Nature Reviews Clinical Oncology* (9:728–737). Edited by Susan Mayor.

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

X-rays

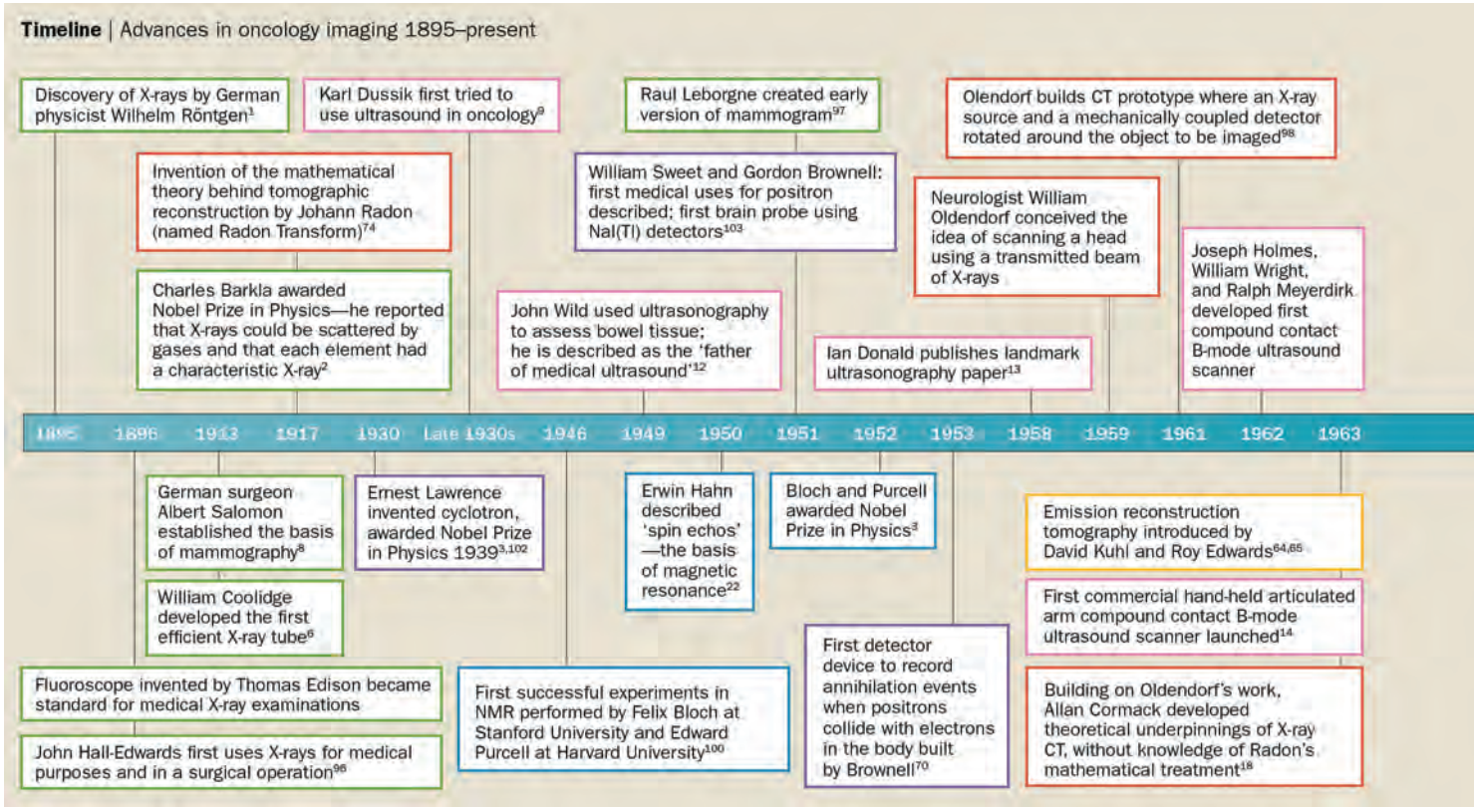
X-rays were discovered in 1895 by the German physicist Wilhelm Conrad Röntgen, who coined the term 'radiation X' for this previously unknown type of radiation. He resisted suggestions from colleagues to use the term 'Röntgen rays' but this is sometimes used in some countries, including Germany. Röntgen was awarded the first Nobel Prize in Physics in 1901 for his discovery.

The advantages of X-rays are that they are rapidly acquirable and easily reproducible. Disadvantages include exposing the patient to radiation and providing only limited oncological information. Over the last 100 years or so, X-ray imaging has been largely superseded by other oncological imaging techniques for a range of different indications, but it remains an important technique to look for complications in cancer patients. Use of X-rays remains a mainstay in certain areas of oncological imaging, including mammography. This technique was first discovered by the German surgeon Albert Salomon in 1913, who observed the different appearance of tumour tissue compared to benign tissue in mastectomy samples. It remains a very useful technique, particularly for screening patients with fatty breasts and to look for microcalcification.

Computed tomography

A British electrical engineer, Godfrey Hounsfield, is credited with being the inventor of CT in 1971. As with many other types of oncological imaging, significant work predated this particular invention. Allan Cormack, a South African physicist, described the fundamental mathematical physics of CT in 1963, but Hounsfield was unaware of his work. Even earlier, the basic mathematics underlying CT was described by Johann Radon in 1917, becoming known as the Radon transform, but Cormack and Hounsfield were both unaware of Radon's work. Subsequently, both Hounsfield and Cormack were recognised for the discovery of CT, and awarded the Nobel Prize in Physiology or Medicine in 1979.

CT is a fundamentally important technique in oncological imaging and has had huge impact. It remains the 'workhorse' modality in oncological imaging units across the world. Key



advances in CT technology include the advent of helical CT in 1987 with multi-detector CT in 1998.

An example of the way CT has changed clinical practice can be seen in lymphoma. Before CT, chest X-ray and lymphography were the main techniques used for patient work-up. Chest X-ray was used to look for mediastinal nodal involvement and lymphography was the crude technique involving injection of dye into the web space in the feet to visualise involved lymph nodes. Staging laparotomy was performed with splenectomy on patients to define whether the spleen was involved. CT changed all this by providing a whole-body imaging technique, which avoided the need for laparotomy and enabled imaging of the entire body to look for enlarged lymph nodes and extranodal sites of involvement.

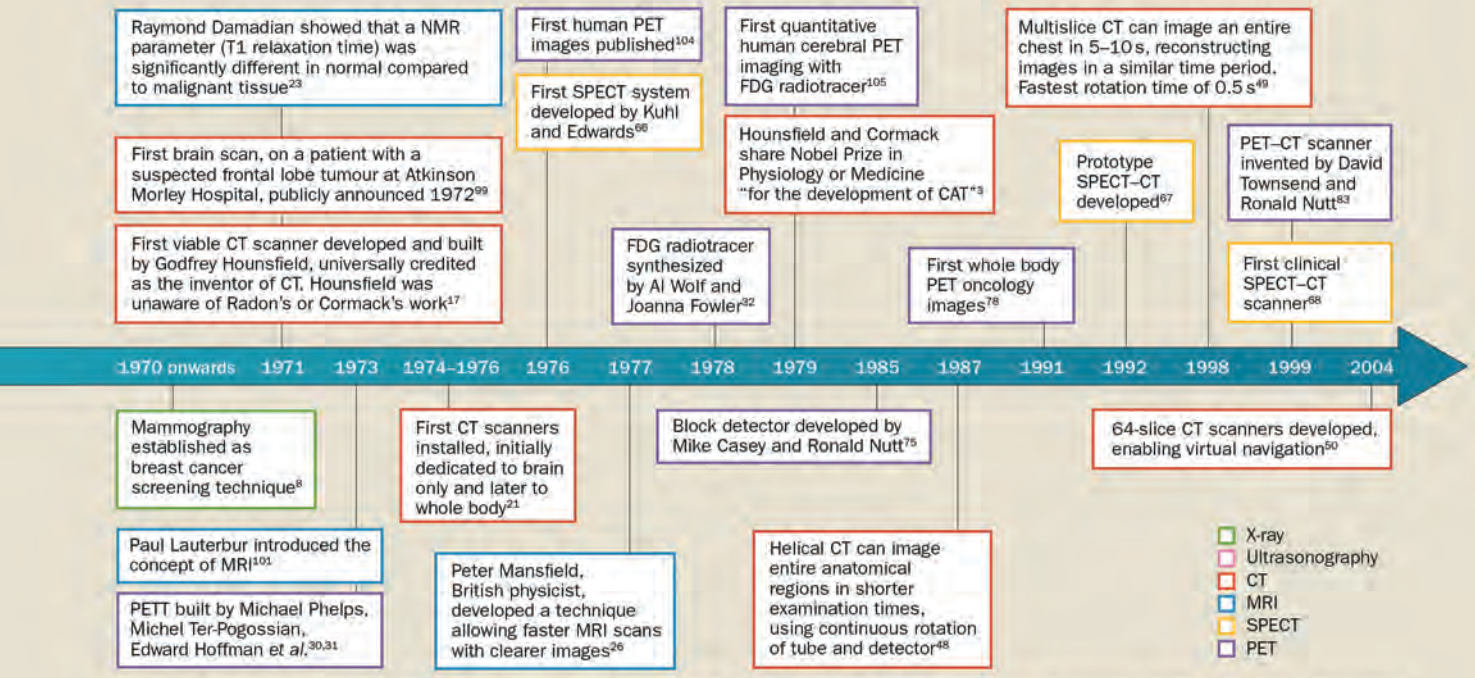
CT has also been very important in allowing the development of image-guided radiotherapy, and the development of response evaluation criteria is allied with the development of CT. The principal disadvantage of CT is the radiation dose, in addition to some clinical limitations discussed later.

Magnetic resonance imaging

Many individuals were involved in the development of MRI. Erwin Hahn described 'spin echoes' in the 1950s, for which he was subsequently awarded the Wolf Prize in physics. In the 1970s, Raymond Damadian reported that nuclear magnetic resonance can distinguish cancer from normal tissue *in vivo*, and the American chemist Paul Lauterbur produced the first MRI image of a mouse in 1974. Damadian went on to perform the first human MRI scan in 1977. British physicist Peter Mansfield was responsible for developing the mathematical techniques leading to faster and clearer MRI imaging in 1977. Lauterbur and Mansfield were both awarded the Nobel Prize in Physiology or Medicine for their discoveries concerning MRI in 2003 but, controversially, Damadian was not recognised for his contribution.

The advantages of MRI include the absence of radiation exposure; the technique provides good contrast resolution and has the ability to provide multiplanar imaging. Limitations include the fact that patients with

Source B Sharma, A Martin, A Constantinidou et al. (2012) *Nat Rev Clin Oncol* 9: 728–737, reprinted with permission from Macmillan Publishers Ltd © 2012



Abbreviations: CAT, computed axial tomography; FDG, fluorodeoxyglucose; NaI(Tl), Thallium doped Sodium Iodide; NMR, nuclear magnetic resonance; PETT, positron-emission transaxial tomograph; SPECT, single-photon emission computed tomography.

metallic prostheses may not be suitable for scanning, and claustrophobia is a significant problem for patients in clinical practice. Nevertheless, MRI quickly gained clinical ground, having been invented from the outset as an oncological imaging technique. It was rapidly taken up for imaging of the central nervous system, particularly for brain tumour. There has also been considerable interest in MRI as a whole-body imaging technique.

Positron emission tomography

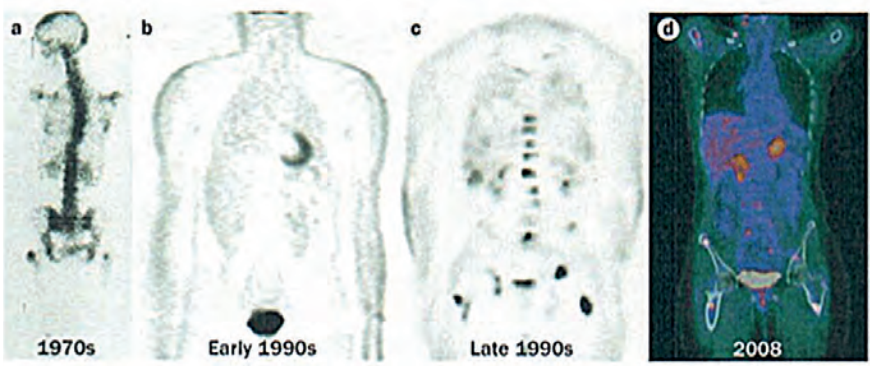
For many years we have used anatomical techniques in oncological imaging, looking for anatomical changes. However, in recent years interest has been growing in the use of functional imaging. Key individuals involved in the development of PET included Gordon Brownell at the Massachusetts General Hospital in the 1950s and 1960s, and work from the Brookhaven National Institute in America in the 1960s. Michael Phelps, Michel Ter-Pogossian and Edward Hoffman produced the first PET instrument in 1973, which enabled transaxial PET images to be obtained.

PET is a functional technique that relies on the injection of a radioisotope, which is linked to a biologically active molecule that targets the site of interest in the body. The clinical tracer that has been in use for several decades is 18-fluorodeoxyglucose (FDG), discovered by Wolf and Fowler in 1978, which is comprised of glucose linked to a radioligand. The initial interest in PET was for neurological imaging, but in the late 1980s the focus moved to cardiac viability, looking at cardiac perfusion and hibernating myocardium. PET was found to be very useful in oncological imaging almost by chance, with the first oncological PET image being presented in 1991, using FDG as a radiotracer. To this day oncological imaging is by far the major use of PET in worldwide clinical practice.

The advantages of PET include the capacity for whole-body imaging, lesion characterisation and accurate staging. Functional imaging provides an early response assessment in the sense that functional changes 'predate and predict' anatomical changes, so early response to a variety of treatments can be evaluated using functional techniques. Limitations include the drawback that FDG is not accurate across all tumour histologies and that tissue changes such as inflammation will also take up FDG, so it is not a truly tumour-specific ligand. The other key disadvantage of PET is that, unlike MRI, it involves a radiation dose.

PET has made a stepwise change to clinical practice in lymphoma and a number of other tumour types, in a similar way to CT. In Hodgkin lymphoma and high-grade lymphomas, PET leads to clinically significant stage migration at baseline staging (i.e. it picks up disease not detected by other imaging modalities, which

EVOLUTION OF CLINICAL PET IMAGING



Four images demonstrating how the resolution and accuracy of lesion detection by PET imaging has increased over the past four decades.

a) 1970s rectilinear ^{18}F-fluouride scan – the pioneering rectilinear scanning technique had been developed by Brownell and co-workers in 1953

b) Non-attenuation-corrected whole-body PET imaging in the early 1990s, using filtered back projection rather than iterative reconstruction

c) Attenuation-corrected (BGO crystal detector) FDG PET image from the late 1990s of a patient with breast cancer. A number of scattered sites of increased FDG accumulation are observed, most clearly within the thoracolumbar spine and bony pelvis region bilaterally, representing metastases; of note, defining the exact anatomical location of lesions in this image is almost impossible

d) PET-CT image of a patient with high-grade lymphoma taken in 2008, leading to stage migration, with PET-CT detecting occult scattered focal bone sites of involvement in addition to known lymphadenopathy

Source: Courtesy of G Cook, King's College London, Reprinted from *Nat Rev Clin Oncol* 9: 728–737, reprinted with permission from Macmillan Publishers Ltd © 2012

has an impact on the proposed treatment). It provides information for early response evaluation and in residual mass assessment, as to whether viable disease is still present or whether the residual mass reflects inactive fibrosis. PET-CT, which was originally envisaged by Townsend and Nutt in 1991, was invented in 1999, and led to a huge change in the use of PET across clinical practice, and widespread acceptance in the clinical community, by combining anatomical with functional information and enabling lesions to be precisely localised.

The figure on the opposite page illustrates the evolution of PET since the 1970s, with the first image demonstrating a crude PET image from the 1970s through to the PET images that were produced in the early and late '90s, and then the stepwise further change with PET-CT in the last decade, leading to much more accurate anatomical localisation of sites of uptake.

The figure *above, right* illustrates some of the strengths and weaknesses of imaging science with PET-CT in images from a patient with breast cancer. Bone staging and response evaluation are real problems in oncological imaging. On anatomical imaging (CT and MRI), 'increasing dense sclerosis' is one feature of bone response to treatment in a number of different tumour types/situations. However, in a proportion of oncology patients a point is reached where 'stable dense sclerosis' is present on CT/MRI, and it is not possible to assess bone disease activity/control. Functional imaging with PET can be very useful in a proportion of tumour histologies.

The coronal CT images shown (*on the right of the figure*) demonstrate diffuse heterogeneous sclerosis throughout the axial and proximal appendicular skeleton imaged, which is stable compared with the previous scan (*not shown*). The colour-fused PET-CT image (*on the left*) shows that the vast majority of the bone infiltration in this patient with invasive ductal breast cancer is not FDG avid, representing a current complete macroscopic metabolic response to systemic treatment. Abnormal ^{18}FDG PET activity is shown only at L3 and the superior right ilium, reflecting sites of metabolically active bone disease. The PET findings implied that an ongoing maintenance (hormonal) treatment approach was suitable in this patient rather than re-institution of systemic cytotoxic chemotherapy.

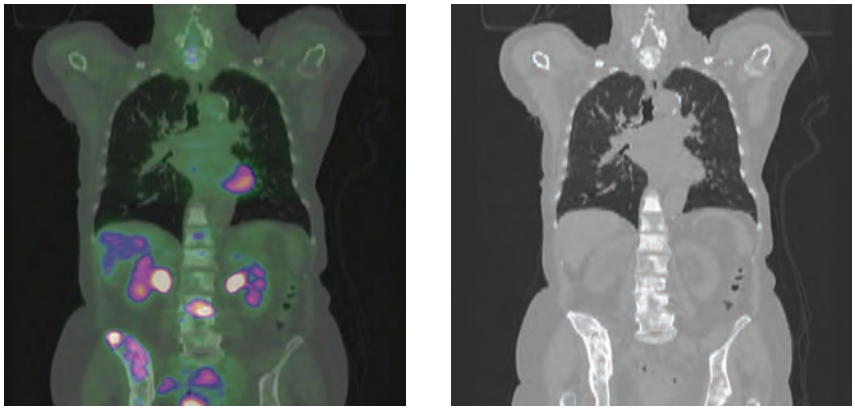
This was the subject of a large retrospective study of PET-CT in breast cancer, illustrating our philosophy regarding the importance of multiparametric imaging for the optimal management of cancer patients (*Ann Oncol* 2011; 22:307–314).

Looking to the future

In terms of future directions, new techniques such as PET-MRI, which comprises a fusion of functional imaging and anatomical imaging, the use of novel targeted PET radio tracers, and the use of whole-body diffusion-weighted imaging are likely to make an important contribution. However, imaging history in oncology teaches us that no single technique is accurate across all tumour types, and in answering all specific tumour questions. Although these new techniques will likely come to the fore, each of them will have strengths and weaknesses and will not provide the universal answer to all of the problems that we have in caring for cancer patients.

There are six fundamental hallmarks of cancer and these can be targeted in a specific way with radiotracers. Although we have been using FDG so far for the vast majority of clinical PET, more specific radiotracers are increasingly being developed, with a number entering the clinical domain. As we develop radiotracers targeted towards specific cell receptors and specific tumour receptors, then PET-CT and PET-MRI will become much more accurate.

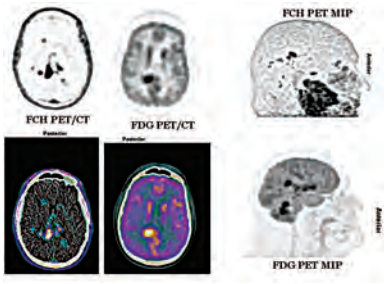
BONE RESPONSE TO TREATMENT



FDG PET-CT *(left)* revealed areas of metabolically active bone disease which could not be detected by comparing the density of sclerosis on this CT image *(right)* with earlier images *(not shown)*

Source: Courtesy of Bhuey Sharma, Consultant Radiologist, Royal Marsden NHS Trust

NOVEL PET RADIOTRACERS FOR MORE ACCURATE ASSESSMENT



The F-choline (FCH) radiotracer appears more accurate than FDG for detecting CNS lymphoma, in part due to high physiological background CNS metabolic uptake of FDG

Source: Courtesy of Sue Chua, Consultant Radiologist, Royal Marsden NHS Trust

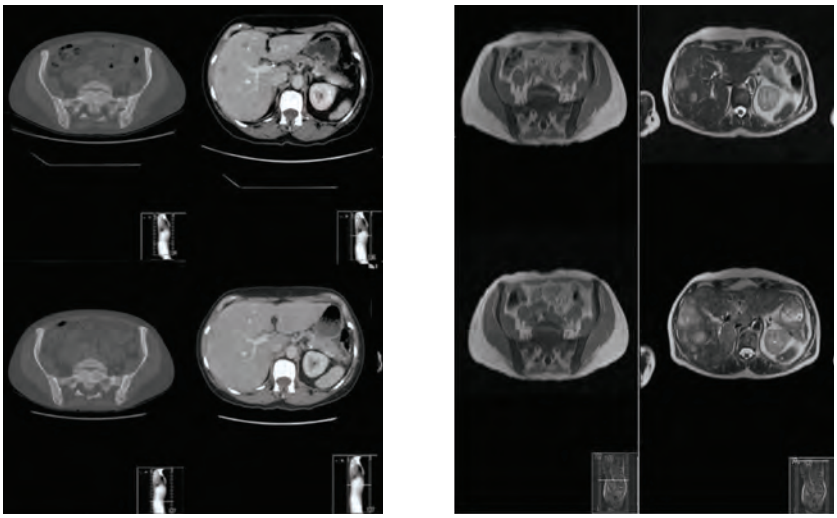
The figure above illustrates the concept of using targeted imaging to provide a more accurate assessment of a patient's oncological status. The FDG PET images (*middle column and bottom right*; inverse grey scale, colour fused and maximum intensity projection images respectively) demonstrate sites of increased metabolic activity in the right posterior cerebral and cerebellar hemispheres in a patient with high-grade lymphoma with involvement of the central nervous system (CNS). Note high physiological background CNS uptake on FDG PET imaging. The F-choline (novel radiotracer) PET imaging (*left column and top right*) demonstrates significantly higher accuracy than FDG PET for the detection of CNS lymphoma, revealing multifocal CNS lymphoma (which was concordant with IV contrast-enhanced MRI, *images not shown*). F-choline is a specific substrate for choline kinase, an enzyme commonly overexpressed in malignant lesions due to its role in cell membrane synthesis. It is therefore a measure of cellular proliferation rather than metabolic rate. To date, choline has found its most important PET application with prostate cancer, where FDG is not generally useful, as prostate cancers can have relatively low metabolic rates. Early work suggests that F-choline may be useful in the context of CNS lymphoma (one area of our current research).

Diffusion-weighted imaging MRI is also likely to be important in oncological imaging in the coming years. The technique is being validated across a number of different tumour types in research, but shows significant promise and is increasingly being used in oncology for brain and liver imaging. It also shows exciting promise for staging and response evaluation in bone marrow and in other problem areas such as assessment of peritoneal disease and brachial plexopathy.

The concept of diffusion-weighted MRI relies on the difference in water movement in different tissues, with restricted water movement in areas of high cellularity contrasting with less restricted water diffusion in areas where tumour has been broken down to a less cellular structure. It is an MRI technique that provides whole-body imaging with no radiation exposure. Data can be quantified with the apparent diffusion coefficient (ADC), providing an objective measure of tumour response (with PET, semi-quantitative analysis can be performed using the standard uptake value, or SUV).

The figure below illustrates the limitations of CT scans (*left-hand images*), in terms of sclerotic bone response evaluation. The top image shows widespread bone disease and the liver image demonstrates a few

CT AND MRI SCANS FROM A PHASE I TRIAL BREAST CANCER PATIENT



Comparing before *(top)* and after *(bottom)* scans to evaluate response to a phase I drug, the MRI scans *(right)* picked up widespread disease progression in the liver that was not evident on the CT scans *(left)*. Bone response was difficult to evaluate with either imaging modality and was considered (subjectively) stable

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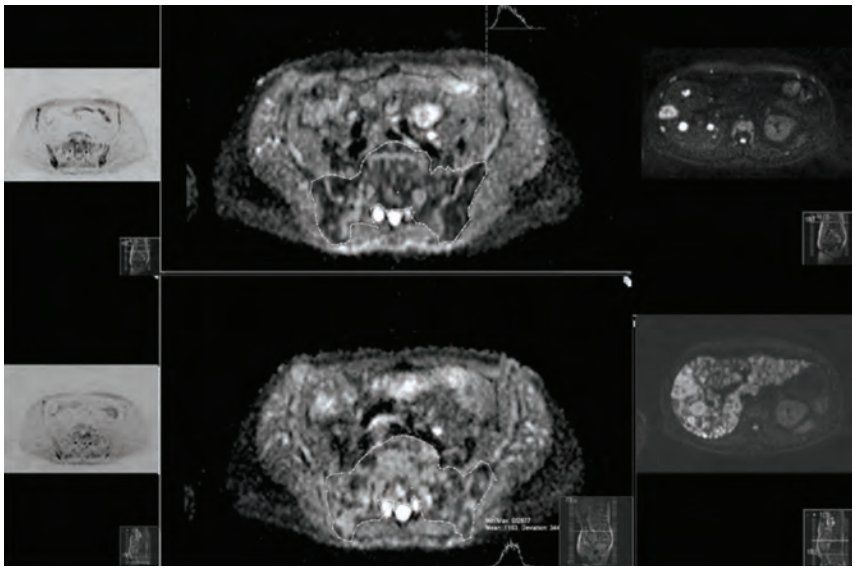
liver metastases. After the phase I drug, the images at the bottom suggest bone disease is stable with no discernable differences on CT imaging; however, based on these images it is really impossible to define whether the patient is responding in the bony skeleton. The liver images demonstrate that there have been some slight changes in the liver metastases, although the liver status overall was considered stable according to the RECIST classification.

The images on the right of the same figure are T2-weighted MRI images for the same patient. The top and bottom images show that the bony sclerosis looks stable – again impossible to define whether there has been a change in the patient's bone status. However, the liver images show marked widespread liver progression, so, in this particular case, MRI was more sensitive than CT in demonstrating liver disease progression.

However, using diffusion-weighted MRI in the same patient, at the same time points, gives a different answer (see figure *above, right*). The left-hand images at the top and bottom of the figure show that the degree of restricted diffusion has reduced. The middle images show that the apparent diffusion coefficient (ADC) values have reduced, with a shift on the ADC map, showing good bone response to treatment, which could not be defined from CT or 'standard' MRI. Conversely, the diffusion-weighted MRI of the liver (*right-hand images*) demonstrates that there has been marked liver progression. This exemplifies a case of a patient who was considered to be stable on CT, while MRI demonstrated stable bone status but liver progression, and diffusion-weighted MRI demonstrated a fundamentally different result, showing that the diffuse bony infiltration has partially responded to treatment, whereas there has been marked liver progression (i.e. a true mixed response). This is an important example of how these new techniques will not only change clinical practice but also change endpoints/patient stratification in research trials. ■

DIFFUSION-WEIGHTED MRI IN THE SAME PHASE I TRIAL BREAST CANCER PATIENT



Diffusion-weighted MRI performed at identical time points in the same patient (pre-treatment *top*, post-treatment *bottom*) revealed a good bone response to treatment but marked liver progression

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Take home message

- There have been tremendous developments in oncological imaging over the past 120 years.
- No single imaging technique can provide all the answers at a given time in any tumour with regard to all tumour questions.
- The persistent challenge from an oncological imaging perspective is to provide an assessment that is 'as close as possible to the truth'.
- The future of oncological imaging will entail multiparametric approaches, using combined anatomical and functional techniques to more accurately guide patient management.
- We need to understand the basic imaging science, including the fundamental weaknesses as well as the strengths of any given technique, to provide appropriate and optimal care for cancer patients.

Complementary or alternative medicine in cancer care – myths and realities

GARY DENG AND BARRIE CASSILETH

Two practitioners of integrative oncology make the case for using non-traditional therapies alongside mainstream care – and for abandoning the term "complementary and alternative medicine" as unhelpful and misleading – in this comprehensive article, which first appeared in Nature Reviews Clinical Oncology.

Imagine this scene: the oncologist concludes an outline of an adjuvant treatment plan to a patient who has recently been diagnosed with stage III breast cancer. The patient asks, "Should I be on an alkaline diet? I heard that alkalising the body kills cancer cells. I've also heard that sugar feeds cancer. Should I avoid sugar? How about graviola, a herb from the Amazon that is supposed to cure cancer? Can I get acupuncture during chemotherapy to reduce side effects?" This not-uncommon scenario brings to mind pressing questions. What are these therapies and remedies that are not traditionally part of Western mainstream medical care? How do we, as oncologists, respond to questions about nontraditional therapies?

Data on the use of adjunctive complementary therapies for symptom control is often confused by the use of the convenient acronym 'CAM' – complementary and alternative medicine – in publications that fail to distinguish between alternative and complementary modalities. The acronym is inherently imprecise. Some therapies, such as vitamins, are part of mainstream medical care when prescribed to patients with vitamin deficiencies or taken in appropriate amounts to maintain general health. However, vitamins are 'alternatives' when used in 'megadoses' as a treatment for cancer, sometimes in lieu of mainstream care. Similarly, 'prayer for health' might be a useful aid during mainstream cancer care in some regions of the world for some patients, but can be selected as a cancer 'treatment' in others. Thus, the terminology and its varying interpretations interfere with accurate reporting and hinder the accurate understanding of survey data.

The interest in therapies outside of mainstream oncology care is not limited geographically or among particular segments of the population. In countries in which modern medicine predominates, 40–50% of patients with cancer use CAM therapies outside the mainstream.[1–6] Among cancer survivors in the US, up to 40% used complementary or alternative therapies during the period following their treatment.[7] The 2007 National Health Interview Survey showed that four in ten adults (38.3% of adults; 83 million individu-

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als) and one in nine children less than 18 years of age (11.8% of children; 8.5 million individuals) in the US used dietary supplements and various mind–body therapy techniques.[8,9]

Largely because the CAM terminology is an admixture of unrelated – often mutually contradictory – concepts, the term has become outdated and is no longer in common use. As accurately stated in a recent publication: "the term 'integrative medicine' is fast replacing that of complementary and alternative medicine, or 'CAM.'"[10] Another publication sums up the terminology problem well: "this controversial term should be changed, since the words 'complementary' and 'alternative' have different meanings and should not be connected by 'and'."[11]

Complementary therapies are those used to complement or use alongside conventional methods of therapy, whereas alternative methods refer to those that are used instead of known conventional therapies. Accordingly, the term 'integrative therapies' accurately describes the complementary treatments being used in medical settings alongside conventional practices. Centres for integrative medicine are being established in many academic medical centres.[11] Indeed, the term CAM is rarely applied in legitimate settings, and virtually every National Cancer Institute (NCI)-designated comprehensive cancer centre in the US has a programme or department using the term 'integrative medicine'. In addition, the US Consortium of Academic Health Centers for Integrative Medicine has a membership of 55 esteemed academic medical centres with medical schools, all of which have integrative medicine programmes.

In this article, we summarise the data on helpful complementary therapies and their appropriate incorporation into cancer care (integrative oncology), discuss nonviable alternative therapies and examine the patient interest in these therapies. We also provide recommendations for how oncology professionals can manage these issues in an evidence-based, compassionate fashion that enhances trust and rapport, strengthens the physician–patient relationship and improves the quality of life for both the patient and their caregivers.

Complementary approaches

Mind–body therapies

Mind–body modalities focus on interactions between the brain, mind, body and behaviour with the intention of reducing symptoms and promoting health. Some of these therapies, such as meditation, relaxation techniques, hypnotherapy, yoga, T'ai Chi, music therapy and qigong have ancient roots; others, more recently developed, include the likes of guided imagery.[12] The common goal of mind–body therapies is to reduce the effects of anxiety, fear, phobia, anger, resentment, depression and pain on the patient while promoting a sense of emotional, physical and spiritual well-being. Mind–body therapies do not treat cancer *per se*.

Numerous clinical trials of variable quality have been conducted to assess the benefits of these techniques. For example, systematic reviews and meta-analyses have consistently shown that mind–body techniques do reduce anxiety and stress, improve sleep quality and overall quality of life, especially when used with other treatments (such as drugs).[13–17] Among such therapies, mindfulness-based stress reduction is the best studied – an approach that focuses on developing the patient's objective 'observer role' for emotions, feelings and perceptions and creating a nonjudgmental 'mindful state' of conscious awareness.[18] Its meditative components of body scan, sitting meditation and mindful movement are taught over a period of weeks.[18] By contrast, yoga, T'ai Chi and qigong, which originated in Asia, are less well studied, despite being commonly used. They combine physical movement, postures and breath control with meditation. A few small trials (20–80 patients) have shown a reduction in anxiety, depression and distress as well as improved emotional well-being in patients with cancer who practice these techniques, as measured by standard validated instruments.[19–21]

Although mind–body therapies are generally safe, their effectiveness requires instructors skilled in conveying appropriate technique and regular practice by the patient. These helpful complementary modalities can be used as part of a multidisciplinary approach to patient care. Major research studies are underway to elucidate the mechanisms by which mental activity exerts control over physiological function,[22–24]

Acupuncture

Acupuncture, an ancient technique with great contemporary interest, involves the placement of special needles at certain body points (acupoints) a few millimetres to a few centimetres into the skin, which can be followed by manual manipulation or the application of heat or electric pulses to the needles.[25] Historically, acupuncture was thought to exert its effect by regulating the flow of energy (called chi or qi) along meridians in the body when inserted into these acupoints.[25] Although anatomical studies have shown that acupoints tend to be located over interstitial connective tissue planes,[26] current evidence does not conclusively support the claim that acupuncture points or meridians are electrically distinguishable.[27] However, substantial data from neuroscientific research suggest that the effects of acupuncture are mediated via modulation of nervous system activity.[28–31] Regulated as medical devices in the US, acupuncture needles are sterile, single-use, filiform, 32–36 gauge and 30–40 mm in length. A typical treatment session is provided by licensed or certified professionals and lasts 20–40 minutes.

Acupuncture is used to treat a wide variety of ailments, although its efficacy has been evaluated with rigorous scientific research methodology only in the past few decades. Clinical trials have shown that the treatment is safe and effective for several symptoms experienced by patients with cancer.[32] Indeed, a Cochrane review of 11 randomised controlled trials (RCTs) encompassing 1,247 patients – most using sham acupuncture as controls – concluded that acupuncture reduces chemotherapy-induced nausea and vomiting.[33] The majority of acupuncture trials have been conducted to determine the efficacy of acupuncture in reducing pain. Recent systematic reviews of RCTs support the analgesic effects of acupuncture for certain types of pain (for example, musculoskeletal pain, osteoarthritis and chronic headache).[34, 35] Furthermore, acupuncture has shown benefit in reducing radiation-induced xerostomia,[36] but mixed results in reducing hot flushes experienced by women with breast cancer.[37–39] The technique is possibly effective in reducing lymphoedema in women with breast cancer who had axillary dissection.[40] Both a systematic review of 46 RCTs and a Cochrane review showed that acupuncture seems effective in treating insomnia, although larger, rigorously designed RCTs are warranted.[41] Acupuncture has also been shown to relieve anxiety in a diverse patient population.[42–44]

Acupuncture is generally safe when performed by qualified practitioners. After 760,000 treatments in 97,733 patients receiving acupuncture in Germany, only six cases of treatment-related serious adverse events were reported.[45] The most common adverse effects (<5%) included minor bleeding

or bruising and pain or unfamiliar sensations at the acupuncture sites. In patients with cancer, acupuncture should not be given to those with severe neutropenia or thrombocytopenia due to their higher risk of infection or bleeding, or at the site of primary or metastatic neoplasm.

Acupuncture is not an optimum first-line treatment for symptom relief. Rather, it can be considered when standard treatment is not satisfactory or not tolerated. In patients with severe chemotherapy-induced nausea, vomiting, pain, xerostomia or hot flushes in spite of optimal medical management, acupuncture can be included as part of a multimodal management plan. Although some insurance companies do cover acupuncture treatment provided by qualified therapists for certain indications, the cost-effectiveness of acupuncture remains to be determined.

Manipulative and body-based practices

Massage therapy and other manual techniques – such as Swedish massage, shiatsu, tui na, reflexology, Thai massage, Ayurvedic massage, lymphatic drainage and myofascial release – are provided by massage therapists, physical therapists and occupational therapists.[46] These practices, which evolved from various cultures, focus primarily on the musculoskeletal system and connective tissues. For example, Swedish massage, the most commonly practised massage therapy in the West, uses five styles of long, flowing strokes – effleurage (gliding), petrissage (kneading), tapotement (rhythmic tapping), friction and vibration/shaking – to manipulate soft tissues.

Most cancer-related clinical trials of massage therapy focus on Swedish massage and reflexology (foot massage using specified parts of the sole thought to relate to bodily organs or locations). Results have been summarised in two systematic reviews that incorporate 14 RCTs and 12 RCTs, respectively, with some overlap.[47,48] The control interventions used in these trials include standard of care, attention (where patients received interpersonal interactions but not massage therapy) or low-intensity bodywork, such as light touch. Although the reviewers indicate that the research methodology of most trials included in both reviews was poor – for example, small sample sizes or the lack of any attempt to control for nonspecific effects – the data do support massage therapy as an effective adjunct in cancer supportive care to reduce anxiety and pain.[47,48]

Massage therapy in patients with cancer must be provided by certified massage therapists who are also trained in working with patients with cancer, to minimise risk of injury. For example, only light-touch massage should be provided to frail patients. Strong pressure should be avoided in areas harbouring tumours or metastases, or to patients with bleeding tendencies. Cases of serious adverse events – including cerebrovascular accidents, ureteral stent displacement, haematoma, nerve damage and posterior interosseous syndrome – have been reported, usually as a result of exotic types of massage (such as application of very strong pressure not appropriate for the anatomical location) or massage delivered by laypeople.[49,50] When delivered appropriately, massage therapy is a valuable, soothing complementary therapy that aids symptom control in patients with cancer and on which many patients rely.

Alternative therapies

Patients might seek alternative therapies for a variety of reasons, including frustration with a lack of improvement using mainstream treatments. In the past, cancer was considered a dire disease with few effective treatments; accordingly, patients sought more-effective, gentler treatments – real or imaginary.[51]

Today, the primary danger of alternative therapies is that patients delay or forego altogether effective cancer treatment. For example, instead of undergoing surgical resection of an early-stage breast cancer, a patient might opt for an alternative 'natural therapy'. By the time it becomes apparent to the patient that the therapy has not controlled the growth of her cancer, it has metastasised, rendering it incurable. Another risk to patients is that most alternative therapies are very costly. And as these are rarely covered by

FACTORS CONTRIBUTING TO PATIENTS' INTERESTS IN ALTERNATIVE THERAPIES

- Poor prognosis and lack of effective treatment – willingness to try 'anything'
- Patient activism – wishing to search for nonmainstream treatments perceived as unknown by oncologists
- Patient empowerment – feeling like an active participant in self care
- Cultural values and belief systems – believing that anything 'natural' is good and 'synthetic chemicals' are bad
- Tradition of using indigenous medical systems – including traditional Chinese, Ayurvedic and Latin American folk medicine
- Conspiracy theories – believing that pharmaceutical companies suppress curative 'natural products' out of profit motive
- The internet and search engine technology – providing quick access to a vast amount of information and misinformation
- Direct-to-patient marketing – promotions by product manufacturers that include attractive packaging and specious 'scientific' jargon
- Viral messages – medical myths, health tips and 'cancer cure secrets' propagated by friends, relatives and others; a patient's willingness to comply

insurance schemes, patients must pay out of pocket for them, often depleting their resources with the false hope that they are receiving effective therapy. The subsequent financial havoc creates tremendous distress for the patient and family. A third risk is that these therapies make false promises to desperate patients – results that cannot be delivered, representing an act of deception and betrayal. As clinicians, we have a moral obligation to dissuade patients from these useless therapies.

Miraculous cancer cures

Proponents of alternative therapies claim to produce 'amazing' results in patients with cancer who have not responded to conventional therapy. The treatment can be as simple as a single product from an exotic source or derived from a 'breakthrough discovery' decades ago yet 'suppressed' by mainstream medicine thereafter. For example, amygdalin (also known as laetrile) is an extract from bitter apricot seeds that is not – despite its other moniker of vitamin B17 – a vitamin. Although clinical studies have shown a lack of efficacy[52,53] and a risk of cyanide toxicity,[54] some patients continue to seek and use it. In our own recent experience, one patient proudly displayed her vitamin B17 pill bottle during a consultation and claimed that someone told her it cured his cancer after he had been told he had only months to live. We are certain other oncologists have been faced with similar situations.

Another touted miracle cure is caesium therapy, in which patients ingest caesium chloride (CsCl) to alkalinise the body. Proponents claim CsCl will kill the cancer cells because cancer cells "perish in an alkaline, high-pH, environment."[55] Unfortunately, ingestion of CsCl can lead to torsade de pointes, a potentially lethal cardiac arrhythmia.[56,57] This alternative treatment can also include an elaborate regimen of special diets, detoxification techniques and large doses of natural products. Furthermore, these therapies rely heavily on testimonials of purported users of the products; the promotional materials are often laden with specious scientific jargon that can appeal to laypersons, but their misleading nature is obvious to anyone versed in cancer biology. Other examples include 'oxygen therapy' (ingestion or injection of substance containing hydrogen peroxide or ozone) and variations of bioelectromagnetism (subjecting the body to electromagnetic field generated by a device), as are various 'energy therapies'.[58]

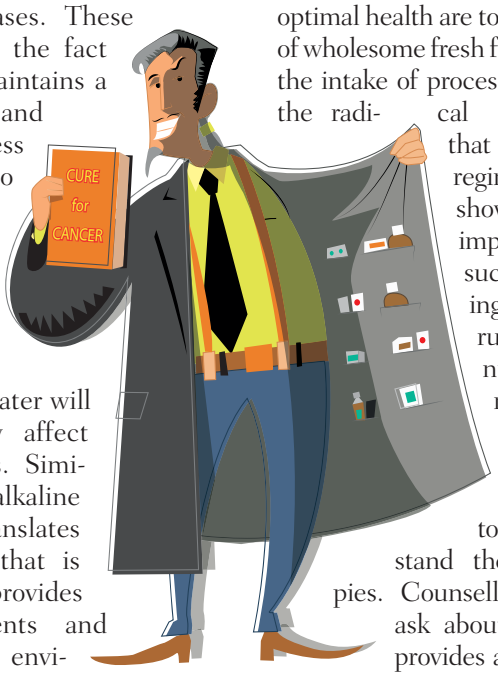
The parties that stand to profit from these products use various tactics to circumvent laws and regulations. They often use carefully worded statements or testimonials to create the impression that the products can cure cancer without literally saying so. Or, they disassociate themselves from the promoters by engaging in multilevel marketing or 'guerrilla marketing' schemes. Although the FDA (US regulatory body) has investigated numerous unsubstantiated claims and the Federal Communications Commission (FCC) investigates such false advertisements, the resources required to gather evidence and initiate legal actions are such that they can only prosecute a small number of violators. Physicians should educate their patients about why these therapies should be avoided.

Anticancer diets

A near-universal patient question concerns diet. Often patients are not satisfied with the usual dietary advice offered by dieticians, and seek 'anticancer' diets – an approach that has spawned its own category of self-help books.

Alkaline diets

One example that is frequently cited in this category is the so-called alkaline or pH diet. This diet is similar to the concept behind caesium therapy, that acidity promotes cancer and cancer cells cannot survive in an alkaline environment. By drinking 'alkaline water', distributed from an expensive device hooked up to a faucet [tap], and eating 'alkaline foods', which happen to be mainly fresh vegetables, fruits, legumes and nuts, one can ward off cancer, arthritis, obesity and other diseases. These claims disregard the fact that the body maintains a tight pH range and eliminates excess acid or alkaline to preserve pH balance. Treated water has little buffering capacity, therefore, drinking so-called alkaline water will not significantly affect blood pH levels. Similarly, glorifying alkaline foods simply translates to eating food that is healthy, which provides essential nutrients and not an alkaline environment toxic to cancer cells.



Other anticancer diets

Many other anticancer diets with little scientific basis circulate among patients, including the Budwig diet, the Gerson diet, the raw food diet and many more.[58] In addition, 'detox' or 'mono' diets (such as those relying mainly on vegetable and fruit juice) can restrict or preclude important food categories that are necessary for a full range of nutrition.

A high-fat, low-carbohydrate ketogenic diet is another popular subject of inquiry. Animal studies suggest that ketogenic diets induce excessive oxidative stress and might enhance the therapeutic effects of radiotherapy.[59] Clinical trials are underway to evaluate their benefits and risks.[60–62]

When responding to diet-related inquiries, oncologists might find it helpful to point to the 'kernels' of truth in the marketing materials for these programmes. The basic requirements for optimal health are to consume a variety of wholesome fresh foods and to reduce the intake of processed food. None of the radical anticancer diets that employ restrictive regimens have been shown to significantly improve survival. As such, patients adhering to these schemes run the risk of malnutrition. Optimal caloric and nutrient intake is very important for patients to be able to withstand their cancer therapies. Counselling patients who ask about these diets also provides a good opportunity to put dietary advice in the context of an overall healthy lifestyle, which also includes regular exercise.[63] The potential for physical activity to improve outcomes,[64,65] including benefits to patients receiving palliative care,[66,67] should be noted. Many leading cancer facilities have exercise programmes tailored to the needs of patients with cancer, with experienced fitness instructors who routinely work with patients across a broad range of abilities and disabilities.

Sugar and cancer

The notion that sugar 'feeds' cancer is frequently cited by concerned patients. Although not entirely without merit – glucose metabolism is an active area of research in anticancer drug development[68] – it is often exaggerated in public perception. Some patients become paranoid about all sugar-containing food, regardless of the amount. Such anxiety by itself is detrimental to the quality of life of patients and should be avoided. Instead, patients should be advised to keep things in perspective: no definitive data have shown that sugar promotes cancer growth. However, excessive intake of refined sugar is unhealthy for many reasons, especially for its association with metabolic syndrome, and should accordingly be minimised. A small amount of refined sugar is not harmful. To meet caloric requirements, patients should consume complex, unrefined carbohydrates and unsaturated fat (unless they have a digestive tract condition that precludes those foods) and avoid large amounts of foods with added sugar.[69]

Natural product dietary supplements

The use of supplements is among the most frequently questioned subjects by patients. Over-the-counter dietary supplements available to patients with cancer include vitamins and trace-element formulations that have well-defined constituents. Additionally, botanical extracts and herbal products that often contain complex compositions of many compounds, some of which are unidentified, are also available. Indeed, botanicals, fungi and marine organisms (such as sea sponges) are a rich source of therapeutic compounds that are used in cancer therapy; chemotherapeutic agents derived from natural sources –

so-called natural products in chemical jargon – include the taxanes (paclitaxel is isolated from the Pacific Yew tree), camptothecin (isolated from of *C. acuminata*, the Chinese 'happy tree') and its analogues, vinca alkaloids (isolated from the periwinkle *C. roseus*) and numerous microbial compounds.[70] However, decades of research are needed to ascertain the clinical safety and efficacy of compounds derived from natural sources in clinical studies. Natural products available as dietary supplements are not viable cancer treatments until their efficacy has been established in such studies.

Patients with cancer often ask about natural products that have been shown to have activity against cancer in animal or in vitro studies, but unconfirmed in clinical trials. Many are readily available as dietary supplements, and patients can use them on their own, often without informing their physicians. In addition, patients might pursue the use of natural products marketed with 'buzzwords' such as antioxidant, immune booster or detox. A comprehensive list of such supplements has been reported.[71] Patients view these products as helpful during cancer treatment because of claims that the products protect 'good' cells from damage, restore suppressed immune function or remove toxins 'left behind' by cancer treatment. Some of these agents might hold promise in cancer prevention or treatment; for example, early-phase clinical trials of polyphenols extracted from green tea have demonstrated benefit in the treatment of chronic lymphocytic leukaemia (CLL)[72] and in the chemoprevention of breast cancer.[73] Similarly, docosahexanoic acid (DHA, an Ω3-fatty acid) has demonstrated positive results in breast cancer prevention[74] and treatment,[75] as has curcumin in slowing progression from monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma.[76] Nonetheless, the majority of the available supplements has not shown a reasonable possibility of meaningful clinical benefits when ingested orally. Many also carry the risk of interacting with prescription medicines or have their own detrimental effects.[77–80] For example, several herbs possess oestrogen-like activity, the intake of which is not advisable for women with oestrogen-receptor-positive cancers.[81] Other supplements can alter drug metabolism, such as St John's wort, leading to serum drug levels higher or lower than intended.[82] Misconceptions held by patients after reading news reports or marketing materials need to be invalidated in a language patients can understand (see Table opposite).

Patient characteristics

Surveys indicate that patients with cancer who use complementary or alternative approaches tend to be female as well as younger, better educated and more affluent than those who do not, representing a health-conscious segment of the population that is proactive in its healthcare, that seeks health information and that has the means to pay for services not typically covered by insurance or public health schemes.[1–6] Given the increased sophistication of patients and physicians in recent years, patients and their oncologists increasingly pursue discussions of integrative oncology, alert to the fact that incorporating complementary (adjunctive) therapies into mainstream cancer treatment can decrease symptoms and improve overall quality of life. Furthermore, such discussions facilitate patients in having an active role in their care.[83]

Patients acquire information about complementary approaches primarily from friends (65%), family (48%) and the media (21%),[1,84] with additional information – as well as misinformation – being delivered via the internet and social networks.[85] The general interest in complementary modalities has increased in recent decades because of increasing supportive data on the value of complementary therapies, as well as growing professional and patient acceptance of the modalities used. Additionally, the emphasis on wellness and survivorship, which incorporates managing long-term adverse effects from cancer treatment and reducing risk of cancer recurrence, has enhanced general interest in complementary modalities.

Impediments to communication

Optimal cancer care demands dealing with issues that are important to patients, including those that are likely to be detrimental if left unaddressed. Proper dialogue about the use and application of therapies is important. The majority of patients want to discuss the topic with their oncologists given the opportunity, yet nondisclosure remains a problem, in part because the opportunity fails to arise.[86] Additionally, patients have also reported being fearful of physician disapproval or disinterest in what they do outside of conventional treatment, or assume that such information is not important or relevant to their cancer treatment.[87,88] By contrast, physicians believe that patient nondisclosure is attributable to patient fears of physician disapproval or lack of understanding.[89] As the prevalence of complementary therapy use is high, initiating a discussion provides an excellent opportunity for the physician to demonstrate compassion, understanding and humanity, in addition to providing high-quality care based on scientific data.

COMMONLY ASKED QUESTIONS BY PATIENTS WITH CANCER AND EXAMPLE RESPONSES

Question, belief or statement	Possible responses	Examples
XYZ was reported to kill cancer cells in a laboratory experiment. Should I take it?	What works in the test tube often does not work in humans because the concentration used in the laboratory is so high that you could never achieve that level in the tumour tissue by ingesting the herb. Many things kill cancer cells in the test tube, but what kills the cancer cells might also hurt the healthy cells.	Paclitaxel is a drug derived from the yew tree. To get the equivalent of one dose, you would need to ingest >100 lbs of tree bark. Taking a few capsules of the tree bark will not do anything. If you add bleach to cancer cells, they will die. However, no one would drink bleach to treat cancer.
Chemotherapeutic drugs are toxins. I want to detoxify my body.	Some 'detox' therapies increase the activity of the enzymes in the liver to remove toxins. These enzymes can also remove chemotherapy drugs faster, meaning you are not getting the correct dose needed.	St John's wort seems to reduce the adverse effects of chemotherapy, but was later found to also lower the level of the active metabolite of irinotecan in the blood.[77]
I have so many adverse effects from my cancer treatment. Can I take XYZ to give me more energy or boost my immune system?	Be careful—some herbs have their own adverse effects or can fight against other medications you are taking.	Some 'energy boosting' herbs can raise your heart rate and blood pressure. Others can make your blood thinner if you are taking anticoagulants. Some might contain oestrogen-like substances, which might reduce your hot flushes, but can reduce the effect of the hormonal therapy you are on. Some herbs elevate your liver enzymes.
I heard that antioxidants have anticancer properties. Should I take them?	Antioxidants can protect DNA from damage by harmful elements in the environment, but they will not revert already-mutated genes back to normal. Antioxidants might have a role in cancer prevention, but they will not treat cancer; their effects in cancer prevention have not been confirmed. A healthy diet is more important than taking individual supplements.	Initial small studies suggested that vitamin E and selenium might prevent prostate cancer. Later, a randomized controlled study with tens of thousands of people showed no cancer preventive effects and even a harmful effect.[78,79]
Antioxidants protect the body from damage caused by chemotherapy and radiotherapy.	For antioxidants to protect from chemotherapy and radiotherapy the antioxidants would need to distinguish between normal cells and cancer cells, otherwise they would protect the cancer cells as well.	High-dose antioxidants given during radiotherapy have been shown to reduce adverse effects during treatment, but also might have made the cancer more likely to recur.[104]

Dilemmas for clinicians

Although most patients use natural products (supplements) hoping to reduce the adverse effects of conventional treatment, support the body through cancer treatment or prevent cancer recurrence, other patients with few or no effective treatment options might want to try anything. This desperation can lead the patient to use natural products that have shown some possible anticancer activity in early preliminary studies. Although the chances of efficacy might be extremely remote, these patients might come to the clinic with information about the benefits of various elaborate, so-called anticancer regimens.

One example is the Bill Peeples cocktail, which is often asked about by patients with advanced-stage sarcoma.[90] This product contains more than a dozen dietary supplemental ingredients that the manufacturer claims have antiangiogenic or antioxidant properties based on laboratory studies, plus a few prescription medicines used off-label. Such a scenario presents a dilemma for the oncologist faced with a patient for whom there is no effective treatment or appropriate clinical trial. How do we provide compassionate care while safeguarding our patient's best interests?

We believe that the answer lies in meeting patients where they are. We can affirm their perseverance not to give up, and tolerate their use of agents that are generally safe and have shown some preliminary evidence of anticancer activity. At the same time, we also need to help the patient work towards accepting whatever outcome he or she will eventually face, despite their best efforts and those of the treating physicians and caregivers. Palliative care often begins too late in clinical practice.[91] Instead, patients' options, goals and preferences should be assessed early in the course of cancer treatment. Personalised care of patients

with advanced-stage cancer should be tailored to the diverse physical, psychological, social and spiritual consequences of cancer for the individual.[92] Using complementary or alternative therapies might help patients feel content that they have explored every possible option, help them to accept the futility of further treatment and facilitate closure. Accordingly, the treating oncologist must take a compassionate approach in accepting these decisions by the patient. Similarly, an effort must be made to minimise the physical, emotional and financial burdens experienced by the patient, discuss and closely monitor adverse reactions and prepare the patient and family for end-of-life issues.

Integrative oncology programmes

Combining helpful complementary therapies with mainstream cancer care to reduce symptoms and improve quality of life constitutes the practice of integrative oncology. Many, if not most, cancer centres have established integrative oncology departments or programmes to provide complementary therapies and to counsel patients about potentially problematic dietary supplements and alternative therapies. Counselling by trained and experienced physicians should include guiding patients away from potentially harmful therapies and addressing their underlying psychosocial or cultural needs.[93,94] Referring patients to qualified specialists, therapists, counsellors or instructors connects these individuals to appropriate sources of facts and sound advice. These qualified personnel can serve as valuable resources for future questions, to provide support for patients' efforts, and to divert energy away from useless and potentially harmful or expensive approaches. Furthermore, as patients gain information about additional symptom management techniques, they experience positive interactions with their physicians, improve self-care skills and enhance their physical, emotional and overall well-being.[95,96]

A structured approach to discussing the use of complementary or alternative medicine with patients in general was described in 1997 and updated in 2002.[97,98] Although written for use in the primary care or internal medicine settings, this approach might be helpful in the oncology setting as well. A similar report focused on discussing complementary or alternative medicine with patients in the oncology care setting.[93] In 2010, a set of comprehensive communication guidelines was proposed on the basis of a systematic literature review of methods for the discussion of complementary modalities for oncologists.[94] Together, these works provided a framework for counselling patients with cancer on complementary or alternative therapies.

At Memorial Sloan–Kettering Cancer Center, each new patient receives an information packet that reminds them to discuss any self-prescribed supplements or medications with their physicians. All patients are asked at each visit to disclose any herbs and other dietary supplements they are taking. Patients who raise questions about complementary or alternative therapies that require discussion – and those who are on supplements at risk of interacting with prescription medicines – are referred to the Integrative Medicine Service for comprehensive counselling. During the counselling (see Figure opposite), physicians well versed in both oncology and integrative medicine make a comprehensive assessment of the patient's needs and address the issues from both the overall cancer care perspective and the patient-specific perspective.

Practice models of integrative oncology vary according to the patient demographics and the societal environment of the medical facility. The integration is not always easy and can be hampered by a lack of awareness or perceived importance by oncologists, a lack of properly trained physicians knowledgeable in both cancer medicine and complementary therapies, a lack of trust between physicians and

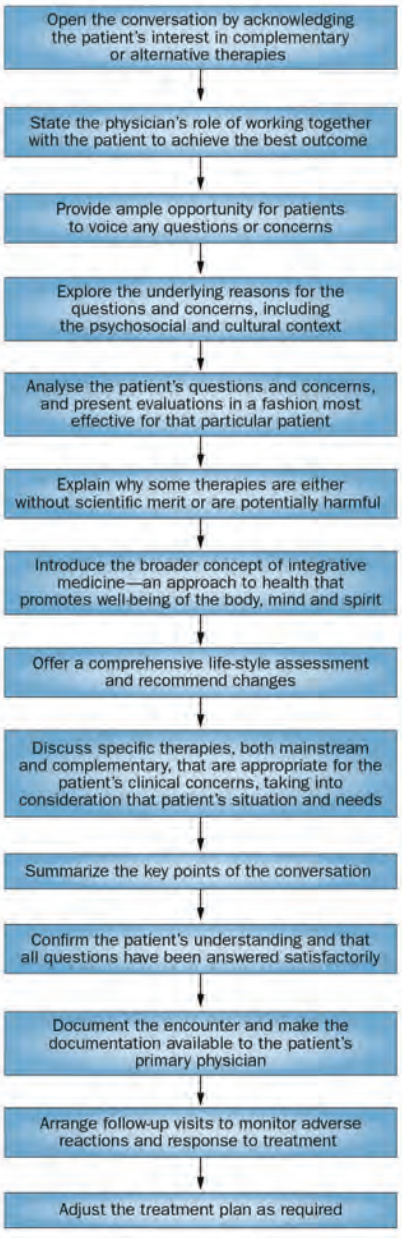
complementary therapies practitioners who are not medical doctors or insufficient funds. An investigation of six integrative oncology programmes across four continents identified several essential elements for a successful programme: location within the oncology department area, oncologist referral to consultation with integrative oncologist, sufficient time for integrative oncologist–oncologist communication, integrative practice that is evidence based, professional complementary medicine practitioners and coverage of the cost for the integrative oncology service.[99]

For busy oncologists, staying abreast of new complementary medicine research results and of the ever-expanding world of alternatives to mainstream cancer treatment is difficult. However, many excellent continuing education materials are available from reputable sources. In addition, the knowledge and expertise available from integrative oncology colleagues can be extremely helpful, especially those dual-trained in mainstream oncology and integrative medicine. National-level and international-level efforts can provide helpful information to practising oncologists. A multidisciplinary nonprofit organisation – the Society for Integrative Oncology – was formed by clinicians, researchers and patient advocates to provide a platform for the advancement of evidence-based, comprehensive, integrative healthcare to improve the lives of people affected by cancer.[100] Using the standard methodology for development of a practice guideline, which consists of systematic review of current literature and multiple rounds of peer reviews, the group evaluated the strength of the evidence for common complementary therapies, as well as any potential risks or burdens. The resulting recommendations were graded, peer-reviewed and adapted by the American College of Chest Physicians[101,102] and the Society for Integrative Oncology.[103] These guidelines represent an initial effort in giving clinicians who might not be familiar with complementary therapies evidence-based assessments of the therapies, and when and how to incorporate them into the care of patients with cancer. With time, these national and international efforts in raising the awareness of integrative oncology and its application in clinical care would improve the overall care of cancer patients.

Conclusions

Complementary or alternative medicine are topics that patients with cancer are highly interested in and also find quite confusing. Safe and beneficial complementary therapies should be integrated into regular cancer care to improve patient quality of life and outcome. However, patients should be steered away from alternative cancer therapies that are risky and do not have clinical value. Integrative oncology combines complementary therapies with mainstream care, trying to optimise the patient's physical, psychological and spiritual well-being, taking into consideration the individual's values and priorities in life. A robust integrative oncology programme should be part of any high-quality cancer care institution, as is the case for virtually all NCI-designated comprehensive cancer centres. By understanding and addressing issues our patients feel are important, compassionate care can be tailored to each patient, and oncology will reach the noble goal of treating each patient as a person with cancer, rather than treating only the cancer in a patient. ■

Steps in advising patients who are interested in complementary and alternative therapies



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Author affiliations

Gary Deng and Barrie Cassileth, Integrative Medicine Service, Memorial Sloan-Kettering Cancer Center, New York

newsround

Selected reports edited by Janet Fricker

Clinical trials lead to cost savings

British Journal of Cancer

On average, non-commercial oncology clinical trials are associated with small excess treatment costs compared to the standard of care, while commercial trials are associated with high cost savings, concludes a UK study conducted in a single centre. Recruitment of patients to clinical trials was found to be associated overall with considerable cost savings.

It has long been thought that conducting clinical trials incurs additional costs above the standard of care. Such perceptions remain a barrier to academic clinical trials being performed in many countries. In the current study, Pippa Corrie and colleagues, from the Cambridge University Hospitals NHS Foundation, explored the financial implications of conducting clinical trials.

Between January 2009 and December 2010 the team undertook a retrospective cost attribution analysis to determine the treatment costs associated with oncology (non-haematology) clinical trials. At the centre, over the two-year period, 357 cancer patients were recruited to 53 different interventional clinical trials, of which 40 were phase II, two randomised II/III and 11 phase II. Altogether 27 of the trials were academic, non-commercial sponsored trials, and 26 were commercial sponsored trials.

For each protocol, the treatment cost difference for the experimental arm(s) was calculated as the difference between the experimental arm treatment costs and standard of care costs. The costs for cancer drugs were obtained from the British National Formulary (2010).

Results show that, in comparison with the standard of care, the average treatment costs were an excess of £431 (€520) for a non-commercial trial (range £6393 excess to £6005 savings) and a saving of £9294 (€11,215) for a commercial trial (range £0 to £71,489). There was an overall treatment cost saving of £388,719 (€469,000) in 2009 and £496,556 (€599,100) in 2010, largely attributable to provision of free drug supplies from pharmaceutical companies. Overall, the treatment cost savings to the NHS were estimated to be approaching £0.5 million (€0.6 million) per annum.

Notably, seven of the non-commercial trials were associated with treatment cost savings. Two of these trials, SCOT (adjuvant chemotherapy in colorectal cancer) and PERSEPHONE (adjuvant chemotherapy in breast cancer), evaluated whether shorter durations of adjuvant treatment (which cost less) were as effective as the standard of care. Such studies, stress the authors, demonstrate the importance of academic trials, addressing questions that would not represent a priority for industry sponsors.

"In our view, this data provides overwhelming evidence to refute any concern that clinical research generates a cost pressure for the health service. On the contrary, we have demonstrated significant financial gains," write the authors. A balanced portfolio of both commercial and non-commercial research, they add, should offer the greatest benefits to patients and the overall health economy.

E Liniker, M Harrison, JMJ Weaver et al. Treatment costs associated with interventional cancer clinical trials conducted at a single UK institution over 2 years (2009–2010). *BJC* 15 October 2013, 109:2051–57

Strain analysis reveals subclinical LV dysfunction following anthracyline treatment

European Journal of Cancer

Myocardial strain imaging proved more sensitive than left ventricular ejection fraction (LVEF) in the early detection of left ventricular systolic dysfunction following

anthracycline chemotherapy in HER2/neu-negative breast cancer patients, reports an Australian study.

While anthracycline chemotherapy has remained the cornerstone of breast cancer treatment for four decades, efficacy has been undermined by its dose-dependent cardiotoxicity. In the current study, Paul Stoodley and colleagues, from Liverpool Hospital, Liverpool, Australia, set out to establish whether strain imaging would reveal LV systolic dysfunction not discernible with LVEF in patients with HER2/neu-negative breast cancer up to 12 months after treatment with anthracyclines.

Between October 2008 and March 2011, 78 consecutive anthracycline-naive breast cancer patients were studied prior to the commencement of anthracycline chemotherapy (T1) and within seven days of completing anthracycline therapy (T2). Then in the second part of the study patients found to be HER2/neu-negative were studied at six months (T3) and 12 months (T4) after the initial exam. At these time points LVEF was measured by Simpson's method according to recommendations of the European Association of Echocardiography, while LV longitudinal peak systolic strain (LPSS) was measured with 2D speckle tracking echocardiography.

Altogether 28 of the original 78 participants (36%) were found to be HER2/neu-positive by in situ hybridisation, and therefore proceeded to trastuzumab therapy and were excluded from the analysis at T3 and T4. This left 50 HER2/neu-negative participants who were studied at four time points over 12 months.

Results show that global systolic strain was significantly reduced from a baseline of -19.0±2.3% to -17.5 ± 2.3% immediately after treatment (P<0.001), rising by six months to -18.2±2.2% (P=0.01). LVEF, on the other hand, remained largely unchanged at both T2 and T3.

By 12 months (T4), global strain had normalised in 84% of patients, with persistent strain remaining in 16% (n=8). A re-analysis of data from patients with persistent global strain showed that they had greater reductions in strain at six months (-17.2%), and had received higher cumulative doses of anthracyclines.

"While HER2/neu positive patients treated with adjuvant trastuzumab are monitored closely, we have demonstrated subclinical LV dysfunction by strain analysis in HER2/neu negative patients, who comprise ~75% of all breast cancer patients," write the authors.

Monitoring HER2/neu-negative patients who receive anthracycline therapy at baseline and six months, they add, would help identify patients with subclinical cardiac dysfunction who would benefit from additional cardiac monitoring and treatment.

■ P Stoodley, D Richards, A Boyd et al. Left ventricular systolic function in HER2/neu negative breast cancer patients treated with anthracycline chemotherapy: A comparative analysis of left ventricular ejection fraction and myocardial strain imaging over 12 months. *Eur J Cancer* November 2013, 49:3396–3403

Model predicts life expectancy in patients with metastatic cancer

■ Cancer

The TEACHH model is able to divide patients receiving palliative radiotherapy into three distinct life expectancy groups. The approach, suggest the US authors, offers the promise to better tailor palliative therapies to the patient's outlook.

Estimating prognosis is one of the most difficult tasks encountered by oncologists, particularly for patients with metastases whose life expectancy can vary between days and years. But predicting life expectancy has important clinical implications. In an earlier study, Edward Chow and colleagues, from the University of Toronto, created and validated a prognostic model that categorised palliative cancer patients into one of three prognostic groups, using the cancer type (breast vs non-breast), Karnofsky performance status (<70 vs >70) and metastasis location (bone only vs other) (*JCO* 2008, 26:5863–69).

In the current study Monica Krishnan and colleagues, from Dana-Farber Cancer Institute, Boston, Massachusetts, set out to build on the model created by Chow to identify patients at the extreme ends of the prognostic spectrum, i.e. those with short (<3 months) and long (>1 year) life spans.

Between June 2008 and July 2011, the records of 862 patients with metastatic cancer receiving palliative radiotherapy at the Dana-Farber Brigham and Women's Cancer Center were retrospectively reviewed.

Results of a multivariate analysis showed that factors significantly associated with shorter life expectancy were cancer type (lung and other vs breast and prostate), older age (>60 years vs <60 years) liver metastases, Eastern Cooperative Oncology Group performance status (2–4 vs 0–1), hospitalisations within three months before palliative radiotherapy (0 vs >1) and prior palliative chemotherapy courses (>2 vs 0–1).

A further analysis showed that patients in group A who had 0–1 risk factors had a median overall survival of 19.9 months (95%CI, 13.9–31.1 months), that patients in group B who had 2–4 risk factors had a median overall survival of 5.0 months (95%CI 4.3–5.6 months), and that patients in group C who had 5–6 risk factors had a median overall survival of 1.7 months (95%CI 1.2–2.1 months).

"By providing LE estimates, this model may help clinicians provide quality palliative care to their patients with advanced cancer and their families," write the authors, adding that the number of prior palliative chemotherapy courses and hospitalisations have not been reported previously as factors predictive of life expectancy.

The TEACHH model can help identify those patients who are eligible for hospice care and guide end-of-life discussions with patients, it can be used to select hypofractionated RT regimens to avoid protracted courses of RT near death, and to identify those patients with longer life expectancies who may be candidates for dose escalation, which has been associated with improved local control for certain palliative disease sites.

The model, they add, requires external validation to assess its accuracy in disparate settings of patients with advanced cancer presenting for palliative radiotherapy.

■ M Krishnan, Z Epstein-Peterson, Y Chen et al. Predicting life expectancy in patients with metastatic cancer receiving palliative radiotherapy: the TEACHH model. *Cancer*. doi:10.1002/cncr.28408

Adjuvant gemcitabine improves overall survival in pancreatic cancer

■ JAMA

For patients with macroscopic complete removal of pancreatic cancer, treatment with adjuvant gemcitabine for six months resulted in a 24% improvement in overall survival in comparison to observation alone, report the latest findings of the CONKO-001 study.

The vast majority of pancreatic cancer patients presenting with localised disease allowing surgical resection relapse within two years, leading to five-year survival rates of less than 25%. Although controlled trials have been conducted in the area of adjuvant therapy for almost three decades in such patients, no consensus has been reached on standard approaches to treatment.

In the current CONKO-001 study, Helmut Oettle and colleagues, from the Charité-Universitätsmedizin, Berlin, set out to compare adjuvant intravenous gemcitabine with observation alone in patients undergoing complete, curative-intent resection of pancreatic cancer. The primary endpoint of the study, disease-free survival, has already been reported.

Between July 1998 and December 2004, 368 patients from 88 centres in Germany and Austria were randomised to adjuvant gemcitabine treatment (1g/m^2 days 1, 8, 15, q 4 weeks) for six months (n=186) or observation (n=182). Altogether 179 patients from the gemcitabine arm and 175 patients from the observation arm were eligible for the intention-to-treat analyses of disease-free survival and overall survival. At randomisation, patients were stratified according to tumour stage (T1–2 vs T3–4), nodal status (N0 vs N1), and resection status (R0 vs R1), based on the TNM classification.

By September 2012 (when 89.3% of patients had died), the median overall survival was 22.8 months for the gemcitabine group versus 20.2 months for the observation group (HR=0.76, 95%CI 0.61–0.95, P=0.01). As reported previously, median disease-free survival was 13.4 months in the gemcitabine treatment group compared with 6.7 months in the observation group (HR=0.55, 95%CI 0.44–0.69, P<0.001). At five years, disease-free survival was 16.6% in the gemcitabine group versus 7.0% in the observation group, while at 10 years, disease-free survival was 14.3% in the gemcitabine group versus 5.8% in the observation group.

The treatment effect was detected consistently across all the pre-stratification subgroups of tumour stage, nodal status, and resection status.

"The statistically significant differences in disease-free and overall survival between treatment groups support the use of gemcitabine as the backbone for future studies of adjuvant therapy following R0/R1 resection of pancreatic cancer," write the authors. Since the study was designed to be applicable to community-based oncologists (without uniform standards for surgery or centralised pathology review), as well as academic centres, they add, the results are likely to be representative of general clinical practice beyond the study countries.

■ H Oettle, P Neuhas, A Hochhaus et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer. The CONKO-001 randomized trial. *JAMA* 9 October 2013, 310:1473–81

START: 10-year data support hypofractionated radiotherapy for early breast cancer

■ Lancet Oncology

Ten-year follow-up results for the START trials continue to support use of hypofractionated schedules of radiotherapy contracting treatment from five to three weeks following primary surgery in early breast cancer.

In the START studies, following primary surgery, chemotherapy and endocrine treatment, women with completely excised invasive breast cancer from 35 UK radiotherapy centres were randomly assigned, between 1999 and 2002 to different radiotherapy treatment regimens.

The five-year results of the UK Standardisation of Breast Radiotherapy (START) trials suggested that lower total doses of radiotherapy delivered in fewer, larger doses (fractions) were at least as safe and effective as the historical standard regimen (50 Gy in 25 fractions). While the results informed the National Institute for Health and Care Excellence (NICE) and American Society for Radiation Oncology (ASTRO) guidelines for breast radiotherapy fractionation, a 2010 Cochrane review concluded that longer follow-up was needed for a more complete assessment. In the current publication, John Yarnold and colleagues, from the Royal Marsden NHS Foundation, London, report on 10-year data.

In START-A, 2236 women were randomised to receive 50 Gy in 25 fractions (the historical standard), 41.6 Gy in 13 fractions, or 39 Gy in 13 fractions – all delivered over five weeks. The 10-year rates of local-regional relapse were 6.3% for the 50 Gy arm versus 7.4% for the 41.6 Gy arm (HR 0.91, *P*=0.65) and 8.8% for the 39 Gy arm (HR=1.18, *P*=0.41). In comparison to the 50 Gy group, women in the 39 Gy group had significantly less moderate or marked breast induration (*P*=0.034), telangiectasia (*P*=0.003), and oedema (0.001). No significant differences were found between the 41.6 Gy and 50 Gy groups.

In START-B, 2215 women were allocated to receive 50 Gy in 25 fractions over five weeks or 40 Gy in 15 fractions over three weeks. The 10-year local-regional relapse rates were 5.5% for the 50 Gy group versus 4.3% for the 40 Gy group (HR=0.77, *P*=0.21). In comparison to the 50 Gy group, women in the 40 Gy group had significantly less breast shrinkage (*P*=0.015), telangiectasia (*P*=0.032), and breast oedema (*P*=0.001).

"The hypofractionated and control schedules at 10 years remain similar to those at 5 years, confirming that appropriately dosed hypofractionated radiotherapy for women with early breast cancer is safe and effective," write the authors.

In an accompanying commentary, Bruce Haffty and Thomas Buchholz, from Rutgers-Cancer Institute, New Jersey, write that widespread use of a three-week course of radiation might provide patients with more convenient treatment schedules, while reducing health-care costs without compromising patient outcomes.

■ J Haviland, J Owen, J Dewar et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* October 2013, 14:1086–94

Sentinel lymph nodes: high false-negative after neoadjuvant chemotherapy

■ JAMA

Among women with clinically node-positive (cN1) breast cancer receiving neoadjuvant chemotherapy, who had two or more sentinel lymph nodes (SLNs) examined, the false-negative rate did not meet the predefined study criteria, the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial has concluded. In the phase II trial, use of dual-agent mapping and sampling of at least three SLNs was associated with a lower likelihood of false-negative SLN findings.

While for patients who initially present with node-negative breast cancer, axillary lymph node dissection (ALND) has been replaced by SLN biopsy, the application of SLN for staging the axilla following chemotherapy for women who initially had node-positive cN1 breast cancer remains unclear due to high false-negative rates reported in previous studies.

In the ACOSOG Z1071 trial, Judy Boughey from the Mayo Clinic, Rochester, Minnesota, and colleagues, explored the false-negative rates of SLN biopsy after neoadjuvant chemotherapy, in women who initially presented with cN1 disease. Between July 2009 and June 2011, the investigators enrolled women from 136 institutions who had clinical T0 through T4, N1 through N2, M0 breast cancer and received neoadjuvant chemotherapy. The study protocol was that all SLNs were excised and submitted prior to the ALND procedure. To maximise the likelihood of SLN identification. SLN mapping with both blue dye and radiolabelled colloid mapping agents was recommended.

Results showed that, of the 756 women enrolled, 649 underwent chemotherapy followed by both SLN surgery and ALND. The researchers found that the false-negative rate was 12.6%, which exceeded the prespecified threshold of 10%.

The researchers found that the false-negative rate was 10.8% when a dual-agent mapping technique was used, versus 20.3% when a single agent mapping technique was used (*P*=0.05). Furthermore, the investigators found that the false-negative rate was 9.1% when three or more SLNs were evaluated versus 21.1% when two SLNs were evaluated (*P*=0.007).

"Given this acceptability threshold, changes in approach and patient selection that result in greater sensitivity would be necessary to support the use of SLN surgery as an alternative to ALND in this patient population," conclude the authors, adding that after chemotherapy the axilla has more fibrosis, making evaluation of lymphatic drainage and surgical dissection more challenging. Using two mapping agents with different molecular sizes and transit times, they suggest, might offer an important surgical standard for SLN surgery after chemotherapy.

In an accompanying commentary, Monica Morrow and Chau Dang, from Memorial Sloan-Kettering Cancer Center, New York, write that as clinicians move away from the 'one size fits all' approach, prognostic information obtained from residual nodal disease following neoadjuvant therapy is likely to become increasingly important in helping to determine the need for additional therapy. "If that is true, research in ways to improve the performance of SLN biopsy after neoadjuvant therapy is needed for this approach to become a viable management strategy," they write.

■ J Boughey, V Suman, E Mittendorf et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer. The ACOSOG Z1071 (Alliance) Clinical Trial. *JAMA* 9 October 2013, 310:1455–61

■ M Morrow, C Dang. Sentinel node biopsy after neoadjuvant chemotherapy a new standard for patients with axillary metastases? *ibid* pp 1449

My World

Bettina Ryll is a patient advocate and founding member of the Independent Melanoma Community Advisory Board. A qualified doctor, with a PhD in molecular biology, she gained a deeper insight into the reality of cancer, and fighting cancer, when her husband Peter was diagnosed with advanced melanoma. She now uses that insight to help others.

Why I chose to be an advocate

I didn't feel I had a choice. Going through the experience of advanced melanoma with Peter made me realise where things go wrong for patients, but also what can be done to make things better. Not doing it now would simply feel wrong.

What are the rewards?

I've learnt so much, not just about melanoma, treatment options and their limitations, but also how details that seem insignificant in health make all the difference when you are ill, about trials and how to access them, the shortcomings of research with regard to patients' needs, how to function under huge psychological pressure, how to live despite having death as part of your life, how to deal with friends and family and their grief, how to tell your children that their father is dying... I wish I'd never had to learn this, but it is rewarding that I can now help others in a situation similar to ours.

What I find hardest

The slow rate of progress. Melanoma patients don't have much time. The combination of slow progress with patients dying quickly is very hard.

What I've learnt about myself

I am far more resilient and less willing to give up than I thought, and I can find something positive in any situation. Peter and I packed goodie bags for our children's birthday party in the radiotherapy waiting room. We celebrated his birthday, just two weeks before he died, with cake and champagne in hospital. It was probably pure defiance, but those were good moments.

I'll never forget...

Our group of melanoma patients – Taron, Quentin, Petr, Patricia and Peter – who all died horrendous deaths but supported each other and made all the difference to the time we had together.

A high point in my advocacy work

At the moment I'm content if I feel that we've come a babystep closer to better trials for melanoma patients!

I wish I were better at...

Time-management. There is always so much to do and so little time!

What I value most in advocates

The ability to turn adversity into strength, courage and compassion and use personal experience to help others.

The most significant innovation for patients in recent years

The recognition that patients are not simply consumers of a service, but possess knowledge that can improve the situation for society as a whole.

Advances I would most like to see

More efficient ways of developing, licensing and reimbursing drugs, to ensure that patients are not denied access to potentially life-saving therapies for the sake of extended risk evaluation (after all, the risk of untreated melanoma is death). They should also not be submitted to inferior treatments or placebos solely to fulfill trial design criteria coming from an era when the exponential increases in efficacy seen in melanoma today were unthinkable.

What I wish health professionals would learn in their training

I wish they were made aware that most of them are future patients and it is in their hands to influence how they themselves will get treated in the future! I would like medical students to get the chance to meet patients as persons, not only as medical cases, because I believe they would then be able to deliver better care. ■