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LESS INVASIVE, LESS TOXIC

Do interventional radiologists merit a place at the multidisciplinary table?

POOR QUALITY CANCER CARE

Is centralisation the answer?

TOBACCO TACTICS IN THE HEADLINES

The story behind *The Independent's* in-depth exposé

Richard Sullivan

Why are we doing this?

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Cancerworld

Shaping the future of cancer care

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Struck by cancer, killed by ageism

KATHY REDMOND EDITOR

Care of elderly cancer patients has improved over recent years; however, younger patients in Europe still survive longer than more elderly patients, and the difference cannot be accounted for by the higher likelihood of dying from all causes as you get older. Evidence suggests that there are a number of reasons why older people with cancer fare worse than their younger counterparts.

A recent study has shown that elderly patients are more likely to have their cancer diagnosed as an emergency, which compromises their chances of surviving. A variety of studies have demonstrated that, after controlling for patient choice, co-morbid conditions and pathological and biological factors, older patients are less likely to receive appropriate treatment than younger patients.

The worry is that clinical decisions are still being made on the basis of a patient's age, leading to significant under-treatment. Such decisions are often underpinned by ageist attitudes and stereotyping of older people. A survey of 155 British oncologists, cancer nurses and GPs, carried out late last year by the cancer charity Macmillan Cancer Support, showed that discriminatory practices persist. Nearly half the respondents indicated that they had been involved with a cancer patient who had been refused treatment because of their age.

In a sign that policy makers are beginning to recognise how serious this problem is, the UK Department of Health, together with Macmillan Cancer Support, have just published a joint report on cancer in the elderly. It noted that older people are becoming increasingly heterogeneous in terms of their life expectancy, their physical and mental well-being and their willingness to undergo aggressive cancer treatments, and it argued that treatment decisions should be based on an objective assessment of the patient's preferences, condition and circumstances, not on assumptions.

The report presents a series of recommendations, key among which are: we must act now because not acting will cost more money in the long term; cancer specialists and elderly care specialists must engage more effectively with one another in planning and delivering cancer services; treatment decisions must be tailored to individual patients using proven assessment methods that differentiate frail from fit elderly patients; and multi-agency working is essential to ensure that the needs of patients with more complex problems are effectively addressed.

Implementing these recommendations, not just in the UK, but all over Europe, could significantly improve the quality of care for many elderly patients. We also need to address the problem of late diagnosis: why are so many elderly patients being diagnosed in an emergency setting and what can we do about it? Discrimination has no place in modern cancer care and determined efforts are required to ensure that age is not a barrier to accessing high-quality diagnosis and treatment. ■

Richard Sullivan: Why are we doing this?

SIMON CROMPTON

Cancer policy is determined by opinions not evidence, with the loudest voice setting the agenda. This is the worry of Richard Sullivan, who is on a mission to open the discussion to voices beyond the "comfortable little world of oncology", and allow new evidence and intelligence in.

Richard Sullivan would like you to ask yourself a question: is what you're doing justified by evidence? Not just you, but everyone in the cancer community, everyone treating patients, everyone developing protocols, guidelines and policy. When you go back to hard data about what benefits people most, are you sure that the things that you do, the assumptions that you make, are built on firm enough foundations?

His demand for a deeply rational approach might make more sense to you when you know that he is the man who led the recent *Lancet Oncology* commission on cancer costs in high-income countries and identified a "culture of excess" in cancer which demanded a radical shift in policy. His controversial report, published in September 2011, concluded that cancer professionals and industry should "take responsibility and not accept a substandard evidence base and an ethos of very small benefit at whatever cost." Specifically, he and his co-authors pointed to the growth of new technologies, over-use of expensive cancer drugs with limited impact, lack of health economic studies, lack of suitable clinical research, defensive medical practice, and a lack of evidence-based socio-political debate.

Their report said that, while the number of cancer drugs available in rich countries had risen from 35 in the 1970s to nearly 100 now, few treatments were "clear clinical winners". It drew flack from cancer patient organisations for criticising the "futile" provision of expensive care to patients during the last weeks of life.

Today, speaking to me in his office in Guy's Hospital, London, where he is based, the Professor of Cancer Policy and Global Health at the King's Health Partners Integrated Cancer Centre wants to take his message still further. What really annoys him, he says, and what he really wants to change, is the fact that cancer policy is still led by opinion, not evidence.

"The loudest voice sets the agenda," he says.

"What's stunning is that as scientists and clinicians, particularly in the academic field, our lives are supposedly dominated by the use of evidence in the way we treat patients and define protocols. And yet we don't apply the same rigour when it comes to designing systems, creating policy."

"I see it at every level, whether it be local, national, European or global, and my biggest mission is to provide intelligence to allow people to have a framed debate about what the reality of the world is, rather than what someone's opinion is."

Sullivan is a big picture man, restlessly inquiring, with some big opinions of his own. Trained as a surgeon, moving straight into academia and then industry, his perspective was shaped by seven years as clinical director at Cancer Research UK, the world's largest independent cancer research charity. Add to that the fact that for 18 years he combined his cancer work with membership of the British Army reserves, and that he has an active interest in ancient medicine, Egyptology, rebuilding conflict zones, conservation biology, science communication and medicinal mushrooms, and you'll get the idea: Sullivan, still only 45, isn't a man with a fusty, limited perspective.

As the thoughts speedily tumble out during our interview, it becomes increasingly clear that the diversity of his experience with various cancer "tribes" as he calls them is also what sets him apart from any particular establishment. He is a bit of an outsider, with a unique overview, and he wants to use that perspective to bring change.

"If you really want to explain the world, you have to see through different lenses, prisms, walk through different doors," he says.

So it is not surprising that his main message in the *Lancet Oncology* report was the need for more debate and open-mindedness. It also makes sense that his message to the medical profession in his *Annals of Oncology* editorial on global health last October was equally hard-hitting. If cancer is to be controlled in low- to middle-income countries, he said, "then we are all going to need to step outside our comfortable 'little' world of oncology to embrace the players

JASON HARRIS

"The people with the loud voices who make the big decisions aren't necessarily the best qualified to do so"

(World Bank, IMF, global commodities, trade agreements, etc.) that will really shape future outcomes for patients."

The problem with the comfortable little world of cancer, he says bluntly, is that the people with the loud voices who make the big decisions aren't necessarily the best qualified to do so.

"Senior people are expected to have insight and opinions on a whole range of public policy issues in which they may never have been trained. They have gained their seniority in relatively narrow areas of clinical medicine or science and are suddenly asked and expected to make public policy, strategy, and political decisions about issues that they have little experience or training in."

Debate around affordability of cancer care has also become stifled, says Sullivan, because funders, governments, industry and other parts of the cancer community have become more closely bound together, making it harder for people to stand outside and criticise.

"We need to challenge policy in cancer that masquerades as public health when it's really being utilised to leverage commercial advantage," he says.

It's Sullivan's job to provoke debate. King's Health Partners Integrated Cancer Centre is an academic health sciences centre, bringing together the expertise of leading London hospitals. Established in 2008, its aim is to create a centre where world-class research, teaching and clinical practice are brought together for the benefit of patients in South East London and beyond. It is a designated centre for the EORTC Network of Core Institutions, and a Member of the Organisation of European Cancer Institutes (OECI).

Sullivan was brought in at the outset to head up the international activities of the centre and develop an international cancer policy and global health theme encompassing clinical services, research and academic arms. At the same time, with the support of the Veronesi Foundation and the online oncology channel eCancer, he developed a new Institute of Cancer Policy – a think-tank-cum-task-force which aims to understand problems and map out solutions for the global cancer community.

It has a programme of daunting breadth, taking on work from a wide range of funders and strategic partners. It is currently helping develop national research and development systems in Chile, South Africa and India, and was the policy research lead in an EU consortium studying cancer communications (ecancerHub). It has a particular focus on affordable cancer care, public health systems in developing countries, and the special problems of countries made frail by conflict, such as Libya, Afghanistan and Syria.

So when Sullivan talks about the work "we" are doing, he's referring not to himself, but to a wide range of experts and partners, mainly drawn from the staff at King's Health Partners, and from disciplines as wide ranging as economics, social science, politics, psychology, global health, anthropology, conflict resolution and communication. Sullivan believes that to solve the problems with cancer you have to look to disciplines outside cancer. The cancer world by itself simply doesn't have the know-how to put global cancer policy and resourcing issues straight.

It's what he calls "democratising" cancer policy, to allow new evidence and intelligence in.

Nowhere is this more true than in the field of finding solutions for the growing burden of cancer in low- to middle-income countries.

His *Annals of Oncology* editorial last year pointed out that cancer had been off the global health menu until the United Nations held a high-level meeting on non-communicable diseases in September 2011. Though 70% of cancer deaths are in low- to middle-income countries, just 4% of global research and development knowledge is applicable to these settings.

"If you think of the amount of money in

national research funds in high-income countries, and how much of that money goes into real global cancer, it's a percentage of a per cent. It's embarrassing. I stood up at UICC last year and said this."

But supplying exciting, expensive, hard-to-maintain innovations and technologies is not the answer.

"I used to believe passionately in technology leapfrogging for the good of global health," he says. "Now we've done a lot of research in low-income countries, I've completely changed my mind. We have almost nothing to teach them. In fact, if anything, it's the other way round. I've seen approaches, pathways, innovations coming out of South Africa and particularly India – places like the Tata Memorial Centre in Mumbai – which frankly all care teams in high-income countries should see."

"There is still a tendency for some parts of the cancer community in high-income countries to act in an imperialist way. They say: 'We're going to have a big meeting and then we're going to set down guidelines for the treatment of x in low income countries,' with little understanding of the country in question. This annoys me so much. Most people who develop cancer will do so in countries with a health trajectory that is completely different from that of high-income countries. This is cancer within the context of a double, triple, quadruple disease burden. But many of the solutions that work seem to get little visibility."

They are often the simplest things: improving systems, organisation, or the availability of very basic treatments.

Twinning arrangements can have a massive impact. Sullivan cites the example of a partnership between Indiana University and Eldoret in West Kenya, which over the last decade has built impressive cancer services and bicultural understanding. Twinning arrangements by World Child Cancer, a charity that has been facilitating and funding international hospital twinning partnerships since 2007, have brought huge advances for children with cancer in emerging and low-income countries, he says.

"It comes down to real partnership. Spending time there to understand culture and what the real problems are, building relationships, having the money available at the back but not just handing it out, making things sustainable, having an exit strategy." Helping countries develop solutions rather than importing them wholesale takes time, money and support from institutions and organisations – but once achieved, they can serve as a model for other countries to follow.

JASON HARRIS

Sullivan and his team are now working on long-term plans for sustainable cancer service development in countries such as Sierra Leone through the King's Global Health Centre. He took colleagues from King's to spend time in

He also began to see some of the 'darker side' of human nature and the limitations of 'big cancer'

Chile (where he is Visiting Professor in Cancer and Public Health at the Universidad Catolica) to help the country establish research management and planning policies and structures. "I'm hoping this could also act as a template for other Latin American countries."

Sullivan's passion for global health – indeed his occupational restlessness – might be explained by his itinerant background. An only child, he was born in Aden in Yemen, his parents employed in the British diplomatic service and oil industry. Their postings took him rapidly across the Middle East and East Africa – "It was very formative to have exposure to so many cultures and environments so soon" – and then, when he was 12, back to the UK. Having adjusted to the cold, it was British prep school and a boarding school in Hampshire, which became "like a new family". He loved the sport, the outdoor life, the cadet force, and learned how to be self-sufficient.

Inspired by the books of James Herriot, he decided he wanted to be a vet. "But my grades weren't good enough, so I went into medicine instead, which wasn't as demanding!" In 1987, he went to St Mary's Hospital Medical School in London, and realised he had made the right decision – he loved lab work, experimental pathology (in which he gained his BSc degree) and most of all working with clever, dynamic people. He admits to finding the rotations during his surgical training "unimaginably dull", and he kept his mind occupied by writing "weird articles" about ancient medicine and the hazards of reproduction in space.

He also had another source of stimulation. During medical school he had joined the army medical corps "while slightly bored", but soon moved into the intelligence group of the British army reserves. Ever since, until 2005, his part-time army activities provided him with a counterpoint to the medical world. They took him all over the world, gave him an expertise in biological weapons that put him on a NATO working group, and primed his abiding interest in the public health issues of countries recovering from conflict (Libya, Syria and Kosovo in particular). He is appalled at how little research has been done on the policies for post-conflict reconstruction, and is today part of the team from King's building a conflict and health focus.

After qualifying as a surgeon, he completed his doctoral research into the regulation of the cytoskeleton and exocytosis by G-proteins at University College London (simultaneously studying the adaptation of mammals to iodine-depleted environments with colleagues from the University of Chile) under the supervision of cell biologists Bastien Gomperts, Anna Koffer and Alan Hall – "brilliant people, who took no prisoners and taught me the fundamentals of molecular biology."

Then, in 1999, he boldly stepped out of vibrant academia into industry, joining the clinical research and medical affairs divisions at Merck KGaA. Why?

"I wanted a taster," he says. "There's no substitute for being on the inside to give you an idea of how pharma thinks, the models, problems and who makes the decisions." As the company developed its cancer portfolio including medicines like cetuximab, it also nurtured Sullivan's interest in cancer. One year later, the insights into drug development became valuable when he began his seven-year stint as clinical director at Cancer Research UK (CRUK), which supports hundreds of clinical trials into new drugs and treatments.

Sullivan was part of the team that developed the organisational framework for the UK's Experimental Cancer Medicine Centres initiative and led the development of the CRUK Cancer Centre initiative. He became the organisation's main contact point with the media, providing expertise on a range of clinical and

JASON HARRIS

Rethinking global strategies. Sullivan with some of the 100 cancer experts and journalists who gathered at the World Oncology Forum, Lugano 2012, to assess the success of current approaches to controlling cancer

policy subjects – which has left him with an enduring interest in communication issues. He admits to having been intolerant of press distortion and oversimplification, until he came to understand how they too were often manipulated by the publicity machines of organisations.

Working at CRUK was, he says, "like fast-forwarding two or three lifetimes in seven years" – he could push on innumerable doors to find out the true story about every aspect of cancer research, policy and practice, and see the world through the eyes of patients, clinicians, academics, researchers, funders, industry and policy makers alike. "I can't think of any aspect of science I wasn't exposed to," he says.

But alongside the passion, he also began to see some of the "darker side" of human nature and the limitations of "big cancer". There were some things that could be better said and done outside the restrictions of the establishment. "It was time to walk across the mountain range and find another tribe," says Sullivan.

The tribe called academia has given him the freedom to speak his mind. Now he can talk openly about the great irrationalities and inequalities that annoy him. Foremost is the way that research and funding is vastly, and irrationally, skewed towards cancer drugs, as opposed to other interventions such as surgery and radiotherapy.

"Every piece of quantitative data you look at – whether it be media articles, bibliometrics, expenditure on R&D – will indicate that medicines dominate the socio-political and cultural space. When I present this data, and show people that funders are now spending nearly 80% of their money on basic biological research and drug development, and then show them research done by an Australian group which shows the public health benefit of all cancer drugs compared to other primary modalities is just 20%, absolute maximum – then everyone starts shuffling their feet."

"But everyone gets excited about drugs because they're where the big science is, and the research funding too. There are 624 new

"They may bring some benefit to some people, but as a population measure they are not where the action is"

Supporting healthcare in Wamba. Sullivan has made three trips to this highly remote community in the Democratic Republic of Congo to deliver medical training, medicine and equipment as part of a joint health-conservation project. He is pictured here with lead medical technician Gilbert Mbonio Poikombela and his team

molecular entities currently in phase I to III trials in high income countries. This is an unbelievable number. They may bring some benefit to some people, but as a population or public health measure, they are not where the action is."

But surely there's a problem with his strictly rational population-based approach to policy, I suggest. Doesn't it continually run up against the clinician's fundamental aim to improve life expectancy and quality for each individual patient? And at a time when the emphasis in the clinic is increasingly on personalisation rather than one-size-fits-all approaches, is it surprising that some in the cancer community find it hard to engage with those who tell them they should stop treatments which still offer hope to individuals?

"But you need an open debate about what the trade-offs are and where we really stand," says Sullivan. "The numbers aren't out there, so people can't make these decisions in the first place. You can't talk about the cost of something without knowing about the losses."

"I absolutely agree with you that in high-income countries there is a growing and serious divergence between society and individualism. But we've found out that, even with the rise of individualism, people are still very socially minded. The public are quite prepared to debate these things. We just assume that adding more and more for smaller and smaller benefit is what they want, and that the doctor–patient interaction can't be done on a rational basis, but the truth is that it can. So if multiple lines of therapy are being provided towards the end of life with little benefit, we need to stand back, examine these systems and ask: why are we doing this?"

Answering these questions is as much about looking at sociology and culture – how people interact, what sorts of systems engage people – as high-level cancer policy. So Sullivan is increasingly working with social scientists at King's, looking at social hierarchies, how patients can be better engaged in policies, and the practical realities of making policy relevant for individuals as well as populations.

It's another example of the way that Sullivan actively seeks out the challenging. Does his questing mind ever manage to go into neutral? His 10-year-old daughter Alice is one diversion. So are skiing and horse riding. But what really provides a therapeutic mental shut-down is another legacy of his army activities: skydiving. He engages in parachute training with the army, and regularly performs HALO (high-altitude low-opening) jumps from 30,000 feet with full oxygen. "You get two and a half minutes of free-fall. It's bloody cold. But it's a complete mental break. It shuts down everything apart from what you are doing, so it's hyper-relaxing!"

Richard Sullivan, then, is not your average health academic. Somehow you feel that the cancer world might benefit from a few more generalist, tribe-swapping, evidence-driven, combat-ready sky-diving professors. But maybe, given the difficult questions he is asking, one is enough to be getting on with. ■

We hit the spot

The new techniques that could bring interventional radiologists to the multidisciplinary table

MARC BEISHON

Less invasive than surgery and less toxic than systemic therapy, will the fast-growing specialty of interventional radiology join the 'big three' as the fourth pillar of cancer care?

Looking at the specialists in the front-line of oncology, the 'big three' of surgeon, medical oncologist and radiotherapist are the dominant forces, and rightly so, as the recognised clinicians in cancer treatment. But other medical disciplines that work alongside them are also increasing their impact on clinical care, none more so than interventional radiologists, who not only are very active now in oncology but are also staking a claim to being among the leaders in new developments – and indeed the 'fourth pillar' of cancer care.

Radiology is most associated with diagnostic procedures that use the array of imaging techniques to examine the body's anatomical structures. But in the past few decades radiologists have also pioneered minimally invasive techniques that are now widely used in clinical practice, such as angioplasty and stents used to open blocked arteries, and embolisation for bleeding. Radiologists invented these procedures because they are imaging specialists, and image guidance is often needed to place devices such as catheters, needles, probes and stents. So successful have they been that some other specialists, such as cardiologists and neurosurgeons, now 'own' the techniques in their fields.

This doesn't worry Brian Stedman, consultant radiologist at Southampton University Hospitals NHS Trust, UK. "My feeling is that interventional radiology is in the front wave of medical technology – we often develop techniques that other specialities take on, such as angioplasty for heart disease and vascular treatments for aneurysms such as carotid and leg stenting, which have taken over from surgery. So surgeons have now trained in these, taken the workload off us and gone on to further develop the procedures. Meanwhile we will go on developing new techniques, some of which will stay in radiology because of their complexity or rarity."

One major field where radiologists are now making their mark is oncology,

CT-guided biopsy. With the help of images taken approximately every second, this interventional radiologist can guide the needle to a precise target located deep in the patient's abdomen

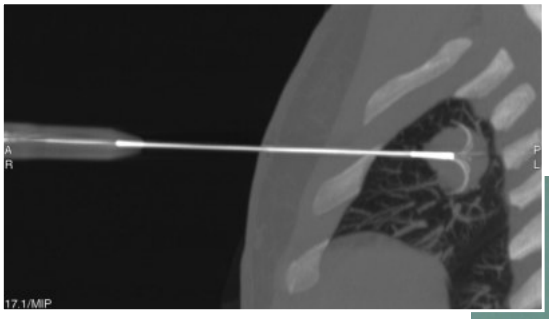
INSTITUT GUSTAVE ROUSSY

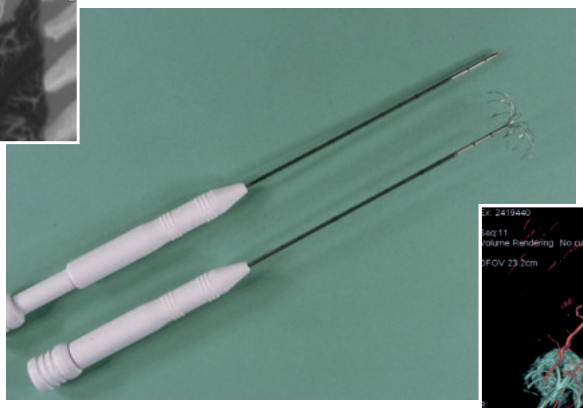
says Stedman. He himself is a specialist in abdominal radiology and a clinical lead for cancer services in his area, and he recently made the news for carrying out the UK's first 'chemo-bath' of the liver for two patients with metastatic melanoma of the eye.

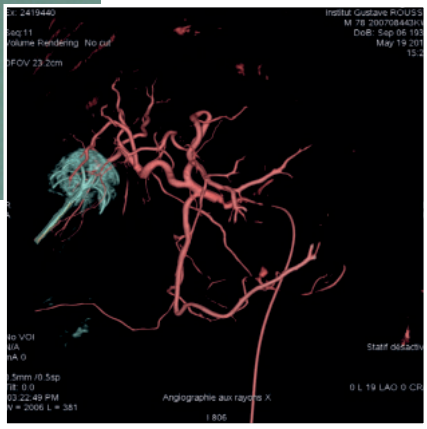
This technique – which isolates the liver for a short period during which chemotherapy is delivered directly to the organ – is not likely to be widespread given the rarity of both the tumour and the expertise needed to carry it out. But for Stedman it points to a key concept in the delivery of drugs. "I think in 20 or so years' time we may look back and see giving systemic chemotherapy as odd. Why inject drugs into a vein for the whole body when you want an effect only in one organ such as the lung, kidney or brain?"

Liver perfusion is just one of many techniques that now make up interventional oncology – a field which, according to Andy Adam, professor of interventional radiology at the University of London (the first such position in Europe), is probably the fastest growing part of his specialty. Adam, who is based at London's Guy's and St Thomas' Hospital, and has been president of the European Society of Radiology among other posts, explains that the early applications of interventional oncology were in supportive and palliative care, and included for

"I think in 20 or so years' time we may look back and see giving systemic chemotherapy as odd"







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Radiofrequency ablation needles (centre) are inserted into the tumour in a retracted position, and can then be opened up to deliver a radiofrequency current to multiple locations. The upper image shows this procedure being carried out in the right upper lobe of the lung. The lower image is a 3D-reconstruction of combined therapy to a hepatocellular carcinoma – the blue colour shows tumour uptake of drug and contrast agent lipiodol, the red denotes the hepatic arterial tree

instance applying stents in the biliary tree for obstructive jaundice. "Such procedures have made a huge difference to people's lives – a stent in the oesophagus can allow someone to eat, for example," he says. Embolising neuroendocrine tumours – cutting off their blood supply – addressed symptoms such as severe flushing and diarrhoea that made patients' lives miserable, he adds, and the effects, though short lived, were real. "Then drugs made this redundant – but it paved the way for new vascular procedures."

Radiologists have also long performed biopsies where it is necessary to place a needle very accurately to take a sample, says Adam, and it is by extending the various techniques to curative settings that interventional radiology is now making its name in oncology. The basic idea is that radiologists can guide a needle or probe to almost any part of the body and then carry out local treatment directly to a tumour or its blood supply.

The two main treatment types in interventional oncology currently fall under the umbrellas of ablation and embolisation. Ablation of tumours is probably the most rapidly growing treatment area. Using energy such as radiofrequency and microwave, or freezing (cryo-ablation), radiologists guide probes directly into the tumour to deliver cell-killing treatment.

Embolisation also has several techniques – on its own, a radiologist can place a catheter in a tumour's blood supply and release embolic agents to block the blood flow. But there is also chemo-embolisation, which combines embolic agents with chemotherapy, and radio-embolisation, which adds radioactive beads to help kill tumours.

There are plenty of variations and other techniques that are attracting attention, such as high-intensity focused ultrasound (HIFU), an ablation method being trialled in prostate cancer; irreversible electroporation, an ablation technique using bursts of electricity that avoids heat damage to surrounding tissue; a technique that uses ultrasound to break up bubbles that release drugs; and the liver chemo-bath, which is more properly known as chemo-saturation or percutaneous hepatic perfusion.

But most of these procedures are recent and still in development. The challenge now is to generate an evidence base for interventional oncology, and for this growing field to find its way into mainstream practice. So far, procedures that are widely carried out are mainly limited to small tumours where the disease is not widespread – typically no more than three tumours <3 cm – in particular in the liver, kidney and lung.

A place in the mainstream?

Interventional radiologists are essentially acting as alternatives to surgeons – they aim to remove or reduce visible tumours. While taking on palliative care is a large part of their practice, they can also be involved in early-stage treatment, where multidisciplinary discussions are required. As with any expanding area of oncology, there are also key questions about combining treatments with other therapies such as radiation and drugs. It's a challenging agenda, especially as there are not many interventional radiologists practising exclusively in oncology in Europe, and the field is fragmented. There are pockets of excellence, mainly at cancer centres and large teaching hospitals, but they often take different approaches to the same techniques, which makes comparisons difficult.

One practitioner who has helped to put interventional oncology on the map

De Baere expects to see radiofrequency ablation increasingly included in guidelines for small tumours

in France and elsewhere is Thierry De Baere, who is based at the country's largest cancer centre, Institut Gustave Roussy (IGR). He is head of an interventional radiology department dedicated to oncology – one of the few in Europe – and was originally trained as a radiologist, joining IGR 20 years ago.

"When I joined most practice was palliative care such as biliary and urinary stenting and embolisation, but a milestone was the first radiofrequency percutaneous ablation, which made us part of treatments with a curative intent. It was a key change because oncologists looked at our practice and saw that we could be involved not only with end-stage care."

De Baere says radiofrequency ablation is now a standard option in the treatment of localised liver cancer (hepatocellular carcinoma) – the latest clinical practice guidelines from EORTC/European Association for the Study of the Liver (EASL) note that radiofrequency ablation can achieve greater than 90% complete response in small early-stage tumours, and the same is true also of another technique, injecting alcohol (ethanol) directly into these small tumours, which is particularly popular in the Far East in countries such as China and Japan. Both techniques can also be used in patients for whom surgery is not an option.

De Baere expects to see radiofrequency ablation increasingly included in guidelines for small tumours in other cancers. "For example, in renal cancer the first option is surgery, but there is a subgroup where there is a borderline situation for surgery and for whom there is a high success rate for ablation. We are also treating metastatic disease as well of course, and there is a sort of competition between surgery and radiofrequency ablation for small lung metastases of less than two centimetres."

Building the evidence

Much of the work is fairly new, with a flurry of activity in the past three to four years, adds De Baere. The next milestone is to provide more evidence that radiofrequency ablation really is as good as surgery, or at least very close to it, for small tumours. There are randomised trials that compare radiofrequency ablation with surgery in hepatocellular carcinoma, which have demonstrated no significant difference in overall and disease-free survival (and given ablation's less invasive nature it is the preferred first-line option in some centres). But there are no such studies yet in lung or kidney cancer and, as he notes, it is difficult to randomise patients, given the high volume needed, although various centres have tried to embark on these comparisons.

"Cohort studies and registry databases will give some lead on survival outcomes, but in any case the situation is not very different from surgery – there are no randomised studies that show surgery is better than something else," says De Baere.

Adam adds that while the evidence in hepatocellular carcinoma is excellent, no one knows yet whether interventional techniques are actually better than surgery. He also notes another barrier to randomising patients – they will often prefer the far less invasive nature of interventional radiology. "The choice could be between a simple one-hour procedure or a major operation with a hospital stay that could end up with someone losing a kidney and going into dialysis."

In kidney cancer, he says, oncologists are now also referring patients with small tumours for radiological removal rather than adopting a 'watchful waiting' approach, given that, although smaller ones are usually relatively benign, they can metastasise if they grow.

Interventional technology is moving much faster than the evidence base, says Stedman. "Our probes used to be limited to the small area of damage they could cause. Now with modern technology such as microwave equipment and cryo-ablation we can kill quickly a bigger lump of tissue under image guidance. If a patient has four or five tumours in the liver, kidney or lung we can now treat them in one sitting – 10 years ago to kill one kidney tumour of 3–4 cm, it took a lot of probes and skill to get it right."

Stedman agrees that good evidence is building for ablation of kidney tumours, and that the debate is moving to whether interventional procedures should be preferred as a first-line option. One key study he mentions, which is ongoing and could substantially raise the profile of interventional oncology, is FOXFIRE, a UK multicentre comparison of adding radio-embolisation to chemotherapy to treat colorectal cancer that has spread to the liver. (An international version of the trial is SIRFLOX, which includes patients in the US, and which has now closed.)

"This is a Formula One race in

oncology, as metastatic colorectal cancer is where many drug companies are eager to gain a foothold. The response rate of first-line chemotherapy has improved but, if radio-embolisation is effective as an addition, it will be a step-change in how interventional radiology is seen. It would be a big example in the front-line delivery of treatment for a common disease."

This pivotal multicentre trial uses technology called Sir-Spheres, from Australian company SIRTeX. These are microspheres labelled with yttrium-90 that are injected into the hepatic artery, which then lodge in the tumours' vascular structures. Only centres with expert interventional radiologists can participate. Earlier studies have shown the effectiveness of just a single injection of the radioactive spheres.

As Stedman adds, the liver has the important feature of having two blood supplies, the hepatic artery and the portal vein, and normal liver tissue is supplied mostly from the portal vein, allowing agents to reach tumours through the arterial supply. This is also how the chemo-bath procedure he has carried out works.

"There have been no great treatment options for ocular melanoma that has spread to the liver – it is resistant to systemic chemotherapy, and surgical attempts to put clamps round the liver and then apply drugs are very invasive and do not work well. Now by placing balloon catheters above and below the liver to block the venous supply we can pour whatever we want into the hepatic artery without it being systemic."

The agent used in this case is actually a mustard gas derivative (melphalan), which at the high doses administered would be highly toxic in the rest of the body, but attacks only melanoma metastases in all parts of the cell cycle and kills them, without affecting the normal liver. Stedman says the treatment lasts about an hour, and the blood leaving the liver is directed outside the body and cleaned and put back into circulation via the jugular vein.

Commenting on the procedure, Peter Naredi, chair of surgery and a liver specialist at Sahlgrenska University Hospital in Gothenburg, Sweden, says: "Isolated liver perfusion for melanoma is something we started 20 years ago, and we are the referral hospital for Sweden. But we do the procedure as open surgery – interventional radiology is promising but has yet to prove it can replace open surgery. And I would instead choose liver embolisation with yttrium spheres as more innovative."

A company named Delcath is marketing the liver chemo-bath system. While it does at present have only limited use in a small population of ocular melanoma patients, it could be applied in other cancers such as colon and breast. Stedman agrees it is not yet a 'finished product'. It is also a complex technology requiring a high level of skill to place three catheters guided by X-ray fluoroscopy and administer the treatment. And as De Baere points out, technical complexity is a barrier to developing the field. "The reason radiofrequency ablation has become widely used is because you just need ultrasound to guide it," he says.

Cost is also an issue, he adds, with expensive new technologies that may not find ready reimbursement by health systems in some countries. "We need to say to providers that paying for, say, radiofrequency ablation in kidney cancer means you can save money because you are not also paying for surgery." Although much interventional oncology has been pioneered in Europe, superior reimbursement has meant the US is now generating about half of developments.

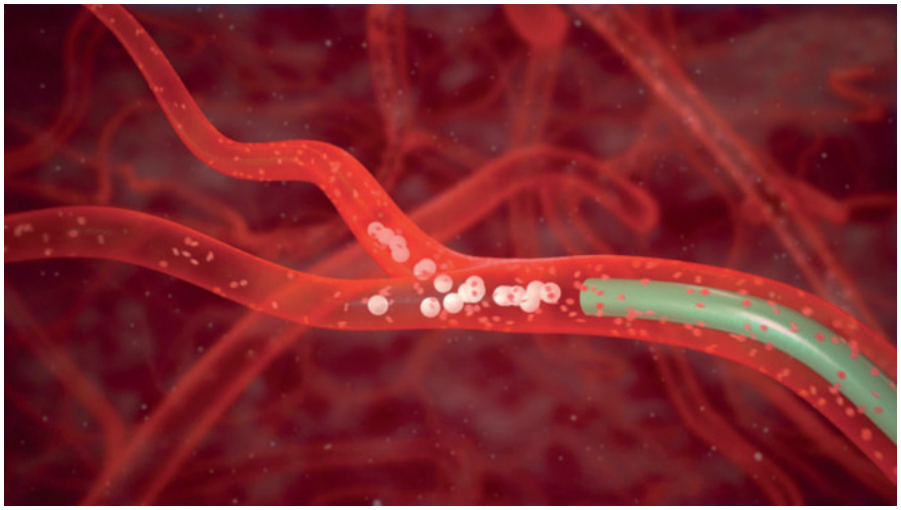
Adam also sounds a note of caution about pushing too quickly for new technology and procedures, as there are not yet enough interventional radiologists with oncology expertise. "You cannot approach oncology as a technician – you have to spend time with patients discussing the options and following up your procedures. You can't delegate this to others as they won't have the knowledge about problems with treatments. You have to be a proper clinician like other oncologists."

At the radiology/oncology interface

The main pathway into interventional radiology is from radiology itself, although there are some who transfer from surgery – Stedman for example – and some surgeons predominantly carry out interventional procedures. The workload for many in interventional radiology can be immense, and a big distraction from developing oncology interests. They are much in demand, for instance, in hospitals with emergency departments, while even in large teaching establishments such as his own, Adam says he cannot attend all the tumour board meetings he would like to, and has to prioritise where he feels the interventionalist's voice is most needed to discuss treatment options. "I don't attend kidney meetings now, because we have that well covered," he says.

Stedman is a rarity – he is the clinical lead for the regional cancer network, a post historically held by surgeons, and he says others find it odd to have a radiologist in charge "It's a sign that interventional oncology is at the frontline of treatment." It is logical to have radiologists playing a central role, he says. "When patients come into our network the imaging interactions are often the most important part of the pathway, with questions such as: is the tumour resectable? or is there another technology we can use for treatment?"

But he is not actually part of oncology, which can be problematic. "Some



SIRTeX

Blockade. These tiny radioactive spheres target the tumour to deliver local radiation therapy; trials are ongoing to see how effective they are used in combination with chemotherapy for treating liver metastases from colorectal cancer

patients are managed by me, some by oncology – but I don't have junior staff and a lot of oncologists don't know about the techniques or potential complications."

At IGR, De Baere's department does have three full-time staff, with another coming, plus two fellows. But the workload is going up by double digits each year – more than 3000 patients were seen by his team last year, many for biopsies as the demand for personalised testing for new biomarkers mushrooms (biopsies went up by 60% last year alone, he says).

Collaboration with oncology is clearly essential, and De Baere says that, because interventional oncology is limited to small tumours at present, this has restricted impact at the multidisciplinary table. He notes that medical oncologists are particularly receptive, because of the ability to downstage and treat people several times, helping also to give patients 'chemo holidays' from systemic drugs.

"But with surgeons we can be treating the same population and they need to accept that they don't need to operate on some small tumours – attitudes do vary by centre." Perhaps the most challenging partnership is with radiation oncologists, as there is again crossover with potential treatments such as brachytherapy, and there could be combined approaches. "This is a difficult field," says De Baere.

There are various local, national and international curricula and training programmes in interventional radiology, such as the European Interventional Syllabus from the Cardiovascular and Interventional Radiological Society of Europe (CIRSE), which has also established the annual European Conference on Interventional Oncology (ECIO), which will convene for the fourth time in June in Budapest, and has Adam and De Baere on its advisory board.

A key role for both CIRSE and ECIO is to look objectively at shortcomings in the evidence base, expand the curriculum, and network with other disciplines such as European radiation oncologists. "We have also set up a multidisciplinary committee with experts such as Liz Kenny, a radiation oncologist from Australia [based at the Royal Brisbane and Women's Hospital], who is a world expert on cancer services," says Adam. "We are not the fourth pillar of oncology yet – our disadvantage is we sit in radiology and it is hard for us to be heard. But our advantage is that we have highly effective procedures that are much less traumatic. We deserve to be there but it will take time."

And Kenny herself adds: "I think it is essential to have interventional oncology as the fourth pillar of cancer care. The potential to do good is high. To have this accepted, however, we need quality outcome data on patient benefit, including quality of life and costs associated with treatment. Interventional oncologists should also work within multidisciplinary teams and they need to develop a good understanding of the natural history of the cancers that they are involved with.

"With an evidence base, interventional oncology techniques are more likely to be incorporated into national and international guidelines and become mainstream options for people with cancer. But if its use is indiscriminate it runs the risk of falling into disrepute and this would be a tragedy." ■

"We have highly effective procedures that are much less traumatic. We deserve to be there but it will take time"

Centralising cancer services:

is this the best way to improve results?

In an effort to improve outcomes, some countries are concentrating the care of cancer patients in a few designated centres, where they can be seen by specialists who work in multidisciplinary teams that are entirely focused on specific types of cancer.

In Ireland, the majority of cancer patients are now seen at only eight centres – fewer if the cancer is particularly rare or complex. Each centre covers a population of at least 500,000. Four are located in the area around the capital city Dublin, on the east coast, where the population density is 1200 people per km^2. The other four are spread around the rest of the country, where population densities are closer to 30 people per km^2.

One consequence is that many patients must now travel much further from home. In more remote areas the journey can take two hours by car – longer by public transport. Help with travel costs is available in cases of genuine financial hardship.

Is this scale of centralisation justified? Could many cancers be treated more locally without compromising safety? *Cancer World's* Anna Wagstaff posed this question to two experts: Susan O'Reilly, Director of the Irish National Cancer Control Programme, and Renée Otter, former Director of the Northern Comprehensive Cancer Centre in Groningen, who made the case to keep services more local when similar reorganisation plans were discussed in The Netherlands.

Susan O'Reilly

The change to more centralised cancer services in Ireland came in response to two drivers. One was a series of 'scandals' highlighted in the media around errors or delays in diagnosis and treatment, particularly in breast and colon cancer. The other was the EUROCARE results, which showed cancer outcomes in Ireland were not very good. As Ireland had already been investing in more and better-trained cancer specialists, the problem seemed to lie in the way services were being delivered, with poor coordination and lack of streamlining.

One of the big challenges we faced was fragmentation of surgical services. This was worst for breast cancer, where surgery was being carried out in more than 32 hospitals. In some hospitals, surgeons were operating on a very small number of cases, and many of them did not have medical or radiation oncologists on site to provide multidisciplinary care.

There is also a body of literature that drove thinking around surgical services, with studies linking better outcomes to specialist training and high volumes.

So the obvious proposal was to stop offering breast cancer services in hospitals that did not have a critical mass of patients or staff to do the job to a high standard. The hypothesis is that you can offer patients an opportunity to be treated in expert hands where you have a well-trained surgical oncologist, or at least a surgeon with a high volume of cancer practice, working with a critical mass of other cancer specialists, including medical and radiation oncologists, and with specialist pathology and radiology.

The first big change we made was in breast cancer, where services were moved entirely into the eight designated cancer centres. The other services were closed and those hospitals are no longer involved in either diagnosis or surgery. Time limits to referral were agreed, for instance two weeks for urgent breast cancer, and compliance is carefully monitored. We then moved on to other cancers, which have now been centralised to a greater or lesser extent.

Renée Otter

I agree it is important to make sure no patient is diagnosed or treated by doctors who work outside a multidisciplinary team, or who do not have appropriate specialist training, or see too few patients to keep up their skills. But for most cancers this can be achieved without a high degree of centralisation.

While very small hospitals should clearly not be involved in cancer, the evidence for centralising all services is not very convincing. It focuses largely on the relationship between outcomes and surgical caseloads, and most of the studies don't take into account other issues such as training, wait times, the input of other disciplines, and whether the patients were cared for by a collaborative multidisciplinary team. Some studies look at surgeon caseloads, others at team or hospital caseloads, and there is little clarity about what the minimum caseload for different types of cancer should be.

There is an alternative. If all teams operate according to national guidelines for diagnosis, staging and treatment, and all specialists have appropriate training and qualifications, and their performance and outcomes are monitored, this would put an end to substandard treatment. Furthermore, we could get some reliable evidence about how few patients are too few, and about the extent of centralisation that is really needed for different types of cancer.

The real problem is that many countries do not have national evidence-based guidelines for diagnosis and treatment. Most countries also have no recognised specialist training for surgeons, for instance in breast cancer, colorectal cancer, urological cancers etc, even though these surgeons call themselves specialists. Very few countries have proper quality control in place to ensure that guidelines are being followed and outcomes are in line with what would be expected. These are the issues that need to be addressed.

It's true that a lot of evidence relates purely to surgical procedures: how many lymph nodes were removed? were the margins clear? what procedure was used (eg meso-rectal excision in rectal cancer)? Or it looks at short-term outcomes such as 30-day morbidity or mortality. But when you do the analysis you see very compelling data that high-volume surgeons and the specialist centres do it better.

There are also practical considerations. To get a critical mass of specialists and sub-specialists you have to have a hospital facility large enough to be able to recruit and retain surgeons, radiation oncologists and medical oncologists and others. They need to feel they have academic opportunities and sufficient volumes of work to keep up their skills. Radiation oncology services anyway tend to be attached to the larger hospitals, because of the capital cost. Then there are other specialties; for example, most smaller hospitals cannot offer immediate plastic reconstruction of a breast following surgery.

I do agree about the importance of national guidelines in reducing substandard treatment, but many countries don't yet have them – including Ireland, where they are in development but not yet finalised. But it's not enough to have them, people need to know they are there, and adhere to them. Monitoring adherence can be done at more sophisticated cancer centres which register patients and their treatment on databases. But this doesn't happen in small communities. It is technologically feasible, but it requires a lot of cooperation by the hospitals, who must do the data capture, and by the clinicians who may feel they are being scrutinised and criticised and may not wish to participate.

In a perfect world of evolving IT and electronic health records it might work. But right now, even cancer registries are spotty across Europe. Some do a great job and gather diagnosis, stage, treatment and date of death, but some of the best health systems, like France, still have no national registry. Good data management is essential, but it takes years to evolve, and right now we need to take care of the patients we have.

I agree that practitioners often resist being obliged to work according to guidelines and don't like their work to be scrutinised, but is that a good enough reason to centralise services, and require patients to travel further?

Remember that more than 65% of cancer patients in Europe are aged over 60 when diagnosed – many are in their 70s and 80s – and many also suffer additional health problems, which can make mobility a problem. Their partner and friends, on whom they may rely for support and assistance, will be of similar age. Furthermore a lot of patients – between 30% and 45% across Europe – are diagnosed when their cancers are too advanced to be curable. For these patients, quality of life, including being able to stay at home, becomes very important.

Centralising cancer services also deprives local hospitals of the skills they need to diagnose the cancer in the first place and to treat patients who are admitted on an emergency basis – which includes almost all patients with colorectal cancer. Palliative care is typically provided at a local level, and should be an integral part of a patient's treatment. It should be provided by people with expertise in the problems associated with particular types of cancer, working as part of the team.

This is why it is better to have the multidisciplinary teams operating as locally as possible, with referral to specialist centres being reserved for very rare cancers or cancers that are highly complex or expensive to treat.

I agree that specialists don't want to be working in an isolated backwater, and will want to participate in discussions about how to improve outcomes and in research. But they can do this if they are part of a national network. It doesn't necessarily mean everyone being physically in the same centre. If necessary to keep their skills up, teams – or some members of the team – can cover more than one hospital in their region.

The key thing is to get the first decisions right – the diagnosis and staging and treatment plan – and the best way to make sure this happens is to go to a dedicated cancer centre.

In reality most practitioners in smaller services don't network in to multidisciplinary teams. It sounds fine to say it, but you can't demonstrate it in most healthcare systems. And while there is debate about what the minimum caseload should be for each particular type of cancer surgery, we know that surgeons who work in smaller services are more likely to provide substandard care. This is because they have to cover a wide range of procedures, they may not have time to assimilate the literature, or they just like to stick to old habits and no-one is looking over their shoulder to make sure they do it right. Before we centralised breast cancer surgery, many surgeons were still not doing sentinel node biopsies.

Of course patients don't welcome having to travel, and there may occasionally be patients who are so frail that referring them to a cancer centre may be inappropriate. But in general, that initial expert multidisciplinary team consultation is essential whether the treatment will be curative or not, and you can't always know whether a cancer really is incurable until you have done sophisticated tests such as PET for lung cancers, which can only be done at larger centres.

A lot of the treatment can then be done closer to home. In Ireland we have 25 hospitals that can deliver some chemotherapy, often under supervision of oncologists, while community nurses are trained to take care, for instance, of infections, and to disconnect a central line or disconnect pumps so patients don't have to go back to the treatment centre. Control of symptoms – pain, nausea, anorexia, fatigue, constipation, all the usual miseries – is best delivered by a palliative care team as close to home as possible.

I am not against cancer centres. I am against a system that obliges all patients to go to one.

Even in a country like Ireland, which has large areas of very low population density, there will be three or four hospitals in every region large enough to have the organisation and expertise to deal with many cancers, provided they work closely with a regional cancer centre, and everyone works to national guidelines.

It is in these hospitals, not the cancer centres, where the "first decisions" are made – the initial diagnostic tests and the first steps of staging. So having national guidelines that set down which tests are appropriate and how they should be done, and ensuring they are followed at every level, is a priority that cannot wait.

The question is then what happens next. There will be patients who should be referred to a regional cancer centre, but there will be many who can be safely managed in a good-sized hospital closer to home. Criteria for referral should be set down in the national guidelines, and where there is any doubt, the decision can be made in consultation with a team at the regional cancer centre.

In some countries with very low population density, such as Wales, videoconferencing is routinely used by local teams to hook up with the regional centre to discuss patients. Multidisciplinary teams can also cover more than one hospital in a locality if caseloads for a specific type of cancer at a particular hospital are deemed to be too low.

The thing about cancer centres is that they are highly oriented towards research. This works well for patients who want to go all out for a cure and get access to all the latest trials. But many patients whose cancers have been picked up too late and who have other health issues – heart, circulation, diabetes – which are not the concern of cancer centres, may want the option of having all their care organised from a single good-sized hospital closer to home. I think there is a danger of looking at things too much from the perspective of specialists who are highly focused on just the cancer, and we don't think enough about the other problems, health or otherwise, that a patient may have. ■

Tobacco tactics in the headlines

PETER MCINTYRE

At a time when the British media has been under the spotlight for its for poor ethical standards, *The Independent's* Big Tobacco Exposed series shows why good investigative journalism remains so important in opening powerful bodies up to public scrutiny. Journalist Steve Connor won a Best Cancer Reporter special merit award for his work.

The day I spoke to Gerard Hastings, director of the Institute for Social Marketing, at Stirling University, the courts had just thrown out a challenge by the tobacco industry to a ban on tobacco displays in shops and bars instigated by the Scottish Executive. Hastings was pleased at the outcome and not surprised that the tobacco industry had gone to court. "The industry always tries to do this – their aim is not so much to win as to delay. Every week they can delay it happening they can earn more profits."

The Institute for Social Marketing is a small but prestigious centre whose activities include research into what influences – or inhibits – young people with respect to smoking. It has conducted several longitudinal surveys based on interviews with 11- to 16-year-olds, and has looked in particular at the impact of advertising. Its research has been used by policy makers when they consider ways to prevent a new generation of young people taking up the habit.

The world's largest tobacco company, Philip Morris International, wanted a close look at the data behind the Institute's research on young people and tobacco. In 2009 an application was made under the Freedom of Information Act, requiring the Institute to release anonymised but detailed interviews with young people, and other information. The tobacco company did not make this application openly; it asked Clifford Chance, one of the world's largest corporate law firms, to do so on its behalf.

There are obvious ironies. The Freedom of Information legislation applies to public bodies, but not to commercial organisations, so Philip Morris was using an act from which it is itself exempt to gain access to academic data, and it did so under a cloak of anonymity.

If the Institute for Social Marketing had been based in England they might have succeeded, but the Freedom of Information (Scotland) Act of 2002 requires applicants to make requests in their own name. The then Scottish Information Commissioner, Kevin Dunion, insisted that Clifford Chance reveal the name of its client.

Nevertheless, staff at the Institute felt overwhelmed. They believed they had a duty of care to the young people not to reveal details of their interviews. This small team found itself working nights and weekends to make their case for withholding the information. Over a two-year period, however, they were not able to convince the information commissioner that their data should be protected.

Picking up the story

In August 2011, Steve Connor, science editor of the British daily newspaper *The Independent*, heard about the application and saw some parallels with stories he had worked on about applications to compel climate change researchers to reveal their data.

Connor recalls: "As with all the best stories, it comes from talking to people. I was talking to someone about something completely different and they mentioned tobacco companies trying to get information from scientists. I write about climate change a lot, and I immediately thought this could be a story. I tracked down the guys at Stirling and they seemed to have an eminently reasonable case about why they should think twice about handing over the material for review."

In Stirling, this approach by a journalist did not go down well at first. "At the time I felt a little uneasy about it," says Hastings. "We had been told by our lawyers that this was not exactly *sub judice* [in which case media coverage could be contempt of court], but it should not be discussed – a wonderful irony given we are talking about freedom of information. It was a source of some discombobulation but ultimately it was good news for us."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Smoked out: tobacco giant's war on science

Philip Morris seeks to force university to hand over confidential health research into teenage smokers

EXCLUSIVE
By Steve Connor
Science Editor

THE WORLD'S largest tobacco company is attempting to gain access to confidential information about British teenagers' smoking habits.

Philip Morris International, the maker of Marlboro cigarettes, is seeking to force a British university to reveal full details of its research involving confidential interviews with thousands of children aged between 11 and 16 about their attitudes towards smoking and cigarette packaging.

The demands from the tobacco company, made using the UK's Freedom of Information law, have coincided with an internet hate campaign targeted at university researchers involved in smoking studies.

One of the academics has received anonymous abusive phone calls at her home at night. She believes they are prompted by an organised campaign by the tobacco industry to discredit her work, although there is no evidence that the cigarette companies are directly responsible. Philip Morris says it has a "legitimate interest" in the information, but researchers at Stirling University say that handing over highly sensitive data would be a gross breach of confidence that could jeopardise future studies.

The researchers also believe that the

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Connor spent a day with the team in Stirling listening to their concerns, and then approached Philip Morris for their side of the story. Based on what he uncovered,

They believed they had a duty of care to the young people not to reveal details of their interviews

"It played badly in the press for Philip Morris. I did wonder about the PR advice they were getting"

The Independent decided that this was an important issue, and broke the story on 1 September 2011 under the headline "Smoked out: tobacco giant's war on science". Connor's story began:

"The world's largest tobacco company is attempting to gain access to confidential information about British teenagers' smoking habits.

"Philip Morris International, the makers of Marlboro cigarettes, is seeking to force a British University to reveal full details of its research involving confidential interviews with thousands of children aged between 11 and 16 about their attitudes towards smoking and cigarette packaging."

Over three days *The Independent* ran a number of stories under the logo "Big Tobacco Exposed", which also spotlighted successful applications by tobacco companies to obtain details of meetings between researchers and officials at the Department of Health.

Hastings had to put a holiday on hold to deal with requests for interviews. "I have done a lot of media in my time but this was the biggest. The tabloids and the broadsheet press were very, very agitated by it.

"That Thursday will live with me till the end of my days. I was supposed to be going south with my wife on a trip home and it just didn't happen because I was talking the whole time. And a lot of it – live radio for example – is not easy to do and is stressful. When the media pick up a story you don't know where it is going to go. But it played badly in the press for Philip Morris. I did wonder about the PR advice they were getting."

By December 2011 Philip Morris had let its application lapse, although it has never formally been withdrawn.

It was Hastings himself who nominated Connor for a Best Cancer Reporter award. "I think he knew his business as well as we knew ours. I think the process was successful." In his nomination, Hastings said: "Cigarette companies spend millions on combating attempts to curb sales and the recruitment of new smokers by targeting those academics involved in understanding the link between smoking addiction and tobacco promotion. [*The Independent's* campaign] …was one small victory in the battle with Big Tobacco and its attempts to gag and intimidate the anti-smoking research community."

A force for good. Steve Connor with ESO's Franco Cavalli at the Best Cancer Reporter award ceremony, Lugano 2012

JASON HARRIS

Use or abuse of the Act?

But why oppose the application in the first place? Should scientific data not be open to scrutiny? Hastings says they felt this would be a betrayal of the young people whose views they had sought. "In essence we are trying to reverse engineer what the tobacco industry is doing and how their activities impact on children. It is worth bearing in mind that the vast majority of smokers start as children. Without

A thorough job. Connor's series of articles presented a damning picture of the lengths to which tobacco companies will go to ensure each new generation becomes hooked on its product. www.independent.co.uk

children the industry is out of business in a generation. Every ounce of their effort must be dedicated towards keeping that recruitment going.

"The challenge is that the tobacco industry will deny to their dying breath that their marketing has an impact on children. When we conduct the research, we are asking young people to collaborate with us in a way that is both difficult for them and risky. They are having to confess to behaviours that they wouldn't want their parents to know about, let alone anyone else.

"In order to do this research, we had to reassure the ethics committee that young people would not be harmed by it and, specifically, that their answers would be treated with confidentiality as well as anonymity. We are in a position of trust with these young people."

But what about *The Independent*, which campaigned vigorously for the Freedom of Information Act to be introduced? Connor saw the tobacco company campaign as turning the principle on its head. "The FoI Act is essentially for individuals to speak truth to power, and this was in a way subverting the Act. This was quite clearly a huge multi-million dollar organisation employing very expensive law firms to use this Act. It was rather like Goliath being given a club to beat David with.

"If the tobacco industry was paying for or commissioning research

"The Act is essentially for individuals to speak truth to power, and this was in a way subverting the Act"

"I had every encouragement, from the editor down. We will give you more time, go ahead and do this"

that involved interviews with underage children about tobacco or smoking habits, there would be uproar because it would be seen as the tobacco industry trying to work out what goes on in a child's mind that can help them to sell their product. They may argue that they wanted to see the raw data on which this research was based for quality reasons, but at the same time it would have been interesting for them to work out how children respond to tobacco advertising or cigarette packet advertising or whatever. That is why we as a newspaper thought it was a good campaign to launch.

"These interviews with teenagers were conducted expressly under guarantees of confidentiality. They said it would make it harder for them to do research in the future if this data was in the hands of the tobacco industry."

Maurice Frankel, director of the UK Campaign for Freedom of Information, wrote to *The Independent* to say that the law was designed to be "applicant blind" – the decision should be about the information not the applicant. "An authority cannot refuse a request because the applicant is opposing its policies, criticising its competence, challenging its decision in court, or in the case of an opposing political party, trying to replace it in government." But he pointed to a specific exemption in the Scottish Act that allows information collected during a continuing programme of research to be withheld if disclosure would substantially prejudice future reports – subject to a public interest test.

Against the public interest

Steve Connor says that the tobacco companies failed that test. "The truth is that when Philip Morris had to justify what they were doing in front of television cameras it was very difficult for them, and that goes to show that they were on a sticky wicket ethically. They would have pursued this if they thought it was ethically justifiable and they could justify it in front of a wider public. To my mind they could not do it and that is why they dropped it."

The Scottish Information Commission, which dealt with the Freedom of Information application, was not asked to rule on the public information test; however, it did not uphold objections to revealing the information on the grounds that Philip Morris's application was "vexatious". It reported that: "While the Commissioner considered that the request would place a significant burden on the University, he found that that fact alone was not enough to make the request 'vexatious'. He found that there was a legitimate reason for the request to be made, and there was no evidence that its purpose was to disrupt or annoy the University. The fact that [Philip Morris International] may disagree with the research being carried out was not enough to make the request vexatious."

He did not have to rule on the next objection – that it placed an unfair financial burden on the University, as by then the application had been dropped.

Strong backing from colleagues on *The Independent* was a big help says Connor. "It is always difficult to get good stories, and then to convince other people in the office that it is a good story. With this I had no difficulty. I had every encouragement from the editor down. They were pushing me – we will give you more time, go ahead and do this."

He admits it is nice to get awards from organisations of repute like the European School of Oncology, but says the buzz is short lived. "It is nice to bask in that reflected glory for a while but you have go into the office the next day and find the next story. Of course, it is nice to know that sometimes doing this job you can do some good as opposed to just reporting on the world at large and being the first version of history. You can maybe be a force for good and I think that this was actually a good outcome."

Connor does, however, have a concern over the ability of serious newspapers to invest time in digging out stories, as economic pressures to cut staff increase. "This is increasingly expensive when newspaper newsrooms are being cut and we are all being asked to sit at our terminals and churn out stuff. So it is more difficult than 10 or 15 years ago when newsrooms were better staffed. It is loosely called investigative journalism but I think all good journalism has an element of investigation about it. This kind of investigation requires taking a risk, putting in the investment in terms of time and possibly money. In the end it did pay off." ■

Skin toxicities caused by targeted therapies

Targeted drugs can result in a variety of skin toxicities that are unpleasant for patients and, if unattended to, can lead them to stop taking their drug as prescribed. Effective teamwork is required to ensure symptoms are identified and managed.

Mucocutaneous adverse events are relatively common with targeted agents, and there is a relationship between skin toxicities and side-effects as a whole. Papulopustular eruption is the commonest skin toxicity, with dry skin, itchy skin and hand-foot skin reaction also being common. The figure overleaf illustrates some of the mucocutaneous reactions that occur with targeted agents. These include trichomegaly (long lashes), which can occur with EGFR inhibitors, and blepharitis (inflammation of the rims of the eyelids), which is a common side-effect with EGFR inhibitors, but has not been reported very widely in the literature because no-one is looking for it carefully. The connection between skin toxicities and mucosal toxicities is illustrated by side-effects affecting both the eyelid (skin) and eye (mucocutaneous tissue).

There is a correlation between stomatitis (inflammation of the mucosal lining in the mouth), hand-foot skin reaction and rash. Their appearance

European School of Oncology e-grandround

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

In this issue Christine Boers-Doets, from the department of Clinical Oncology at Leiden University Medical Centre in The Netherlands, reviews the occurrence and management of skin toxicities caused by targeted therapies. Annie Young, from the University of Warwick, in Coventry, UK, poses questions arising during the e-grandround live presentation.

Written by Susan Mayor.

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

is similar, with round ulceration and an erythematous halo (see upper figure opposite), underlining the connection between these side-effects, which can occur with targeted agents.

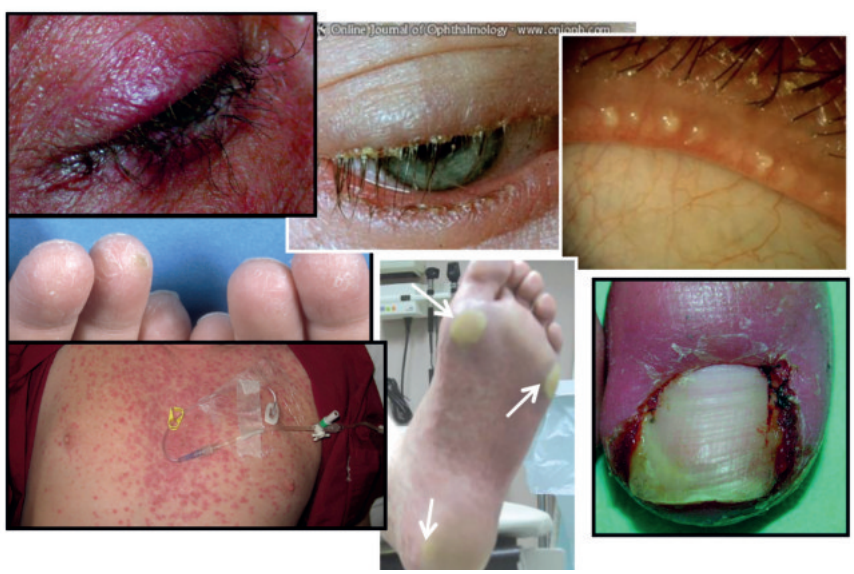
The connection between hand-foot skin reaction and stomatitis is illustrated in a study of patients treated with sunitinib: of the 13 patients who had grade 3 hand-foot skin reaction, 10 also had stomatitis (*Br J Dermatol* 2009, 151:1045–51). Of the 76 patients who did not have hand-foot skin reaction, only 18 had stomatitis. This tells us that if you see severe stomatitis or severe hand-foot skin reaction in a patient, you should look at their feet or in their mouth to see whether there are other mucocutaneous side-effects. The same connection between cutaneous side-effects and stomatitis occurs with mTOR inhibitors (*Cancer* 2010, 116:210–215).

Most common mucocutaneous adverse events with targeted agents

- Papulopustular eruption ('rash') 45–100%
- Xerosis cutis (dry skin) 7–35%
- Pruritus (itchy skin) 8–35%
- Hand-foot skin reaction 5–59%
- Periungual inflammation (nail) 12–16%
- Abnormalities in hair growth 14–21%
- Eye/eyelash abnormalities >30%
- Mucosal changes 12–69%

Source: Y Balagula et al. (2011) *Int J Dermatol* 50:129–146 © 2011 John Wiley and Sons

MUCOCUTANEOUS TOXICITIES



Clockwise starting from top left: trichomegaly; blepharitis; meibomitis; paronychia; hand-foot skin reaction; papulopustular eruption; fissures on the hands.

Courtesy of Leiden University Medical Center, Leiden

AY: *Do all agents have similar side-effects?*

CB-D: *There are differences between the agents. When side-effects occur, the appearance is basically the same, but the grade and duration is different. There is less of a rash with mTOR inhibitors, but the appearance is the same as with other agents and treatment is the same.*

AY: *You mentioned the relationship between the mucosa and dermatological toxicities; do you have any idea why the pathology underlying this relationship makes them occur together?*

CB-D: *It is because the agents bind to receptors in the skin and mucosa as well, so the side-effects develop at both these locations.*

AY: *Do you think that you will see the same relationship between mucosal and skin toxicities with EGFR inhibitors?*

CB-D: *Yes. I did not find evidence for this correlation in the literature, but we see it very often in daily practice. It is important to ask the patients, because the focus tends to be on rash and paronychia, while there is very little awareness about other side-effects.*

Papulopustular rash

This was previously termed acneiform rash or eruption, but it is now known as a papulopustular rash, because patients have papules (small raised pimples) and pustules (small pus-filled blisters). When patients just have papules, the rash appears red, while pustules appear yellow. The picture of the nose in the upper part of the bottom figure opposite shows a crust developing, which is a good sign, because it means that the rash is fading and the patient can continue therapy.

Papulopustular rash first appears on the face. Later it disappears from the face and scalp, but occurs on the

stomach, legs and arms. The patient in the lower part of the figure did not tell us that he had a rash. We did not see anything on his face and he did not tell us about the rash on his body and legs, so we nearly missed it. He only told us when we noticed that he had difficulty in walking and sitting down and we asked why. Treatment of symptoms should be tetracycline twice a day.

The best evidence we have today indicates that tetracycline should also be used prophylactically (the STEPP trial, *JCO* 2010, 28:1351–57). The limitation of this study is that tetracycline was used in combination with sunscreen and topical steroid, so we do not know whether the effect was due to tetracycline alone or whether the sunscreen and topical steroid also played a role. Other treatments being trialled for treatment of skin rash include vitamins K1 and K3, sun protection and pro-vitamin B5 (Bepanthen cream).

AY: *A team from Belgium uses doxycycline 100 mg once a day. Is that alright for the management of skin rash?*

CB-D: *The literature says 100 mg once or twice a day given prophylactically is required. In my opinion, and the opinion of members of MASCC [Multinational Association of Supportive Care in Cancer], 100 mg once a day is enough for prophylactic use. However, when you are managing side-effects you need to increase the dose to 200 mg. If there is no response after 14 days, take swabs and check for resistance and prescribe antibiotics based on culture results.*

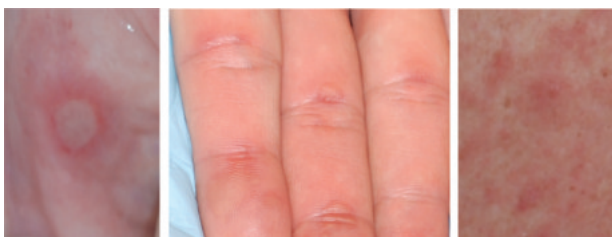
AY: *Should vitamin K ointment be used prophylactically for rash?*

CB-D: *I am performing a Cochrane review on this topic, so I have read all the publications on it. We assessed which products help and which do not. When we put the information together, we only know that we have to use an ointment to reduce rash. Results are conflicting for the use of vitamin K ointment and we need more studies to gain further information. I think the problem is that the right tools were not available to assess the benefit.*

AY: *Do you have any experience with any vitamin K ointments or treatments?*

CB-D: *Here in The Netherlands we give them to patients treated with cetuximab. I am performing a study with pro-vitamin B5 (dexpanthenol) with 160 patients. We will find out whether we can reduce antibiotics, because these have side-effects too. Results with vitamin K1 and pro-vitamin B5 are positive so far, but we need more data.*

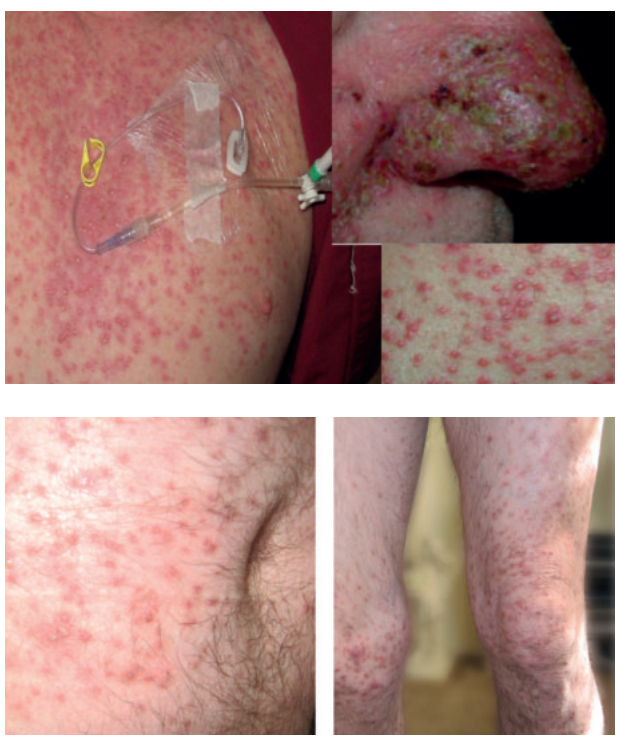
RELATED SIDE-EFFECTS



Stomatitis in a patient on an mTOR inhibitor (left), and hand-foot skin reaction (centre) and rash (right) in patients on sorafenib. These side-effects often occur simultaneously, and if any one of these is found, the patient should be checked for the others.

Courtesy of ME Lacouture, Memorial Sloan Kettering Cancer Center

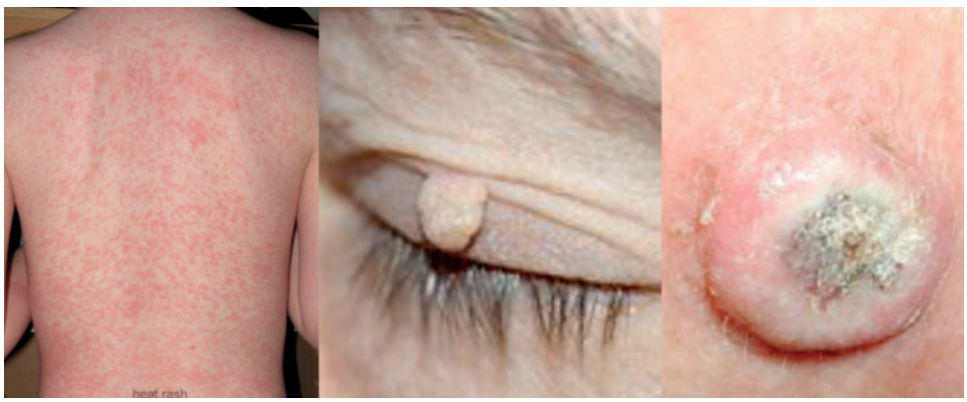
PAPULOPUSTULAR RASH



This rash starts on the face but then moves to the stomach, legs and arms. It is important to ask patients, because they may have rash where you cannot see it, and they may not tell you.

Courtesy of Leiden University Medical Center (upper images), CB Boers-Doets (lower images)

BRAF-SPECIFIC SKIN REACTIONS



BRAF inhibitors cause a rash over the whole body (left), as well as stem warts (centre), which can be burnt with nitrogen, and squamous cell carcinoma (right), which must be excised.

Courtesy of the Netherlands Cancer Institute

BRAF-specific skin reactions

There are a greater number of side-effects with BRAF inhibitors, including some new types of side-effects (see figure above). The rash is similar to that seen with other targeted agents, but the whole body is affected. Patients may develop stem warts, which can be burnt off with nitrogen. Squamous cell carcinoma is a very common side-effect with vemurafenib, which is used against BRAF-positive melanoma. In addition to these unique side-effects, patients on BRAF inhibitors may also suffer side-effects associated with other targeted agents, such as hand-foot skin reaction and sensitivity to sunlight.

Dry skin

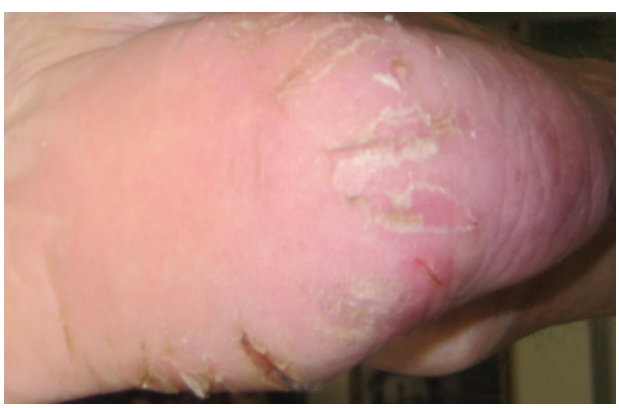
Dry skin (xerosis cutis) is a very common side-effect with targeted agents, and is associated with many other skin toxicities such as rash, photosensitivity, scaling of the skin, fissures and hand-foot skin reaction. To prevent dryness and rash, cleansing with mild soaps and moisturising twice daily with thick, emollient creams is recommended (*Clin J Oncol Nurs* 2008, 12:283–290). Patients should be advised to avoid prolonged hot showers and use only products that are alcohol-, fragrance- and dye-free (*Oncol Nurs Forum* 2008, 35:103–111). Cool or lukewarm water should be used for bathing or washing, and moisturisers should be applied immediately afterwards. In addition, patients need to stay hydrated by drinking plenty of fluids.

Patients may also develop flakes on the skin, which are itchy and, if severe, can be removed by treatment with salicylic acid. Patients with dry skin may also have fissures, which result in cracking. This can be treated with greasy creams and ointments.

AY: *Which cream or ointment is optimal for patients?*

CB-D: *You need a greasy cream or ointment in a pot. The others are too watery and they will not hydrate enough.*

DRY SKIN – FISSURES



Greasy creams and ointments can help keep skin hydrated and avoid fissures and cracks

Courtesy of CB Boers-Doets

Skin infections

The pain from skin infection can be very severe. The patient with scalp infection shown in the figure opposite could not take showers or comb his hair because of his painful scalp. He was treated with tetracycline, but this did not help. Taking a culture showed his infection was resistant to tetracycline, so treatment was changed to another antibiotic. The scalp infection was cured, but the infection reappeared on the patient's leg. Taking a swab showed he had *Staphylococcus*

aureus infection that was resistant to clindamycin, erythromycin and tetracycline. An antibiotic was chosen based on the sensitivity results. Before we learned about looking at the sensitivity to the antibiotics, we used to increase the dose of tetracycline or add topical corticosteroids, but that seldom resolved the skin side-effects.

Nail fold changes

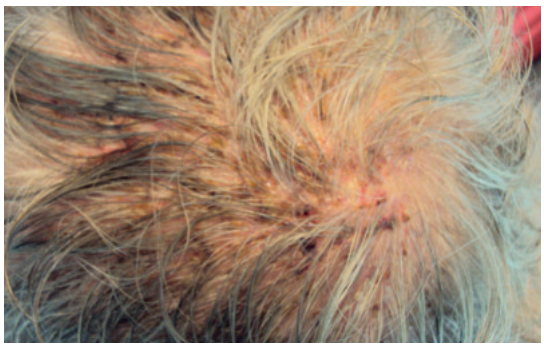
Nail fold changes (paronychia) are very common side-effects that affect the fingers or toes. Paronychia is very painful, and patients whose toes are affected cannot wear shoes or socks, and therefore have to wear slippers. It can become infected, which appears as redness.

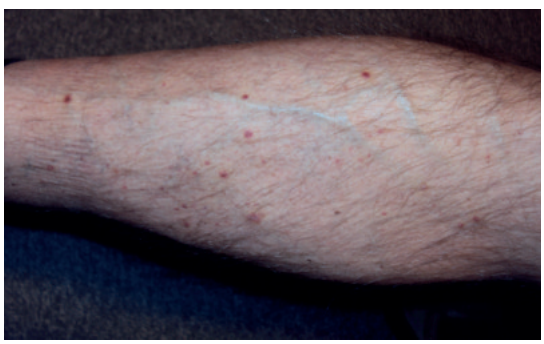
The figure overleaf shows a case of paronychia with pyogenic granuloma (an overgrowth of tissue). A dermatologist may identify this incorrectly as an ingrown nail and try to remove the nail, but this is not an appropriate management option, since the skin overgrowth can be managed by patients themselves.

We recommend that patients with nail fold changes bathe affected nails with table vinegar and water (1:1) twice a day for 15–30 minutes. This will help to reduce the paronychia. In the case of ulceration, or if there is evidence of the situation becoming more severe, a culture is needed to find out if it is infected. It should be checked for antibiotic resistance to guide antibiotic selection.

When pyogenic granuloma is present, silver nitrate applicators can be used once or twice a week. Patients must be warned to apply treatment only to the granuloma and not to the nail or the nail fold, because it will stain them black.

INFECTIONS





If skin infections like these do not respond to tetracycline, it is important to take a swab to identify a suitable antibiotic.
Courtesy of CB Boers-Doets

Special challenges in the elderly

Due to ageing, elderly patients tend to have dry skin and mucosa when they begin therapy. This increases the risk of more severe dermatological side-effects, and more eye and oral problems. Older people also have an increased risk of skin trauma because they are more likely to slip, and this risk is increased further with hand-foot skin reaction. Neuropathy is another problem more common in older people; it can lead to worsening of fissures because it lowers awareness of skin cracking.

Measuring and managing skin toxicities

It is very important that patients with cancer receive optimal treatment with targeted agents, at the optimal dose and for the planned duration. There is a lot of literature showing rapid tumour growth in patients who stop treatment or who have a break for a few weeks, so reducing the dose is not a desirable option. It is therefore essential to avoid having to stop therapy because of skin reactions.

In general, younger patients have a lower overall health-related quality of life than older patients with the same adverse events. This means they are more likely to stop treatment early because of the side-effects, and it is important to avoid this happening (*Cancer* 2010, 116:3916–23).

The physical domain has the greatest impact on health-related quality of life. Patients with a rash have a lower health-related quality of life than patients without rash, primarily because of the burning sensation the rash causes. (*JCO* 2007, 25(18)S19532).

Patients may have multiple problems, and it is very important to enquire about them all. For example, most patients will not report skin or scalp bleeding unless they are asked. Most report skin bleeding when asked specifically, including skin bleeding on their bed sheets during the night, when they take showers and when they are changing their clothes. Skin bleeding is very distressing because it is painful, occurs frequently and it marks clothing.

Assessing health-related quality of life is very important, and can be done with a variety of tools.

Dermatology-specific health-related quality of life tools used in studies with targeted agents include the SKINDEX-62, -29 and -16, which is the most commonly used, and the Dermatology Life Quality Index (DLQI).

Health-related quality of life tools have been developed for use specifically in patients prescribed EGFR-inhibitors, based on the SKINDEX-16. The Functional Assessment of Side-effects to Therapy–EGFRI (FAST-EGFRI-38) had 38 questions and was too long. A shorter version was therefore compiled – the Functional Assessment of Cancer Therapy–EGFRI-18 (FACT–EGFRI-18), with 18 questions, which is a good questionnaire to use.

It is a patient-reported outcome questionnaire that consists of 18 items arranged in three health-related quality of life dimensions: physical (7 questions); social and emotional (6 questions) and functional wellbeing (5 questions). It is important to assess all three domains. The questionnaire is very easy for patients to use, with a five-point Likert-type response scale. It assesses only skin, nail and hair side-effects, and does not include mucosal side-effects, so questions need to be added to cover this area.

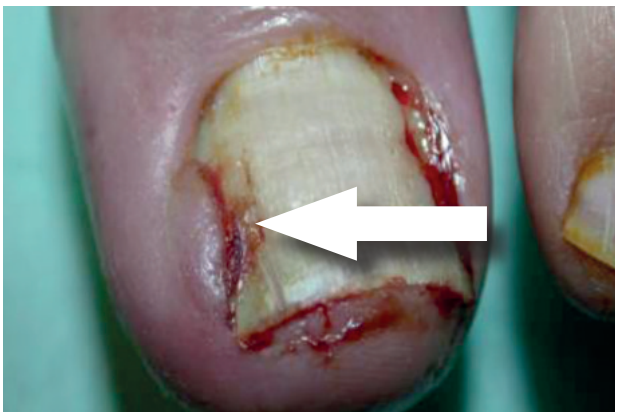
FACT-EGFRI-18 was developed in the USA in English. We are carrying out a clinical trial with this tool, so we have translated it into Dutch, and it is currently being formally validated after linguistic validation. It has also been translated into German, but we are looking for colleagues to carry out linguistic and formal validation.

In our linguistic validation we found that it was the symptom burden – and not cosmetic appearance – that affected health-related quality of life in the first month. Patients said the worst symptoms were increased sensitivity to sunlight, because of the burning sensation. Itching of the skin and scalp and bleeding of the skin were also major problems.

We need to focus on these side-effects because they interfere most with patients' quality of life. Our results are consistent with a previous study in a similar group of patients (*Oncology* 2007, 21 S5:34–36), so both studies provide useful information to guide daily practice.

We are also evaluating the Vanderbilt Head and Neck Cancer Symptoms Survey (VHNSS2.0) for side-effects associated with mTOR inhibitors and mouth ulcerations associated with tyrosine kinase inhibitors.

PYOGENIC GRANULOMA



It is important to be aware of the potential for nail fold changes to avoid patients being misdiagnosed and wrongly treated for ingrown toenail.
Courtesy of CB Boers-Doets

AY: *Which is the best tool to use in the clinic? Do they take a lot of time?*
CB-D: *The SKINDEX-16 is very short, with only 16 questions. It is translated into many languages, but there are different questions for different countries, so the data from different countries cannot be compared.*
AY: *Do you use the FACT–EGFRI-18 in practice in your clinics?*
CB-D: *Yes. I use it because I want to know which side-effect is most distressing for the patient, so we can focus on that.*
AY: *Can you do a symptom cluster? Can you assess all the symptoms as well as skin toxicities at the same time? Or are there different tools for different side-effects?*
CB-D: *The questionnaires we have now are only for side-effects with EGFR inhibitors, not for all targeted agents. In my opinion we need a broader questionnaire. Also they assess only the health-related quality of life and not the grade of side-effects, which means they do not assess symptom burden. We need another questionnaire for that.*

Take home messages

It is very important to keep the skin hydrated in patients treated with targeted anticancer agents. When infected skin rash is suspected, start treatment with tetracycline, but if this does not help it is important to take swabs and select antibiotic therapy based on microbial sensitivity. ■

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Aprepitant and control of emesis induced by five-day chemotherapy

RICHARD J GRALLA

Addition of aprepitant, an NK-1 receptor antagonist, to dexamethasone and a 5-HT3 receptor antagonist contributes substantially to emetic control in patients receiving five-day cisplatin-containing chemotherapy, a new trial shows. Some needs in antiemetic therapy remain unmet, including control of emesis with multiple-day chemotherapy and control of nausea.

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The past few decades have seen remarkable progress in antiemetic control of patients receiving highly and moderately emetic chemotherapy. Well-designed trials supported by thorough neuropharmacological research have led to the development of convenient antiemetic regimens that target relevant neurotransmitters.[1] These trials have enabled safe administration of chemotherapy in an outpatient clinical setting for most patients. An almost-universal use of effective antiemetic regimens has helped to preserve the quality of life of patients while they receive chemotherapy and has had concomitant financial benefits through a reduction in the number of hospitalisations and urgent care visits. A study by Albany and colleagues[2] now brings a new dimension to the prevention of chemotherapy-induced emesis. The researchers demonstrate that addition of NK-1 receptor antagonist aprepitant to dexamethasone and a 5-HT3 receptor antagonist improves antiemetic control in patients receiving five-day cisplatin-containing chemotherapy. The trial provides new information with important implications for evidence-based guidelines for antiemetic treatment, and the results highlight areas where well-designed studies are required to improve treatment strategies in many oncology settings.

In this double-blind phase III crossover study, patients with germ-cell tumours receiving two cycles of five-day cisplatin-based chemotherapy were randomly assigned to aprepitant (125 mg on day 3 and 80 mg once a day on days 4–7) or placebo; both arms also received dexamethasone (20 mg daily on days 1 and 2 during acute emesis phase, and 4–8 mg twice a day on days 6–8 during the delayed emesis phase) and a 5-HT3 receptor antagonist (once a day on days 1–5) on first cycle and were crossed over to the other treatment arm on the second cycle. Addition of aprepitant (three-drug treatment arm) resulted in substantially better prevention of

vomiting on each day of chemotherapy, in both the delayed emesis setting (days 6–8) and acute emesis setting (days 1–5), compared with the control (two-drug arm). Patients expressed preference for receiving aprepitant in this double-blinded crossover design. Additionally, no difference was observed in adverse effects between the three-drug aprepitant-containing arm and the two-drug control arm. The fact that a 42% complete emetic control is achieved with aprepitant add-on over five days of chemotherapy versus 13% in the control arm provides sufficient evidence to call for an update of the evidence-based guideline recommendations for antiemetic treatment in patients receiving multiple-day chemotherapy.

The findings of Albany et al.[2] not only expand our knowledge of how to treat emesis in patients receiving multiple days of chemotherapy, but also illustrate that in many common chemotherapy settings antiemetic control is not sufficient. We still need better approaches to prevent chemotherapy-induced nausea and limited information is currently available for anti-emesis treatment in many common oncology settings including chemotherapy given with radiotherapy. Furthermore, the study reveals that optimal schedules have not been defined for use of corticosteroids as antiemetic drugs or for the dosing and scheduling of NK-1 receptor antagonists.

Addition of aprepitant resulted in ... better prevention of vomiting on each day of chemotherapy

As the authors also acknowledge, the study has several limitations. An inherent problem in prevention of emesis induced by multiple days of chemotherapy is that several emetic phases (acute emesis, delayed emesis, and even anticipatory emesis) potentially coexist on the subsequent treatment days. This problem is observed in the dexamethasone dosing schedule. For treating acute emesis, dexamethasone is given only on the first two days of chemotherapy to avoid potential adverse effects with longer treatment. The results indicate that patients experience increased nausea and vomiting after the first two days. Albany and colleagues are rightly concerned about adverse effects associated with dexamethasone treatment when given daily for multiple days, but these potential side-effects with short courses of steroid treatment should be weighed against the benefit of control of emesis. Several trials have indicated a carry-over effect of delayed emesis control even when dexamethasone is stopped after the first day of chemotherapy.[3,4] However, whether this carryover effect would hold in multiple-day chemotherapy regimens is not clear.

Another limitation of the Albany et al.[2] trial is that aprepitant treatment is not given until day 3 of chemotherapy. Earlier studies indicated that treatment with an NK-1 receptor antagonist on the first day of chemotherapy has beneficial effects on emetic control on the subsequent days[5] and that higher single doses of an NK-1 receptor antagonist might provide long-term emetic control.[6] Therefore, initiation of aprepitant treatment on the first day of chemotherapy could lead to better control of both acute and delayed emesis, and perhaps of nausea.

In the Albany et al.[2] study, participants received 5-HT3 receptor antagonists other than palonosetron as part of the antiemetic regimen. Randomised trials have demonstrated better emetic control with palonosetron when used as monotherapy[7] or in combination with dexamethasone,[8] compared with older 5-HT3 receptor antagonists, such as ondansetron and granisetron. Indeed, a phase II trial, conducted by two of the researchers involved in the Albany et al. study, using palonosetron in a multiple-day intermittent administration schedule (on days 1, 3 and 5),[9] demonstrated that palonosetron plus dexamethasone treatment might improve control of emesis in patients with testicular cancer receiving multiple-day cisplatin-based chemotherapy, and might allow an every-other-day dosing schedule with this agent. These data are supported by results

Key points

- Oral aprepitant added to dexamethasone and a 5-HT3 receptor antagonist regimen improves five-day complete emetic control in patients with germ-cell tumours receiving cisplatin-containing chemotherapy
- Aprepitant-containing three-drug combination therapy has no additional side-effects compared with the two-drug (dexamethasone and a 5-HT3 receptor antagonist) regimen
- More research on drug scheduling and dosing of the aprepitant-containing three-drug combination regimen might lead to enhanced emetic control
- The new trial highlights several issues in antiemetic therapy that need further research, such as the requirement for improved control of nausea in many emetic chemotherapy settings.

of other studies using palonosetron.[7,8]

Unfortunately, although aprepitant addition treatment in the present study results in meaningful improvement in control of emesis, the majority of patients in the three-drug treatment arm still experienced vomiting. Even more surprisingly, only 13% of patients in the control arm were free of vomiting. These results demonstrate that aprepitant should be used in antiemetic regimens, and that studies are urgently needed to investigate whether other aprepitant and dexamethasone treatment schedules could improve emetic control.

The findings of this trial have additional implications. The control of nausea is only marginally improved with the aprepitant-containing regimen, and on several days nausea is not well controlled. This problem also exists with single-day chemotherapy, especially in the delayed emesis setting, and with different types of chemotherapy.[4,6,8] Given that the control of nausea lags behind the control of vomiting, future studies should focus on controlling nausea as the primary endpoint in major trials.

Even considering the remarkable progress in controlling emesis, it should be noted that few trials have been performed in chemotherapy settings other than in those with single-day chemotherapy administration. More antiemetic trials are needed in many chemotherapy settings, including those in paediatric oncology, those using oral chemotherapy or new molecularly targeted agents, those in patients previously treated with chemotherapy, and those using concomitant chemotherapy plus radiotherapy. These studies should also include multiple-day treatment settings.

The Albany et al.[2] study is a useful contribution to the knowledge of antiemetic treatment. It provides evidence for a new approach for controlling emesis in multiple-day chemotherapy and highlights many unmet needs in the complete control of emesis for all patients on each cycle of chemotherapy. ■

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Competing interests
The author declares associations with the following companies: Eisai, Helsinn and Merck. Please see the original article online for full details of the relationships

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

newsround

Selected reports edited by Janet Fricker

Laparoscopic colon resection delivers comparable results to surgery

■ Annals of Surgery

A trial comparing laparoscopic-assisted colon resection (LCR) and open colon resection (OCR) for patients with colon cancer found no differences in five-year overall survival, recurrence-free survival or freedom from recurrence, the Australasian Laparoscopic Colon Cancer Study has reported.

With widespread dissemination of laparoscopic surgical techniques into surgical practice, it has been necessary to ensure that short-term benefits of this type of surgery can be achieved safely without survival disadvantages for patients. Similar studies have been conducted across different economic, cultural and geographical backgrounds (such as the North American Clinical Outcomes of Surgical Therapy trial, and the European Colon cancer Laparoscopic or Open Resection trial) to ensure conclusions are generally applicable.

In the Australasian Laparoscopic Colon Cancer study, Philip Bagshaw and colleagues, from the University of Otago, Dunedin, New Zealand, randomised 601 patients with potentially curable colon cancer in a 1:1 ratio to receive LCR (n=290) or OCR (n=297).

Between January 1998 and April 2005 patients were recruited by 33 surgeons working across 31 participating centres in Australia and New Zealand. Significant differences between the two trial groups were that LCR patients were older at randomisation, with pathology specimens showing smaller distal resection margins, while OCR patients had worse pathology parameters, but no difference in disease stage.

Results show that the five-year overall survival was 77.7% for patients treated with LCR versus 76.0% for those treated with OCR (P=0.64); the recurrence-free survival was 72.7% for LCR versus 71.2% for OCR (P=0.70); and freedom from recurrence was 86.2% for LCR versus 85.6% for OCR (P=0.85). The subgroup of 43 patients who converted from LCR to open surgery had a five-year disease-free survival of 55.7%, in comparison to 76% for the LCR group and 71.7% for the OCR group (P=0.002 for both).

Secondary endpoints (described elsewhere) showed LCR delivered significant improvements in the return of gastrointestinal function and length of hospital stay, but with an increased operative time and no difference in intra-operative and postoperative rates of complications.

"The Australasian Laparoscopic Colon Cancer Study trial confirms that laparoscopic-assisted resection of colon cancer is not inferior to open resection. This contribution of long-term outcome data from another geographical region adds to the evidence supporting the place of laparoscopic surgery in the treatment of colon cancer," write the authors.

The finding of worse outcomes for patients converted from LCR to open surgery, they add, may be due to the fact that 12 of the 43 patients in the group had advanced disease. "Thus, outside the context of a randomized controlled trial, more accurate preoperative imaging, initial laparoscopic assessment, and stringent patient selection might consequently reduce the LCR conversion rate," they write.

■ P Bagshaw, R Allardyce, C Frampton et al. Long-term outcomes of the Australasian randomized clinical trial comparing laparoscopic and conventional open surgical treatments for colon cancer. *Ann Surg* December 2012, 256:915–919

Molecular profiling improves outcomes in carcinoma of unknown primary

■ Journal of Clinical Oncology

Molecular tumour profiling predicted the tissue of origin in most patients with carcinoma of unknown primary site (CUP), a prospective phase II trial has found. The authors of the US study, which represents the first use of molecular profiling in clinical management of patients with CUP, also showed profiling directed site-specific treatments and improved survival.

Approximately 3–5% of all cancers have no identifiable primary site, with recommended treatments including trials of empiric chemotherapy (usually taxane/platinum or gemcitabine/platinum regimens). But as treatment for specific types of advanced cancer improve, it has become increasingly likely that accurate identification of the tissue of origin and subsequent site-specific therapy would result in improved treatment for patients with CUP.

Molecular tumour profiling is a new diagnostic technique enabling prediction of the tissue of tumour origin by detecting site-specific gene expression profiles. However, no prospective trial has been undertaken in CUP patients to confirm that molecular predictions result in the selection of more effective therapy or improved survival.

In the current study, between October 2008 and December 2011, John Hainsworth and colleagues, from the Sarah Cannon Research Institute, Nashville, Tennessee, enrolled 289 previously untreated patients with CUP from 14 sites in the Sarah Cannon Oncology Research Consortium. Tumour biopsy specimens were tested against a 92-gene reverse transcriptase polymerase chain reaction cancer classification assay, and when a tissue of origin was predicted, patients who were candidates for treatment received standard site-specific first-line therapy.

The four most commonly predicted tissues of origin were biliary tract (21%), urothelium (12%), colorectal (11%) and non-small-cell lung cancer (11%). For the 194 patients who received biopsy-directed site-specific treatment, median survival was 12.5 months versus "historical survivals" of 9.1 months for patients who received empiric therapies. Furthermore, results showed that patients with CUP predicted to have responsive tumour types treated with site-specific therapy had a median survival of 13.4 months versus 7.6 months for patients with less responsive tumour types.

"Molecular tumor profiling offers the potential to identify the tissue of origin in patients with CUP and, therefore, may substantially change the management and outcome of these patients," write the authors. It is difficult, they add, to know how much additional clinical evidence is necessary before molecular profiling should become accepted as a standard part of diagnosis for patients with CUP. While randomised phase III trials are the only accepted way of providing unequivocal answers to this question, confounders for molecular profiling include therapies that can be identical for each treatment group and physician and patient reluctance regarding randomisation.

In an accompanying commentary, Adil Daud, from the University of California, San Francisco, writes that limitations of the study include use of historical controls, which could lead to overestimates of benefit, the time taken for biopsies to be processed, which could weed out rapid progressors, and the observation that 12.8% of patients had insufficient tissue for molecular testing. "While the data presented in the current trial is far from conclusive, it appears to be a rational direction for CUP and should lead to greater advances in survival in the future for this otherwise dismal disease," he concludes.

■ J Hainsworth, M Rubin, D Spigel et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon Research Institute. *JCO* 1 October 2012, doi:10.1200/JCO.2012.43.3755

■ A Daud. Removing the unknown from the carcinoma of unknown primary. *ibid*, doi:10.1200/JCO.2012.45.7630

Ovarian cancer: HE4 serum levels predict successful cytoreduction

■ Gynecologic Oncology

For patients with ovarian cancer, preoperative measurement of serum HE4 levels proved the best predictor for achieving optimal cytoreduction, an Italian study has found. HE4 delivered better sensitivity and specificity than serum levels of CA125.

Surgical cytoreduction followed by platinum/taxane chemotherapy provides the cornerstone of advanced ovarian cancer management, with optimal surgical outcomes shown to be one of the most powerful determinants for survival.

Currently, laparotomy provides the most accurate way to evaluate tumour burden and establish whether or not patients are suitable for optimal surgery, but it is an aggressive approach that can

postpone the start of chemotherapy. No general consensus exists about the best approach to preoperatively establish the cytoreducibility of ovarian cancers.

In the current study, Roberto Angioli and colleagues, from the University of Rome, Italy, set out to evaluate whether HE4, a novel biomarker for the early detection of ovarian cancer, offers a good predictor for optimal cytoreduction in advanced ovarian cancer and to determine the 'cut-off' level with the maximum prognostic power.

Between January 2011 and June 2012, 57 patients with advanced ovarian cancer had serum CA125 and HE4 levels measured preoperatively and then underwent complete laparoscopy to assess the possibility of achieving optimal debulking surgery, defined as no visible residual tumour after cytoreduction (RT=0). The investigators calculated accuracy, sensitivity, specificity and the positive and negative predictive values (PPV and NPV) of CA125 and HE4 alone and combined, and HE4 and ascites combined, at given cut-off values, using standard mathematical formulas.

Altogether, after diagnostic open laparoscopy, 36 patients underwent primary cytoreductive surgery and 21 were directed to neoadjuvant chemotherapy. Results showed the HE4 value of <262 pmol/l provided the best cut-off to identify candidates for optimal cytoreduction with a sensitivity (proportion of positives correctly identified) of 86.1% and a specificity (proportion of negatives correctly identified) of 89.5% (PPV=93.9% and NPV=77%). This compared with CA125 at a cut-off of <414 UI/ml, having a sensitivity of 58.3% and a specificity of 84%. The best combination for predicting cytoreduction was the combination of HE4 <262 pmol/l and ascites <500 ml, which had a sensitivity of 100% and a specificity of 89.5%.

"Based on our results, the introduction of HE4 as new preoperative tool in predicting cytoreduction may be helpful to select patients for the proper type of surgery," write the authors.

Ultimately it may be possible, they add, to combine preoperative CA125 and HE4 levels with both clinical and radiological findings to create a formal predictive scoring system that would indicate the likelihood of optimal primary surgical cytoreduction.

"In the future we could even combine the preoperative HE4 levels with less invasive instruments to obtain histological diagnosis, such as the CT-guided peritoneal or ovary biopsy, in order to avoid unnecessary surgery," they write.

Further larger studies are needed, stress the authors, to confirm the concordance of preoperative cytoreduction evaluation with serum markers CA125 and HE4 alone or in combination with diagnostic imaging and laparoscopic outcomes.

■ R Angioli, F Plotti, S Caprilione et al. Can the preoperative HE4 level predict optimal cytoreduction in patients with advanced ovarian carcinoma? *Gynecol Oncol*, published ahead of print on 7 December 2012, doi:10.1016/j.ygyno.2012.11.040

PET/CT imaging identified clear cell renal carcinoma

■ Journal of Clinical Oncology

Clear cell renal carcinoma (ccRCC) can be identified using PET/CT imaging with high sensitivity and specificity, the phase III REDECT study has found. To the best of their knowledge, write the investigators, the study represents "the first clinical validation of a molecular imaging biomarker for malignancy."

ccRCC has a poor prognosis (largely due to its high metastatic potential), making differentiation of this phenotype from indolent renal tumours (papillary and chromophobe carcinoma) with limited metastatic potential important for clinical decision making. Until now the standard for definitive characterisation of a renal mass has been surgical histopathology.

However, the development of the chimeric antibody cG250 (girentuximab), which binds with carbonic anhydrase IX, a cell-surface antigen expressed in more than 95% of ccRCC, opens the way for use of PET/CT studies.

In the open-label REDECT study, between May 2008 and November 2009, 204 patients with renal masses scheduled for nephrectomies at 14 medical centres underwent imaging with both iodine-124 (^{124}I)-girentuximab PET/CT and contrast-enhanced CT scans (CECT). PET/CT was obtained two to six days after infusion with ^{124}I-girentuximab and prior to surgery, with scans evaluated for evidence of radioactive uptake in the tumour by a panel of three blinded independent reviewers. In all, 195 patients were included in the analysis by Chaitanya Divgi and colleagues, from Columbia University Medical Center, with complete data sets comprising histopathologic diagnosis, PET/CT and CECT results.

Surgical biopsy was considered the standard of reference against which the imaging modalities were compared, with a central pathologist, blinded to all imaging results, categorising tumour specimens as positive (ccRCC present) or negative (ccRCC absent), according to WHO classification.

The ^{124}I-girentuximab PET/CT tests showed an average sensitivity of 86.2% versus 75.5% for the CECT (P=0.023) and an average specificity of 85.9% versus 46.8% (P=0.005) for the CECT. Inter-reader agreement was high (range 0.87– 0.92 for PET/CT; 0.67 to 0.76 for CECT), as was intra-reader agreement (range 87% to 100% for PET/CT; 73.7% to 91.3% for CECT). ^{124}I-girentuximab was well tolerated with

no evidence of allergic reactions or drug intolerance.

"This multicenter trial demonstrated that ^{124}I-girentuximab PET/CT could provide information on the presence or absence of ccRCC with accuracy at least comparable to that of biopsy, while obviating the need for this procedure with its inherent risks," conclude the authors. Moreover, they add, since chromophobe and most papillary (type 1) cancers – which account for up to 15–20% of all RCCs – are largely indolent, a negative ^{124}I-girentuximab PET/CT scan might allow risk-stratified management and avoid surgery in this group of patients.

"Such an approach would add 'confidence and clarity' to rational therapeutic recommendations for the surgically fragile, elderly, or comorbidly ill patient," they write.

■ C Divgi, R Uzzo, C Gatsonis et al. Positron emission tomography/computed tomography identification of clear cell renal cell carcinoma: results from the REDECT trial. *JCO* 10 January 2013, 31:187–194

Inaccurate beliefs around chemotherapy

■ New England Journal of Medicine

Patients receiving chemotherapy for incurable lung and colorectal cancers may not understand that chemotherapy is unlikely to be curative, compromising their ability to make informed treatment decisions.

While chemotherapy remains the primary treatment for patients with metastatic lung or colorectal cancers, survival benefits are usually measured in just weeks or months, and palliative effects are associated with substantial treatment-related toxic effects. Although several studies have suggested some patients with metastatic disease believe palliative chemotherapy can be curative, the prevalence and determinants of such misunderstandings have not been well characterised.

To understand factors playing a role in such "misplaced optimism", Jane Weeks and colleagues, from the Dana-Farber Cancer Institute, in Boston, Massachusetts, surveyed 1193 patients with stage IV lung and colorectal cancer at diagnosis who had opted for chemotherapy. They were asked about personal characteristics, decision-making, experience of care, and outcomes. Patients were identified from the National Cancer Care Outcomes Research and Surveillance study, which had enrolled more than 10,000 patients receiving a diagnosis of lung or colorectal cancer between 2003 and 2005. Questions addressed patients' perceptions of the likelihood of chemotherapy being able to cure their disease and extend their lives.

Results showed that, overall, 69% of patients with lung cancer and 81% with colorectal cancer gave answers that were inconsistent with the understanding that chemotherapy was unlikely to cure their cancer. In multivariable logistic regression, factors associated with a greater likelihood of misunderstanding were a diagnosis of colorectal cancer compared with lung cancer (OR 1.75, 95%CI 1.29–2.37; $P<0.001$) and non-white race or ethnic group as compared with white race ($P<0.001$), including Hispanic or Latino patients (OR 2.82, 95%CI 1.51–5.27), black patients (OR 2.93, 95%CI 1.80–4.78), and Asian or Pacific Islander patients (OR 4.32, 95%CI 2.19–8.49). Furthermore, patients were less likely to provide inaccurate responses if they received care in integrated networks or if they reported lower scores for physician communication. This latter finding suggests that patients "perceive physicians as better communicators when they convey a more optimistic view of chemotherapy," note the authors.

"Our results suggest the need for targeted education to help all physicians learn to communicate honestly while also maintaining patients' trust and regard. Efforts to incorporate earlier and more effective end-of-life care must address honestly and unambiguously patients' unrealistic expectations about the outcomes of chemotherapy," write the authors.

The argument can be made, they add, that patients without a sustained understanding that chemotherapy cannot cure their cancer have not met the standard for true ongoing informed consent to treatment.

In the accompanying commentary, Thomas Smith and Dan Longo, from John Hopkins University School of Medicine, in Baltimore, Maryland, write that chemotherapy near the end of life, is still common, does not improve survival, and is one preventable reason why 25% of all Medicare funds are spent in the last year of life.

■ J Weeks, P Catalano, A Cronin et al. Patients' expectations about effects of chemotherapy for advanced cancer. *NEJM* 25 October 2012, 367:1616–25

■ T Smith, D Longo. Talking with patients about dying. *ibid*, pp 1651–52

Corrections and clarifications

25 by 25 target for cutting NCD deaths

Agreement on a target of cutting premature deaths from non-communicable diseases by 25% by 2025 was reached at the World Health Assembly in May 2012, and not at the UN Summit on Non-Communicable Diseases held in November 2011, as was incorrectly stated on page 22 of the January/February issue of *Cancer World*.

Is there an app for that?

JUSTIN GAINOR

Smartphones give patients the technology not only to record a consultation but also to share it privately, post it on a social network or even upload it to a public website. What does this mean for doctors and their relationship with patients?

Smartphones are everywhere – the subway, coffee shop, and even my clinic. As smartphones have gained popularity, I have seen their potential to improve my patients' lives and experiences with illness. I have also witnessed how these devices can simultaneously complicate and even damage the patient–doctor relationship.

Like my patients in the clinic, the benefits of smartphone technology are diverse. Mr Monte, a 61-year-old gentleman with metastatic pancreatic cancer, liked to show his infusion nurses pictures of his family during chemotherapy; he explained that the photographs were reminders of why he continued to fight so vigorously. Ms Gold, confined to one room for her month-long hospital stay following a stem cell transplant, passed the time playing various board game apps with family members all over the country. Mr Stephens, a soft-spoken, recent college graduate with Hodgkin's lymphoma, found a haven during his chemotherapy infusions by closing his eyes and listening to music on his phone. Ms Jacks, a patient with warfarin skin necrosis, arrived in haematology clinic without hospital records, but used her smartphone to show me pictures of her evolving skin lesions.

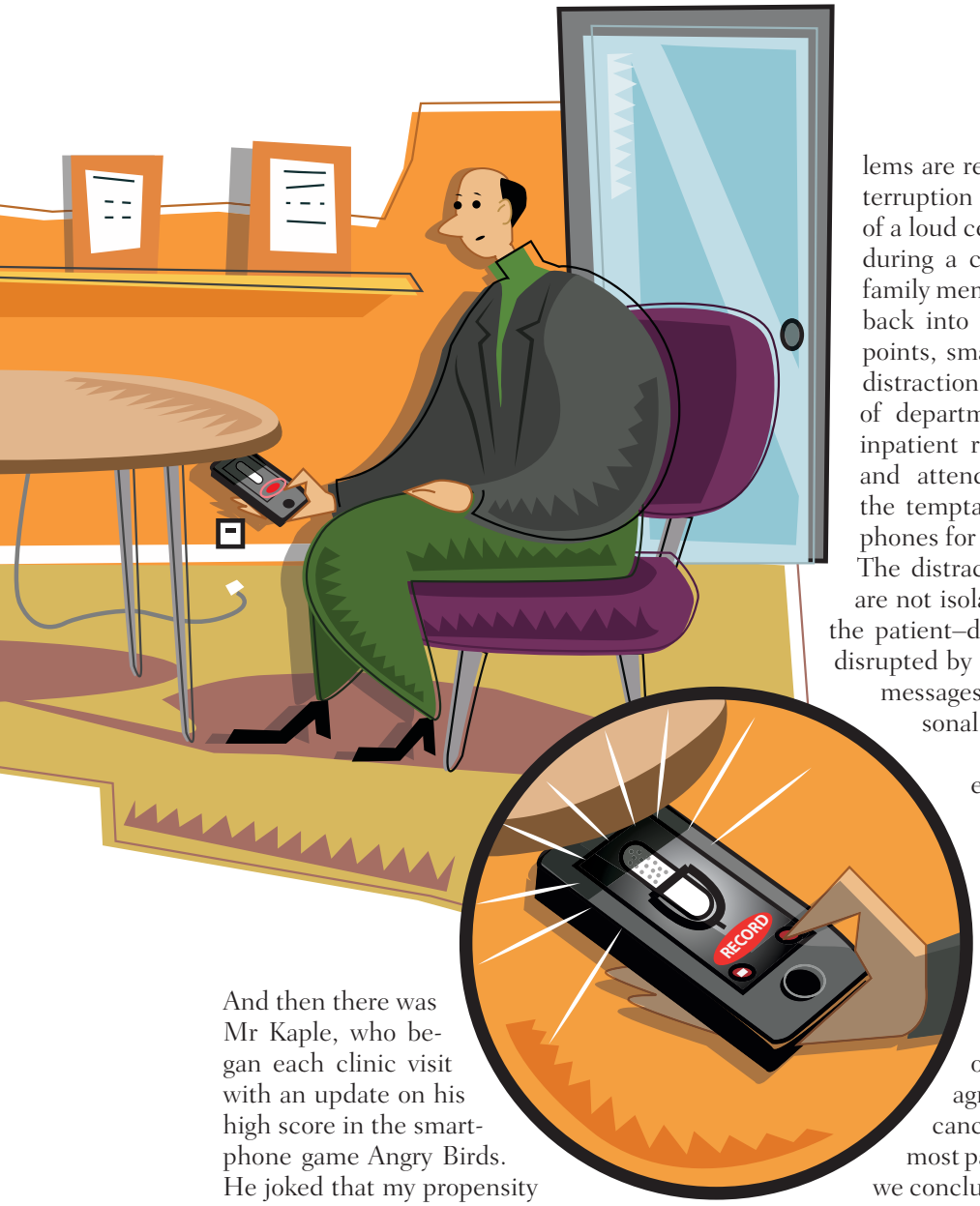


ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

And then there was Mr Kaple, who began each clinic visit with an update on his high score in the smartphone game Angry Birds. He joked that my propensity for running late gave him extra time to practice.

Just as smartphones provide opportunities for amusement, information, and access for patients and providers alike, the same devices can introduce new problems into the practice of medicine. In a majority of cases, these problems are relatively minor, such as the interruption of a patient visit by the ringing of a loud cellular phone or the brief delay during a counselling session to allow a family member with bad reception to dial back into the encounter. Still, at other points, smartphones can prove powerful distractions. Whether it is in the middle of departmental conferences or during inpatient rounds, students, house staff, and attendings are not impervious to the temptation of checking their smartphones for email, news, or other updates. The distractions invited by smartphones are not isolated to these settings. Indeed, the patient–doctor encounter itself can be disrupted by a physician responding to text messages, e-mail notifications, or personal calls.

Recently, I became acquainted with another potential 'side-effect' of smartphone technology that I found much more disturbing, because it served to paradoxically disrupt the lines of communication and trust between patient and doctor. My initial consultation with Mr Brown, a 63-year-old gentleman with newly diagnosed metastatic oesophageal cancer, began and proceeded like most patient encounters. However, as we concluded the visit, I recognised that Mr Brown's seemingly idle smartphone had just recorded our entire conversation without my knowledge.

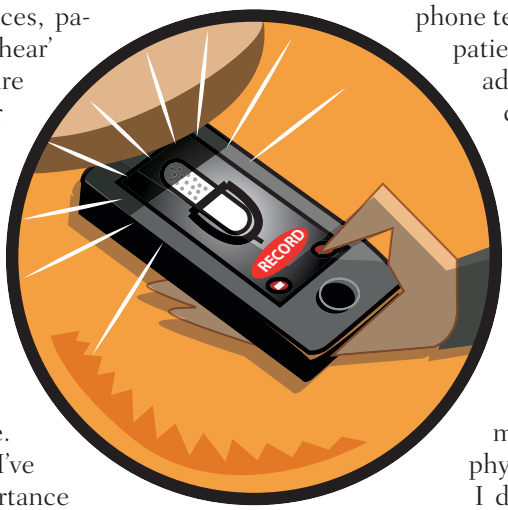
The realisation that one of my patients had secretly recorded our visit using his smartphone was simultaneously surprising, confusing, and deeply unsettling. Frankly, I was so caught off-

Mr Brown's seemingly idle smartphone had just recorded our entire conversation without my knowledge

The intimacy of our clinic visit was now overshadowed by the handheld elephant in the room

guard at this realisation that I hesitated and said nothing. In the days that followed, I replayed the visit with Mr Brown in my mind. Why did he feel the need to record our conversation? And why did I not vocalise my concerns?

Prior to meeting Mr Brown, I have had requests to record appointments, usually with a smartphone. Although it sometimes made me feel slightly more self-conscious, especially as a first-year oncology fellow, I have always consented. In these instances, patients often cite a desire to 'hear' the whole visit or capture details or instructions for family members. Indeed, meeting an oncologist for the first time can be a surreal and overwhelming experience. Often, patients need to process the details of a visit at their own pace, distilling fragments of information as they are emotionally able.



Over the past year, I've quickly learned the importance of repetition and the need to encourage patients to bring family members to each visit to assist with filtering information. Perhaps then, there may be situations in which patients derive a great deal of benefit from having a recorded copy of a clinical encounter? Care must be taken, however, to do so with openness, mindful of the trust necessary for a successful patient–doctor relationship. Indeed, many states, including my own, have specific laws precluding the recording of individuals without explicit permission.

In the case of Mr Brown, I don't know his reasons for recording our conversation or why he didn't mention the smartphone. I hope that it was a simple oversight on his part. Regardless, the incident was upsetting, not because of the recording itself but because of the act of concealment. It felt like a violation of trust between patient and doctor. I began thinking: If he didn't tell me about the smartphone recording, were there other aspects of his medical history that he was leaving out? The intimacy of our clinic visit was now overshadowed by the handheld elephant in the room.

My experience with Mr Brown has also made me think of other ways that smartphone technology might impact the patient–doctor relationship. In addition to simple audio recording, smartphones have the capacity to videotape. Indeed, one of my colleagues recently learned that his last patient encounter had been filmed – without his knowledge – with a smartphone. Where might this video end up: on a blog? social media website? YouTube? physician rating website?

I do not know for sure if my visit with Mr Brown was unique, but I suspect it was not. He has since returned to my clinic many times, and I have yet to see his smartphone back on my desk. I am, however, cognisant that I look for it. For me, this is a subtle reminder that, just as smartphone technology can broaden my access and ability to play a role in the lives of my patients, these same devices can introduce new complexities into our relationships. ■

All patient names have been changed to protect patient confidentiality. The author, Justin Gainor, is an oncologist at Massachusetts General Hospital Cancer Center, Boston, Massachusetts.

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My World

Jacob Scott uses approaches from his previous life as a physicist and engineer to build models of cancer biology and evolution from first principles, in the hope of generating novel, translatable hypotheses. On leave from his post as a radiotherapist, he is a researcher at the H Lee Moffitt Cancer Center's department of Integrated Mathematical Oncology, and DPhil candidate at Oxford University's Centre for Mathematical Biology.

Why I chose to work in cancer

I was drawn to radiation oncology initially because it allowed me to use physics, a discipline I had studied all my previous life. What now keeps me in oncology is the patients, and their bravery in the face of the unknown.

What I love most about my job

As a physician scientist working in theoretical and mathematical oncology, I love being able to draw insights into complex biological processes from abstractions and mathematical reasoning, and being able to generate novel biological hypotheses from these.

The hardest thing about my job

Helping patients tread the fine line between hope and realism.

What I've learned about myself

I am extremely lucky, and no matter where I go, there is someone smarter, braver and harder working than I am just around the corner.

I'll never forget...

My first cancer patient, at the Cleveland Veterans hospital, who was admitted for pneumonia, but was otherwise a picture of health. It turned out to be advanced lung cancer, and he never left the hospital. The bravery shown by him and his family taught me, at a critical point, about the responsibility we have as physicians to facilitate or keep respectful watch over families as they go through end of life issues.

A high point in my career

The amazing opportunities I have had to share with the world the new field of theoretical oncology, at gatherings such as the World Oncology Forum (www.worldoncologyforum.org) and TEDMED (www.tedmed.com).

I wish I were better at...

Mathematics. I am quite good at understanding where the big questions lie, and how mathematical techniques can be applied, but I still struggle with hard sums.

What I value most in a colleague

An open mind. The most important thing for the coming generation in cancer will be to admit that we know *very little*. While we have learned much, our lack of progress against cancer as a whole speaks volumes about how much more there is to learn – and in some cases unlearn.

The most significant advance in my specialty in recent years

Greater acceptance and funding for physical-science-based approaches in cancer research, such as the new Physical Sciences in Oncology Centers programme, launched by the US NCI, which is designed to bring mathematicians, computer scientists and physicists into the fray.

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

Make a habit of talking with scientists and clinicians from outside your discipline. Working towards finding a common language will bear fruit in the long run. It is these conversations that will yield the next big advances.

What I wish I'd learned at medical school

I wish that I *hadn't* learned most of the molecular biology that I was taught. We should be taught the general concepts, but to learn specific mechanisms is of little use to the physician in training. The time could be better spent with master teachers of anatomy and physical diagnosis, learning skills that are relevant to all physicians, and are hard to get from books later on. ■