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A RECIPE FOR SUCCESS

Negotiating the fine line between hope and realistic expectations

SEARCHING FOR A CURE

How can academia and industry collaborate more effectively?

GOOD PATHOLOGISTS SEEK ADVICE

A guide to improving diagnostic accuracy across Europe

Agnès Buzyn

Protecting France's AAA rating for cancer care

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Cancerworld

Shaping the future of cancer care

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Don't play with numbers

KATHY REDMOND EDITOR

Seven simple lifestyle 'steps' can cut your risk of getting cancer by 51%. This carefully crafted message, recently publicised by the American Heart Association, was guaranteed to receive enormous media attention because of its simplicity coupled with the promise of halving the risk of contracting a highly feared disease. It is perhaps a good example of linking causes to promote healthier lifestyles. How far it helped anyone understand their own particular risks of getting cancer and how best to manage them, however, is more debatable.

Most of us, when we hear that something halves our risk, tend to think we have understood something meaningful. But if we have little idea about what level of risk we currently face – as is generally the case – then being told that our risk will halve is in practical terms meaningless. Am I halving my risk of ever getting this cancer from 2 in 100,000 to 1 in 100,000? In which case it may make sense to keep the lifestyle and accept the higher risk. Or do I have a 2 in 10 chance of getting that cancer within the next five years, in which case halving that risk to 1 in 10 might be worth some fairly major changes in lifestyle.

If we are to help people understand and take sensible precautions to manage their risk, we need to stop communicating 'simple' but often meaningless figures about relative risk – and think about how we present figures that help people get some perspective about what their actual (absolute) risk levels are, from which risk factors and for which cancers.

There is evidence to show that the statistical format used to present health information influences how well people understand it, and their perception of risk. Changes in risk appear much larger and more impressive when using a relative risk format, and this can lead people to believe that an intervention is more effective than the available evidence demonstrates. This applies equally to the risk reduction benefits associated with preventative behaviours, screening and cancer treatments.

Talking in terms of absolute risk reduction is far more informative. Thus it is better to say: "If you do X you will reduce your chance of getting this cancer over the next 10 years from 3 in 1000 to 2 in 1000," rather than: "If you do X it will reduce your chance of getting this cancer over the next 10 years by about one third."

Using statistical formats everyone can understand is also advisable. It is better to use frequencies rather than percentages where possible – thus 60 out of 100 patients rather than 60% of patients. Graphs and other visual formats are also highly effective at conveying information involving probabilities.

Cancer has always suffered from disinformation and sensationalist claims and scares. The only way to counter this is through consistent and accurate information that is presented in a way that people can easily make sense of. This should become a standard for all educational literature that communicates risks about different aspects of cancer. It should also apply to press releases, so that news about cancer prevention, screening and treatment communicated by the mass media will be genuinely informative and less likely to lead to inaccurate beliefs about the potential of any intervention. ■

Agnès Buzyn: protecting France's AAA rating for cancer care

MARC BEISHON

France's relatively low profile on the European cancer stage belies a creative and innovative approach to research and care that other countries could learn from. Agnès Buzyn lifts the lid on how French cancer services continue to earn their ranking among the best in the world.

On the first day of her job as president and chief executive of INCa (Institut National du Cancer – France's cancer institute), Agnès Buzyn had to field calls from journalists keen to get comment on a new report that raised the risk level of cancer from using mobile phones. "That took me by surprise, as I had not yet seen the report," she says. It was a taste of the wide ranging issues she would have to deal with as the head of a national institute dedicated to both care and research – anything related to cancer, including public concerns about risks that are often wildly out of step with reality.

In its mainstream work, INCa has direct responsibility for commissioning and organising research, says Buzyn, which puts it in the same camp as other national agencies such as the NCI in the US. "But the NCI does not deal with organising cancer care – I think we are the only large state cancer agency in the world that has not only research but also care and prevention in its remit," she says. "While other countries have a division between research and care, France has been a leader in saying that they have to be very closely linked."

France has for some time delivered some of the best five-year survival rates in the world, ranking in the top five alongside Australia, Canada, Japan and the US. Though an achievement in itself, it is the progress made in building on this success, since the formation of INCa and a national cancer strategy, that Buzyn wants to emphasise. Key initiatives include rapid implementation of genomic mutation testing for personalising treatment, the establishment of seven regional research networks

(called cancéropôles, which are now certified by INCa), and the imposition of quality standards, which has led to fairly brutal cuts in the number of clinics allowed to treat cancer patients (more than half have gone). The target of all patients being seen by multidisciplinary teams is now met in more than 90% of clinics.

Personalisation is a key theme where France appears quietly to be taking a lead in Europe. "We were able to quickly convince our ministry of health that detecting patients with mutations could save a lot of money by avoiding inefficient treatments, which is why most patients are now tested in France, and we are also now moving on to wider molecular sequencing," says Buzyn. Coupled with a focus on key populations where networking and multidisciplinary working are especially needed – such as older people, teenagers and young people, high-risk patients and those with rare cancers such as sarcomas – the 'landscape' of cancer care in France has perhaps changed more rapidly in recent years than in most countries, and INCa has been instrumental in this.

That said, Buzyn stresses that there are formidable obstacles stemming from inequalities, including in access to high-quality healthcare. "The ministry of health is in charge of our national cancer plan and we are able to pilot only half of the plan's measures ourselves," she says. "When we are in charge of our half, it works well, but it gets much more complicated where there are wider social aspects beyond our power, such as insurance for people recovering from cancer, whether people can return to work or not, and changing systems for reimbursement of treatment, such as arranging for radiotherapists to be paid the same where we have shown that fewer doses are just as effective.

"We are a coordination agency and have to work with many different stakeholders, from charities to professional societies to other government agencies. We have the power to bring everyone to the table, but finding solutions often takes time and a lot of patience."

She is candid about the main failure she sees so far: that of addressing inequalities. "It's in our plan but it's been a disaster – the only part we have had success with is in early detection in breast cancer, where we have done a lot of work with isolated women such as those who don't speak French. Here we have pro-

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"Although France has good overall figures, they do mask a lot of inequality"

duced materials in various languages and worked with associations in city suburbs to explain about screening – but it's the only field where we have substantially reduced inequalities so far. Although France has good overall figures, they do mask a lot of inequality, especially in areas such as the north of the country."

Buzyn took the job at INCa in June 2011 as the third head of the agency, and its first woman president. The institute was established in 2004 after the publication of the first French cancer plan, one of the legacies of President Jacques Chirac. She arrived midway through a second plan, due to end this year, which was funded at more than €730 million. "Last December at our annual cancer congress President François Hollande announced that we will have a third plan starting in 2014," says Buzyn, "although it is likely to receive less funding. But all our stakeholders were glad to hear about the third plan, as we need to keep on setting objectives to bring everyone to the table – I told the President that we needed another plan to go further."

Hollande also addressed inequalities at the announcement. "The cancer plan is a plan to fight against inequality," he said, noting that the risk of dying from cancer among 30- to 65-year-olds is twice as high for workers than professionals.

Setting five-year plans and sticking to comprehensive reviews and reshaping of objectives regardless of party political lines – especially now in a time of austerity – also sets French cancer planning apart from most others. While most countries recognise cancer as a priority, it is more usual for national plans to lack the deadlines and renewal that France now enjoys. To be fair, however, Buzyn says that the early years of INCa were very much those of an organisation feeling its way forward, and it is only recently that its achievements are starting to reach a wider audience internationally. And as she comments, "Other health professionals in France outside of cancer have questioned the special status of INCa – but of course I agree that cancer is different."

Buzyn has a background in cancer. Her pathway into medicine was set in train when she worked alongside her father, an orthopaedic surgeon, in her school holidays – handing him instruments during operations. "It was natural for me to go to medical school and I thought I would be a surgeon too, but it's not an option well suited to a busy family life, so I looked for a specialty in a hospital, as I didn't want to go into private practice.

"I wanted to deal with a 'real' disease and chose leukaemia partly because when I was five my best friend disappeared from school and the teachers told me she had died from leukaemia. I found a strong woman mentor in Eliane Gluckman, who started bone marrow transplants here and was the only woman chief of department in France, and went on to specialise in haematology and transplants – but I'm not an oncologist and only really found out a lot more about solid tumours when I came to INCa."

Most of her clinical career has been at Necker hospital in Paris, where she still has one morning clinic a week to keep contact with patients. Though known as a paediatric centre, it also has adult departments, and Buzyn decided to work only with adults and teenagers. "During my residency, when I worked with Eliane Gluckman, a child died in my arms – I was eight months pregnant with my first baby and I just found it too hard to work with children."

A milestone in bone marrow transplants during her time, she says, has been a huge expansion in the donor population. "When I started we only had about a million – now we have 15 million from many countries. Another big advance has been that we can perform transplants with incompatible donors – now almost all patients can have one."

Buzyn has also pursued a research career in leukaemias and immunotherapy at institutes in Paris. Given the advances in immunotherapy that are finally coming to fruition, she has some regrets about leaving the field. "I was specialising in chronic myeloid leukaemia (CML), and when Glivec came along people told me immunotherapy wasn't interesting anymore. But I'm sure now it will

be part of the mix of therapies we need to treat cancer," she says. In other research work she has helped to show how patients with certain mutated acute lymphoblastic leukaemias (ALL) do not need bone marrow transplants.

In the clinic, a big issue she only now has the power to address is the needs of teenagers and young adults with cancer. "It is a special population group, as the diseases are very different and the young people are sometimes very mature but often angry – it takes a lot of time and energy to take care of them. I had a lot of young people referred to my department, and 15 years ago I wanted to open a special unit for them – but I wasn't able to. Now at INCa we are finally making plans for such units."

FRANÇOIS GUILLOT/AFP/GETTY IMAGES

A trusted source of information. Agnès Buzyn fields questions from the media about the potential cancer risk posed by leaking Poly Implant Prosthèse (PIP) breast implants, December 23, 2011

Although France is not seen as a rigidly patriarchal society, Buzyn says that, in academic medicine especially, there was and still is some reluctance among men to see women in senior positions – something she encountered when she was appointed professor of clinical haematology at Paris Descartes university. "It's still hard for women to have an academic career – men just don't see women as taking their place even if you have all the diplomas and research papers and are equivalent to them. I had lots of jealousy from colleagues at the hospital after my appointment as a professor. There are many women working in labs and in specialties such as pathology and geriatrics – but there is resistance to us becoming heads in what are seen as major disciplines such as haematology. Other women colleagues and I even thought of setting up a pressure group to highlight this issue."

To its credit, it was the right-wing Sarkozy government that wanted a woman as the third head of INCa after the then chief executive was asked to manage a new drug agency. Buzyn came to the fore because she had also participated in a number of French agencies, and was in any case on INCa's executive council at this point. "I was first involved in a number of scientific councils such as at the French blood agency. I like being involved in society as a citizen, and I also like politics – it means you have a chance to change things. But I didn't think I could be involved at a higher level."

The appointment that brought her national attention was to the board of the French radiological protection agency. "This was my first real administrative experience and I enjoyed it very much. As a scientist I brought input from the research and university sector. But I then had to deal with the Fukushima crisis, which was very big in France." Previously, she says, the meltdown at Chernobyl had caused a scandal in France after the public were advised that there was no fallout over the country. "That was not true and people got thyroid cancer after eating wild produce. So when Japan's Fukushima crisis happened – and with our own background with nearly 60 nuclear power plants – it was a big concern here, although this time there was no danger.

"With the media going crazy I had to go on TV almost every day and explain what was going on, and say there was no need for people to buy iodine pills. I'm a leukaemia specialist so that was part of the reassurance, as I was not seen as part of the nuclear lobby. I didn't want to do it, but I realised that the journalists wanted to hear from me." They still want to hear from her now she is at INCa – and possible leukaemia associations with power plants are another ongoing and controversial issue.

When she was a full-time clinician, the cancer plan did not concern her much, she says. "But the one thing that was really interesting was that any patient with cancer had to be discussed first in a

"It's a sobering thought that more than 1000 places were deemed not qualified to work with certain cancer patients"

The second cancer plan 2009–2013

The second cancer plan covers five areas, 30 measures and 118 actions. Here are some of the key planks:

Research

- Increase resources for multidisciplinary research; accredit five multidisciplinary cancer research integrated sites.
- Increase patient participation in clinical trials by 50%, prioritising the most vulnerable populations.
- Devote more than 15% of the research budget to analysing environmental and behavioural risks.
- Contribute to the full genome sequencing of the five most common cancers.

Observation

- Produce and communicate information on cancer and cancer research and treatment on an annual basis.
- Produce an analysis of cancer distribution across the country each year.

Prevention – Screening

- Increase participation in organised screening programmes by 15%. The level of increase should be 50% in the départements experiencing most difficulties.

Patient care

- Individualise patient care and expand the role of the referring doctor. Ensure that 80% of patients benefit from at least one individualised care plan.

Life during and after cancer

- Develop individualised social support during and after cancer. Ensure that 50% of patients benefit from at least one post-cancer plan.

The cancer plans are available in English and INCa also publishes major documents in English such as its yearly activity reports and scientific reports on research. The latest scientific report is for 2011–12 and has detailed descriptions of national and international projects with graphics and tables. See www.e-cancer.fr

multidisciplinary team – no oncologist in France is allowed to see patients on their own in private practice. That is real progress for quality of care and security for patients, and for me one of the main achievements of the first plan."

That plan, she adds, was also about structuring oncology from a fairly uncoordinated state. "It was decided to organise research and care networks in the regions and accredited centres to take care of patients – we fixed the minimum numbers of patients a year to maintain quality." That led to a dramatic reduction in the number of clinics treating various cancers. "Ten years ago there were more than 2000 establishments – now there about 800," says Buzyn. It is a sobering thought, she adds, that more than 1000 places have been deemed not qualified to work with certain cancer patients.

Overall, the first plan had 70 ambitious areas in six main themes to cover, but it lacked rigorous indicators to monitor progress, says Buzyn. This has now evolved into five areas, 30 measures and no fewer than 118 actions – including 'flagships' with specific targets (see panel). Buzyn mentions research as an area where they achieved particu-

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lar success. "We've put a lot of energy into developing phase I and II clinical studies, and have increased by 70% the number of patients in trials. That is much more than the plan objective of 50%," she says, noting that these trials have a focus on vulnerable populations such as children, older people and those with rare and the most serious cancers.

Another success has been the accreditation of eight multidisciplinary research centres under the SIRIC banner (sites de recherche intégrée sur le cancer), including the Institut Gustave Roussy (IGR) and the Curie, both in Paris. "Our ambition is to organise translational research in hospitals integrated with care and prevention," she says.

Molecular profiling of tumours for personalising therapy is now being done in 28 regional centres, notes Buzyn, and is at the heart of a wide number of initiatives. "We have started a programme for phase II trials for targeted therapies that are just approved or about to be approved – we want to open trials to patients who have a mutation such as BRAF in cancers other than melanoma, for which vemurafenib is approved. We will see whether drugs are effective in other indications, and if so, we will ask the industry to open an official trial. Many oncologists want to see this, because it will help them avoid giving off-label drugs without knowledge of their effectiveness and side-effects." The project is called AcSé (for secured access to drugs) and is run at INCa's CLIP^2 (accredited early-phase clinical) centres. The institute is proposing it as a possible European model for public–private partnership.

Meanwhile, the testing network for mutations in common cancers has ramped up to cover most patients, identifying key markers such as KRAS in colorectal cancer and EGFR in lung tumours, as well as possible new targets. Buzyn reports that €69 million has been saved at a cost of only €1.7 million by ensuring, for instance, that lung cancer patients without mutated EGFR are not treated with gefitinib.

Having reference centres for pathology is also driving a mandatory second opinion system for rare cancers such as sarcomas, where at least 15% of diagnoses are changed when reviewed (France is one of the few countries with a mandatory review – see also When in Doubt, Ask an Expert, page 30). This process also admits patients into clinical networks of specialists in rare disease. There are currently 17 such networks, which include rare cancer types as well as rare events such as cancer in pregnancy.

This in turn is feeding research, by building up tumour banks and registries, and trial participation. "For example, we participated in a multinational chondrosarcoma trial run from the US and we were the first country to finish our inclusions, identifying 45 patients in less than a year, who were detected through our network. Most other countries do not have this level of organisation. We know almost every patient with, say, a chondrosarcoma in France." For more on initiatives in molecular pathology, see Testing the Testers (*Cancer World* November–December 2012) and also the key paper led by INCa on the French tumour profiling programme (*Nat Rev Clin Oncol* 2012, 9:479–486).

INCa also helps fund large-scale academic research, such as the PHARE trial that aimed to find whether 6 months of Herceptin is as effective as 12 months for adjuvant therapy in breast cancer. The trial enrolled some 3380 patients across more than 150 centres in France.

Another pilot from INCa focuses on supporting patients by providing them with a personalised therapeutic 'project' and post-cancer personalised project, to give them a proper explanation of their treatment plans, identify what supportive and social needs they have and prepare the ground for life in the community after treatment ends. "It will be part of our third plan to put more emphasis on ambulatory care in the community, involving GPs and perhaps creating a new type of profession such as coordinating nurse," says Buzyn.

An overall aim of the third plan, she adds, is to speed up innovation for patients. Though France has a good record of introducing drugs early – as they did, for instance, with Herceptin – Buzyn considers the overall pace of innovation to be too slow, noting again that areas less in INCa's influence can hold things up. A higher proportion of radiotherapists than medical oncologists work in private practice in France, for example, and not only are they likely to be slower to make changes, they are also

"I really want to work more on quality of care, as it is unforgiveable if patients lose the best chances they have"

less well represented in wider research networks (France is one of the membership 'black holes' for ESTRO, the European radiotherapists' society).

Radiotherapy has received more attention, however, since a major scandal about overdoses given to more than 5000 prostate cancer patients in Epinal, north-east France. Three professionals received prison sentences this year for their part in this.

Other disciplines allied to oncology, such as interventional radiology, also need to be integrated much more into strategy, says Buzyn, and new avenues with truly 'outside' professionals, such as mathematicians, physicists and engineers, need to be explored – a call for proposals from these disciplines has been made by INCa and several have been funded.

To help break down barriers, Buzyn has reorganised INCa's 150 staff into two main directorates – public health and organisation of care, and research and innovation. "The idea is to encourage translational actions and fewer 'vertical' actions," she says.

Although public health messaging is handled by another agency, INCa does have a role to play in prevention messages on issues such as tobacco and risky behaviour, she says. "French people tend to think all things are equally risky – we need to do more to show them that about one-third of cancer risk is related to tobacco and alcohol, and not to pollution in cities, for example." INCa is exploring whether to make research in areas such as behaviour change a priority for the next few years.

Regarding risk, Buzyn's reassuring presence was called into play again recently during the PIP breast implant scandal, as not only were many cancer reconstruction patients affected, but there was alarm about a possible association with developing lymphoma (one woman did die of the disease). "We approached this as an expert group to show what the evidence was," she says.

She places great store on INCa giving independent advice, noting that the experts it uses for recommendations must demonstrate they are not compromised by involvement with industry.

Internationally, Buzyn is keen to do more to talk about the French experience, recognising that there is not enough representation at present. "But French oncologists are well connected in research networks, and I gave a presentation at ESMO last year on our progress and plans in personalised care," she says. There is, however, much more to tell about how the French model is doing across the entire patient journey, she feels.

INCa is a member of the European Partnership for Action Against Cancer (EPAAC) working group on cancer research, and recently hosted a meeting in Paris where Buzyn discussed possible pilot projects to better coordinate European research, such as a healthcare knowledge network, public–private partnerships in early-phase clinical trials, and prevention research. It is and has been active in various other EU projects; for example it was the coordinator of CoCanCPG (Coordination of Cancer Clinical Practice Guidelines in Europe), and is active now in programmes such as TRANSCAN (the network on translational cancer research). However, the very fact that she is not using English as much as when she was a researcher is an indicator of the need for more international work, Buzyn adds.

Two key people spring to mind in her life. One is her husband, Yves Levy, an HIV/AIDS specialist in charge of the French HIV vaccine programme. "We talk a lot about research and he helps me a lot," she says. The other is Jean-Paul Vernant, a retired professor of haematology and well known to Buzyn – which is advantageous because he has been charged with drawing up the third cancer plan for 2014–2018.

Her appointment is for a five-year term and she is clear about her priority. "I really want to work more on quality of care for everyone, not just access to care, which is in the current plan, as it is unforgiveable if patients lose the best chances they have. I receive a lot of letters from patients and families and some are so sad, and I always answer them – but I want to be able to reassure them that they had the best care." ■

Finding breakthrough treatments:

how do we fix the broken model?

The business model for developing new cancer drugs is broken and needs replacing with more efficient forms of public–private collaboration. This was a key message from the Stop Cancer Now! appeal made to governments and policy makers on February 4th, World Cancer Day. It reflects a growing concern that the relations between industry and academia need to change if we are to translate the impressive advances in our knowledge and understanding of cancer into breakthrough treatments.

This concern was also addressed in an EORTC position paper in January 2013 (*EJC* 49:1–7). The authors call for a new model of partnership between industry and academia to allow each to play to their "core competencies" to improve drug development by ensuring better integration of standardised, quality-controlled clinical, biological and imaging data into the decision-making process. Are they right? If so, what should the new partnership look like? *Cancer World's* Anna Wagstaff put the question to Lex Eggermont, director of the Gustave Roussy cancer institute in Villejuif, Paris, and Bill Hait, global head, Janssen Research & Development.

Lex Eggermont

We should first acknowledge that our ability to identify targets and develop drugs against those targets is a major scientific breakthrough. Our lack of progress in clinical terms reflects the complexity of cancer. The initial reasoning was that a drug that works against a given target, e.g. mutated BRAF, would work across different diseases defined by that particular target. This would have meant that the old-style pharmaceutical business model of finding 'blockbuster' drugs that work over large populations might have remained viable. But this does not seem to be supported by the evidence, because we now know that the organ of origin – the tumour environment – plays an important role, so a BRAF inhibitor that shows a good response in BRAF-mutated melanomas, for instance, shows no such response in colorectal cancers with the same mutation.

The challenge for industry is to find a financial model that can sustain developing drugs that work well in small populations. The challenge for all of us is to find a way to make the science work. The clinical side of the drug development programmes has become far more important, and I think the EORTC is right to focus on the need to ensure better integration of standardised, quality-controlled clinical, biological and imaging data into the decision-making process. The work must be led by medical oncologists and imaging oncologists, because they are trained to have that broad vision and understand multiple tumour types. They have to use all their knowledge about the disease, and programmes must be science driven – with multiple biopsies, multiple evaluation points and multiple investigation techniques, such as functional imaging. Everything has to be worked out in phase I and early phase II, and only if you see convincing and consistent effects will you take a drug into a phase III trial.

Such work can only be carried out at centres of excellence, which have the experience, expertise and infrastructure. These are the centres that, together with industry, will make the discoveries but will also kill many drugs that are not good enough to be moved into later phases. Our dependency on one another is now much greater.

Bill Hait

A lot of oncology drugs have been approved in the last two years, some of which make a big difference, but there's no question that we haven't cured as many cancers as we might have hoped.

I think part of the problem is that we became too enamoured with the technology. The ability to clone genes, express proteins, make crystals, and use those crystals to conduct structure-based drug design became so 'easy' compared to the old-fashioned way, that we got carried away. We assumed that as soon as we made a drug against an identified target it would solve the problem. I agree with Lex that it just hasn't turned out that way, but I don't think lack of interactions between academic institutions and industry on clinical trials is the major problem – clinical trials are collaborative by their very nature.

I believe the big problem centres on how you translate a fundamental discovery into an active drug. Pharma companies are experts in developing drugs, but have very limited understanding of the biology and pathophysiology of disease. Academia, on the other hand, has very little expertise in drug development, but has very deep expertise in disease. We need to be able to sit down together and look, for instance, at drug resistance in acute myeloblastic leukaemia and ask: what are the drivers of those cancer cells? What are those

pathways? What are those antigens? How do we get closer to knowing that this pathway and the targets in this pathway are most likely to have a pay-off in those patients if we could make a good drug?

We should come together in robust and meaningful collaboration bringing our expertise to the table and not be ships passing in the night. A good example is the agreement Stephen Friend negotiated with the Lee Moffitt Cancer Center in Florida, when he was at Merck. Merck funded the setting up a of network of hospitals that would provide Moffitt with tissue samples for cancer genome analysis. It was a very large investment on Merck's part, and a sizeable investment in time and effort by the Moffitt Cancer Center, but because of that partnership they now have probably more information and data than they could ever have imagined.

An example we are very much involved with is a partnership with the Koch Institute for Integrative Cancer Research at MIT, where we work together on the tumour microenvironment and immunologic microenvironment, which are areas of mutual interest.

I agree that the big challenge is to understand more about drivers and resistance mechanisms in different cancers, and that requires collaboration. But the elephant in the room is how to get around the intellectual property [IP] restrictions so that the data that is generated can be shared. Once the data is out in the public domain, anybody in this world who has a scientific brain and analytic power can analyse it and come up with ideas. In fact Stephen Friend left Merck to set up Sage Bionetwork, a non-profit organisation that promotes open data sharing, and sets open challenges to encourage interested scientists to focus on particular problems and data sets, to see who can come up with the most discriminatory bioinformatic analytical models.

Most cancer centres are involved in programmes and partnerships exploring a lot of different avenues and they are creating huge data warehouses. But if we don't know how to resolve the IP problem around data generating and data sharing, it's hard to see how you can develop a partnership model that will make it possible to explore all the data that already exists but is locked away.

That said, I don't think the disappointing performance of targeted drugs can be ascribed entirely to failures at the more fundamental level of research. Resources are being wasted because too many drugs make it into clinical trials without convincing data that they have the potential to make a big difference. I think one reason is that many preclinical programmes are conducted too much in isolation rather being tested in a broader range of models. I often see data presented as very hopeful and promising, and I am totally underwhelmed by what I am looking at. This can be a particular problem with biotechs that have everything riding on the success of just one or two molecules, but it can play a role wherever scientists' future prospects are linked in some way with the success of the project.

When you analyse data from 20 experiments, it's easy to focus only on the better results and find excuses for why some didn't turn out so well. People with a broader perspective on the disease may be more cautious about proceeding until more is understood about the reasons for the inconsistent results. Better collaboration, particularly at the preclinical stage, could ensure a more critical evaluation of the strengths of a particular molecule.

I agree that the failure rate is too high, but I don't see the problem as a lack of robust interaction or use of enough preclinical models. Between all of us, we still lack adequate knowledge to predict with greater certainty which drug will work and which will fail. In my experience, teams that work on a compound spend an enormous amount of time working with many molecules and many sites of interaction with the target. These people live and die for their compound and by the time a drug is ready to enter clinical trials there has usually been significant input from external experts on advisory boards. These experts won't have seen only the good data, because companies tend to seek advice on the areas where they are uncertain, so are more likely to focus on the less convincing data.

On the issue of IP and sharing data: would things would go better if relations between industry and academia were more open, as Lex suggests, so that everybody could pitch in? It sounds reasonable when you first hear it, but there is also the other possibility of too many cooks spoiling the broth. If I make an observation that I think is critically important, I would be much more interested in finding the best person or people in the world that I can collaborate with on it. It is more manageable, it is not going to create a lot of noise, and I think it would be more productive. Take Herceptin. The discovery of HER2 neu was made by Bob Weinberg at MIT in a cell line that came from a brain tumour. Denis Slamon observed that HER2 neu was being overexpressed in breast cancer and that it portended a very poor prognosis, and Genentech gave Denis Slamon the tools to explore the space of HER2-positive breast cancer. Then some fantastic scientists at Genentech went on to develop Herceptin.

It's easy to say: let's ignore IP. But at the end of the day, we have to preserve a pharmaceutical company's ability to be profitable, so that it will have the funds to reinvest in the important and innovative research that impacts the health and welfare of people in the world. As in all highly innovative industries, IP is essential for this model to work. You have to be sensitive to that.

The problem is that the model that worked for developing Herceptin has not worked as well as we had hoped for other types of disease, because most solid tumours have turned out to be far more complex, with multiple drivers. But we're not going to solve the problem if we keep so much data, particularly all the sequencing data, behind closed doors. We have to open up at some point, and earlier than now, to the benefits of the unparalleled analytic power that is around. We should also bear in mind that most institutes where we are working run on tax payers' money, so the public should have some right of access to the information we help generate.

For me, the question is how you can construct partnerships that protect IP rights while still putting a whole lot of raw data on the internet where other people can try their hand at making sense of it. That could be a very technical discussion about where IP starts and where it ends, but if the industry doesn't open up to more open partnerships and data sharing, I don't see how it will survive. We can die together or live together, but we will certainly need a big change to live together. If we can't change the paradigm to create open partnerships and publicly shared data, then I think it will just suffocate. Cancer is too complex to be solved by pharma alone, and too complex to be solved by academic institutions working alone. We have to invite in all the analytical power and infrastructure that is out there.

That sounds right until you get into specific examples. We've had instances where an academic person requested raw data for a particular project. He had good academic credentials and we were about to turn over the data when our attorneys found out that this person had just started a company that was trying to produce a competitor drug. We were about to give that person the raw data.

You need to be aware that there are noble people out there who want to do the right thing. Then there are others who may have ulterior motives, and companies need to protect themselves from that.

We came up with an idea a couple of years ago called an I-SPORE (SPORE being a grant scheme run by the US National Institutes of Health). We said to leaders of a couple of universities: we'll put on the table all of our reagents, capabilities and drugs, in return for you, the academic leaders, helping us understand in greater detail the drivers of a particular type of cancer.

In the end it didn't come to anything, because it was very hard to reach agreement on some of the details – the usual barriers of how quickly you publish, who gets what credit when you work as a team, royalties, protection of IP. I think it's basically a good idea and none of those barriers are insurmountable.

Could such an agreement incorporate provision for open sharing of some of the raw data? Quite possibly. Under the proper circumstances, proper investigators opening up the books to raw data could be very useful for both the industry and the investigators, but there has to be some care in doing that. We need to continue to ask these questions and work together to find a solution. ■

What counts as a 'successful' outcome?

SIMON CROMPTON

Every patient wants to be cured. But a culture that defines success as 'cure' condemns many patients and doctors to failure. Should the cancer community be looking to broaden the concept of success to better reflect how well care plans deliver the best possible outcome tailored to each patient's personal priorities.

What does treatment 'success' mean in cancer? Does it only mean curing the cancer? Or controlling it? Extending life? Or providing a good quality of life, even for a short time?

How we define success and failure is important because it has a profound impact on the goals that patients and their doctors set themselves and the experience of the cancer journey. Developing a shared understanding of what success means is also essential for informed public debate about the value of different interventions in different settings and how to get the best outcomes from the resources we have.

Roger Wilson, who has lived with sarcoma for 13 years, has pondered deeply on these issues. He says there is an urgent need for the cancer world to address the cultural influences that affect treatment decisions in advanced cancer: "We need to look at the patient demand for a 'right to live', the medical attitude that 'success equals cure' and the funder's view that a dying patient is just a financial burden," says Roger, who is a founder and President of Sarcoma UK.

Somewhere, amid these influences, what's right for the individual can get lost.

Perspectives from patients and family on these issues provide a rich vein of insight for professionals and policy makers. In all their variety,

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

they offer a central message: for a treatment to be 'successful' patients and their families must be properly engaged.

Negotiating expectations

Kathy Oliver says that when her son Colin was diagnosed with a brain tumour in 2004 at the age of 24, her only measure of success was cure. "I didn't know any better then," says Kathy, who is co-director of the International Brain Tumour Alliance.

"When the diagnosis was given to us, we were sitting in a tiny room in a London hospital, but we may as well have been sitting on a planet in outer space. We had no map, no compass, no anchor to steady us. In our naïvety, we believed at that stage that treatment success could only be measured in terms of cure: we anticipated that neurosurgery would remove nearly all the visible tumour, followed by radiation that would eliminate every last cruel cancer cell, and then chemotherapy to guarantee a long and healthy life. Unfortunately, it didn't work out like that."

"As my son's journey progressed, and his tumour's level of malignancy did too, each successive treatment carried with it a different measure of success and expectation. With each treatment stage, the successes became more modest, but at the same time the availability of each treatment represented renewed hope."

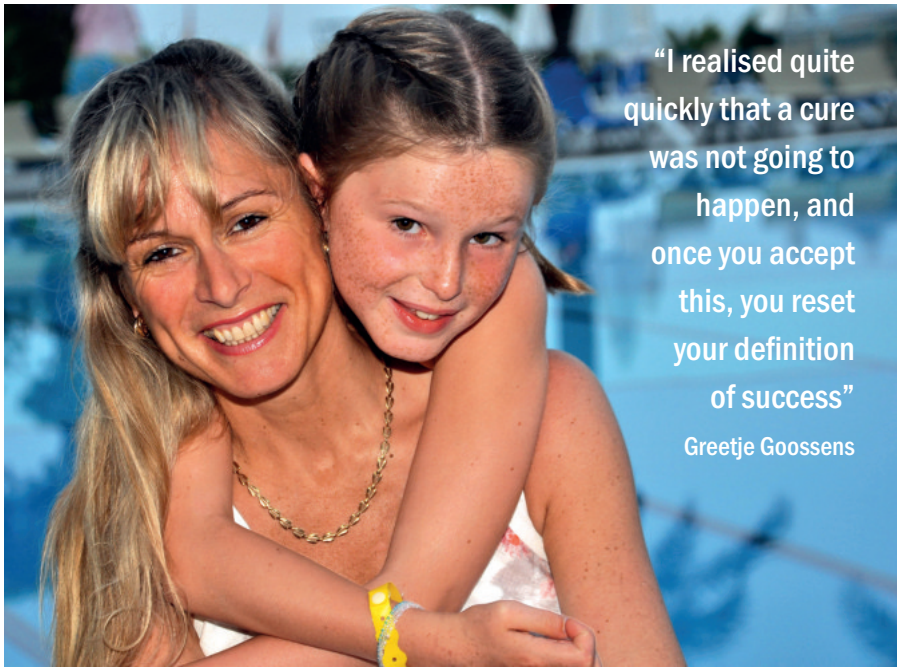
Greetje Goossens from Belgium,

diagnosed with multiple myeloma in 2002 at the age of 37, tells a similar story of revising expectations. Since it is a disease "that doesn't go away", she says, patients often have a lasting relationship with their doctor, with treatment options being constantly discussed and renegotiated.

"My idea of success has definitely changed over time," she says. "After my diagnosis, we discussed whether I should have more aggressive treatment which would extend life, or softer treatment that would give me better quality of life. At that stage, I was ready to go for the aggressive treatment – to go as close to a cure as was possible, because I had just given birth, had two young children, and I wanted to be with my family for as long as possible. But then I realised quite quickly that a cure was not going to happen, and once you accept this, you reset your definition of success. Now success means reaching certain milestones, to get the children through adolescence, and now to bring them to graduation.

"For someone over the age of 70, the objectives might be very different," says Greetje, a board member of Myeloma Patients Europe. "And people late on the journey sometimes say they're fed up with treatment and just want not to suffer and to be with their families."

Expectations, and thus definitions of success, are also heavily shaped by cultural and social influences, says Luzia Travado, head of the psycho-oncology unit at the Champalimaud Cancer Centre in Lisbon, Portugal. Patients with advanced cancer who come from lower socio-economic groups tend to be more passive recipients of care, she says. Their expectations of treatment 'success' may be far less ambitious than better educated patients with higher incomes, who tend to want more control, and push more not only for a right to live but a right to a good quality of life.



What doctors do will be partly defined by this. Those working with higher socio-economic groups are more likely to propose active treatment towards the end of life.

"There are some patients who want to control, and some who are happy that the doctor controls," she says. "But if you want properly responsive health systems, you have to keep asking people questions, whichever group they fall in, so that they can be involved if they want to. That doesn't always happen."

Buying time

The question of when active treatment should cease will always be difficult to negotiate, but with health services operating under ever tighter cost constraints, many patients now feel they are being denied a worthwhile shot at achieving a valuable added few weeks or months not because their expectations are unrealistic, but because they are considered unaffordable.

Bettina Ryll, whose husband Peter died of melanoma in February last year after treatment in Sweden and the UK, is one among many representatives of cancer patients who worry that, despite high-level debate about 'best' treatment towards end of life, what actually happens is often dictated by economic considerations.

She has watched with interest as academics and policy makers have grappled with the cost of new cancer drugs, and she stands alongside the many patient groups who criticised the 2011 report of the Lancet Commission on cancer costs. This claimed that giving expensive care to patients during the last weeks of life is 'futile' and argued that too many of the new cancer treatments only extend life by a few weeks.

"Terminally ill people are members of society too," says Bettina, who jointly founded the Melanoma Independent Community Advisory Board – an international network and resource for people affected by melanoma – in 2011. "They have paid into their health system, have made their contribution to their health care, and as a society we have a duty to honour that. I think it's shocking to see how, suddenly, people who are no longer in the 'healthy club' are considered not worthy of receiving any more from the health system."

Bettina, who trained as a doctor herself, questions how far doctors really understand what a few extra weeks can mean to families, and she rejects the way active treatment tends to be counterposed to palliative care, arguing that treatments that extend life can also improve the quality of life.

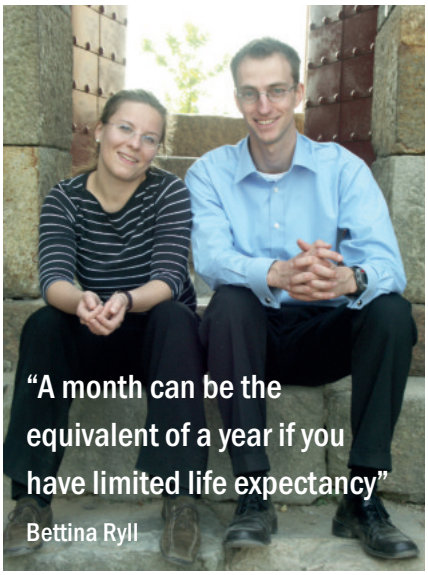
"Peter's melanoma was extremely aggressive," she says. "It was diagnosed in February and by April the tumour had encased his whole arm so that he couldn't move it and it was very painful. We didn't expect him to see the summer.

"Then he went on a trial for a new drug and the tumour regressed – so much so, that he could even start rowing again. He died in February last year, so being on that drug bought us nearly a year. I remember thinking, before he went on the trial, 'What's the point of another month or so?' But it gave us a chance to adjust, to say goodbye, to give our two daughters a chance to prepare, to get things in order. I think that year was the most valuable year of my life."

"As healthy individuals, I think we underestimate the value of time for the person with cancer and their family. A month can be the equivalent of a year if you have limited life expectancy."

Something to hope for

Kathy Oliver stresses that encouraging realistic expectations must be tempered with giving patients and their families something to hope for. If there is nothing to hope for there can be no hope of success.



"I wish that in the early days of my son's diagnosis we had not faced such nihilism from some of the medical professionals we met," she says.

"We often think of successful treatments that are either swallowed, injected, zapped or surgically performed. But to be given hope is just as important a treatment, and brings benefits not just for the patient, but for the family too. I cannot stress enough how important it is to maintain hope for patients facing devastating diagnoses.

"I know that in my son's case, when there were no more surgeries, no more chemotherapies, no more radiation to be done, he still insisted that there was a plan for him. He kept receiving experimental therapy until the day he died, and in the last days kept reminding us not to forget to give him his treatment. Was the treatment futile in terms of medical benefit? Yes, it probably was. But what was important to my son, and also to us, was that there was a plan even towards the end."

Of course, the experience of each family will be very different. Treatment plans will be influenced by the nature of the disease, its stage, and according to the character, socio-economic background, circumstances and wishes of the patient. With all those variables, doctors have a task on their hands when it comes to managing expectations while keeping hope alive.

Towards personalised measures of success

Roger Wilson says that a way forward is to provide doctors with "prognostic/risk assessment tools" that will give them the means to look at living with cancer in a rounded manner, not just in terms of medical treatments. This kind of personalised approach

Many patients now feel they are being denied a shot at achieving a valuable added few weeks or months

could yield a new integrated idea of treatment success for each patient.

"Such tools could be based on biological, behavioural, social and psychological markers: 'this patient will do better if treated this way, another patient will need treating another way, and a third yet another way' – even when clinically they are at the same stage with the same disease. Each treatment may involve lifestyle elements, would draw in expertise from non-cancer healthcare specialists, and would include practical support tuned to the needs of patients' families."

There have been tentative steps towards this kind of patient-centred research, he says, and it would sit very neatly with personalised cancer therapy approaches. "If we could reach the two objectives together, that would be a genuinely new definition of success."

For Greetje Goossens a good relationship with their doctor remains the key for patients to perceive their treatment as successful. "It's about partnership. I didn't feel on the same wavelength with my first doctor and felt very unhappy, but when I changed I could accept my situation much better."

However, a study published recently in the *New England Journal of Medicine* warns against jumping to the conclusion that a 'good relationship' necessarily improves the chances of patients achieving an outcome they perceive as 'successful'. Quite the reverse in fact.

JOHN FLOWERDEW WWW.STUDIOJ.CO.UK

The surprise findings show that misunderstandings about treatments and their objectives are more common, not less, when doctors and patients have a good relationship.

The study, published in October last year, examined the expectations of 1193 patients receiving chemotherapy for metastatic lung or colorectal cancer. This can prolong life by weeks or months, or relieve symptoms, but does not cure. However, 69% of patients with lung cancer and 81% of those with colorectal cancer did not understand that chemotherapy was unlikely to cure their cancer. Surprisingly, perhaps, the risk of reporting inaccurate beliefs about the chemotherapy was higher among patients who rated their communication with their physician very favourably.

The implication is that the cost of a good relationship between doctors and their patients is an inability to face up to difficult facts – or at least a tacit agreement to collude in unrealistic expectations. The consequences of this may only come home to roost when patients and doctors are both faced with a sense of failure late in the cancer journey.

A planned and transparent transition

Bettina Ryll believes that altering the emphasis at medical school would go a long way. "At medical school you still have a rose-tinted view of how medicine saves lives, and maybe more could be done to demonstrate how palliative care is an important part of medicine too, and about the palliative ability of advanced treatments."

Luzia Travado agrees that both patients and doctors find it difficult to acknowledge when cure is no longer possible. But it is up to the doctor to regulate expectations, right from the point of diagnosis. "It's difficult," she says. "Patients cling to any hope, and doctors want to avoid their patients getting too emotional. I've seen some

"So it all depends on establishing a proper partnership, and negotiating where you are heading at different stages"

patients who want to continue with their chemotherapy whatever the circumstances, because their coping mechanism is to not even consider the possibility of death.

"So it all depends on establishing a proper partnership and negotiating where you are heading at different stages. That's why it's so important that doctors are given the communication skills, and understand, for example, the SPIKES six-step protocol for delivering bad news.

"Patients need to be helped to understand that the doctor can do something for them at all stages, even if they can't cure. Here, we have abolished the phrase 'There's nothing more I can do for you.' If there isn't open communication from the start, patients and their families can easily feel frightened and isolated when the language doctors use changes, and doctors stop talking about 'active' treatment."

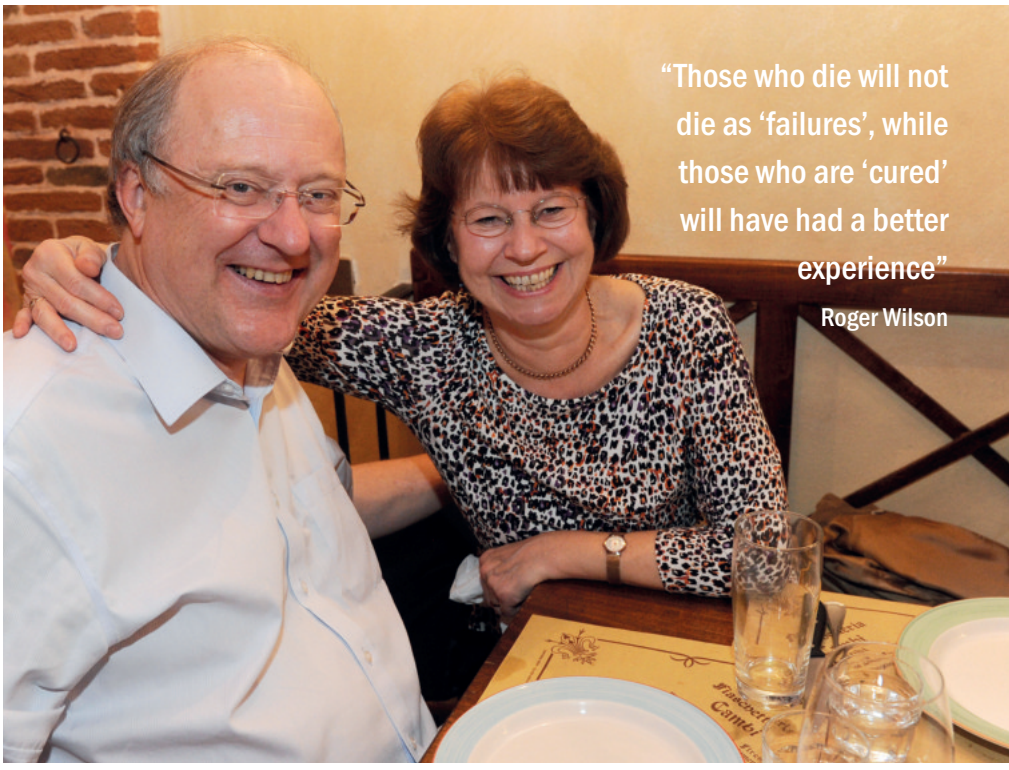
Roger Wilson agrees with that prescription. But given the cultural influences that make it so difficult for doctors and their patients to look forward and discuss dying, he believes we have to look further than training time-strapped doctors. Healthcare systems need to plan for greater involvement from palliative care experts with psychological training from early on in the cancer journey.

"The truth is that we do not do communication well, but is unfair to look at it solely as a clinical problem best resolved by training cancer doctors better than we currently do," he says. "Our healthcare systems have a general lack of will to support cancer patients with professionals who have had psychological training first and have then learned about cancer.

"A treatment approach which starts as curative but which recognises the 'point of no return' in a positive way would go a long way to challenging the current cultural influences on doctors and patients. The transition to palliative treatment should be planned and transparent. Expert palliative support should be seen as constructive and introduced to the patient long before there is the recognition that curative treatments are no longer feasible. Those who die will not die as 'failures', while those who are 'cured' will have had a better experience."

Such planning could redefine everyone's ideas of treatment success, he says. And it might mean that people with cancer and their families are helped to make decisions that are better suited to them as life reaches its end.

"It might mean that a few more patients die a few days earlier than they might otherwise have done, but the whole family experience and remembrance of dying would be more positive," says Roger Wilson. "That would also be a benefit to society." ■



ULI DECK

When in doubt, ask an expert

MARC BEISHON

No pathologist can be an expert in every type of cancer. But there is a lot that can be done to greatly improve the accuracy of diagnoses, particularly in rare cancers, as a recent European survey has shown.

The best quality treatment based on clinical guidelines carefully adapted to the individual patient can be worthless if the pathology report is wrong about the diagnosis. But getting the pathology right is becoming harder as more and more new molecular subtypes are identified, many with important implications for treatment options. This is a particular challenge with cancers that occur only rarely, because most pathologists see too few to gain any familiarity with them, let alone expertise.

In an effort to address this challenge, Rare Cancers Europe and the European Society of Pathology conducted a survey last year to find out more about how cancer pathology is practiced across Europe, and to try to identify opportunities for improvement.

Responses from 123 pathologists from 37 European countries indicate that while two-thirds rate the current pathology standards in their countries as high or very high, about half from eastern and southern European countries said standards were average or low. The survey also revealed cause for concern over how well pathologists are integrated into multidisciplinary teams, the proportion of 'atypical' or 'suspicious' findings that are sent for an expert second opinion, levels of clinical feedback from clinicians about their pathology reports and participation in quality assurance conferences.

The implications are at first sight alarming, says Angelo Paolo Dei Tos, director of anatomic pathology at the General Hospital of Treviso, Italy, and an expert involved in many soft tissue and bone pathology groups, who helped organise the survey. This is particularly so, he adds when seen alongside findings of an earlier study, published last year in the *Annals of Oncology* (23:2442–49), which compared initial diagnosis of sarcoma with an expert review in three European regions, and showed that up to 40% of diagnoses are inaccurate. Other studies have shown that a discrepancy level of around 30% is probable in most European countries. "The rate does not seem to have changed much over the years," Dei Tos says. He is keen to stress, however, that the answer lies with constructive engagement with healthcare systems rather than casting blame.

CUSTOM MEDICAL STOCK PHOTO / ALAMY

Second opinion

"Pathologists know that when you see a rare cancer, you have two options – you either ask for a second opinion or you don't," says Dei Tos. "In the US, it is almost standard practice to send out for a second opinion, especially in private practice, because it is usually paid for by insurance and there is a strong incentive to avoid litigation for mistakes. But in most of Europe the decision is almost always dependent on the goodwill of the pathologist. So far, only France and Sweden have mandatory systems for second opinions."

The *Annals of Oncology* study sent histological data from sarcoma patients in two regions in France and one in Italy for a second opinion from regional or national experts over a two-year period. It was a follow-on from a study conducted in one area of France that showed that "only 54% of included patients had full concordance between primary diagnosis and second opinion." A key point about the study is that the data were sent to sarcoma experts – a second opinion can of course also be obtained from within the same institution or from another laboratory or institution that may lack expert knowledge. Here again, the authors also stress that any discrepancies are not viewed as errors or "misdiagnosis", but as "acknowledged need for assistance".

The detailed results from the three-region study are that full concordance between the first diagnosis and expert second opinion was reached in 56%

"The complexity and rarity of these tumours can make diagnosis almost impossible outside of expert centres"

"Many times I see a perfect molecular test performed on the wrong tumour"

of cases (824 in total), partial concordance in 35% (the same diagnosis of the actual tumour but different grade or histologic subtype) and complete discordance was reached in 8% of cases (including over whether the tumour was actually benign rather than malignant).

As Dei Tos points out, the major issue with sarcoma is that the number of identified subtypes has exploded over the past 10 years or so. "There are now as many as 90 histological subtypes that all look different and can need sophisticated immunohistochemistry and molecular genetics to arrive at the correct diagnosis. But the complexity coupled with rarity of many of these tumours – most pathologists simply won't see them in years – can make diagnosing them almost impossible outside of expert centres."

Morphology before molecular pathology

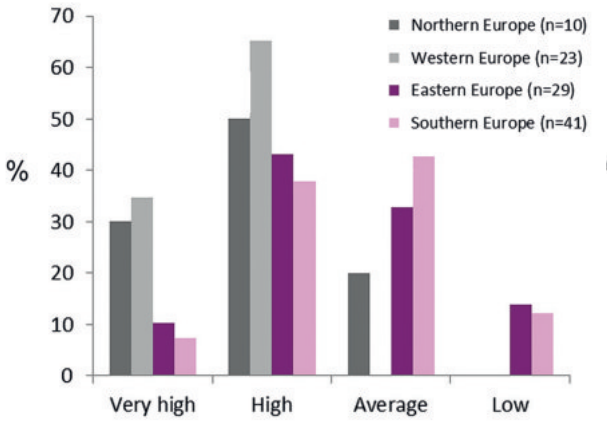
Good pathology, starts with examining tumour slides on a microscope, says Dei Tos, and not rushing into sophisticated testing. This is where expert knowledge is critical. "When we put a slide on the microscope at our centre we develop a differentiated diagnosis in our minds from the morphology of the cells – such as their size and shape. Only afterwards do we use immunohistochemistry or molecular testing to prove it and exclude other things. Our pathologists are exposed every day to rare diseases that others may not see at all – so they are routine for us, but our expertise then becomes rather unique, especially as some of us have very detailed knowledge of particular subtypes."

Rare sarcomas can also mimic carcinomas and lymphomas, he adds, and attributes such as necrosis and mitotic activity can look malignant but may not be, while lesions that look indolent and benign may actually be highly aggressive cancers. Looking for expressions such as cytokeratin can also lead to confusing sarcomas with other cancers that also express it.

In a paper on pathology and genetics published in the *Annals of Surgical Oncology* (2010), Dei Tos noted: "Even in the presence of state-of-the-art molecular techniques,

PATHOLOGY STANDARDS

On an international scale, how would you rate the current pathology standards in your own country?



The Pathology in Rare Cancers International Survey (2012) was a joint initiative of Rare Cancers Europe and the European Society of Pathology. The findings shown here and in the subsequent graphs are based on 123 responses from across 37 European countries

Source: The Pathology in Rare Cancers International Survey (2012) http://tinyurl.com/cancerpathologysurvey

SECOND OPINIONS

When you come across a case that is "atypical" or "suspicious", what do you usually do?

Goodwill. Paolo Dei Tos and colleagues at Treviso respond to requests like this one for second opinions, on an informal basis and free of charge – only Sweden and France have mandatory systems in place

accurate morphologic assessment should still represent the diagnostic mainstay… for two very simple reasons: no distinctive genetic aberration is present in 100% of cases of a given tumor… and the same genetic aberration may be present in unrelated entities."

"Medical oncologists are starting to believe that molecular pathology is the gold standard – but I tell them that many times I see a perfect molecular test performed on the wrong tumour. But genetics can be very valuable when based on good morphology."

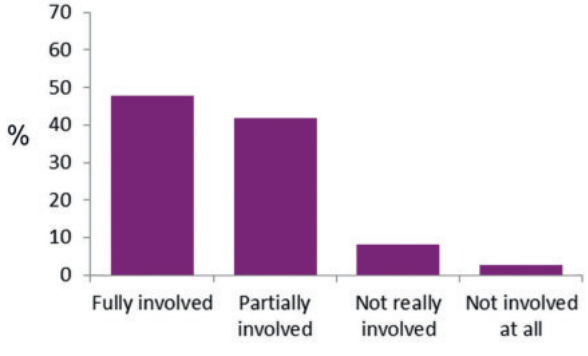
The implications of incorrectly diagnosing the type of sarcoma, or failing to identify it is a sarcoma at all, are becoming all the more serious with the marked increase in the options available for treatment. Not long ago, the options were limited mainly to surgery and possibly radiotherapy, with standard chemotherapy having only a limited effect across all sarcoma types, says Dei Tos. Now the molecular and cytotoxic landscape for targeting subtypes has opened up dramatically, with evidence, for instance, that angiosarcoma – a particular interest for Dei Tos – responds to chemotherapy such as taxanes as well as anti-angiogenic drugs, while other subtypes respond to other drugs, including targeted therapies such as imatinib (Glivec).

In the three-region study, although there was a high inaccuracy rate, major misdiagnosis with direct impact on patient care was less than 10%, and related mainly to grade and type. Grade in particular could determine whether adjuvant or neoadjuvant chemotherapy is given. But it is also not unusual, adds Dei Tos, for a tumour such as GIST (gastrointestinal stromal tumour, a type of sarcoma), for instance, to be misdiagnosed as a leiomyosarcoma (which looks similar). Patients can thus miss the chance to have the "stunning" success that imatinib can give with GIST (equally, patients misdiagnosed with GIST can be prescribed imatinib for a tumour that would only benefit from classic cytotoxic therapy). "Sadly there are stories of patients sitting on the wrong diagnosis and treatment for years," he says.

A wrong diagnosis could have immediate severe consequences. As Han van Krieken, professor of pathology at Radboud University Nijmegen Medical Centre, Netherlands, and president elect of the European Society of Pathology, notes: "We had an example only recently. A patient was referred for amputation of his arm based on a diagnosis of sarcoma in an academic centre, but this centre had little experience with sarcoma and thus also the pathology. Upon review it was a benign lesion and amputation obviously was not needed. There are studies on melanoma, lymphoma and sarcomas showing that such expertise is really needed, but we see it more and more in other tumour types too."

INVOLVEMENT IN MD TEAM

To what extent are you involved in the multidisciplinary medical team caring for the patient?



Improving rare cancer pathology

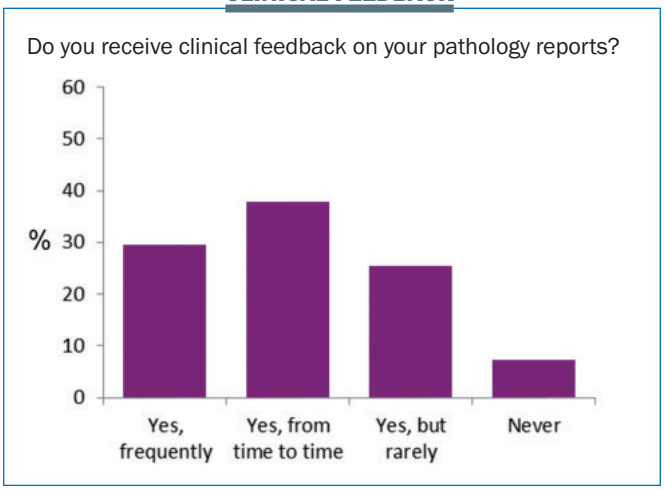
The conclusion that Dei Tos draws is that robust second opinion systems should be implemented in all countries to give extra help in correct diagnosis of rare cancers. Given that it is likely that only a few countries will actually mandate such systems, he feels that continuing to build evidence and provide education about

"It's not because they are not good pathologists – it's a lack of day-to-day expertise on these rare subtypes"

the issues is the best way forward. "Certainly, medical oncologists in our rare cancer network in Italy want second opinions because the revisions can and do change their practice," he says.

Pathologists themselves, according to the Rare Cancer Europe survey, feel the need for better training and education; this was the most frequently cited recommendation, along with better integration of pathologists into multidisciplinary teams.

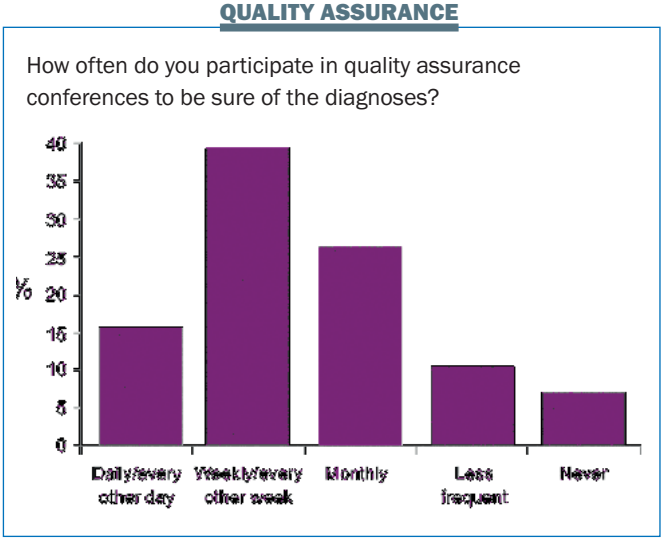
CLINICAL FEEDBACK



But as Dei Tos says, training is no substitute for familiarity: "We do have pathologists who come to us for experience and may spend two or three months here, but when they go back, after six months or so, when they send us samples it is clear that they are starting to lose confidence as they simply do not see enough cases. It's not because they are not good pathologists – it's a problem intrinsic to lack of day-to-day expertise on these rare subtypes."

Van Krieken adds that, although training and teaching are available, it is simply not feasible for individual pathologists to cover the whole cancer field, which makes it particularly important that pathologists work very closely with the treating team. This makes the lack of multidisciplinary working indicated by the survey particularly worrying, he says – assuming it is a true reflection (the number of respondents was not high). He would like to see the European Society of Pathology place greater emphasis on multidisciplinary work. "At this point the [Society] has no policy other than providing high-quality training, working with other organisations such as ESMO, EORTC and ECCO, and providing quality assurance programmes for molecular testing, which are not specifically for rare cancers." (See also Testing the Testers, *Cancer World* Nov–Dec 2013.)

QUALITY ASSURANCE



Meanwhile Dei Tos and his team give second opinions at Treviso on an informal basis, and it is only recently that the Italian government has allocated some funding for such work through the country's rare cancer network (called Rete Tumori Rari, which itself has reported treatment-relevant discordances in more than one-third of the sarcoma cases reviewed by pathology in the network). "But from the start I decided to provide all second opinions free of charge – it's important not to see them as a way of making money, because I believe that would generate an unfair system where cash buys access. In Europe most health systems are public and they should look to fund a proper second opinion system to support expert centres." ■

Chronic and late effects: how physical activity can help

An exercise programme can improve patients' physical ability to function, lift their mood and may even lower their chance of recurrence. The coordinator of the ground-breaking Glasgow study presents the evidence in favour of including individualised exercise interventions as an integral part of patient care.

Four million people will be living with a diagnosis of cancer in the UK alone by 2030 (www.macmillan.org.uk). This is equivalent to more than 7 out of every 100 members of the adult population – a proportion that will be reflected across much of Europe, where incidence and survival rates are broadly similar. The challenge in ensuring that these survivors enjoy a good quality of life is to address the chronic or late-appearing side-effects of cancer and cancer treatments. These include fatigue, which is one of the most debilitating long-term effects of cancer; weight changes (either weight gain or loss); loss of bone density, including osteoporosis; cardiotoxicity; lymphoedema; psychological problems including anxiety, depression, fear of recurrence and cognitive dysfunction; and limited range of movement.

A US study showed that more than half of cancer survivors (53%) had problems functioning, with at least one functional limitation, compared

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 Anna Campbell, University of Dundee, Scotland, reviews the latest evidence on the role of exercise in cancer rehabilitation. Dominik Berthold, University Hospital of Canton Vaud, Lausanne, Switzerland, poses questions arising during the e-grandround live presentation, which was held in collaboration with the European Oncology Nursing Society (EONS).

Summarised by Susan Mayor.

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

to only 21% of people of the same age who had not had cancer (*Ann Epidemiol* 2006, 16:197–205). The study was undertaken with an elderly population, and the common functional problems were: crouching/kneeling; standing for two hours; walking quarter of a mile (0.4 km); lifting or carrying a load of 10 lb (4.5 kg); and standing up out of a chair. These movements are all the basis of daily activities needed for housework, shopping and similar tasks, suggesting that functional aspects of quality of life tend to be quite dramatically reduced after a cancer diagnosis.

Exercise-based cancer rehabilitation: the evidence

The number of high-quality studies in this field is increasing exponentially each year. They show that physical activity can reduce the functional loss (cardiovascular and muscular) that occurs with cancer and its treatment, and can reduce some of the chronic or late-appearing side-effects of treatment, including fatigue, depression and weight gain. Exercise-based rehabilitation can also reduce some of the long-term reliance on health services. Emerging epidemiological evidence suggests that being physically active reduces the risk of the cancer recurring, as well as all-cause mortality, for breast, prostate and colorectal cancers. As rehabilitation programmes are already available for coronary heart disease, diabetes, preventing falls and the lung disease COPD, programmes for cancer survivors can tag into or copy programmes that have been tried and tested for other chronic conditions.

During treatment

A systematic review of high-quality, randomised controlled studies of physical activity as an intervention during adjuvant treatment for cancer – during chemotherapy, radiotherapy or after surgery – shows that physical function, in terms of cardiovascular function and muscular strength, improves significantly (grade A evidence; *J Cancer Surviv* 2010, 4:87–100).

The 17 randomised controlled trials all showed a small to moderate effect in improving cardiovascular fitness or muscular strength in patients taking part in a physical activity programme during adjuvant treatment.

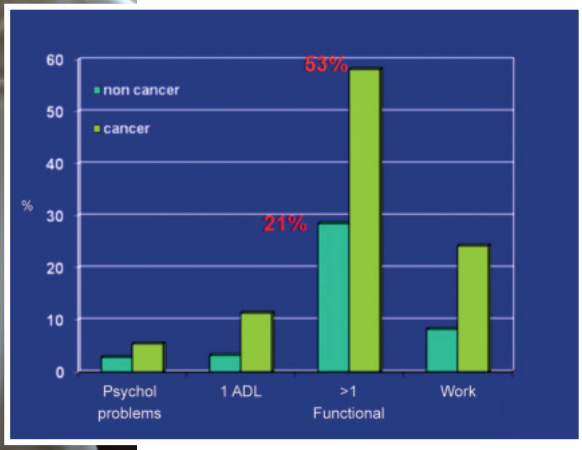
Some studies have shown physical activity can reduce fatigue during treatment, but the overall effect is not very large. However, the good

FUNCTIONAL LIMITATIONS ARE THE BIGGEST PROBLEM

CORBIS

More than half of the cancer survivors surveyed reported problems functioning – most involving activities essential for daily life

Source: Reprinted from KK Ness et al (2006) *Ann Epidemiol* 16:197–205, with permission from Elsevier; ADL – Activities of Daily Living



news is that being physically active during treatment does not *increase* tiredness. Anxiety, self-esteem, quality of life and depression show small improvements with physical activity during treatment. Also exercise interventions aid in significantly reducing body fat and increasing lean muscle mass. The overall take home message is that it is safe and effective to give an appropriate programme of physical activity while on adjuvant treatment. This can help prevent the functional decline that can occur during and after cancer treatment.

Question. *There is a modest increase in physical function with physical activity. Do you have any information on age subgroups? Will a patient who is 80 years old benefit as much as a younger person with non-Hodgkin lymphoma at the age of 20?*
Answer. *The majority of studies mentioned in this report are with women with breast cancer with an average age of 50–60. I believe that a similar effect will be found irrespective of age, but perhaps a younger person with non-Hodgkin lymphoma would gain more fitness from a physical activity intervention, while a frail elderly person might gain more active daily living and confidence. The results will vary with the cancer type and the patient's age and condition.*

After treatment

What about giving an exercise intervention in a patient who has finished adjuvant treatment? Results here are more significant. Exercise interventions achieve large increases in muscle strength (effect size [ES] 0.90 in seven randomised controlled trials) as well as significant improvement in cardiovascular fitness (ES 0.32 in 14 RCTs). For many but not all patients, this timepoint, just after treatment, is when they are ready to start an exercise programme. Fatigue levels also show a significant reduction with exercise interventions. Wellbeing improves more significantly with activity after treatment, and there are small reductions in body fat and increases in muscle mass. It is important to note that these trials involved only an exercise intervention; studies incorporating both exercise and diet may give even better results for positive changes in body composition.

Finally, some new studies have looked at the effect of exercise on bone density. Reduced bone turnover can occur with hormonal therapies, potentially reducing bone density. Resistance exercise programmes can help reduce the risk of bone thinning, but the results of different trials to date are inconsistent.

Other benefits of exercise are being explored in relation to some of the late effects of cancer treatment. As well as improving bone health, studies have shown exercise programmes can improve range of movement. Activity programmes designed for individual patients may prevent lymphoedema, and studies have shown that exercise does not exacerbate lymphoedema in patients who already have the condition. Further studies have shown improved mood, better regulation of insulin, reduced cardiotoxicity and improved immune system function with exercise.

A smaller number of studies have looked at the effects of exercise in people with advanced or terminal cancer. A systematic review of six small studies investigating physical activity during palliative care showed some benefit. One study showed that home-based, seated exercises prevented decline in quality of life (*Oncol Nurs Forum* 2004, 31:977–983). Supervised group exercise for six weeks improved fitness, functional ability, emotional wellbeing, fatigue, dyspnoea and anorexia (*J Pain Symptom Manage* 2006, 31:421–430). The key message in a palliative setting is that the patient's preference is important. The aim is not necessarily to improve fitness, but to maintain independence and wellbeing towards the end of life.

Impact of physical activity on cancer recurrence: the evidence

Kenfield and colleagues followed 2705 men diagnosed with prostate cancer over 10 years, monitoring activity levels. Results showed that the number of deaths in total was 36% lower in men who walked an average of one hour each day (7+ hours per week). It was 49% lower among men taking three or more hours of vigorous activity each week, with 61% fewer cancer deaths (*JCO* 2011; 29:727–732).

The strongest beneficial effects of physical activity on disease recurrence and risk of death has been observed in longitudinal studies of breast cancer survivors. A systematic review of nine high-quality, prospective cohort studies following breast cancer survivors over time showed that undertaking leisure-time physical activity involving moderate-intensity exercise for 30 minutes most days each week was associated with a 30% reduction in breast cancer mortality risk when compared to a sedentary lifestyle with virtually no physical activity (*Maturitas* 2010, 66:5–15; *Med Oncol* 2011, 28:753–765). Two longitudinal studies have shown that colorectal cancer recurrence risk and mortality is reduced by about 50% with six hours of moderate-intensity physical activity each week (*JCO* 2006, 24:3535–41).

Why might exercise be protective?

Research is starting to explore why people who are physically active may be protected from cancer recurrence. Exercise may have a beneficial impact on energy balance and fat distribution, and this is important as obesity is strongly associated with higher risk of cancer recurrence. Secondly, physical activity can influence sex steroid hormones, such as oestrogen and testosterone, which affect some hormone receptive cancers. Insulin, insulin-like growth factor and its binding protein IGF-BP3 seem to be involved in cancer cell growth, and their levels can be influenced by physical activity. Inflammatory markers (such as CRP and interleukins) and immune system components (such as natural killer cells) may also play a role in cancer and can be regulated by exercise. Finally, physical activity may impact on the antioxidant defence system, DNA damage and apoptosis.

What do guidelines recommend?

During cancer treatment (surgery, chemotherapy and radiotherapy), guidelines recommend that patients should exercise to tolerance (*Med Sci Sports Exerc* 2010; 42:1409–26). This means that interventions should be individualised for each patient according to how fit they were before developing cancer, their current treatment, and the side-effects they encounter. After treatment, and when patients are feeling stronger, they should try to accumulate about 20–30 minutes of moderate-intensity cardiovascular fitness training three to five days per week, and also incorporate muscular strength and endurance training twice a week. Activity to maintain balance and flexibility is also beneficial. Physical activity programmes should be individualised, based on a patient's needs, goals and exercise preferences, and taking account of any barriers to exercise, including long-term side-effects related to their treatment and disease. Brisk walking is a great simple and easy cardiovascular activity that patients can do to get health benefits – even five to ten minutes' walk round the block or to the shops can be enough to make a difference.

Physical activity programmes can help:

- Improve functional status before treatment or prevent/delay functional decline during treatment:
  - Maintain/optimise cardio-respiratory function
  - Maintain muscle mass (lean body mass) and strength
  - Maintain joint range of motion/muscle/connective tissue length.
- Address treatment-specific impairments during and after treatment, including: pain, fatigue, muscular weakness (specific), deficits in joint range of motion, poor balance or co-ordination, lymphoedema, peripheral neuropathy, bone thinning and steroid-induced cardiomyopathy.
- Optimise general health in the recovery period after cancer treatment.

Question. *Research shows a risk reduction of 30% or 40% with exercise for the three most common cancers, and this exercise does not need to be intensive but can just be walking for 20–30 minutes a day. To me that just looks amazing. It's extremely cost-effective compared to the costs of cancer treatments. Why isn't there a major programme in the UK or elsewhere to help cancer patients take exercise?*

Answer. *There are now a number of programmes that are beginning to emerge throughout Europe. Here at Dundee we have a programme called MoveMore, available for any person living with cancer – it offers home-based programmes with a DVD and booklet, one-to-one consultations, gym instruction and group- and water-based exercise programmes. A sample of approximately 12 different types of programme (e.g. hospital-based, home-based, individual, group, etc) is being evaluated by Macmillan, a UK cancer charity, for improvements in quality of life, active daily living and cost–benefit.*

PHYSICAL ACTIVITY LEVELS ON AND OFF TREATMENT

ALAMY

Only a minority of people meet daily recommended levels of physical activity even when they are healthy

Source: JKH Vallance et al (2006) *Eur J Cancer Care* 14:34–43

Question to the live webcast participants. *Patients at my centre have no formal access to exercise rehabilitation. Do yours?*
Responses. *Yes: 44%. No: 56%.*
Question to participants. *In your opinions, how many patients could benefit from such an intervention?*
Responses. *Most participants considered 30–50% of cancer patients would benefit.*

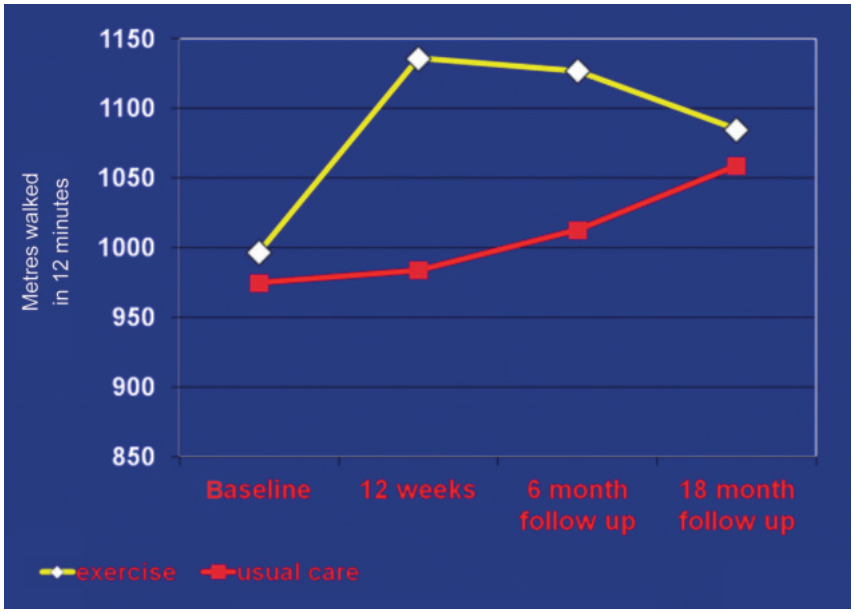
For a lot of people who have not participated in any structured physical activity for a long time, a cancer diagnosis can be 'a teachable moment' (*JCO* 2005, 23:5814–30). Being diagnosed with cancer can increase a person's motivation to make lifestyle changes, including incorporating exercise into their lives. However, figures for the US – which are very likely to be true also for other countries – show the number of people doing the recommended level of 30 minutes moderate-intensity activity on most days of the week is very low (*Eur J Cancer Care* 2006, 14:34–43).

Only 30–40% of the population take the recommended amount of exercise before being diagnosed with cancer, and this falls to only about 5% of patients on treatment and 20% off treatment.

Putting the evidence into practice

In 2000, I carried out a small pilot study which showed that 'rest is not best' during breast cancer treatment, but that physical activity could improve quality of life. In 2003, my colleagues and I began a larger study funded by Cancer Research UK – the Glasgow Study – that randomised 203 women on chemotherapy or radiotherapy for breast cancer to attend group exercise classes (a combination of cardiovascular and strength training) twice a week for 12 weeks, or to the usual care group of no structured exercise. After 12 weeks, women taking part in the exercise programme (held in community-based settings) had improved significantly in walking pace, weekly activities, shoulder mobility, breast cancer specific quality of life, and positive mood. Six months later, women who had been randomised to the exercise intervention during treatment still had better overall quality of life in terms of physical functioning, positive mood, and

LONG-TERM BENEFITS OF AN EXERCISE PROGRAMME



It took 18 months for women in the control group to catch up with those on the exercise programme in terms of sustained walking speed. Five years on, women on the programme were still doing 2.5 hours more physical activity a week on average and reported more positive mood

Source: Courtesy of Anna Campbell, University of Dundee

less fatigue and depression than the usual care group (*BMJ* 2007; 334:517)

Analysing the cost-effectiveness, the NHS (National Health Service) cost of the intervention was £400 (€470) per woman for a safe and effective intervention that provided short- and long-term physical, functional and psychological gains. Participants spent fewer nights in hospital and had fewer GP visits than the usual care group, giving a saving of £1507 (€1750) per patient. Overall, the intervention achieved conventional standards of cost-effectiveness (unpublished data).

Following the women for five years showed those in the exercise group could walk much further in 12 minutes after the intervention, and this was sustained until the 18-months' follow-up timepoint. For the 87 women (out of the original 203) who attended the five-year follow-up, those originally randomised to the exercise group still reported significantly more leisure-time physical activity (2.5 hours more per week) and a more positive mood than the control group. Those taking part in recommended amounts of physical activity, irrespective of original group, recorded a greater decrease in depression levels at all follow-up points. This showed that the 12-week exercise programme gives lasting effects, and staying active can reduce depression after cancer (*J Cancer Surviv* 2012, 6:420–430).

In light of the results of that study, the city of Glasgow has now introduced the Active ABC – Active After Breast Cancer – programme for any woman diagnosed with breast cancer in the past five years. It provides 24 free sessions led by trained fitness professionals followed by sessions on health behaviour change. The programme works by self-referral, but patients can be signposted by health professionals. A national vocational qualification has been developed to train people to become cancer rehabilitation specialists (www.canrehab.co.uk) and there are now more than 200 qualified cancer exercise specialists in the UK. Dundee University is setting up a cancer rehabilitation centre for training, research and practice. The aim, as mentioned earlier, is to make exercise-based rehabilitation a sustainable part of every cancer survivors' care pathway.

Summing up

Keeping physically active after a cancer diagnosis appears to be a safe and effective way of improving physical, functional, social and emotional aspects of quality of life. Programmes should be individualised. The key message for patients is that a little physical activity is better than nothing, and they should avoid being sedentary. Right from their diagnosis, patients should have information that being active can be helpful and health professionals need to be aware of the strong evidence for the benefits of exercise. For the future, more research is needed on cancer-specific guidelines for physical activity, into mechanisms and into ways to improve behaviour change. ■

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Investment biobanking – increased returns from tissue samples

VALERIE SPEIRS AND ADRIENNE MORGAN

Researchers now expect that samples obtained from biobanks are accompanied with well-annotated clinical data. Opened in 2010, the Breast Cancer Campaign Tissue Bank takes this criterion a step further: researchers obtaining tissues are required to return the data they generate from every sample back to the Tissue Bank.

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Biobanks are secure storage facilities that typically contain biological samples ethically collected from human donors. These samples are made available to the biomedical research community with the aim of helping to advance research into human disease. The nature and purposes of biobanks can differ extensively, and include diverse examples such as the US Navy Tissue Bank (which was established in the 1950s and is widely regarded as the first major biobank)[1] in Bethesda, Maryland, and the Egyptian Mummy Tissue Bank at the Manchester Museum, UK.[2] In recent years, a number of biobanks have been developed to respond to the growing needs of the biomedical research community for greater access to human tissue samples for laboratory-based research.

In 2008, a gap analysis conducted on behalf of the UK charity Breast Cancer Campaign[3] identified the lack of access to well-annotated breast cancer samples as a considerable limitation to the research and, in particular, to the rapid transfer of promising laboratory findings to the clinic. To help bridge this gap, the Breast Cancer Campaign Tissue Bank was set up in 2010 as part of a coalition of four core academic centres of excellence in breast cancer research across the UK; Barts Cancer Institute, London, and the Universities of Dundee, Leeds and Nottingham, in partnership with the National Health Service. The Tissue Bank is the first widely available specialist breast cancer biobank in the UK.[4]

To make the best use of the tissues curated by biobanks, researchers require that tissues are accompanied by well-annotated data. Although there are no universally agreed guidelines, this annotation is now routine practice for most biobanks and usually includes anonymised information relating to each tissue donor, such as date of birth and gender plus follow up and survival data. More-specialised, disease-specific information is often also available. For breast cancer samples this expanded information includes tumour type, tumour grade, lymph-node involvement

and hormone receptor status in addition to the information on disease-free survival and overall survival of the patient. However, the tissues represent a rich source of data that is only generally revealed by investigators when using these tissues in their research. Currently, this type of data is usually made available to the public via peer-reviewed publication, a process that is limited by the fact that published studies tend to report 'positive' findings because negative results are generally more difficult to publish.[5] Furthermore, the requirement to anonymise data in research publications means that even positive data cannot be associated with the relevant individual tissues by future researchers. As a result, potentially important data generated from tissues procured from biobanks is not routinely available to future researchers; certainly not in a way that permits correlative analysis across a whole series of studies investigating the same tissue set. This loss of data association could result in unknown duplications of effort as well as the wasting of the valuable tissue resources, monies provided by funding bodies and efforts of the researchers.

During the establishment of the Breast Cancer Campaign Tissue Bank we aimed to maximise the use of data derived from the available tissue samples. In addition to acknowledging the value of a large tissue resource that could cater to the challenges of research into tumour heterogeneity, we also recognised that it was crucial to develop a solution whereby data generated using these tissues could be returned to the bank and made available to other researchers. We developed this policy following discussions with the UK patient advocate group Independent Cancer Patients' Voice,[6] whose members expressed a desire to see the best possible use of the data obtained from donated tissues to benefit future patients with breast cancer.

The policy requires researchers who obtain tissues from the Tissue Bank to return data generated from every sample back to the curators of the Tissue Bank in its raw form within two years.[7] We reasoned this would give researchers sufficient time to complete their research on these tissues and publish their data, although there is some flexibility in the timelines. To our knowledge, the Breast Cancer Campaign Tissue Bank is the first biobank to operate a data-return policy, adding considerable value to our sample holdings. As outlined in our consent forms, we do not return individual research findings to patients or their clinical team. We appreciate that many patients consider it their right to receive feedback of incidental findings and this topic has been – and continues to be – debated extensively.

To complement the data-return policy, the Breast Cancer Campaign Tissue Bank also uses a purpose-built interoperable bioinformatics platform that is freely available as an online resource.[8] This tool enables the mining of data from the breast cancer literature and the integration of different types of 'omics' and clinical data with publicly relevant annotations from various resources, including common portals such as the NIH's National Center for Biotechnology Information, Ensembl, UniProt and Reactome. Over time, this online resource will enable additional mining of the data arising from research using tissues obtained from the Breast Cancer Campaign Tissue Bank. By making this information available to the wider scientific community these tissues will gain even greater value.

Much like in a normal bank, where investment portfolios take time to mature, we recognise this increase in value will not happen overnight; accumulation and maturation of data will be a slow process taking many years, but remains a key component for research. Nevertheless, the more the Tissue Bank is used the more valuable its contents will become for researchers. The processes we have adopted will enable the efficient and co-ordinated use of banked tissues, providing a rich source of data that will be invaluable for the breast cancer research community. We are keen that other biobanks follow the blueprint we have adopted at the Breast Cancer Campaign Tissue Bank as it offers a simple way of adding extra value to the samples held by biobanks. ■

Key points

- Samples donated by patients to biobanks are a very valuable resource for biomedical research that potentially enable accelerated translation of laboratory results to the clinic
- Returning the data derived from such samples back to the biobanks offers an efficient way of mining information from these samples, adding considerable value to the biobank holdings

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

newsround

Selected reports edited by Janet Fricker

Scandinavians show better awareness of age-related cancer risks

■ British Journal of Cancer

Large international differences exist in the extent to which people are aware that cancer risks increase with age according to the first study ever to examine differences in cancer awareness and beliefs between high-income countries. Symptom recognition appears more uniform, however.

International comparisons have shown wide differences in cancer survival between high-income countries with good cancer registration systems and good access to health care. For cancers of the lung, breast, bowel and ovary diagnosed between 1995 and 2007, the International Cancer Benchmarking Partnership (ICBP) found that Australia, Canada and Sweden had the highest survival, Norway had an intermediate rate, and Denmark and the UK had the lowest rates.

In the current study, Lindsay Forbes and colleagues, from King's College, London, set out to examine differences in cancer awareness and beliefs across ICBP study countries and to explore how these might contribute to patterns of survival. Between May and September 2011, investigators carried out a population-based telephone survey of 19,079 men and women aged 50 years or more in Australia, Canada, Denmark, Norway, Sweden and the UK. The survey measured cancer awareness and beliefs using the newly developed Awareness and Beliefs about Cancer (ABC) measure.

Results show that the mean number of symptoms recognised (out of 11) were 8.22 for the UK, 8.35 for Denmark, 8.49 for Norway, 7.71 for Sweden, 8.34 for Australia and 8.70 for Canada. Awareness that cancer risks increase with age was 14% in the UK, 13% in Canada, 16% in Australia, 25% in Denmark, 29% in Norway and 38% in Sweden.

In the UK, 14.5% of respondents said embarrassment put them off going to the doctor with symptoms that might be serious, compared to 5.8% in Denmark, 9.4% in Norway, 9.2% in Sweden, 11.6% in Australia and 9.6% in Canada. Additionally, 34.3% of respondents in the UK said they would be worried about wasting their doctor's time compared to 11.7% in Denmark, 10.9% in Norway, 9.3% in Sweden, 14.2% in Australia and 21.1% in Canada. In the UK, 27.5% were concerned about what the doctor might find, versus 23.9% in Denmark, 19.8% in Norway, 23.1% in Sweden, 22% in Australia and 25.4% in Canada.

"The pattern of differences in cancer awareness and beliefs between the participating countries did not follow the pattern of differences in survival, but there was some evidence that it followed cultural/language demarcations: Scandinavian people had lower levels of barriers to symptomatic presentation and better awareness of age related risk than people in the Commonwealth countries," write the authors.

The findings, they add, have specific implications for individual countries. In Denmark, poor cancer survival rates are unlikely to be due to poor cancer awareness; while in the UK interventions to promote early presentation might usefully focus on addressing awareness of age-related risks and increasing people's confidence about approaching GPs with possible cancer symptoms.

■ L Forbes, A Simon, F Warburton, et al. Differences in cancer awareness and beliefs between Australia, Canada, Denmark, Norway, Sweden and the UK (the International Cancer Benchmarking Partnership): do they contribute to differences in cancer survival? *Br J Cancer* 5 February 2013, 108:292–300

Bioradiotherapy does not benefit larynx preservation

■ Journal of Clinical Oncology

In patients with cancer of the larynx there is no evidence that bioradiotherapy with cetuximab delivers benefits over chemoradiotherapy with cisplatin for larynx preservation, the phase II TREMPLIN study has found.

To date, two main approaches have been evaluated for larynx preservation: induction chemotherapy followed by radiotherapy in good responders, and concurrent chemotherapy and radiotherapy. In Europe induction chemotherapy based protocols have tended to be preferred; while in the US concurrent chemotherapy and radiotherapy has been regarded as the best approach for avoiding total laryngectomy. For each approach pros and cons have been identified: with induction chemotherapy only good responders have a chance of avoiding surgery, while with the concurrent approach all patients avoid surgery, but treatment is

associated with acute and late toxicities. In a recent randomised trial, bioradiotherapy with cetuximab delivered improvements in overall survival in comparison to radiotherapy alone, suggesting bioradiotherapy might offer an alternative to chemoradiotherapy.

The French Groupe Oncologie Radiothérapie Tête et Cou set out to compare the efficacy and safety of induction chemotherapy followed by chemoradiotherapy or bioradiotherapy for larynx preservation. Between March 2006 and April 2008, 153 previously untreated patients with stage III to IV larynx/hypopharynx squamous cell carcinoma, from 20 centres, received three cycles of induction chemotherapy (docetaxel and cisplatin on day 1 and fluorouracil on days 1 through 5). All 116 patients who responded (i.e. who achieved >50% response rate) received conventional external beam radiotherapy and were then randomly allocated to the cisplatin arm (chemoradiotherapy, *n*=60) or the cetuximab arm (bioradiotherapy, *n*=56). Patients achieving less than 50% response rates were not eligible for random assignment, and underwent immediate salvage total laryngectomy.

Results showed there were no significant differences between the two groups for the primary and secondary endpoints. At three months, larynx preservation was achieved in 95% of patients in the cisplatin arm versus 93% in the cetuximab arm. At 18 months, larynx function preservation was achieved in 87% in the cisplatin group versus 82% in the cetuximab group, and overall survival was 92% for the cisplatin group versus 89% for the cetuximab group. For both toxicity was high, while treatment compliance was higher in patients receiving cetuximab than cisplatin.

"There is no evidence that one treatment was superior to the other or could improve the outcome reported with induction chemotherapy followed by radiotherapy alone," conclude the authors.

In an accompanying commentary, Everett Vokes, from the University of Chicago Medical Center, Illinois, writes, "We cannot conclude that cisplatin-radiotherapy and cetuximab-radiotherapy are equivalent because the favorable survival observed in both arms was likely a function of TPF (docetaxel, cisplatin, fluorouracil) induction and subsequent patient selection and not as a result of the intensification of radiotherapy."

The major challenge for organ preserving protocols, he adds, is not to increase already good outcomes of responders, but to improve outcomes for non-responders, which will not be achieved by excluding them from randomisation. "The TREMPLIN trial... reminds us that, when designing clinical trials, we must prioritize the specific deficiencies of current standard approaches that we need to address," writes Vokes.

■ J Lefebvre, Y Pointreau, F Rolland et al. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized phase II study. *JCO* 1 March 2013, 31:853–859

■ E Vokes. Competing roads to larynx preservation. *ibid* pp 833–835

Wide variation in lung cancer survival

■ Thorax

While differences in stage at diagnosis explain some international variations in lung cancer survival, wide disparities in stage-specific survival suggest factors such as treatment also play an important role, a population-based study in nearly 60,000 patients has found.

Stage at diagnosis has often been suggested as one of the primary explanations for lung cancer survival being low in certain countries (such as the UK), on the grounds that patients go to see their doctors too late for treatment to be effective. Understanding why these survival differences occur is considered helpful, since it would facilitate policy changes to bring survival up to the highest international standards.

In the current study, Sarah Walters and colleagues, from the London School of Hygiene and Tropical Medicine, obtained population-based data that had been routinely collected on 57,352 patients, aged between 15 and 99 years, diagnosed with lung cancer between 2004 and 2007, whose details had been recorded in national cancer registries in Australia, Canada, Denmark, Norway, Sweden and the UK. The authors then monitored patients to estimate survival at one year and 18 months after diagnosis, for each diagnostic stage, for both non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC).

Results showed that, after adjustment for differences in age and death from other causes, one-year survival rates after a diagnosis of lung cancer were 46% in Sweden, 42% in Australia, 42% in Canada, 39% in Norway, 34% in Denmark, and 30% in the UK. Taking the example of patients diagnosed at stage IV for NSCLC, one-year survival rates were 16.8% in Canada. 21.4% in Denmark, 25.9% in Sweden and 15.5% in the UK. Taking the example of SCLC, the one-year survival rates for patients with a diagnosis at stage IV were 18.3% in Canada, 23% in Denmark, 26.8% in Sweden and 14.4% in the UK.

"International differences in survival were also evident within each stage of disease for both types of lung cancer: generally low in the UK and high in Sweden," write the authors.

Differences in the thoroughness of staging, they suggest, may have contributed to international variation in stage distributions and stage-specific survival, with the proportion of histologically verified tumours ranging from 74% in the UK to 94.8% in Sweden. In the UK, report the authors, elderly patients have been less likely to undergo invasive procedures due to concerns about frailty.

"Low stage-specific survival in the UK could conceivably arise in part because of suboptimal staging, and this misclassification of stage in a proportion of patients could lead to inappropriate treatment and therefore overall lower survival," they write.

In order to understand the impact of different staging procedures on international

differences in survival, stress the authors, cancer registries in future will need to capture information on staging procedures used for each patient, for example whether investigations such as PET-CT were used.

The authors are currently examining how far differences in treatment between the six countries may explain survival variations.

■ S Walters, C Maringe, M Coleman et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population based study 2004–2007. *Thorax*, published online 11 February 2013, doi.org/10.1136/ thoraxjnl-2012-202297

Long-term functional outcomes: no difference between prostatectomy and radiotherapy

■ New England Journal of Medicine

At 15 years' follow up, no significant differences in functional outcomes for urinary incontinence, erectile dysfunction and bowel urgency were found between men treated for early prostate cancer with surgery and those treated with external beam radiotherapy. These findings contrast with earlier two- and five-year data from the same study, showing advantages in urinary incontinence and erectile function for patients undergoing radiotherapy, and advantages in bowel urgency for patients undergoing prostatectomy. Regardless of treatment, the study shows the risk of suffering functional decline at 15 years is considerable.

As the median life expectancy after treatment for prostate cancer is 13.8 years, a long-term analysis to understand outcomes for men choosing between radiotherapy and surgery is considered important. The literature, however, largely reports short-term (1–3 years) or intermediate term (4–5 years) outcomes, which may not reflect the long-term experience of men undergoing prostate cancer treatment.

In the current study, to assess the long-term effects of localised prostate cancer treatment, David Penson and colleagues, from Vanderbilt University Medical Center in Nashville, Tennessee, analysed the Prostate Cancer Outcomes Study (PCOS), which followed 3533 men with prostate cancer diagnosed in 1994 and 1995, who underwent either surgery or definitive radiation therapy within a year of diagnosis. The final analysis included 1655 men aged between 55 and 74 when diagnosed with localised prostate cancer, of whom 1164 underwent surgery and 491 underwent radiotherapy. Functional status was assessed at baseline and 2, 5 and 15 years after diagnosis.

Results show that 15 years after diagnosis, 322 of the men who underwent prostatectomy (27.7%) and 247 of the men who underwent radiation therapy (50.3%) had died.

At two years, patients undergoing prostatectomy were more likely to have urinary incontinence than those undergoing radiotherapy (OR 6.22), at five years they were still more likely to have urinary incontinence (OR 5.10), but at 15 years no significant difference could be found between the two groups.

At two years, patients undergoing prostatectomy were more likely to have erectile dysfunction than those undergoing radiotherapy (OR 3.46), at five years they were still more likely to have erectile dysfunction (OR 1.96), but at 15 years no significant difference was found between the two groups.

At two years, men in the prostatectomy group reported significantly lower rates of bowel urgency than those in the radiotherapy group (OR 0.39), at five years they were still less likely to have bowel urgency, but at 15 years there was no significant difference (OR 0.98).

"Men undergoing prostatectomy or radiotherapy for localized prostate cancer had declines in all functional outcomes throughout early, intermediate, and long-term follow-up.

"Whereas short- and intermediate-term data reveal differences in functional profiles among men undergoing prostatectomy and radiotherapy, at 15 years we observed no significant relative between-group differences," conclude the authors.

Given the absence of an untreated age-matched control cohort, they acknowledge that the precise contribution of prostate cancer treatment to age-dependent changes in urinary, sexual, and bowel function remains unknown.

■ M Resnick, T Koyama, K Fan et al. Long-term functional outcomes after treatment for localized prostate cancer. *NEJM* 31 January 2013, 368:436–445

MEK inhibitors renew efficacy of radioiodine

■ New England Journal of Medicine

Administration of selumetinib delivers clinically meaningful increases in iodine uptake and retention for patients with thyroid cancer refractory to radioiodine, a pilot clinical study funded by the American Thyroid Association has concluded.

While radioiodine (iodine-131) remains the mainstay of therapy for patients with metastatic thyroid cancer of follicular origin, many patients have tumours unable to concentrate iodine, resulting in radioiodine resistance. The result is a poor prognosis, with 10-year survival rates of around 10% among this group of patients, versus approximately 60% among patients with metastatic thyroid cancers that retain iodine.

Approximately 70% of papillary thyroid cancers have gene mutations encoding the growth factor receptors RET or NTRK1, and the three isoforms of RAS and BRAF. Activation of these proteins stimulates mitogen-activated protein kinase (MAPK) signalling, which inhibits the expression of thyroid hormone biosynthesis genes, thereby facilitating iodine uptake in organs.

James Fagin and colleagues, from the Memorial Sloan Kettering Cancer Center in New York, set out to determine whether selumetinib, which inhibits the MEK1 and MEK subtypes of MAPK kinase, might reverse refraction to radioiodine.

For the study, performed between August 2010 and December 2011, after stimulation with thyrotropin alfa, 24 patients with differentiated thyroid carcinoma of follicular cell origin who met criteria for radioiodine refractory disease, underwent dosimetry with iodine-124 PET both before and four weeks after treatment with selumetinib (75 mg twice daily).

Of the 20 patients evaluated (two of the original 24 had baseline QT levels outside the study range and two dropped out), 12 had iodine-124 uptake that was new, increased, or both after selumetinib. In eight of these, the second iodine-124 PET study indicated that the absorbed radiation dose in the lesion would equal or exceed 2000 cGy with 300 mCi of radioiodine or less; these patients continued to receive selumetinib, and they received therapeutic radioiodine. It is noteworthy that the 12 patients included four out of nine patients with BRAF mutations and five out of five patients with NRAS mutations. However, while all five patients with NRAS-mutant tumours exceeded the dosimetry threshold for receiving therapeutic radioiodine with selumetinib, this was the case for only one of the patients with BRAF mutations.

Of the eight patients treated with radioiodine, five had confirmed partial responses and three had stable disease; and all patients showed decreases in serum thyroglobulin level, with a mean reduction of 89%. No toxic effects of grade 3 or higher attributable to selumetinib were observed, add the authors. One patient, who was treated with 139 mCi of radioiodine during the study, received a diagnosis of myelodysplastic syndrome more than 51 weeks after radioiodine treatment, with progression to acute leukaemia.

"These results provide a proof of principle that MEK inhibitors can induce iodine uptake and retention in thyroid tumors. An advantage of this therapeutic strategy over long-term treatment with small-molecule kinase inhibitors alone is that only a short course of drug therapy is required to elicit a durable clinical effect," write the authors.

Enhanced iodine uptake, they add, was also observed in bone and nodal metastases, both of which have been found to be comparatively refractory to treatment with kinase inhibitors.

■ A Ho, R Grewal, R Leboeuf et al. Selumetinib enhanced radioiodine uptake in advanced thyroid cancer. *NEJM* 14 February 2013, 368:623–632

Study questions value of tumour boards

■ JNCI

The presence or absence of tumour boards in a large integrated health system does not influence service quality or survival "in any meaningful way", a study in the US Veterans Affairs (VA) health system has found.

Tumour boards involve the discussion of newly diagnosed cancer patients by multidisciplinary teams involving medical, surgical and radiation oncologists, in addition to pathologists, diagnostic imaging specialists, palliative care doctors, and social workers. Tumour boards are perceived to be so important that the American College of Surgeons' Commission on Cancer Program Accreditation requires cancer programs to have multidisciplinary cancer conferences to prospectively review cases. Despite widespread use, no data exist on the benefits of tumour boards for cancer care.

In the current study, Nancy Keating and colleagues, from Harvard Medical School, in Boston, Massachusetts, assessed whether the presence of a tumour board (either general or site-specific) was associated with recommended care and with survival outcomes. Information gathered from 138 VA medical centres was linked to cancer registry and administrative data to gauge the receipt of stage-specific recommended care and survival in patients with colorectal, lung, prostate, haematologic, and breast cancers. Patients were diagnosed between 2001 and 2004, and followed through to 2005.

The results showed that 103 (75%) of the 138 hospitals surveyed had at least one tumour board, 62 centres had a single tumour board that discussed cases from multiple cancer sites, and 41 had more than one disease-specific tumour board. The presence of a tumour board was associated with only seven of 27 measures assessed (all $P<0.05$). When researchers applied a Bonferroni correction (a method used when several dependent or independent statistical tests are performed simultaneously), only one measure was associated with tumour boards. The measure was that patients with limited-stage small-cell lung cancer reviewed by tumour boards were statistically more likely to undergo chemotherapy or radiation than those not reviewed ($P<0.00185$).

The authors comment that the lack of association of multidisciplinary tumour boards with measures of use, quality or survival could mean that tumour boards do not influence the quality of cancer care. "It might also mean that tumor boards are only as good as their structural and functional components and the expertise of the participants, and because tumor boards likely vary in their efficacy depending on these factors, measuring only the presence of a tumor board may not be sufficient to understand their effects," write the authors. Additional research, they add, is needed to understand the structure and format of tumour boards leading to the highest quality care.

In an accompanying commentary, Douglas Blayney, from Stanford University School of Medicine in California, writes that there should be no surprise that improved performance on the process or outcome measures of quality is not predicted by the existence of team meetings. "Anyone who has ever played a team sport, worked with a laboratory team, led a clinical trial team, or led a patient care team soon realizes that huddles, lab meetings, cooperative group meetings, or attending physician rounds don't get the job done."

■ N Keating, M Landrum, E Lamont et al. Tumor boards and the quality of cancer care. *JNCI* 16 January 2013, 105:113–121

■ D Blayney. Tumor boards (team huddles) aren't enough to reach the goal. *ibid* pp 82–84

Once upon a loss

JOHN M CORMAN

The Oncologist

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As physicians, we are trained to expect loss. Every disease has the ability to develop, to progress, and ultimately to cause a patient to succumb. We protect ourselves from the pain of such an experience by steeling ourselves from the self-condemnation that accompanies wondering, "What more could I have done?" We are rarely able, however, to ever completely absolve ourselves.

As surgeons, we are fortified to deal with such events. We are invincible. We invade a body and put it back together. We are supermen. We make hundreds of critical, life-altering decisions before most people have had their morning coffee. Each of our decisions affects a patient's life, both the quality and quantity. But how many are correct? Just one error, one poorly placed suture, one inaccurate assumption can result in disaster.

Just as disastrous is not feeling responsible or guilty after a complication or death. Our guilt, although perhaps self-indulgent, is redolent of our humanity. We employ every means to protect ourselves: defiance, arrogance, logic, and rationalisation – an alphabet of protective shields. Humour is a common mechanism for coping. However, the jokes are never particularly funny and are far from comforting.

We take classes to educate us in the stages of grief. We recognise the importance of the process for our patients and their families: the anger, the denial, and finally the acceptance. Although these stages are acceptable for others, we as physicians strive to remain stoic. By taking our feelings out of the equation, we somehow feel we are better able to help patients and their families through the ultimate emotional event. We effectively step back and isolate ourselves through the use of science and technology, protecting ourselves behind the armour of our white coats. To absorb every bit of grief that we observe during daily rounds would surely make our shoulders sag.

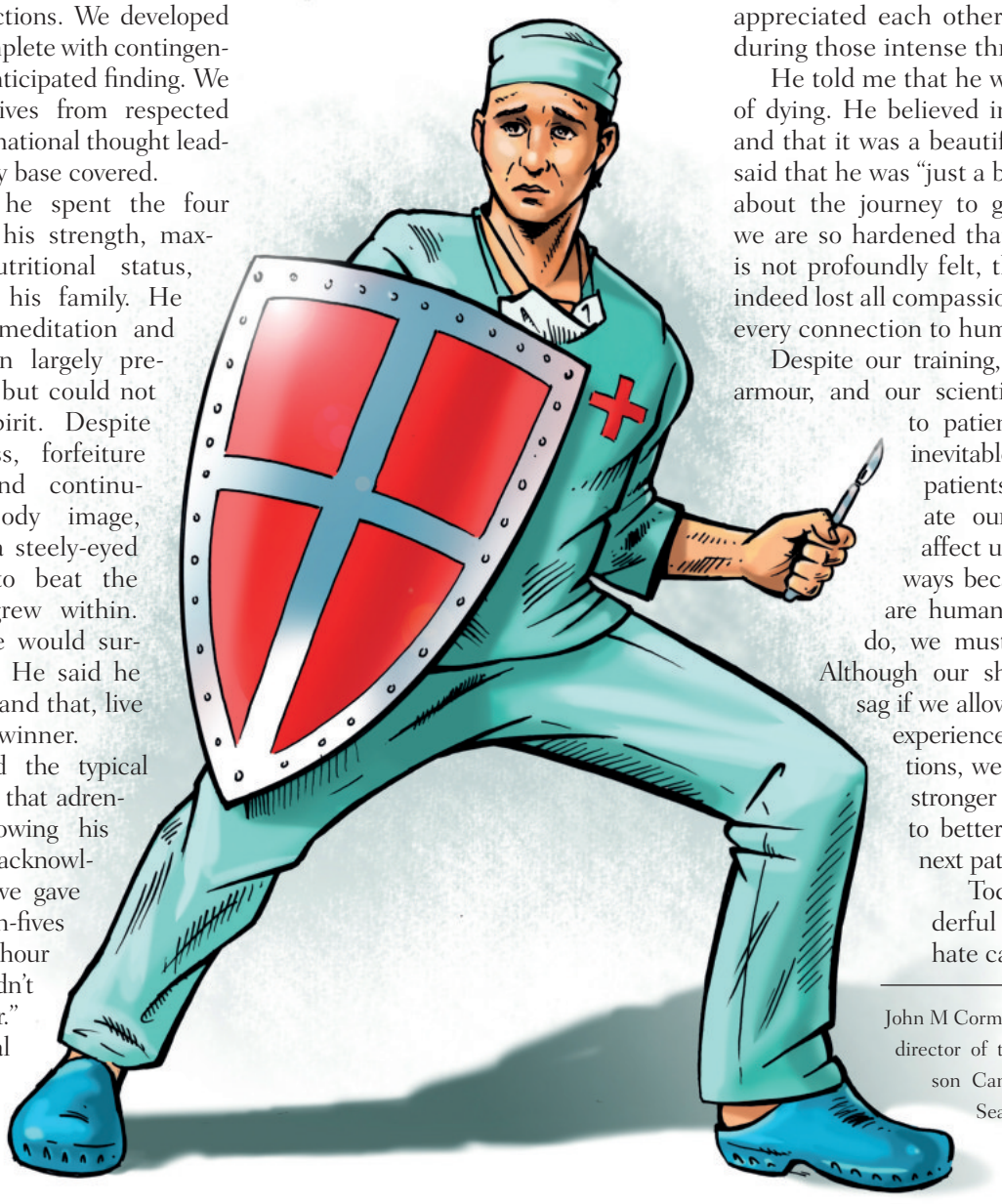
I was asked to see a patient by a colleague leaving for sabbatical. The patient was a vibrant, active, yet self-reflective man deteriorating daily from the effects of a massive pelvic tumour. Despite his wasting body, his eyes shone with his desire to do whatever possible to extend and improve his life. We entertained the idea of chemotherapy or perhaps palliative radiation treatments to buy him some time. In the end, he was simply too

ill for either, but something had to be done. He was not ready to palliate.

We spent four weeks organising the surgical team for a heroic operation. It was an all-star team and six of us would operate: urologists, general surgeons, orthopaedists, and vascular surgeons. We spent hours reviewing anatomy, histology, and three-dimensional reconstructions. We developed a game plan, complete with contingencies against unanticipated finding. We sought perspectives from respected consultants and national thought leaders. We had every base covered.

Meanwhile, he spent the four weeks building his strength, maximising his nutritional status, and embracing his family. He spent time in meditation and prayer. His pain largely prevented mobility but could not dampen his spirit. Despite the weight loss, forfeiture of strength, and continually altered body image, he maintained a steely-eyed determination to beat the monster that grew within. He said that he would survive the cancer. He said he was an optimist and that, live or die, he was a winner.

We exhibited the typical surgical audacity that adrenaline fuels following his operation. With acknowledged conceit, we gave each other high-fives following his 10-hour surgery: "Couldn't have gone better." "That was a real surgery." "One in a million." We had completely removed the 5 lb sarcoma that was causing such pain. He had been bedridden and nauseated. Now, he'd be walking and eating within days. Perhaps our false bravado was emboldened by the knowledge that, although we may have been the victors in the battle, the war was not nearly over.



He spent the holidays at home, but the cancer came back. It was unremitting, vulgar, and obtrusive. We were going backwards. Despite the cancer's recurrence, his family said that his illness had been an incredible spiritual journey. They were amazed by the outpouring from their community and had never loved or appreciated each other as they did during those intense three months.

He told me that he was not afraid of dying. He believed in an afterlife and that it was a beautiful place. He said that he was "just a bit concerned about the journey to get there." If we are so hardened that such a loss is not profoundly felt, then we have indeed lost all compassion and with it every connection to humankind.

Despite our training, our medical armour, and our scientific approach to patient care, it is inevitable that some patients will permeate our shield and affect us in profound ways because we, too, are human. When they do, we must also grieve. Although our shoulders may sag if we allow ourselves to experience these emotions, we will rebound stronger and inspired to better care for our next patient.

Today, this wonderful man died. I hate cancer. ■

John M Corman is the medical director of the Virginia Mason Cancer Institute in Seattle, Washington

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

We protect ourselves behind the armour of our white coats

My World

Fedro Alessandro Peccatori is director of the Fertility and Reproduction Unit at the European Institute of Oncology in Milan. He specialises in breast and gynaecological cancers and tumours of young adults, and has particular responsibility for the care of women who have cancer while pregnant, and patients with fertility problems after a cancer diagnosis.

Why I chose to work in cancer

At medical school I was fascinated by the *Pathologic Basis of Disease* (Robbins' 'bible' on morbid anatomy) and cancer looked like the perfect one – beauty may be found also in evil... I started by specialising in gynaecology because I felt that female cancer patients are especially in need of care as well as cure.

What I love most about my job

When I wake at 6.30 am and ride my bike to work, I really look forward to getting into action. Speaking with colleagues from different scientific backgrounds, trying to resolve difficult situations and the smiles of patients are what makes this profession worthwhile.

The hardest thing about my job

When I know that I cannot do something significant for my patients, that I will have to fight with bureaucracy for most of the day, and that I will not see my family until 7.30 pm. There is nothing heroic about being a doctor, but sometimes it is quite hard.

What I've learned about myself

I have found that I can be quite stubborn when the stakes are high. Modern medicine requires commitment, and I have learned not to give up – with colleagues or diseases.

I'll never forget...

At the start of my internship in gynaecology, when I was asked to care for a patient dying from a resistant germ cell tumour of the ovary. I had lectured the same day about the astonishing results of cisplatin in improving cure rates in this disease, and had ended with the triumphal phrase: "the paradigm of success". How wrong I was! Since then, I have learned that science is nothing without care.

A high point in my career

When I gave a presentation in 1995 at the International Gynecologic Cancer Society Meeting. Afterwards, Bob Young, whom I looked to as a demi-god, said: "Good job, son." Unforgettable!

I wish I were better at...

Reconciling work and family. I often feel guilty about my wife, my daughter and my four sons. I'm trying to find the solution, but there's a long way to go.

What I value most in a colleague

Boldness and creativity when talking about science. Empathy and time when talking about patients. Intellectual honesty when talking about me.

The most significant advance in my specialty in recent years

In breast cancer, the use of anti-HER2 therapies. In gynaecologic oncology, the better understanding of the relationship between BRCA1 mutation and ovarian cancer. For young female patients, effective fertility preservation.

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

Be compassionate with your patients and passionate for their rights. Don't be afraid to share your emotions with them. Be knowledgeable and keep pace with the fast-changing world of cancer science. Be honest with colleagues and prioritise collaboration over competition.

What I wish I'd learned at medical school

That open mindedness and curiosity are talents that must be carefully cultivated throughout professional life. And that medicine is not just diagnosis and cure, but entails pharmaco-economics and resource administration, with the goal of giving every human being equal access to prevention and treatment. ■