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A temple for translational research

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Cancerworld

Shaping the future of cancer care

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Europe's cancer drugs shortage is hurting patients

KATHY REDMOND EDITOR

Hospital pharmacies across Europe are reporting difficulties getting hold of a range of commonly used cancer drugs, including 5-fluorouracil, carboplatin, cisplatin, doxorubicin, etoposide, melphalan, methotrexate, oxaliplatin and vincristine. Medicines used for pain relief including morphine are also reported to be in short supply in some countries.

The problem is not a new one, but has only recently come to light thanks to a survey carried out by the European Association of Hospital Pharmacists (EAHP), which was sent to 600 hospital pharmacies across 36 countries.

Although there were significant differences between European countries in the frequency and nature of shortages experienced, none were spared this problem. Denmark, Iceland, Malta, Romania and the UK all reported that medicines shortages are a daily occurrence. Only 14% of respondents said they never had trouble getting hold of vital medicines, while 66% reported this as a daily or weekly problem. Cancer drugs were ranked as the second most commonly affected area for shortages (55% of respondents) after anti-microbials (57%).

Difficulties and delays in getting hold of the right cancer drugs can seriously damage patient care. Medicines shortages lead to delayed or interrupted treatment, or dose reductions, which can have life-threatening consequences. The use of an alternative medicine increases the likelihood of a medication error and can result in the patient experiencing unnecessary side-effects. There is also a cost associated with the time hospital pharmacists have to spend in sourcing and procuring an alternative medicine, which is often more expensive than the one originally prescribed.

The situation is not unique to Europe – drugs that are crucial for treating cancer have been found to be in short supply across the world, and the problem appears to be getting worse. In the US the number of reported prescription drug shortages nearly tripled between 2005 and 2010. There are multiple causes for these shortfalls, including manufacturing difficulties, problems with suppliers, parallel imports and differences in national stock keeping requirements.

According to the EAHP, this problem has been swept under the carpet for far too long, and it's time for the EU to take action. In Europe, medicine shortages are mostly dealt with at a national level; however, the European Medicines Agency (EMA) can be involved in certain situations, such as when a medicine shortage affects several Member States. The EMA maintains a catalogue of shortages, but this is very limited and so far there has been little or no coordinated European response to the problem.

The EAHP is now calling for a more reliable cataloguing of medicines in short supply across Europe – comparable to the list recently established by the EMA's American counterpart, the FDA, which details the reasons for, and possible duration of, drug shortages, as well as suggesting potential alternatives. Such a list would provide health professionals with the information necessary to anticipate and manage the problem. It would also flag up to European policy makers the true extent of shortages of essential drugs, and the need for urgent action to protect the health and wellbeing of patients. ■

George Coukos

A temple for translational research

SIMON CROMPTON

Switzerland wants a cancer centre that will promote "opportunity, integration and innovation", focused tightly on delivering major benefits to patients. George Coukos is the man charged with making it happen.

Within 15 years, says George Coukos, treatment advances in immunotherapy will mean that cancer cure rates could rise from 50% to 75%. "I'm quite optimistic about that," says the recently installed director of the Oncology Department at the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne, Switzerland.

Such hopeful predictions are viewed with caution by the cancer community. They raise too many questions. It's all very well having promising research, but how do you build on early hope? How do you make fundamental science applicable in the clinic? How do you make innovation widespread, affordable, replicable? There have been false dawns before, particularly in the field of immunotherapy.

Coukos, a world-leading investigator in tumour immunology and ovarian cancer, is aware of all that. In fact, addressing those questions is central to the role he was specifically headhunted to perform at Lausanne – to build a comprehensive cancer centre for Switzerland, integrating research that will result in clinical advance. He has a recipe for progress, and it centres around a simple principle: bringing people together.

Coukos has a history of creating innovative translational research programmes within clinical services, having done just that at the University of Pennsylvania where he spent 22 years establishing the Penn Ovarian Cancer Research Center and directing it for seven years.

Appointed in Lausanne in July 2012 and put in charge of a multi-million euro budget, he has assembled a team of high-flyers from around the world to help him put in place a vision jointly agreed and funded by hospitals, universities, NGOs, Swiss government and philanthropic bodies to create something of global significance on the shores of Lake Geneva.

The Swiss Cancer Centre, federating research groups in oncology from CHUV, the University of Lausanne (UNIL), Ludwig Cancer Research, and the École Polytechnique

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Fédérale de Lausanne (EPFL) and others in nearby Geneva, is now a reality. At its core are Coukos's beliefs about making things happen: maximise access, get people interacting together, combine data. With government and institutional commitment behind it, the big cancer project in Lausanne may indeed provide an antidote to the 'silo' culture that has slowed progress in cancer innovation for decades. In doing so, it could provide a model internationally.

Coukos has worked closely with Doug Hanahan, who directs EPFL's cancer research institute (ISREC), to develop the partnerships.

"The vision is to create a vibrant environment that gives opportunity for wide communication and access – patient access to innovation, access of researchers to the clinical pathway, access of life scientists to cutting-edge technology and engineering. We want to totally integrate engineers, clinicians and life scientists. The principles are opportunity, innovation and integration."

What is striking in Lausanne is that these principles will have a very physical manifestation. George Coukos and I talk in the oncology administrative suite just across the road from the giant block of CHUV. Right behind us is the ghostly presence of a spectacular – but as yet unbuilt – translational cancer research centre.

The Agora Cancer Centre (named in reference to gathering places in Ancient Greece), a sweeping arc of glass and steel perched on the woody slopes surrounding CHUV and overlooking Lausanne and Lake Geneva, will bring together fundamental research and clinical practice. Coukos says it will be a "temple of true translational research" – an emblem for all that he is trying to achieve at Lausanne. It will cost 80 million francs (€67 million).

"Translational research is interpreted many ways, but true translational research has a direct impact on the way we manage patients. The key word is 'impact'. It has the eyes really focused on a specific problem, and assembles teams and approaches to make a dent into this problem."

But it has to be made to happen. That means taking account of the way people really behave. Despite good intentions, good research is often not translated into good clinical practice because clinicians feel too busy to spend time talking to researchers, or hospital budgets won't stretch to

"In these times when we don't even have time to check our emails, bumping into people is critically important"

allowing clinicians the luxury of research.

So the centre, which will house around 400 researchers, is located just 100 yards from the main hospital. "This is important because it has to be linked functionally with the clinical development programme at CHUV," says Coukos. Equally important is that clinicians are being given protected time to be in this research environment – to think, read, talk and write.

The very design of the centre, which Coukos and Hanahan have been closely involved in, will "make people bump". There will be offices and laboratory space for groups from CHUV, UNIL, Ludwig Cancer Research and EPFL concentrated at the two ends of each floor in the building – and between them will be spaces for sitting, talking, having coffee, creating 'neighbourhoods' on each floor.

Each laboratory will be without walls and doors. "That allows a continuous flow of information – people end up talking to each other and a culture of trust can develop," says Coukos. "The experiments and the data are not locked behind doors, but resources are wide open for everyone to access. This design also creates flexibility because programmes can expand or shrink depending on the opportunity."

To create vertical as well as horizontal interactions in the building, there will be plentiful open staircases creating a kind of 'matrix organisation'. Large atria, with seating, vegetation and refreshments, will connect the centre with auditoria and other departments such as pathology.

"There will be a buzz. It's the collective exchange of ideas that ultimately gets you somewhere and in these busy times where we don't even have time to check our emails, bumping into people is critically important.

"There's a new top-down determination, a strategic reassignment at institutional level, to say we're going to support physician scientists, we're going to develop translational scientists, we're going to build resources to allow them time."

He acknowledges that money – and lots of it – is as important as change of culture. It's particularly needed to bridge what Coukos calls the 'Valley of Death' between a laboratory idea and a phase I clinical programme.

"It's absurdly expensive," he says. "There are so many good ideas, but you can count on one hand the programmes that develop products for the clinic and take them into the clinic. A true translational programme must have – in addition to a critical mass of discovery labs – a very strong laboratory infrastructure for complex tissue analyses, biobanks, a mouse hospital platform with sophisticated imaging, many supporting technology cores, and an advanced clinical research infrastructure with data management, interventional radiology capabilities, imaging, manufaturing cores, regulatory support, and nurses and doctors dedicated to phase I studies, for advancing the clinical protocols – so all of that means investing in people and structures."

The commitment of the Swiss Cancer Centre's funding partners was certainly one reason why coming to Lausanne seemed "the opportunity of a lifetime" to Coukos, even though it meant leaving a settled family life and successful career in the US. But then, Coukos' globetrotting life so far hasn't provided much indication that he's one for settling with what he's got.

Born and raised in Greece, he decided to go to medical school in Italy, having fallen in love with the country's culture and sophistication during family visits. The medical school at Modena was "very didactic and comprehensive", and he stayed on to complete a PhD in reproductive medicine and take up a residency in obstetrics and gynaecology at the University of Modena Hospital.

But it wasn't enough: Coukos wanted more training, more hands-on work, so he went to the US in 1991 at the age of 29 to take more research training, then a second residency at the Department of Obstetrics and Gynecology at the University of Pennsylvania Medical Center. In 1999 he completed a fellowship in gynaecologic oncology, realising that it was the side of gynaecology which "needed most help". The problems were

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complex, the patients were touching and rewarding – and in terms of ovarian cancer research, there was a big black hole to fill. Even today, Coukos laments that more progress hasn't been made in ovarian cancer therapeutics.

"This seemed a very important area to spend energy and resources – mine in particular. I decided to spend the rest of my life working in cancer." He stayed at Penn for the next 22 years.

He made his mark in the US as a researcher, clinician and administrator. By 2007 he had established the Ovarian Cancer Research Center, and become Penn's Celso-Ramon Garcia Chair in Reproductive Biology and Associate Chief of the Division of Gynecologic Oncology. All the while his clinical practice offering innovative therapies like immunotherapy drew acclaim.

So it is hardly surprising that when a coalition of government, universities, leading hospital and the Swiss Institute for Experimental Cancer Research (ISREC) started searching for the right person to create a world-class comprehensive cancer centre in Switzerland, his name went on the shortlist.

"I think it was my experience in building innovative translational programmes that were well integrated into the clinic that attracted them," he says. But there was another factor that made the fit particularly good: Coukos' passion for immunotherapy. Lausanne has a long history of expertise in cancer immunology, partly by virtue of the presence of Ludwig Cancer Research, which is today part of UNIL (Coukos, among his other posts, was appointed its director when he came to Lausanne). With so many Swiss cancer research bodies federating, there was a critical mass of immunotherapy researchers on the ground. Coukos was the man to take them forward.

His own interest in immunotherapy began in the late 1990s when he decided that the immune system was of key relevance in developing new treatments. Then Carl June's arrival at Penn to start an immunotherapy programme provided inspiration. No one had seriously investigated immune responses in ovarian cancer before.

"It was a time when many had given up on tumour immunotherapy. At first, I found it hard to

"Immunotherapy is the only therapy that has long-term memory, because it engages the patient's own defences"

convince people that this area was of any importance, and many of my colleagues tried to dissuade me from going into this field because nothing would ever come of it. Many attempts with vaccines had failed. But I thought there were important opportunities, so we pursued them."

The research programme that he developed at Penn discovered a spontaneous immune response in ovarian cancer – and that it had an impact on outcome. His paper in the *New England Journal of Medicine* in 2003 had an international impact, reviving the cancer community's interest in anti-tumour immunity and its therapeutic potential.

"I think that it contributed to shifting the attention of the scientific community to spontaneous cancer immunity. Then additional papers started coming out about colon cancer and other tumours, and it became quite obvious that there is an immune response to most tumour types, and it has to mean something. It sparked additional investment in cancer immunotherapy, including efforts to mobilise endogenous immunity with the new antibody drugs that we have now."

That work led to his team in Penn developing the first personalised vaccines for women with ovarian cancer based on dendritic cells, which elicit T-cell antibody responses against tumours. In addition, he built a programme studying T cells, especially tumour infiltrating lymphocytes (or TILs) extracted from patients' own tumours. This work is now being built into an ambitious research and clinical programme in Lausanne.

Autologous TIL therapy has already proved successful in melanoma. US National Cancer Institute research on TILs, started ten years ago, showed that of 93 patients with metastatic melanoma treated with TILs, 20 had complete tumour regression and 19 had ongoing complete regressions beyond three years. The five-year survival rate for the responders was 93%. Coukos believes that similar results may be achieved with the majority of solid tumour types, so a comprehensive research plan for TIL therapy is being developed at Lausanne.

"We now know that about 50% of patients in all disease types have T cells in their tumours at time of diagnosis, and in some patients you can increase those T cells by therapies such as radiation – so you can then harvest the TILs when you surgically remove the tumour, identify those TILs that have activity against the tumour and then use them for therapy."

CHUV is building a cellular manufacturing facility to produce several hundred vaccine or T-cell products a year, so that they can be "seriously tested" on all solid tumours.

"A patient will come to CHUV, have surgery to remove their tumour, then we will harvest the T cells, give them conventional chemotherapy and/or radiation as indicated by standard care, and then after that we can prescribe vaccine or T cells to boost the chance for long-term disease control. The expectation will be that the new

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therapy will eradicate the residual tumour and minimise the risk of recurrence. This is going to be a very important part of therapy in the future."

With non-cell-based immunotherapy being pursued by the pharmaceutical industry – for example the highly effective immune checkpoint blocker drugs – he is confident that treatments modulating immune response could transform the prospects for curing cancers of all types within 10 years.

"There is the prospect of developing drugs that are universal to touch the majority of patients," he says. "Immunotherapy is the only therapy that has long-term memory because it engages the patient's own defences. So after surgery, radiation and targeted therapies have reduced or removed the tumour, the immune system can be activated to clear the residual cells which are always responsible for relapse. In a decade we could be in a position where, for the first time, we could see a drastic reduction in the relapse rate, and therefore a drastic increase in the cure rate."

Unfortunately, highly promising personalised therapies such as TIL therapy hold little allure for the pharmaceutical industry. The only way personalised vaccines are going to get the considerable investment they need is through independent funding. Which is why the massive amounts being invested in the Swiss Cancer Centre is good news globally.

But is the model sustainable? I put it to Coukos that the world may well look on enviously at what is happening in Switzerland, but conclude that such a model of collaboration and research investment could only happen in wealthy countries. Will personalised immunotherapies ever go beyond high-income countries – or even high-income patients?

The investment and running costs come from the usual sources open to everyone, he explains – grants, institutional support, contracts and philanthropy.

"Certainly, the fortunate aspect of being in Switzerland is that public funding is sufficient to allow us to start with our own research agenda. We want to partner with the pharmaceutical industry to bring our innovations to patients, but clearly there are aspects they would not support, and that's where institutional support and fundraising matters a great deal.

"With T-cell therapy, once we have demonstrated success, we can hopefully convince insurance companies or the state to reimburse this kind of approach – this has already happened in some cases in Germany, UK and the United States.

"With the involvement of more and more medical centres, and growing success, one then brings in the engineers to help automate and simplify the process, which brings a reduction in cost and greater availability. This happened with bone marrow transplantation, which used to be only available in a few institutions but now every major hospital has a unit. So in a few years, we hope to be able to deliver a T-cell programme in an automated way so that we can really contribute to the health of the masses."

Coukos hopes strong buy-in from university clinical teams and practising clinicians in the periphery will help ensure long-term sustainability. He is working with clinicians and administrators to

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create a regional cancer network, the cancer network of Suisse Romande (the name for French-speaking western Switzerland, a region of approximately two million people).

His confidence in the future is partly founded on an international team he has hand-picked from the US and Europe to take the Swiss Cancer Centre project forward. Eric Raymond, Head of Medical Oncology, came from the Bichat-Beaujon University Hospitals in Paris in 2013, and Jean Bourhis, Head of Radiation Oncology, came from the Institut Gustave Roussy in Paris in 2012. Coukos' own arrival in 2012 followed a job-offer out of the blue and some soul-searching. His wife (a doctor) and two sons were settled in the US, his work was booming: "Nobody could believe I made the decision to move at this stage."

Has he found it difficult parachuting in to take the helm in a health environment very different from the US? There has been a cultural transition, he acknowledges, but he quickly grew to appreciate the way that the Swiss value stability, meritocracy and equal opportunity, and take the long view in their decision-making. "They're very important if you want to build solid programmes."

"In the United States planning is more on an individual basis, and it's less long term. If you're a good investigator or clinician, you have freedom to make a successful programme. But often there is no long-term vision from the institution about how to make it sustainable."

Vision is a word Coukos uses a lot. Creating it, communicating it and empowering people so that the vision becomes theirs is the key to ending fragmentation and getting things done. So what's the intended outcome?

"I always set myself five-year goals. So in five years' time, we should have got some major advance in immunotherapy into the clinic, made major advance in radiation therapy and created opportunities for integrating immunotherapy with molecular targeted therapies or radiation therapies. And we should have a solid network of clinical and translational oncology in the French-speaking western Switzerland region. That's my short-term goal, to bring important collaboration and innovation into the clinical space. I think it will happen." Long term, who knows what may emerge. "The important thing is that a good idea will have a chance to make an impact." ■

Right drug, right patient, wrong dose?

MARC BEISHON

Dose too strongly and the patient gets more harm than benefit, too weakly and the drug can't do its job. Could oncology learn from other fields about using pharmacokinetics in the clinic to hit it right in each patient?

Personalised medicine is about tailoring treatment and care to the individual patient and their specific disease. However, oncology has so far largely resisted the idea of personalising dose levels, despite what is known about wide variations in individual pharmacokinetics, which govern how patients' bodies absorb, metabolise, distribute and clear therapeutic drugs.

Conventionally, dosage of anti-cancer drugs has been calculated according to the patient's body surface, which can be estimated by weight and height or more simply by weight alone.

Leading pharmacologists, such as Silvio Garattini of the Mario Negri Institute in Italy, have been arguing for some time that oncologists need to pay more attention to pharmacokinetics (eg *EJC* 2007, 43:271–282). Poor responses – or indeed unexpectedly severe side-effects – they argue could be the result of a conventional approach to dosing that fails to take this into account.

One consequence, they say, is that patients may be wrongly taken off drugs that could benefit them, if used at the optimal dose. Another is that potentially valuable experimental drugs could be wrongly discarded for lack of efficacy or too high toxicity.

Calls are now growing for oncologists to monitor the drug levels circulating in the body as an essential element of personalising treatments.

Therapeutic drug monitoring (TDM)

NICOLO' ASSIRELLI

is already commonly used with a number of agents, including anticonvulsants for epilepsy, anti-coagulants such as warfarin, drugs that treat arrhythmia (cardiac disorder), lithium, some antibiotics, and immunosuppressants.

It is usually done by measuring drug concentrations in blood samples, with the timing and analysis of these tests done to suit the particular behaviour of a drug and its administration.

The main criteria for its use are where the drug has a narrow therapeutic window (i.e. a narrow dose range for which benefits outweigh risks) and a significant variability among patients in pharmacokinetics. There should also be a strong correlation between blood levels and therapeutic effect (ideally oncologists would like to know the drug levels in tumours, but that's much more ambitious), and of course suitable tests and facilities must be available.

Another criterion could be where there is a reason for monitoring variations in dose within a single patient over time, for instance to help patients with adherence when the drug is taken over long time periods. Chronic myeloid leukaemia is the obvious example, and indeed imatinib (Glivec) is so far the only targeted drug for which the routine clinical use of therapeutic drug monitoring has been suggested.

Limited clinical use

Until now, clinical application of therapeutic drug monitoring in cancer patients has been limited to cytotoxics, including methotrexate (given for cancers such as acute lymphoblastic leukaemia) and 5-fluorouracil (given for common cancers such as colorectal and head and neck, and the object of study in one of the few major controlled trials of therapeutic drug monitoring). It is also used in treating children with highly toxic agents such a carboplatin.

Lately, however, there has been a revival of interest in the potential for greater use of therapeutic drug monitoring in cancer, sparked by a pan-European group of pharmacologists convened by the French Society of Oncology Pharmacy. Last August, for instance, the *European Journal of Cancer* ran a series of position papers on the issue, with the lead paper posing the question: 'Therapeutic drug monitoring in cancer – are we missing a trick?' (*EJC* 2014, 50:2005–09).

While pharmacologists may lack experience in introducing new techniques into clinical practice, they do have the specialist knowledge – and they make a strong case.

Jan Beumer, a pharmacologist at the University of Pittsburgh Cancer Institute, wrote a provocatively titled paper last year, 'Without therapeutic drug monitoring, there is no personalised care' (*Nature Clin Pharm Ther* 2013, 93:228–230). He says that pharmacokinetics – a longstanding science – has become marginalised today amid the boom in interest in and funding for all the 'omics' in oncology. "Clearly genetics has a role – without certain mutations, such as BRAF in melanoma, you know a drug won't work. But drug exposure is the end result of a lot of variables, and blood concentration can be much more informative."

He mentions 5-fluorouracil (5-FU) as a good example. Not only does it have the prerequisite narrow

"Age, gender, liver and kidney function, interactions with other drugs and foods and smoking are all factors"

"Where there is toxicity we lower the dose, but we never upgrade the dose if there is no toxicity"

therapeutic window, but its pharmacokinetics also vary widely between patients. Most of this variability is the result of the activity of an enzyme, DPD, which clears 5-FU and if low can lead to a toxic build up that can be fatal. There is a test for the gene mutations that cause DPD deficiency, but most of the people who have severe side-effects have a negative result, says Beumer. Therapeutic drug monitoring, he argues, offers a way to address this variability (without having to explain it).

A randomised trial of therapeutic drug monitoring, currently the landmark trial for its use in oncology, was carried out on 5-FU by medical oncologist Erick Gamelin and colleagues in France, and published in 2008 in the *Journal of Clinical Oncology (JCO* 2008, 26:2099–2105). Ten years earlier they had found that, using standard dosing, a startling 43% of patients were not given the right dose – 33% being underdosed and 10% overdosed. Given that several studies had also shown a relationship between blood levels of 5-FU and the therapeutic window, they divided more than 200 patients into two groups – one receiving a standard dose and another a dose individually adjusted according to the pharmacokinetics. The results showed a significantly improved response rate, a trend to a higher survival rate, and fewer severe toxicities.

Ron Mathijssen, who is both a medical oncologist and pharmacologist at Erasmus Medical Centre in Rotterdam, and professor of individualised oncologic pharmacotherapy, says much of the new enthusiasm for therapeutic drug monitoring comes from understanding the role played by drug concentrations, thresholds of activity, and also huge variability among patients.

"For many years we just didn't know about these factors," he says, noting that there are many physiological factors that affect exposure apart from genetics, especially with oral targeted drugs. These could include age, gender, liver and kidney function, interactions with other drugs and foods, smoking, and differences in drug absorption with oral agents. A high-fat meal alone can give a large exposure effect on a drug such as lapatinib for breast cancer, says Mathijssen.

Because so many factors play a role there are few biomarkers that can predict drug exposure in cancer, unlike some other conditions (such as cholesterol levels for statins). "Kidney function is one which we use in drugs such as carboplatin, and the only option we have in current practice," says Mathijssen. "There have been attempts to use genotyping for certain enzymes to see whether they lead to variations in concentrations, but in practice it can be too complicated. If there is variation in an enzyme (such as *UGT1A1*28* for irinotecan), a medical oncologist is more likely to switch to another drug that doesn't have that enzyme variation, which is unfortunate as it means we are not using drugs in an optimal way."

Dose calculations

In the absence of therapeutic drug monitoring or other biomarkers, for cytotoxics, oncologists rely on dose calculations based on body surface area (BSA), as used in the control arm of the 5-FU study. And going further back to drug development, dosing is set in phase I studies and fine-tuned in phase II, says Beumer, by setting the maximum tolerated dose (MTD) for the whole population from only a few patients. "Just one in six patients at phase I who get toxicity set the MTD," he says.

The starting doses for the trials come from interspecies extrapolation of BSA – from mice up to humans – which scales well with metabolic capacity. "But it doesn't work within a species," says Beumer. "There's an assumption that someone with a bigger liver metabolises more so can receive a bigger dose, but in fact a small 60-year-old woman may have much more metabolic activity than me, a much younger man well over six feet tall." Beumer and colleagues have written that BSA-based dosing "gives the false impression that we are practising personalised medicine by using a patient-specific metric."

This, he says, has resulted in several drugs such as paclitaxel and capecitabine being approved at doses that are too high for most people, and oncologists know to take the dose down. Both he and Mathijssen comment that oncologists obviously like their patients to feel good during treatment. "Where there is toxicity we lower the dose say by 25% or 50%, but we never

AWARD-WINNING SERVICE FOR CHILDREN

Gareth Veal, co-author of the *European Journal of Cancer* series on therapeutic drug monitoring (2014, vol 50, pp 2005–09) and head of pharmacology research at the Northern Institute for Cancer Research, Newcastle, UK, specialises in both adult and paediatric pharmacology and has led the introduction of an award-winning therapeutic drug monitoring service for children treated with carboplatin. As he says, although a lot of drugs used with children have a good response rate they can be very toxic and difficult to manage in small children with developing organs. Many protocols therefore try to maintain response whilst minimising the side-effects of treatment, which is where therapeutic drug monitoring approaches can have an impact.

"In the UK we now routinely carry out carboplatin therapeutic drug monitoring from our reference centre in Newcastle, based on datasets we've built up from monitoring treatments over a number of years and from well-designed clinical trials. Two or three blood samples taken two hours after administration are sent to us and we have the results on dosing back to oncologists the next morning. We do it for groups where there is a high risk of toxicity or lack of response, and for neonates and infants, where drug disposition can be more difficult to predict."

SIOPE

Veal says the carboplatin service is the only one he is aware of in Europe for this drug, but centres with similar expertise are working on other important drugs in children, such as busulfan at Gustave Roussy in Paris.

upgrade the dose if there is no toxicity say by trying 50% more," says Mathijssen. "Wearing my pharmacologist's hat I don't think this is right, but it is hard to change as many medical oncologists like it when the patient has no complaints. The result though is that we are underdosing almost all our patients, in a certain way."

Though, as Beumer points out, if a patient on a drug such as 5-FU does suffer toxic side-effects, even reducing the dose does not necessarily mean that the drug becomes tolerable, and patients can drop out of treatment and lose a chance to respond. "We have tried dosing up to toxicity in trials but it has not been successful," he adds. "Then if you go too low people tolerate it, but the tumour progresses and you go to the next line, which may mean using more expensive drugs."

Practicalities

There are a number of barriers and objections to using therapeutic drug monitoring in oncology. Jaap Verweij, a medical oncologist and now dean and vice-chair at Erasmus MC in Rotterdam, argues that practical difficulties mean it's currently hard to apply in clinical practice. "While we can do beautiful studies in an academic setting, where we can get an almost immediate answer to the questions we ask, these facilities just aren't available to most clinicians, and if you wait several days for test results that's a big limitation."

Organising patients for testing can also be hard, says Beumer: "My oncologist colleagues say therapeutic drug monitoring is great, but when they try to implement it they find that a patient may live two hours away, and it would be hard to get them to come in for an extra blood draw say for 5-FU."

Cost is also an issue, and there are also regulatory barriers, which may be one reason pharmaceutical companies are not promoting its use. Beumer points to a warning letter sent in 2010 from the US regulator, the FDA, to Novartis

"It would be hard to get them to come in for an extra blood draw say for 5-FU"

"Prospective randomised trials will be needed to validate the significant effects seen in retrospective work"

about claims made on company-sponsored sites about the use of therapeutic drug monitoring with imatinib, which "urged physicians to measure the plasma concentration of tyrosine kinase inhibitor in their patients' blood, and then use that information to individualise the drug's dosage or schedule."

The FDA said it was not aware of "substantial evidence or substantial clinical experience to support a correlation between patient outcome and plasma levels of imatinib," and that the prescribing information has no provision for monitoring and increasing drug doses, only reduction or discontinuation for adverse events.

Building an evidence base

More evidence has arrived since then, but to get therapeutic drug monitoring accepted for widespread clinical practice it is likely that prospective randomised trials will be needed to validate significant effects that are seen in current retrospective work. Funding and interest for such trials, however, may be hard to come by, especially for older off-patent chemotherapy drugs.

Trials are more likely in oral targeted agents, not least because of their sheer cost – healthcare funders may well ask more questions about whether these expensive drugs are being efficiently deployed. Verweij notes that exposure studies after first doses in a drug such as the immune therapy ipilimumab for melanoma could save a huge amount of money by identifying earlier who are the 20% of patients who respond.

In their review of therapeutic drug monitoring of targeted therapies in the *European Journal of Cancer* (*EJC* 2014, 2020–36), the pan-European group note that it could provide additional information on efficacy, adherence and safety compared with clinical evaluation alone. Most studies so far have focused on TKIs, which in the case of imatinib have led to clinical recommendations, with the European Society for Medical Oncology currently suggesting that therapeutic drug monitoring may be important in all patients and is recommended for some, such as those who have suboptimal response.

Mathijssen notes that imatinib has a fairly well-established threshold of activity that lends itself to such recommendations – studies look at the 'trough' concentrations of the TKIs, which are easier to assess than the more intensive monitoring needed for cytotoxic drugs.

Verweij is doubtful about the clinical applicability of therapeutic drug monitoring at least for chemotherapy, and says it is certainly of limited use for 5-FU. "5-FU has a very short half-life so you need a test close to the bedside, it is very cheap so economic benefit is low, and its efficacy is limited. And it's hardly ever used on its own, so there is the added complexity of what a patient may be responding to," (though Mathijssen says it is still important to set optimal doses in combinations).

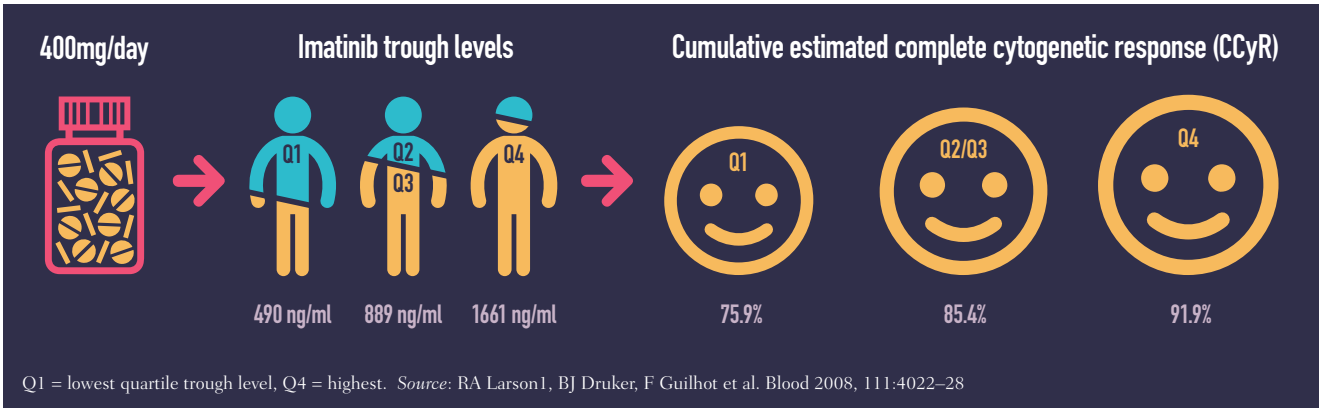
Michèle Boisdron-Celle, a pharmacologist colleague of Erick Gamelin, disagrees, saying that, given the right tools, therapeutic drug monitoring is relatively easy and not costly. They have set up a company in France, ODPM, which provides calculators for predicting the risk of toxicity of the fluoropyrimidine family of drugs (5-FU, capecitabine, etc) and for dose adaptation, which they consider give clinicians tools for better managing patients – not least to avoid deaths caused by toxicity.

"The literature on TDM is conclusive as far as we are concerned," says Boisdron-Celle, and while there "may be some data missing in terms of randomised controlled studies, if there is a clinically proven method for avoiding risks there is a serious ethical question that is raised by asking for RCTs."

In Rotterdam, Mathijssen's group is doing feasibility trials for therapeutic drug monitoring trials on other TKIs such as sunitinib and pazopanib, and is carrying out drug concentration work for a new trial in Switzerland, Austria and Germany on cabazitaxel, a new taxane chemotherapy for prostate cancer. Tamoxifen, an old targeted agent for breast cancer, is also a good candidate, he notes.

There is much exasperation about the lack of interest and understanding of therapeutic drug monitoring among healthcare providers, oncologists and drug companies. Boisdron-Celle is particularly concerned by the pharmaceutical industry. "The benefits of TDM have been clear to all pharmacobiologists and pharmacogeneticists for over 20 years. It's simply

THE CASE FOR THERAPEUTIC DRUG MONITORING OF TKIs IN CML



Q1 = lowest quartile trough level, Q4 = highest. *Source*: RA Larson1, BJ Druker, F Guilhot et al. Blood 2008, 111:4022–28

A 2008 study (*Blood* 2008, 111:4022–28) showed a 25-fold variation in trough levels of plasma concentration of imatinib (Glivec) in 351 patients treated for chronic myeloid leukaemia (range 153–3910 ng/ml). Patients who achieved the best possible outcome of complete cytogenetic response had significantly higher trough levels than those who did not (*P*=0.01). Patients with high imatinib exposure also had better rates of major molecular response and event-free survival.

While some serious (grade 3/4) adverse events increased at higher imatinib exposures others decreased. Over a five-year period, serious fatigue, fluid retention, myalgia and anaemia were all more common in patients in the highest exposure quartile (Q4) than the lowest (Q1), but patients with the lowest exposure suffered more serious joint pain, haemorrhage, rash, neutropenia and thrombocytopenia.

The study was a retrospective subanalysis of the IRIS trial (*NEJM* 2003, 348:994–1004), which five years earlier had compared imatinib against interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukaemia.

The US drug regulator, the FDA, has warned manufacturer Novartis against advising doctors to monitor imatinib plasma levels and adjust the dose accordingly, on the grounds that it was not aware of "substantial evidence or substantial clinical experience to support a correlation between patient outcome and plasma levels of imatinib". Incorporate these pharmacokinetic studies in the pivotal trial design seems to be the message from the FDA.

easier for the industry to give a standard dose to everyone," she says.

In the US, an equally forceful commercial voice is Salvatore Salmone, who runs a company called Saladax that currently offers assays for 5-FU, docetaxel and paclitaxel, and who points to solid data in the pharmokinetic literature that tends to pass oncologists by.

Beumer, who has done some work with Saladax, says sessions on therapeutic drug monitoring at major cancer conferences tend to get sidelined. He hopes the International Congress of Therapeutic Drug Monitoring and Clinical Toxicology (ICTDMCT), a small organisation for which he helped found an oncology section, will contribute to improving the situation.

Mathijssen expects progress as tests and protocols become better suited to clinical practice. "It will be part of practice in ten years' time I believe, because by then it should be possible to measure just one sample with cheaper assays at nearby facilities. I really think it's important – although we don't have the evidence of where the exact threshold might be for a lot of drugs, if we do measure a concentration below the lower limit of quantification we would know the drug is below the therapeutic range and is therefore inactive." ■

"The benefits of TDM have been clear to all pharmacobiologists and pharmacogeneticists for over 20 years"

The price of survival

PETER MCINTYRE

Broadcaster Katrin Zöfel showed the value of good journalism with her half-hour broadcast for Deutschlandfunk, German national radio, which told the stories of people living with long-term effects of being treated for cancer.

More than 2 million people who live in Germany today were treated for cancer ten or more years ago, according to estimates from the Robert Koch Institute. A further 1.5 million underwent treatment between five and ten years ago. Of these long-term survivors, 30,000 had cancer when they were children or teenagers.

Medicine has cured many of them. But there is another side to this. Nobody in Germany has an overview of how well survivors are doing today, or of the impact of the after-effects of treatment with powerful chemotherapy and radiotherapy.

The need to address and attend to late effects of cancer treatment is increasingly (but insufficiently) recognised. Many patients are left with long-term fatigue, pain, infertility, memory loss, depression and other symptoms – and a proportion are diagnosed with second cancers caused by treatment. The landmark Childhood Cancer Survivor Study published in the US in 2006 showed that almost three-quarters of childhood cancer survivors have at least one chronic health problem 30 years later, and that 42% live with a severe, disabling or life-threatening condition.

Germany has follow-up data on those who had cancer in childhood and on adults treated for Hodgkin lymphoma, thanks to the German Hodgkin Study Group. According to Peter Borchmann, who heads the group, 20–30% of Hodgkin survivors have late effects from treatment, ranging from infertility, early menopause and chronic fatigue to heart attacks, breast cancer and leukaemia.

For most adult cancer patients there are no follow-up surveys or clinics once active treatment is over.

Radio reporter Katrin Zöfel was alerted to this issue by Christiane Knoll, her science editor at the national public sector radio network Deutschlandfunk in Germany. She spent the next 15 months researching the issue, finding the right patients and doctors to explain late effects and what can be done. The resulting half-hour programme, *Price of Survival, the Late Consequences of Cancer Therapy,* was declared runner-up in the European School of Oncology's Best Cancer Reporter Award for 2014, with a citation that paid tribute to tackling an important under-recognised problem.

A constructive approach

Zöfel was determined that her story would suggest ways forward – not just highlight problems. "I don't like stories that blow up into a scandal and I was a bit worried that it could be like that. I did not want this to be a story about mean doctors who don't treat patients right. I didn't want to write a story about finger-pointing and blaming."

Zöfel found patients and scientists through support groups and via Deutsche Krebshilfe (German Cancer Aid) and Stiftung Deutsche Kinder-

Striking the right note. Katrin Zöfel wasn't interested in just pointing a finger of blame, so she took time to understand the root of the problems and explore possible ways forward

Deutschlandfunk

Krebshilfe (for childhood cancers).

"After the first interviews with patients, it became very clear that I couldn't cover this topic without plunging deeply into the stories of the individuals involved. What stayed with me was the abrupt and merciless change that cancer meant for the lives of the patients, the absolute way in which they had to turn themselves over to the care of physicians, not knowing whether the treatment would cure them or harm them… At the same time, I felt a clear awareness about how helpless medicine still often is in the face of cancer."

Holger Bassarek was treated with a bone marrow transplant for acute lymphoblastic leukaemia 16 years ago. He was cured but he struggles to remember names and faces and is often exhausted. "The battery is empty, and the normal recharging cycle is never enough." He has poor blood circulation and damage to his peripheral nerves. Fortunately, he insisted on freezing his sperm, and is a father of two boys, despite the treatment destroying his fertility.

Philipp Volkerts, now 26, had a brain tumour the size of golf ball removed when he was 19. Last year Volkerts needed another operation to remove a non-malignant cyst in his head, and Zöfel later accompanied him to Münster where he told his paediatric oncologist, Gabriele Calaminus, how he was feeling. "No headaches, but there was something … it was something like depression. How can I say it? My self-esteem went down. I had mood swings, mainly after the surgery last summer, for maybe one or two months."

Zöfel was struck by the changes below the surface. "He looks very healthy – a sporty guy. He was studying, he has a girlfriend, and now he has a very nice job. Still you could feel the impact that this illness still has on him six or seven years afterwards."

Borchmann and Calaminus both have a long-term commitment to their patients. But Zöfel was shocked by what she heard from some adult oncologists. "Many said: 'I am here to save

the patient and late effects are not my problem.' I also found some people saying: 'We don't want to follow up those patients because we want them to forget that they had cancer.'

"The ones I reached in the end are the ones who really care for their patients, and they were saying: 'I did this to my patients and now it is me who has to follow up on this.' I would say they have a sense of responsibility."

A sensitive issue. As a science journalist with an interest in ecology, Zöfel felt a bit wary about handling a story of such importance to patients

Zöfel notes that some European countries have registers for former patients at the end of treatment. Epidemiologist Flora van Leeuwen, who recently opened a clinic in The Netherlands for people who survived Hodgkin lymphoma as adults, says that it is crucial to know which areas of the body were irradiated and details about the chemotherapy. If her project goes well, similar clinics will open for survivors of breast and prostate cancer.

Zöfel also detailed work by the European PanCare network, which is compiling data on heart problems, secondary tumours and mortality, and is working on European therapy guidelines and a survivor 'passport'.

However, she senses a worrying absence of political will in Germany to close the gap in knowledge and aftercare. She fears that the Third Reich poisoned the well for setting up databases. "It is really hard to have good registries where we can follow up and track people 30 years later, because registries were used in a really bad way in our history. Childhood cancer is an exception, but for adult cancer patients it is practically impossible to follow up on a large scale."

Even patients with doctors committed to long-term care have many needs outside their specialist knowledge. "I found a very strong relationship between some patients and their doctor, and a big reliance on them. But is the oncologist always the right person to care for people with late effects? Maybe they need an internist or someone who knows about hormones."

Where science gets personal

As a science journalist with an original interest in ecology, Katrin Zöfel had to step outside her comfort zone. "It was the first time that I had done a story that mattered so much to patients. I was wary of doing that because I knew it would affect me. If I talk to patients about almost dying and surviving I knew that would not be like talking about the ecology of bats."

But when *Price of Survival* was broadcast in January 2014, it had an impact. "I got more feedback than for any other story. It was posted on several patient advocacy pages. Inside Deutschlandfunk I got feedback that I got the right tone." Zöfel has since broadcast pieces for a Berlin programme and on Swiss public radio and is working on a piece for television. *Price of Survival* was repeated in November 2014 as part of a cancer awareness day.

The Best Cancer Reporter Award has confirmed to Zöfel that she got the balance right. "The award is reassuring; an encouragement to go on. It suggests I was able to hit the right tone. If I was able do it once I might be able to do it again."

Journalists often get a bad press ("sensationalist, superficial, inaccurate") so there are some interesting lessons from this example. One is the time it took – 15 months in all to put the material together. Partly this was because, as a freelancer, Zöfel had to keep taking short assignments to pay her bills. "It must have been pretty annoying for my editor, but I had to earn money in between," she said.

She also admits that she did too much research – because she wanted to get it right. "The work and passion I put into this feature went far beyond what I usually put into my daily work. I talked to one expert and thought, 'OK I understand the topic,' and then I talked to a second one and she basically said the opposite. I needed another two or three experts to figure it out and get an overview and really understand who is right."

In the end, Deutschlandfunk and Katrin Zöfel delivered on quality. In an era where many expect to get their news free online, this is a useful reminder that good journalism requires the same qualities as good clinical practice: expertise, time, commitment, teamwork and trust. ■

A life worth living: we could do much more to help patients with depression

LIZ BESTIC

A new model for caring for depression in cancer patients shows how much can be achieved even on a tight budget.

That being diagnosed with cancer carries an increased risk of depression is perhaps not unexpected. What comes as a surprise to many people, however, is how effectively even major depression in cancer patients can be treated, provided it is done in the right way.

This was demonstrated most recently with the results of a randomised controlled trial that showed impressive results for a new approach to treatment that integrates care for depression with the other aspects of the patient's cancer care (*Lancet* 2014, 384:1099–1108).

The SMaRT Oncology-2 trial randomised 500 outpatients with cancer, diagnosed with major depression, to the new integrated "depression care for people with cancer" or to usual care.

Using a primary outcome measure of 50% or greater reduction in depression severity, scored on the self-rated Symptom Checklist Depression Scale SCL-20, almost two-thirds of patients (62%) randomised to the new approach responded to treatment.

This compared with a response rate of fewer than one in five (17%) of those randomised to the control arm. Treatment for these patients was left in the hands of the patient's oncologist and general practitioner (GP), who were informed that their patient had been diganosed with major depression, and were asked to treat them as they normally would.

A smaller, parallel, randomised controlled trial – SMaRT Oncology-3 (*Lancet Oncology* 2014, 15:1168–76) – looked at the effectiveness of the same intervention specifically in cancer patients with a poor prognosis. It found a significantly better response among patients randomised to the integrated treatment, even in this more challenging group, using average depression severity over the patient's time on the trial as the primary outcome measure.

The results are important because they show policy makers the value of including psycho-oncology within cancer services, and they challenge nihilistic attitudes about the potential for successfully treating depression in cancer patients.

"We have got rock solid evidence

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now, and believe this is the way forward in ensuring people with depression are treated effectively," said Mike Sharpe, a professor of psychological medicine at the University of Oxford, and joint first author of the two studies.

Delivery of the treatment programme relies heavily on specialist cancer nurses, who are given intensive 12-week training in depression care for people with cancer. They work in a team with supervising consultation liaison psychiatrists, working in collaboration with the patient's oncology team and GP.

The study authors attribute the success of the model to a number of factors. It was intensive – a combination of regularly reviewed drug treatment together with psychological therapy delivered in up to 10 sessions, mainly face-to-face, over a period of four months. The training and delivery was done systematically, with regular supervision of sessions using videorecordings, and regular monitoring of patient outcomes. And it was integrated with the patients' cancer and primary care to promote acceptability and adherence.

They also draw attention to the surprisingly poor results in the control arm, where more than four out of five patients failed to respond to "usual care".

A welcome approach

The principle of delivering psychological support as an integrated part of patient's cancer care has wide support among the patient advocacy community. Europa Donna, the European Breast Cancer Coalition, has long been campaigning for all breast care to be delivered by certified specialist units or centres, with access to psycho-oncology services

21 of the 27 countries include psychosocial services in their national cancer plan, but half have no budget for it

among the criteria for certification.

Stella Kyriakides, a former president of Europa Donna and a member of the House of Representatives in Cyprus, says: "It is vital that psycho-oncology is part of a multidisciplinary approach from day one," but she recognises that for many patients this simply isn't happening.

"It is true patients don't get the help they need at the moment. Very few centres have this multidisciplinary approach and not all countries have units which allow for this type of care." The situation for people with rarer types of cancer is far worse, she points out, as they are even less likely to be treated within a multidisciplinary team.

There are wider problems too, she argues, particularly in southern Europe, where mental health care is often seen as a luxury and is ignored. "It is not a luxury for patients, but a right," says Kyriakides.

The German model

In some countries, such as Germany, integrated approaches similar to the one proposed in the SMaRT studies are already up and running. Guidelines published in January this year on diagnostic and treatment approaches recommend a three-step system, which involves screening, counselling and treatment.

Treatment can involve relaxation techniques or psycho-education where the distress is not severe, and psychotherapy combined with anti-depressants or anti-anxiety pharmaceutical treatments in cases of severe depression. "If the patient is over the threshold then they are referred to see a psycho-oncologist. If they are under the threshold they will simply get basic information about their cancer," explains Joachim Weis of Department of Psycho-oncology at Freiburg University.

The German system of psycho-oncological care, he says, is mostly based around psychology and psychotherapy. There are very few psychiatrists working in this field. More importantly, there is a big difference between inpatient and outpatient care. Most cancer patients are treated on an inpatient basis, within certified cancer centres, where integrated psychosocial care is obligatory.

Here patients may see a psycho-oncologist, psychotherapist, psychologist or even a social worker with further education in that field. The nurses in Germany, particularly those who are highly educated in psychosocial competency, are mostly engaged in screening rather than diagnosis.

Germany is unusual in offering cancer patients three weeks at one of the country's 130 specialist rehabilitation centres after their last oncological treatment, where they have access to interdisciplinary teams including psycho-oncologists, social workers, physicians and nurses.

Around 30–40% of all German cancer patients choose these aftercare programmes, which provide high-quality care, says Weis. "During this period we often have a better opportunity to identify if they have a high level of psychosocial distress or psychiatric disorders… It is often in this early rehab phase where patients are identified as having depression or problems coping," he says.

But like everywhere else, health budgets are being squeezed and reimbursement for psycho-oncology services is becoming an increasing issue. There are ongoing discussions with the insurance companies and the Ministry of Health to ensure that it can be paid separately, says Weis, because it is more than the basic budget allows.

"In Germany the focus of the medical system tends to be more on technical aspects, so there is never any problem finding money for high-tech equipment. Since the recession, however, we are struggling to get the money for psycho-oncology, because it comes quite low on the shopping list of cancer treatments."

The European picture

In other parts of Europe the picture is very different. A recent survey conducted by the International Psycho-Oncology Society IPOS, as part of the European Partnership for Action Against Cancer (EPAAC), mapped the needs and resources in communication skills and psychosocial care in 27 countries across Europe.

"Whilst many European countries have integrated psychosocial care into their national cancer plan it is clear there is still much to do in terms of allocating resources and delivering the care equitably," says Luzia Travado, the newly elected head of IPOS.

Travado was a key player in developing the survey and believes there is still huge resistance to recognising mental health or distress as a major component of oncological care, despite intense national and international campaigns by professional organisations.

The slogan "distress is the sixth vital sign," has been a focus of campaigns for better psychosocial care across Europe. IPOS has now enshrined in its International Standard of Quality Cancer Care the requirement that cancer services must integrate the psychosocial domain into routine care and that distress should be measured as the 6th vital sign after temperature, blood pressure, pulse, respiratory rate and pain.

"To improve patients' outcomes it is necessary to integrate psycho-oncology into standard routine cancer care, from diagnosis, across treatment and all phases of disease and survivorship as a vital part of comprehensive high-quality cancer care," says Travado.

Although 21 of the 27 countries in the EPAAC survey already have psychosocial services as part of their national cancer plan, only half of them actually have a budget for the treatment.

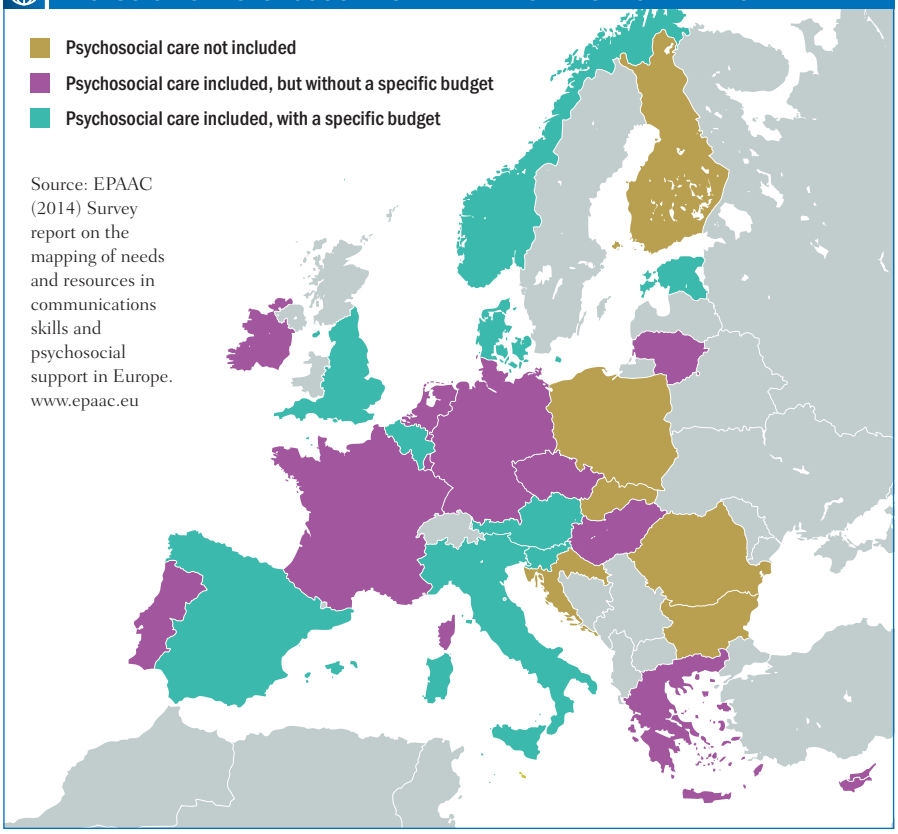
The survey threw up other barriers too. Many psychosocial services in Europe are only available in cancer centres, university hospitals and cancer rehabilitation centres and only rarely in general hospitals. Referrals to these services have been reported as inconsistent, and in some countries the availability of these services is still scarce or completely absent.

One consequence, says Travado, is that doctors feel more reluctant to tell their patients the truth about a cancer diagnosis. She cites Bulgaria, as an example: "Here where there are no psychosocial cancer care services available, doctors tend to be more silent about the diagnosis. Doctors have more confidence in disclosing a diagnosis to a patient where there is a psycho-oncology service in place to refer to."

The EPAAC survey also showed that only 16 European countries have a national psycho-oncology society affiliated to IPOS, which may in part account for the lack of specialist professionals and low levels of interest in fostering psycho-oncology in those countries.

"There is a clear need for improving training and certification in psychosocial cancer care as well as developing a national policy which recommends the use of existing clinical guidelines," says Travado.

INCLUSION OF PSYCHOSOCIAL CARE IN NATIONAL CANCER PLANS



Source: EPAAC (2014) Survey report on the mapping of needs and resources in communications skills and psychosocial support in Europe. www.epaac.eu

"There is a clear need for improving training and certification in psychosocial cancer care"

"It seems quite obvious to switch some of the budget from prolonging life to making life more tolerable"

In 2013 IPOS piloted training workshops in Romania as part of its EPAAC activities. These included demonstrations of best practice in communication skills and psychosocial care, using a stepped model that matches levels of interventions to different levels of need.

"We ran this programme nationally with the help of local government. We included training for the trainers, including psychologists and oncologists, who were then able to cascade this training into regional areas. We also invited nurses to participate, but their English was not good enough so we realised it was important to have Romanian people providing the training," says Travado.

Funding psychosocial care

The worry is that pressure on health budgets is making it harder to secure the funding to ensure all cancer patients have access to the psychosocial services they need – or even to defend existing services, as in the case of Germany.

Aware of this problem, the team behind the SMaRT trials included an analysis of the cost of delivering the proposed integrated approach to treating depression in cancer patients, which came out at a surprisingly low £600 (750 euros) per patient.

Mike Sharpe, principal investigator, argues that this represents very good value for money. "If you don't treat depression in cancer patients you get cancer care that is painful, hugely disruptive, expensive and people come out of that care and say, 'I wish I had died.' That can't be a good outcome can it?" he says.

On top of the benefit to the patient's quality of life, there could also be savings for the health service and the economy if better mental health helps patients engage more effectively with decisions about their care, adhere better to their treatment, and function better in terms of their work and family lives.

Certainly the proposed integrated care model has been warmly received by the Chief Medical Officer in England, and there is even talk of a pilot scheme starting at a large teaching hospital in London.

Whether other countries will be as keen to embrace such a model remains to be seen. Key to keeping the costs low is the prominent role given to specialist cancer nurses, who tend to be paid less than psychologists and psychiatrists. But many countries do not educate and train nurses for such specialist roles.

Kyriakides believes such a central role for nurses is a sensible way to go. "Nurses are at the frontline with cancer patients, not the oncologists, and it makes sense that they are part of any integrated approach to cancer care," she says. "In the case of breast cancer in Cyprus and other parts of Europe, we already have breast cancer nurses and they are key to the emotional care of the patients. I think that nurses have already become such an important part in support and treatment in many areas of health including mental health. A well-trained nurse would make a huge difference to cancer patients, and I do think it would translate to Europe," she said.

Securing funding for this type of care to be delivered across cancer services will, however, require taking the argument to policy makers, particularly in countries that currently have no budget at all for psychosocial services.

"Surely we are all agreed in 2014 that people's outcomes should not be measured just by length of life but also by quality of life. So it seems quite obvious to switch some of the budget from prolonging life to making life more tolerable," says Sharpe.

Travado agrees. "We need to make a case to the politicians that it is more worthwhile to them to have better adjusted citizens that are survivors of cancer than just not pay attention to their needs. When you introduce a psycho-oncological dimension to a patient's care you actually reduce costs, because fewer people drop out of work as a result of their psychological suffering," she says.

But it's not just policy makers who need convincing, says Sharpe. Introducing this integrated approach to care will also require cancer professionals who want to pick up the idea and run with it, and are willing to change their practices and champion new ways of working. Travado agrees. "We cannot simply parachute into other countries in Europe with new ideas without having champions on the ground there who are willing to drive it forward," she says. ■

Overdiagnosis under the microscope

SIMON CROMPTON

A new conference looks at the social as well as individual implications of how we use diagnostic tests that cannot accurately pick out real from apparent threats.

Improving the way we spot, report and explore genuine danger signs is a priority in cancer. But what happens if the tools that we use are poor at distinguishing the tigers from the pussycats – true threats from harmless or low-risk abnormalities? What if the more we screen healthy populations, the more we expose people to unnecessary and potentially harmful treatment?

These questions have already given rise to high-profile and heated arguments in the fields of PSA tensting for prostate cancer and mammography for breast cancer. But they are now part of a much wider debate about the value and dangers of screening populations for signs of disease. It has major implications for policy and practice in cancer and most other fields of medicine.

With new knowledge and technologies continually opening up possibilities for detecting early signs of potential problems, an annual international conference has been launched to respond to pressures to 'overdiagnose'. Convened by the *British Medical Journal*, the US Dartmouth Institute for Health Policy and Clinical Practice and the Oxford University Centre for Evidence Based Medicine, the second event in Oxford, last September, attracted 350 international delegates from a wide spread of medical specialities, many of them working in cancer.

FRED VAN DEELEN, WWW.ORGANISART.CO.UK

A modern problem

Though the idea of 'overdiagnosis' first reared its head in the late 1960s, the possibility that screening for disease could sometimes do more harm than good – identifying and treating abnormalities that would never lead to clinical disease – has been until now "shadowy", according to Alexandra Barratt, a professor at the Sydney School of Public Health, in a keynote address.

"It has been the subject of vitriolic debate, professional division and public confusion, misunderstanding and disbelief," she said.

Today it is under the spotlight. And if the views of the conference delegates are anything to go by, there is a growing conviction that the modern technological expansion of healthcare in rich nations is making overdiagnosis a genuine cause for concern.

One of the speakers, Barry Kramer from the US National Cancer Institute, has likened overdiagnosis to an iceberg. It is, he says, the result of two factors: a reservoir of indolent "disease", and tools that can dip into the reservoir ever more deeply as skills and technology improve.

In cancer, screening tests are the most efficient way of dipping below the water into the iceberg's mass of potential illness. They are used to identify and treat people who have "silent disease" – heading off the prospect that the disease will one day break the surface of the water, appear as symptoms or threaten life. The problem is that the more you dip into the iceberg's bulk, the more silent disease you will find that would never have broken the surface.

Key here is evidence showing that increased care intensity in developed countries isn't always associated with lower mortality rates. One of the most striking examples comes in studies of breast cancer incidence and mortality. For example, the rate of breast cancer in France has increased from 56.3 per 100,000 in 1980 to 90.9 per 100,000 in 2010, coinciding with an eight-fold increase in the number of mammography machines in France. Yet mortality rates have remained more or less stable, at 16–20 per 100,000 for the whole period.

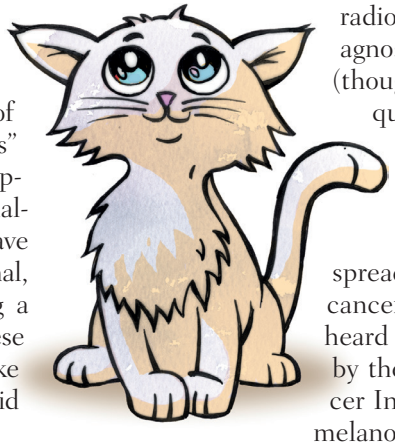
Presenting the information, Bernard Junod, from the independent research organisation Formindep, in France, said that by picking up more disease we are not necessarily stopping more people dying. In fact, we may be exposing more people to damage from treatment.

Though debates persist about how to interpret the evidence – better treatment outcomes will have had some impact on keeping mortality rates steady – and about how many overdiagnoses can be justified for the sake of identifying an additional real threat, the figures quoted by Junod illustrate

The issue is how to get the balance correct – how to set the boundary between 'normal' and 'abnormal'

an issue that demands attention.

Another striking example came from Rustam Al-Shahi Salman, Professor of Clinical Neurology at the University of Edinburgh, Scotland. He said that magnetic resonance imaging was increasingly used as a diagnostic tool in high-income countries because of its alluring safety and sensitivity. But its dangers were easy to overlook. For those having brain scans – for example as part of a private health screen – there is a one in 37 chance of discovering a vascular abnormality which is currently producing no symptoms. Some of these "incidentalomas" – for example an unruptured arteriovenous malformation (AVM) – have the potential to be lethal, for example by causing a brain haemorrhage. "These incidentalomas feel like ticking time bombs," said Al-Shahi Salman.



But the potential harms of intervening may outweigh the benefits, he said. Al-Shahi Salman's research shows that the annual rupture risk of an AVM is 1.3%. But treating AVMs has an annual risk of death or stroke of 7%. At five years, the risk of death or stroke without treatment is 14 in a hundred, the risk of death or disability after treatment is 37 in a hundred.

"Warnings about the unintended consequences of brain MRI should be given to patients with a low probability of disease, research volunteers and those tempted to purchase health check-ups using brain MRI," said Al-Shahi Salman.

In a similar vein, it is the harm that many cancer treatments inflict that makes overdiagnosis so problematic. Junod quoted a study showing that in France in 2010 there were 843 unnecessary deaths as the result of overdiagnosed breast cancer – attributable to cardiovascular damage caused by radiotherapy. He believes there may also have been 169 cases of invasive cancer resulting from radiotherapy of overdiagnosed breast cancer (though some delegates questioned the statistical methods that brought him to these findings).

The evidence is spreading beyond breast cancer. The conference heard an analysis of data by the US National Cancer Institute showing that melanoma incidence has been increasing since 1975, while mortality has remained stable, suggesting overdiagnosis. It heard about concerns that improved screening with blood tests and ultrasound is leading to increased detection of borderline ovarian tumours that might never present clinically in the lifetime of a woman.

And it heard about a population-based study of thyroid cancer patients in Ontario, Canada, between 2000 and 2008, which showed that this "essentially benign" cancer is now increasing at an "epidemic" rate. The increase is confined to more affluent areas, and closely related to the availability of diagnostic ultrasound. Some more affluent regions of Ontario have four times the rate of thyroid cancer of poorer regions.

"This is explained by the increasing use and availability of diagnostic tests in regions where there is a population of higher density, better income, better education," said Stephen Hall, Professor of Otolaryngology, Oncology and Public Health Sciences at Queen's University, in Kingston, Ontario.

A cause and effect of inequality

The study illustrated a common theme that emerged from many presenters. Overdiagnosis is borne of wealth and inequality. Yet poorer less educated populations also feel its effects, because limited health resources that could be used to promote access to evidence-based interventions that would help large numbers of people are being diverted to interventions that are poorly supported by evidence and likely to help only a few.

Margaret McCartney, a Glasgow-based general practitioner and *BMJ* columnist, spoke of how powerless she can feel when trying to help patients from deprived areas with complex problems, because of scarce resources and time. Doctors in the UK are being pushed into routes that are not necessarily in their patients' interests, and which promote overdiagnosis, she said.

For example, they operate in a "climate of fear", constantly having to ask themselves whether they might be blamed if they don't intervene or

run diagnostic tests. Medicines and tests are being "overhyped", and there are few good evidence-based decision making tools that patients and doctors can use together. All of these, she argued, contribute to overdiagnosis.

"Overdiagnosis is the result of industrial tick-box medicine," said McCartney. It focuses on simple solutions for populations, rather than dealing with complexity and uncertainty in individuals. "Preventing overdiagnosis is crucial both to curb avoidable harms and reduce health inequalities," she said.

Part of the problem, said David Haslam, Chair of the National Institute for Health and Clinical Excellence in the UK, is that the public health interventions (such as prevention projects) that have the biggest impact are perceived as dull – whereas interventions and tests that help the few have a glamour that gives them popularity.

He pointed out that both overdiagnosis and underdiagnosis are problems. The issue is how to get the balance correct – how to set the boundary between 'normal' and 'abnormal'. This prompted the question: is medicalisation harmful, or a failure to medicalise harmful?

"We must rely more on individuals making decisions for themselves. Doctors need time to explore individual patient beliefs."

Political drivers

According to John Yudkin, Emeritus Professor of Medicine at University College London, the issue of how we define 'normal' and 'abnormal' is crucial. Decisions made at the highest levels delineating what constitutes illness are not always in the patients' interest. The current 'epidemic' of pre-diabetes (intermediate hyperglycaemia) can be put down to politics, he said.

The American Diabetes Association has recently expanded its definition of intermediate hyperglycaemia to include people with raised fasting glucose or glycated haemoglobin concentrations. The result, said Yudkin, is that half of all Chinese adults and one in three Americans can now be defined as having pre-diabetes.

There is no evidence that treating people in these groups reduces morbidity or mortality, he said. Yet labelling people as "pre-diabetic" brings problems with self-image, insurance, healthcare costs and exposure to drugs with potentially damaging side effects.

"The United States is dominating international opinion. We are talking about starting people on a lifetime of treatment that will provide no benefit."

Several speakers warned that overdiagnosis is likely to become a bigger problem, as technological advances enable medicine to dig deeper and deeper into the iceberg.

Nowhere is this more true than in the field of cancer. John Burn, Professor of Clinical Genetics at Newcastle University, UK, said that since May 2013 the demand for testing for harmful BRCA gene mutations had soared because of publicity about film star Angelina Jolie's double mastectomy. And while identifying such monogenic causes of cancer might be effective and economical, the increasing availability of DNA sequencing is raising the prospect of more complex genetic variants being identified in millions of women.

"We face variant inundation," said Burn. "But the predictive power of gene testing in polygenetic traits is overstated." Genetic testing will not provide an accurate prediction of whether a woman is likely to get cancer or not, yet demand is still going to be high.

"We are heading for the biggest traffic jam in history," he said. ■

The third Preventing Overdiagnosis Conference, scheduled for September 2015, will be hosted by the US National Cancer Institute and National Institutes of Health.

"We are talking about starting people on a lifetime of treatment that will provide no benefit"

Lymphoedema following treatment for breast cancer: a new approach to an old problem

Screening breast cancer patients for lymphoedema makes it possible to identify problems early and take action to halt its progression. Oncologists have an important role to play, particularly given the rise in lymphoedema rates that may be expected due to greater use of regional radiotherapy in early breast cancer.

In the past, lymphoedema was relatively common in women following treatment for breast cancer. It could be severe, with arms swelling up to one and a half times their normal size, which is referred to as 50% lymphoedema. Thankfully it is rare to encounter problems of this scale today.

The aim of this review is to change the way we think about breast cancer-associated lymphoedema.

I would like to propose that we detect swelling early, at a level of around 7–10%, which increases the possibility of treating it successfully.

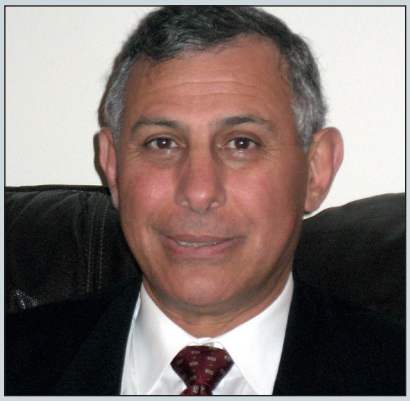
How do we think about lymphoedema today? We think about it in terms of an impairment-based model. This means that when we see lymphoedema, we start to treat it. Treatment is generally unsuccessful in more severe cases, and physicians tend not to be very involved. As soon as we see swelling we just send the patient to a physical therapist to

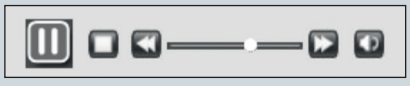
European School of Oncology e-grandround

The European School of Oncology presents fortnightly 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 Alphonse Taghian, of the Massachusetts General Hospital, in Boston, Massachusetts, reviews the challenge that lymphoedema poses following treatment for breast cancer, and suggests a new approach to its management using screening to improve early detection and treatment.

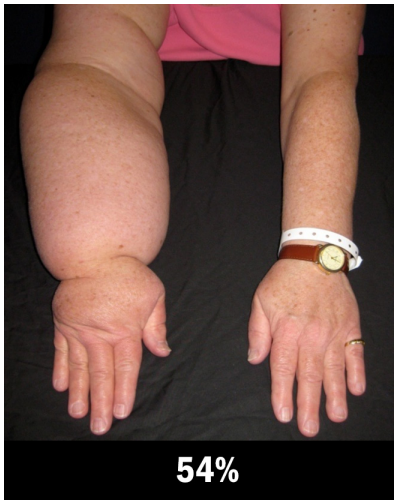
Edited by Susan Mayor.

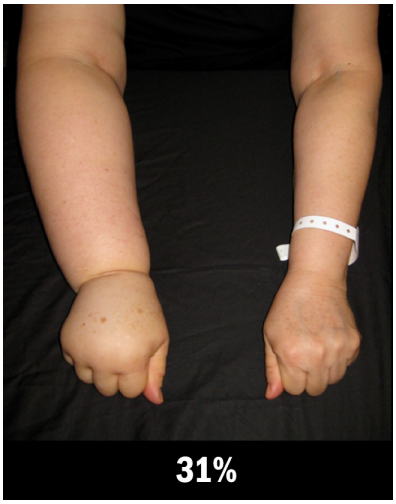


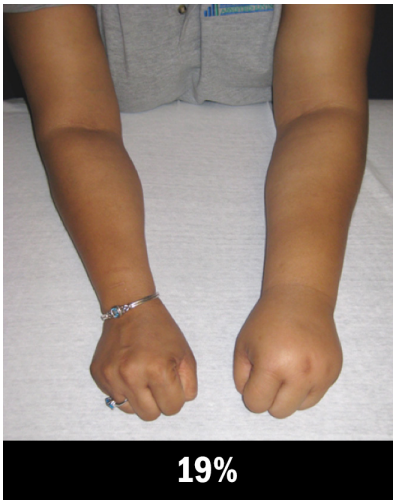


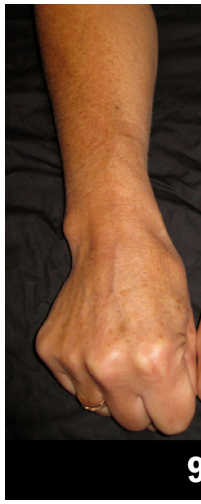
The recorded version of this and other e-grandrounds is available at www.e-eso.net

LYMPHOEDEMA FOLLOWING TREATMENT FOR BREAST CANCER









provide massage or other therapy, but the success rate is fairly low. Limitations hampering improved management are that we do not have a universal definition of lymphoedema or an accurate method to measure it, and there is no level 1 evidence – no phase III randomised trial – on the best way to treat lymphoedema.

For the future, I would like to change the model for lymphoedema to a screening-based model in which we no longer wait until we see that a patient's arm has swollen but, instead, we screen for the problem, detect it early on and then test the best way to treat it. Oncologists should take a lead in this approach because we see the patient very early on during their treatment, while a physical therapist sees them once the problem is already there.

We need to come together to define lymphoedema, agree what degree of swelling we call lymphoedema, and the optimal method to measure it. We need to determine when we should intervene: should it be when there is minimal swelling, a 3–5% difference in volume for example, or 5–10% or more than 10%? We also need to generate level 1 evidence with phase III randomised trials to determine the standard of treatment. And we need to be very mindful of the cost of the treatment.

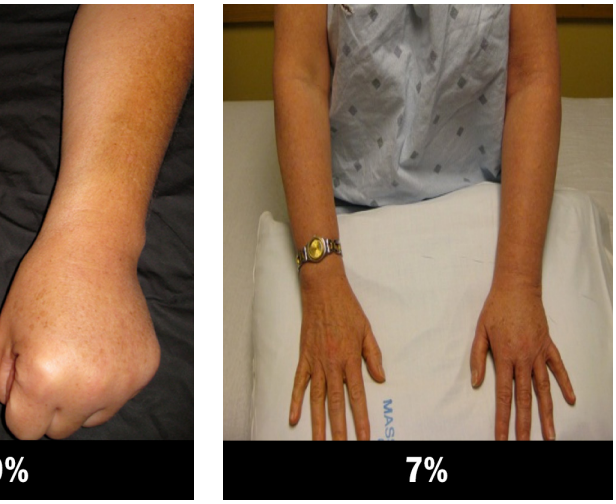
Our department has been interested in lymphoedema for some time and considers that the only way to move this field forward is to work as a team. The Massachusetts General Hospital lymphoedema team, initially formed in 2005, includes: a breast radiation oncologist, physical therapist, surgical oncologist, clinical research coordinator and a patient advocate, all of whom came together to think how best we can address lymphoedema. The goals are to:

- identify lymphoedema as early as possible
- empower patients to manage lymphoedema with as little burden as possible, keeping their goals central to decision making
- contribute to the scientific literature by generating level 1 evidence
- see if early detection leads to early intervention and whether this results in better outcomes.

What do we know about lymphoedema?

The incidence of clinical oedema is 20–25% in patients undergoing axillary node dissection, and 5–9% in those undergoing sentinel node mapping. Subclinical oedema is experienced by almost half of patients with axillary node dissection (47%) and by 15% of patients undergoing sentinel node mapping. There is no doubt that improving surgical technique has greatly reduced the risk of lymphoedema, although it is still high in regions that use lymph node dissection.

Established risk factors include: axillary dissection, wound infection, axillary radiation and high body mass index (BMI). A BMI of 30 or more greatly increases the risk (*Breast Cancer Res Treat* 2013,



142:59–67). Potential risk factors include the number of nodes removed (although this has not been found in patients undergoing sentinel lymph node biopsy alone (*Ann Surg Oncol* 2010, 17:3278–86) and the number of positive nodes (*JCO* 2008, 26:3536–42).

The negative impact of lymphoedema on patients' quality of life is very well established. It can also have a negative impact on body image, with the patient having to live with a permanently swollen arm constantly reminding her about her breast cancer. When lymphoedema is significant, it can decrease the upper extremity function, which also impairs quality of life.

Several studies show that exercise is good for lymphoedema and does not exacerbate the problem (*NEJM* 2009, 361:664–673; *Breast Cancer Res Treat* 2008, 109:9–26; *Biol Res Nurs* 2008, 10:34–43). There are a lot of myths in the lymphoedema field, such as that repetitive arm movements can generate lymph and compromise lymph drainage and can cause more swelling. These still appear in the brochures that we give to patients, but we now know it is completely wrong. The data support exercise, in particular weight lifting, carried out in a well-controlled and progressive manner.

What is the best method to quantify changes in arm volume?

There are four different techniques in the literature:

Tape measurement. The most popular way of measuring lymphoedema is by measuring the circumference of the arm with a tape measure (*Cancer Investigation* 2005, 1:76–83). Unfortunately, physicians are not usually very thorough, measuring only one or two points of the arm, such as 10 cm above or below the elbow. This method has poor reliability and is unable to quantify swelling in the hand or the breast. A more thorough approach is to measure the circumference of the arm every 4 cm, and use software to generate the volume of the arm.

Water displacement. This is the second most commonly used way to measure lymphoedema, and requires the patient to put her arm in a large glass cylinder. The water displaced reflects the arm volume. This method is commonly used in clinical trials; however, it is messy and unhygienic, it takes time, and the reliability is questionable.

Bioimpedance. This relatively new method was developed in Australia. It calculates an impedance value, which reflects the ability of an electrical current to pass through the limb. It is quick and very convenient, simply requiring a small machine that can easily be taken from one consultation room to another. However, as it is rather new there are limited data.

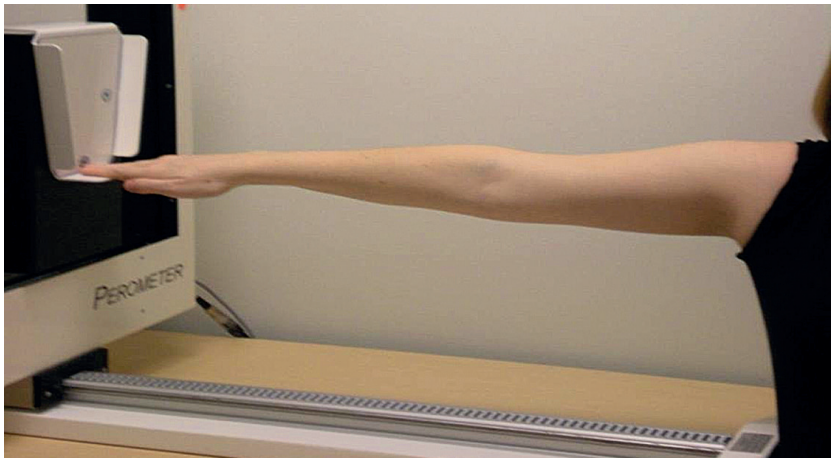
Perometer. This equipment uses infra-red technology to quantify lymphoedema. The patient extends her arm horizontally while a frame moves back and forth producing an image of the volume of the arm on a computer screen (see figure overleaf). This can be compared with the other arm, or baseline measurements, to give the percentage of swelling. We are currently using this method in our lymphoedema screening programme. It is convenient and accurate but the equipment has to be installed into a dedicated room.

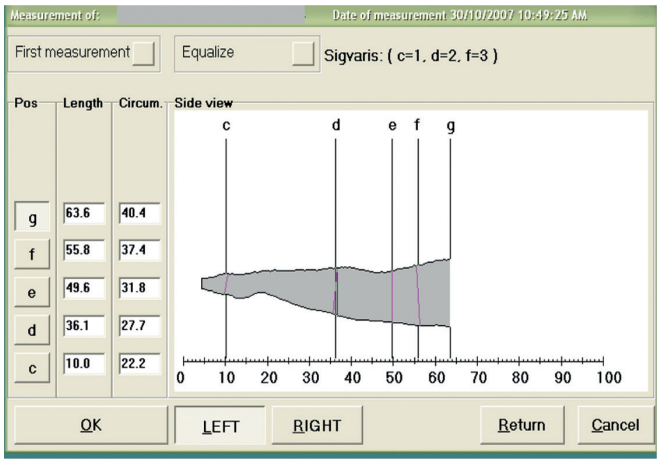
What is the definition of lymphoedema?

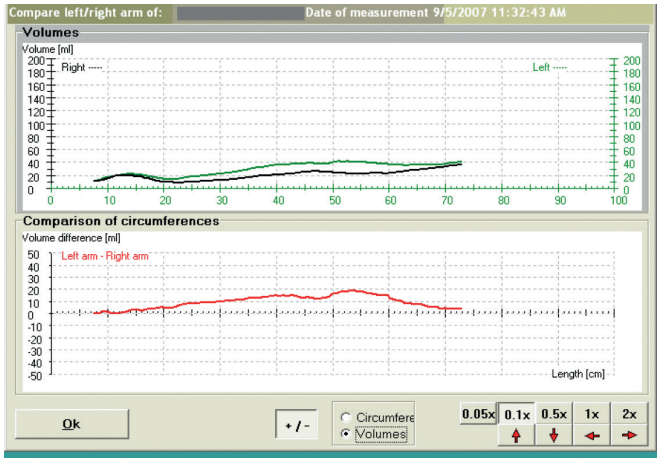
The consensus in the literature, which we use in our programme, defines lymphoedema as a 10% increase in volume compared to the arm volume in the non-treated side. However, several other definitions are in current use, which I believe are less useful.

For instance, lymphoedema is often reported as >2 cm difference in circumference by tape measure at a certain location in the arm (*Lymphat Res Biol* 2005, 3:208–217), or as a volume increase of 150–250 ml *Mayo Clin Proc* 2005, 80:1480–84). Both of these are absolute values, which is unhelpful because they don't take into account the wide variation in normal arm size. A patient with thin arms who shows a volume increase of 180 ml will not meet the definition of 200 ml increase even though her arm has swollen to 15%

USE OF A PEROMETER TO QUANTIFY LYMPHOEDEMA







Perometry uses infra-red beams to measure arm circumference at 4–6 cm intervals (*top*), allowing arm volume to be calculated (*middle*) for the purpose of comparing a patient's affected arm with their opposite arm (*bottom*) or with a baseline measurement taken preoperatively

larger than the opposite arm. She will not be diagnosed as having lymphoedema so will miss out on treatment. A patient with a very large arm, on the other hand, may show a swelling of 220 ml, so meeting the definition of lymphoedema, even if this represents a difference of only 3.5%. This patient might therefore be overtreated (*Breast Cancer Res Treat* 2012, 135:145–152).

Defining lymphoedema on the basis of a percentage increase in volume is therefore more useful. Various thresholds have been suggested (see below); the consensus in the literature is on 10%, which is what we use.

How do we calculate the volume of lymphoedema?

One important thing that many people forget is that at least one in five women have one arm larger than the other; and one in 20 have a volume difference of as much as 10% at baseline. If you don't have this information upfront, you might over- or under-estimate the level of lymphoedema. We studied this in 677 consecutive patients undergoing unilateral breast cancer surgery, measuring relative (percentage) volume change in the at-risk arm compared to pre-operative baseline, using the other arm as a control. The results generated the following relative volume change (RVC) formula:

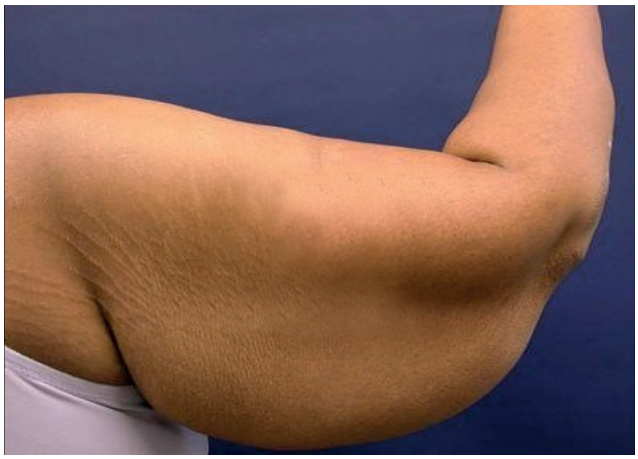
$$RVC = (A_2U_1)/(A_1U_2) - 1$$

(where A_1, A_2 are at-risk arm volumes at pre-op baseline and post-op follow-up, and U_1, U_2 are arm volumes on the contralateral side at corresponding times) (*Int J Radiat Oncol Biol Phys* 2011, 79:1436–43).

In bilateral breast cancer, there is no control arm, and both sides have

MEASUREMENT SHOULD BE BY RELATIVE NOT ABSOLUTE VOLUME CHANGE

Arm vol: 1200 ml + 180 ml = 1380 ml =15% increase classified as 'no lymphoedema'



Arm vol: 6000 ml + 210 ml = 6210 ml = 3.5% increase classified as 'lymphoedema'

Using an absolute value of 200 ml increase in arm volume as the definition of lymphoedema means that women with thin arms will be underdiagnosed and those with larger arms will be overdiagnosed

swelling, so we measured the relative change in at-risk arm volume compared to the pre-operative baseline in a study of 265 unilateral surgery patients and obtained the following weight-adjusted volume change (WAC formula):

$$WAC=(A_2W_1)/(A_1W_2) - 1$$

(where A_1, A_2 are at-risk arm volumes at pre-op baseline and post-op follow-up, and W_1, W_2 are the patient's weight at corresponding times) (*Lymphology* 2013, 46:64–74).

What is the appropriate threshold to initiate intervention?

The aim is to intervene at an early stage, before the patient's arm becomes very enlarged. Should we intervene at 3%, 5%, 10% or 20%? We don't yet know.

Based on symptoms, different investigators have recommended intervention at 10% volume difference (*Palliat Med* 2005, 19:300–313); 20% (*Eur J Cancer* 2003, 39: 2165–67); 200 ml (*Breast Cancer Res Treat* 2002, 75:51–64); 250 ml (*Am J Surg* 1999, 178:311–315); or 2 cm circumference difference. These are all a bit too high. The NIH study, which included only 43 patients, intervened at more than 3% volume increase (*Cancer* 2008, 112:2809–19). However, we consider this too small because a volume increase of 3–5% might represent temporary swelling after surgery.

We looked at the best threshold to intervene in a study of the natural history of almost 1500 patients, carrying out repeat measurements and following them over time. We did not intervene in patients with less than 10% difference. We found that women who had 5–10% swelling, some with very minimal, sub-clinical swelling, progressed to have more severe lymphoedema. Most patients with a volume increase of less than 3% recovered. This suggests the threshold for intervention could be a 5–10% volume increase, but a trial is needed to test whether intervention in these patients is beneficial or not. The trial should randomise patients with a volume increase within this range to observation or intervention (a simple sleeve).

It is important to remember that transient lymphoedema, which resolves without intervention, is common. A trial of 918 patients showed transient lymphoedema in 71% of patients, with a relative volume change of 5% or more for at least three months. It was persistent in the remaining 29% (J O'Toole et al, Congress of Lymphology, International Society of Lymphoedema, 19-23 September 2011).

Why is lymphoedema so important today?

Two very big studies, one from Canada and one from Europe, showed that women who have a small number of positive lymph nodes (1–3 positive lymph nodes) or high-risk node negatives benefit from regional radiation (T Whelan et al, ASCO 2011 Abstract LBA 1003), but this increases the risk of lymphoedema.

We can therefore expect regional radiation to be used more often, which is likely to increase the rate of cases of lymphoedema over the next 5–10 years.

The risk factors for lymphoedema (defined as an increase in volume of ≥10%) that we have found from analysing our data are:

Measured arm volume changes, (where RVC = relative volume change):

- RVC 3% – <10% in the first 3 months after surgery indicates high risk of lymphoedema
- RVC 5 – <10% any time after 3 months post-surgery indicates possible risk of developing lymphoedema.

Clinical and treatment-associated factors:

- BMI ≥30 at the time of surgery
- Axial lymph node dissection
- Regional lymph node radiation

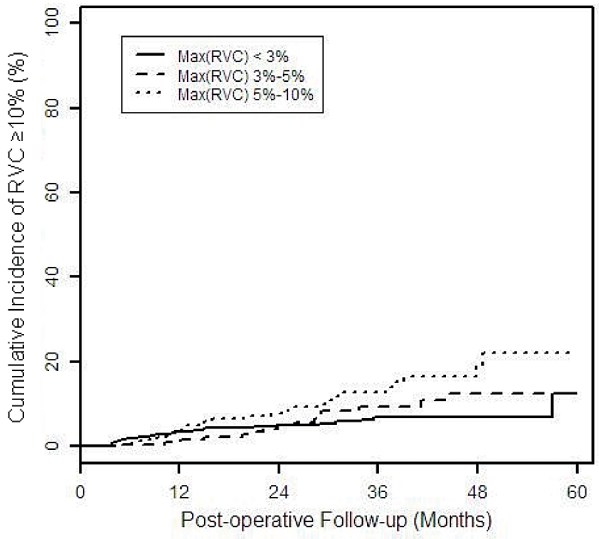
Overall, one in every four or five patients with these risk factors will develop lymphoedema.

What is the appropriate treatment for low-volume lymphoedema?

The question for the future is whether early intervention will prevent progression to more severe lymphoedema. One of the ideas we are considering is a study randomising patients with early swelling to three groups:

- a control group who receive the standard management, such as counseling and stretching but no specific treatment, and are observed to see whether lymphoedema develops
- intervention with a compression sleeve, worn for at least 12 hours a day for 12 weeks, or
- interventional exercise to stop lymphoedema from progressing, including cardiovascular exercise and progressive weight lifting (30 minutes, 3–4 times each week for 12 weeks).

WHAT LEVEL OF VOLUME INCREASE PREDICTS PROGRESSION?



Patients with a maximum relative volume change (RVC) of 5–<10% at more than three months following surgery had the highest rate of progression to ≥10%

Source: MC Specht et al. (2013) *Breast Cancer Res Treat* 140: 485–494, republished with kind permission from Springer Science and Business Media

	HR	95% CI	*P*-value
3–<5% RVC	1.55	0.92–2.61	0.10
5–<10% RVC	2.97	1.75–5.04	<0.0001
No. of measurements/year	1.29	1.16–1.44	<0.0001

Conclusions

We have to change the way we manage lymphoedema. It is not acceptable to wait until a patient develops a large swollen arm, because of the negative impact this has on the quality of her life for the rest of her life.

Sleeves are not curative; they can only provide a control measure to help mitigate the ongoing problem.

Instead, we need to screen for lymphoedema, define it early and then intervene with the aim of preventing progression. There is a great need to study early intervention to generate level I evidence, such as conducting a randomised study. ■

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nature REVIEWS CLINICAL ONCOLOGY

EU data protection regulation – harming cancer research

DAVID J KERR

The cancer community is deeply concerned about the unintended consequences of the current wording of the European Union (EU) draft Regulation on Data Protection, which may challenge the survival of retrospective clinical research, biobanking, and population-based cancer registries in the EU. This directive could negatively affect Europe's competitiveness in cancer research.

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One of the traditional strengths of European cancer research has been the quality, depth and coverage of its cancer registries, which offers the potential to link demographic, clinical and genetic data to explore phenotype–genotype correlations. The Northern European registries in particular have made consistent and important contributions to the international literature on epidemiology and outcome studies.[1] These resources are all predicated on convention and the societal urge to share knowledge, and ultimately wisdom, so data can be pooled and can contribute to 'big science'. The identity of individuals is anonymised and is, therefore, protected; nevertheless, when asked directly, the vast majority of patients with cancer are keen to contribute in any way they can to the wider research agenda.[2]

The European Union (EU) has undertaken a review of data confidentiality and data protection given the extraordinary advances that have been made in transnational electronic data transfer and the potential for data sharing to infringe on an individual's rights to privacy. The current EU Data Protection Directive (95/46/EC) did not consider important technological developments, such as social networks and cloud computing; therefore, legislators determined that new guidelines are required and have proposed an amendment in the form of the General Data Protection Regulation (GDPR).

Paolo Casali[3] has produced a position paper on the EU GDPR, endorsed by Europe's leading cancer research organisations, in response to anxieties induced by the wording of one of the amendments (191 to Article 81) to the GDPR. The amendment could be interpreted as imposing the requirement for researchers to ask for a patient's 'specific' consent every single time new research is carried out on already available data and/or tissues.

Consent would also be required for the recording of data in population-based disease registries, which by definition need be all-inclusive – that is, collection of all of the data for all individuals belonging to a given population is mandatory if the information is to be truly reflective.

All of us in medicine understand the need for confidentiality and data protection, but this legislation could have a far-reaching set of unintended consequences. Apart from deconstructing world leading cancer registries, it will place an enormous barrier to translational cancer research. In Oxford, the cancer trials office has led the UK's adjuvant colorectal cancer trials portfolio for the past 15 years, generating a bioresource comprising 5,000 to 6,000 germline DNA and tissue samples that have been pseudo-anonymised and linked to the trials databases. Such a resource enables clinically relevant outcomes, such as survival and toxicity, to be captured. This repository has proven to be an enormously powerful biobank, which has been used in international collaborations across four continents, providing insights into the genetics and biology of colorectal cancer susceptibility, prognosis, and genesis of chemotherapy-induced toxicity.[4–7] All samples were gifted by patients recruited to these trials through a separate process of consent (98% of patients recruited to the trials also consented to sample collection and storage) for future research, which was broadly specified, given the relative impossibility of defining what future technical innovations might drive the research agenda. This resource has generated several patents and provided the evidence base for two of only three biomarkers that are sufficiently clinically validated for routine use in the management of colorectal cancer.[8,9] Approximately 35% of patients recruited to the trials have suffered recurrence, and have died; thus, such patients are of course beyond the means of re-consent. This biobank could potentially be rendered redundant by the proposed amendment to the Data Protection Directive, which would create a significant practical barrier to the development of companion diagnostics for novel anticancer drugs.

Companion diagnostics or predictive markers are often validated in so-called retrospective–prospective studies, whereby a prospective trial of the relevant anticancer drug and associated biobank are interrogated at some interval after the trial has closed, to explore the relationship of some new marker with drug efficacy or toxicity. Having to regain consent from every patient every time researchers want to test a new hypothesis, using a biomarker that might not even have been on the horizon when the trial was performed, places an impossible burden of care on the research team and runs counter to the initial gift made by the patient. Of course we must put in place a legislative framework that protects data confidentiality, allied to transparent mechanisms to oversee retrospective research projects (for example, the Local Research Ethics Committee or Institutional Review Board) and storage of patient tissue in biobanks, but most EU Member States have existing laws that function perfectly well in this regard.[10]

> **"Having to regain consent from every patient ... places an impossible burden of care on the research team..."**

Casali finishes his article with a strong plea, and one which I echo, "The European cancer community urges all EU decision makers to save research, as well as to protect the right of patients to donate their data and tissues to advance research and find cures. EU decision makers are urged to change the European Parliament Amendments 191 and 194 to Articles 81 and 83, as they would impair public health research within and across EU Member States." ■

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newsround

Selected reports edited by Janet Fricker

Statins improve survival in colorectal cancer

Journal of Clinical Oncology

Using statins after a diagnosis of colorectal cancer was found to be associated with improved survival, finds a large population-based cohort study. The study, funded by the Northern Ireland Public Health Agency, also showed a dose-response association, with more marked reductions for cancer patients using statins longer than one year.

Accumulating preclinical evidence suggests statins, widely used to manage and prevent coronary heart disease, also exert anticancer properties by inhibiting cell proliferation, inducing apoptosis, or inhibiting angiogenesis. Epidemiologic studies have recently demonstrated reductions in both cancer recurrence and cancer-specific mortality among statin users with breast and prostate cancer.

In the current study, Chris Cardwell and colleagues, from Queen's University in Belfast, Northern Ireland, investigated the effect of statin use among a cohort of 7,657 people who, between 1998 and 2009, had been diagnosed with stage I to II colorectal cancer. The cohort was identified from the National Cancer Data Repository (comprising English cancer registry data), and the records were linked to prescription records from the United Kingdom Clinical Practice Research Datalink, and to mortality data from the Office of National Statistics. The time-dependent Cox regression models took into consideration potential confounders, including year of diagnosis, age at diagnosis, sex, cancer stage, surgery within six months, radiotherapy within six months, chemotherapy within six months, site (colon or rectum), comorbidities prior to diagnosis, and use of other medications (including low-dose aspirin, ACE inhibitors, and metformin).

Results showed that statin users overall had a 28% reduction in rate of colorectal cancer-specific mortality compared with nonusers (HR=0.72, 95%CI 0.64–0.81). For those who used statins for less than a year the reduction was 21% (HR=0.79, 95%CI 0.68–0.93); while for those who used statins for more than a year the reduction was 35% (HR=0.65; 95%CI 0.56–0.77).

Associations were slightly more marked in men than women, with men showing an adjusted hazard ratio of 0.64 (95%CI 0.52–0.78) compared to 0.85 (95%CI, 0.66–1.09) in women, but the difference was not statistically significant (*P* for interaction =0.50). Associations were also slightly more marked among patients with BMIs greater than 25 kg/m² (HR=0.68) than in those with BMIs less than 25 kg/m² (HR=0.85), but the difference again was not statistically significant (*P* for interaction = 0.13).

"In this large, population-based colorectal cancer cohort, statin use after diagnosis of colorectal cancer was associated with increased time to cancer-specific death," conclude the authors, adding that potential differences in association between statins and cancer-specific mortality by BMI and sex merit further investigation.

Before randomised controlled trials of statins as an adjuvant cancer therapy can be recommended, add the authors, the association requires confirmation in large, well-conducted observational studies. A trial randomly allocating patients with stage II and III colon cancer, to receive statins to investigate the effect on polyp prevention, is currently ongoing, and "may provide further evidence on the potential of statins as cancer therapy."

■ C Cardwell, B Hicks, C Hughes et al. Statin use after colorectal cancer diagnosis and survival: A population-based cohort study. *JCO* October 1 2014, 32:3177–83

Optimal duration of anticoagulant treatment determined for cancer patients with DVT

Journal of Clinical Oncology

In cancer patients with a first deep vein thrombosis (DVT) treated for six months with low-molecular-weight heparin (LMWH),

absence of residual vein thrombosis (RVT) identifies those at low risk of recurrent thrombotic events, reports the DACUS study.

For patients with cancer, venous thromboembolism (VTE) represents a frequent complication, but management of DVT and pulmonary embolism is considered challenging due to the high risk of recurrent events and haemorrhages. LMWH, it has been reported, is more effective than Vitamin K antagonist therapy, with the result LMWH is recommended as the first option for cancer patients experiencing acute VTE.

While recommendations suggest patients with cancer-related DVT should be treated for six months or longer, this is not based on randomised trials. Among non-cancer patients, easily determinable markers, such as RVT and the D-dimer test, have been proposed to support safe withdrawal of Vitamin K antagonist three to six months after DVT.

In the DACUS study, Sergio Siragusa and colleagues, from the Università degli Studi di Palermo, Italy, evaluated use of RVT to assess optimal duration of anticoagulant treatment in cancer patients with lower-limb DVT. The presence of RVT, measured by compression ultrasound, reflects venous stasis and vessel-wall damage, both important in pathogenesis of venous thrombosis.

For the study, between October 2005 and April 2010, 347 patients with active cancer, with a first episode of DVT treated with LMWH for six months, were assessed for RVT.

Next, the 242 subjects found to have RVT were randomly assigned to continue LMWH for an additional six months (group A1, *n*=119) or to discontinue treatment (group A2, *n*=123); while patients without RVT stopped LMWH (group B, *n*=105).

Results showed recurrence occurred in 22 of the 119 patients in group A1 who continued LMWH compared with 27 of the 123 patients in group A2 who discontinued LMWH treatment, giving an adjusted hazard ratio for group A2 versus A1 of 1.37 (95%CI 0.7–2.5; *P*=0.311).

Of the 105 patients in group B, three developed recurrent VTE, giving an adjusted hazard ratio for group A1 versus B of 6.0 (95%CI 1.7–21.2; *P*=0.005).

"Our results indicate that, after 6 months of standard treatment with LMWH for DVT, the absence of RVT identifies patients with cancer at a low risk for recurrent thrombotic events," write the authors, adding RVT testing could help select patients who might benefit from shortened periods of anticoagulation.

In an accompanying commentary Punam Rama and Mark Levine, from Henderson Research Center, Hamilton, Ontario, write, "Further research is required to define the utility of RVT for guiding the optimal duration of anticoagulant therapy in a patient with cancer with VTE... At the end of the day, the optimal duration of anticoagulant therapy in patients with cancer is an open question."

■ M Napolitano, G Saccullo, A Malato et al. Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis. *JCO* November 10, 2014:3607–12

■ P Rama, M Levine. How long to treat acute venous thrombosis in cancer: can treatment be personalized? *ibid*, pp3586–87

Low-dose CT screening cost-effective for lung cancer

■ Journal of Thoracic Oncology

The average cost to screen individuals at high-risk of developing lung cancer with low-dose computed tomography plus the average cost of curative treatments, such as surgery, is lower than the average cost of treating advanced lung cancer, concludes the Pan-Canadian Early Detection of Lung Cancer study.

Screening programmes are driven by the hypothesis that lung cancer may be cured if disease is detected at an early stage, and that benefits include not only reduced mortality but also averting potentially expensive treatment courses in the advanced setting, associated with low success rates. Given that approximately 8.6 million people in the US meet the criteria for enrolment in the National Lung Screening Trial based on their age and smoking history, the cost of national screening programmes could be significant.

For this study, between September 2008 and December 2011, a publicity campaign was run across seven major cities in Canada, with advertisements in newspapers, on the radio and physician offices, directed at people at risk of developing lung cancer due to age and smoking history. Using a web-based lung cancer prediction tool, volunteers found to have 2% or greater lung cancer risk over three years were invited to join the study.

Altogether 2537 eligible participants were enrolled and scheduled for screening with at least two low-dose CT screening tests: CT-S-1 at baseline and CT-S-2 after 12 months. Lung nodules deemed suspicious for lung cancer were referred for further investigation, which may have included diagnostic imaging, bronchoscopy, percutaneous biopsy, or a surgical procedure.

Altogether 83 cases of lung cancer were detected and confirmed within 30 months of CT-S-1, with 67% being stage IA non-small-cell lung cancer (NSCLC), and 75% early-stage (I or II) NSCLC.

Results show that the average per-person cost for at least two annual low-dose CT screens and all the necessary follow-up or repeat scans for those without lung cancer was $453 for the entire study period versus $2248 for those with lung cancer. The mean per-person cost for diagnostic workup, curative intent surgical treatment, and two years of follow-up was $33,344 for those diagnosed with lung cancer in comparison to $47,792 for those treated for advanced

lung cancer with chemotherapy, radiotherapy, or supportive care alone (P=0.061).

"This is the first prospective resource utilization and cost analysis of a lung cancer screening study that may be used to inform program evaluation and cost-effectiveness analyses (CEAs)," write the authors. "Lung cancer screening is going to be a major policy issue and accurate information on the costs and benefits of screening are urgently needed to inform future cost effectiveness models and the overarching policy debate."

■ S Cressman, S Lam, N Tammemagi et al. Resource utilization and costs during the initial years of lung cancer screening with computed tomography in Canada. *J Thorac Oncol* Oct 2014, 9:1449–58

Study defines minimum number of cases for oesophageal surgery

■ Annals Surgical Oncology

Performing 40–60 oesophagectomies per centre per year is the minimum number of cases for achieving the highest two-year survival rate, after which a plateau is reached, finds a study funded by the Dutch Cancer Society.

Surgical resection is the cornerstone of curative treatment for oesophageal cancer, with compelling evidence suggesting that patients achieve better short- and long-term outcomes when treated in hospitals with high annual surgical caseloads. Recent literature, however, has proposed varying definitions of 'high-volume', ranging from more than five to more than 86 annual oesophageal cancer resections. In consequence there is no consensus about what should be considered a high-volume hospital.

In the current study, Daniel Henneman and Johan Dikken, from Leiden University Medical Centre in The Netherlands, set out to define a meaningful 'cut-off' point for annual hospital volume for oesophagectomy. Using data derived from the Netherlands Cancer Registry, reviewing 10,025 patients who underwent oesophagectomy between 1989 and 2009, the relationship between annual hospital volume and outcome was calculated using Cox regression analysis. Annual hospital volumes varied between one and 83 procedures per year, increasing with time.

Results showed that, in comparison to centres performing 20 resections a year (considered the baseline), those performing 40 resections per year had a hazard ratio for six-month mortality of 0.73 (95%CI 0.65–0.83); for those performing 50 resections a year the hazard ratio was 0.68 (95%CI 0.6–0.78), for those performing 60 resections a year it was 0.67 (95%CI 0.58–0.77), and for those performing 70 resections a year it was 0.67 (95%CI 0.54–0.83).

At two years, in comparison to centres that performed 20 resections a year, those performing 40 resections had a hazard ratio for mortality of 0.88 (95%CI 0.83–0.93), for those performing 50 resections per year the hazard ratio was 0.86 (95%CI 0.79–0.93), for those performing 60 resections per year it was 0.85 (95%CI 0.71–1.05), and for those performing 70 resections per year it was 0.86 (95%CI 0.71–1.05).

"The current study showed a continuous, nonlinear decrease in HRs for 6 month and 2 year mortality, until hospital volumes of up to 40–60 esophagectomies per year, implicating that centralization of esophageal cancer resections to hospitals performing 40–60 resections per year may lead to an improved 6 month mortality and 2 year survival," write the authors.

The findings, they add, may be used to guide national and regional centralisation efforts worldwide.

■ D Henneman, J Dikken, H Putter et al. Centralization of esophagectomy: How far should we go? *Ann Surg Oncol* December 2014, 21:4068–74

PET–CT more accurate than conventional CT for follicular lymphoma

■ Lancet Haematology

Positron emission tomography/computed tomography (PET-CT) is more accurate at predicting survival in patients with follicular lymphoma than conventional CT scanning and should be considered the standard approach for response assessment, finds a pooled analysis of three clinical trials.

While PET-CT has been incorporated into response criteria for diffuse large B-cell lymphoma and Hodgkin lymphoma (both curable disorders requiring urgent management), follicular lymphoma was not included due to the paucity of data. Although initially sensitive to rituximab chemotherapy, follicular lymphoma is characterised by recurrent relapses and risk of histological transformation. Current practice uses CT imaging to evaluate treatment response, but CT cannot easily distinguish patients who are likely to remain in remission for several years from those at high risk of early relapse. PET-CT utilises the tracer 18F-fluorodeoxyglucose (FDG), which is highly concentrated in lymphoma cells.

In the current study, Judith Trotman, from the University of Sydney in Australia, and colleagues, evaluated the scans of 246 patients from three studies who underwent PET-CT within three months of their last dose of therapy. For the PET-CT scans patients were analysed by independent reviewers according to the five-point Deauville scale (5PS) evaluating FDG uptake on PET images on a scale of 1 to 5, with 1=no uptake, and 5 showing that uptake in lesions is higher than in the liver. Altogether 41 patients (17%) were considered to have a 'positive' post-induction PET scan according to the 'cut-off' of 4 or higher on 5PS.

Results show that median progression-free survival was 74 months for patients

with a negative scan versus 16.9 months for patients with a positive scan (HR=3.9; *P*<0.001). Four-year progression-free survival was 63.4% for patients with a negative scan versus 23.2% for patients with a positive scan (*P*<0.0001) and four-year overall survival was 97.1% for patients with a negative scan versus 87.2% for patients with a positive scan (*P*<0.0001).

"Our analysis has shown that PET-CT provides better assessment of therapeutic response and prediction of progression-free and overall survival than does contrast-enhanced CT and bone marrow-based response assessment," conclude the authors, adding that achievement of a negative PET status after first-line therapy for high-tumour-burden follicular lymphoma provides considerable reassurance for patients.

Future clinical trials, they suggest, could study a change to salvage chemotherapy and autologous stem-cell transplantation in patients with a positive PET scan, or a change to a non-chemotherapeutic approach with the immune modulatory agent lenalidomide, BCL2 inhibitors, or drugs targeting B-cell receptor signalling pathways.

In an accompanying commentary, Bruce Cheson, from Georgetown University in Washington DC, writes, "That patient outcome can be predicted with molecular imaging is good news; the question is, what should be done with this information?" In clinical practice, he adds, patients with positive scans should be followed up more closely, but there are no data yet demonstrating that more intensive treatment leads to better outcomes.

■ J Trotman, S Luminari, S Boussetta et al. Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. *Lancet Haematol* October 2014, 1:e17–27

■ B Cheson. PET-CT restaging: a surrogate for follicular lymphoma. *ibid*, e2–3

Pancreatic cancer outcomes better at high-volume centres

■ British Journal of Surgery

Performing pancreatic surgery in high-volume centres delivers improvements in survival, reports a Dutch study.

While centralisation of pancreatic surgery has been shown to reduce postoperative mortality, it is unknown whether this has led to improvements in long-term survival. In The Netherlands around 500 pancreatic resections for neoplasms are performed annually. In 2006 agreement was reached in two of eight Dutch health regions for performance of pancreatic surgery to be restricted to two or three hospitals in that region.

In the current study, Marc Wouters, from Leiden University Medical Centre, and colleagues, set out to analyse the impact of nationwide centralisation of pancreatic surgery on resection rates and long-term survival.

Between January 2000 and December 2009, 11,160 patients were identified by the Netherlands Cancer Registry with cancer of the pancreatic head. For the patients who underwent classical or pylorus-preserving pancreatoduodenectomy, multivariable regression analysis was performed to assess the impact of hospital volume on survival. For the study, hospital volumes were categorised as low (fewer than 10 procedures per year), medium (10–19 procedures per year) or high (20 or more procedures per year).

Results showed that 1,465 patients (13.1%) underwent resection, and that the resection rate increased from 10.7% in 2000–2004 (567 of 5301) to 15.3% in 2005–2009 (898 of 5859) (*P*<0.001). The increased rate of resection, however, had little impact on survival, with median survival being 15 months for those diagnosed between 2000 and 2004, and 16 months for those diagnosed between 2005 and 2009 (*P*=0.135).

The proportion of patients undergoing resection in a high-volume hospital increased from 30.1% (82 of 272) in 2000–2004 to 47.2% (175 of 371) in 2005–2009. High-volume hospitals had a median survival of 18 months versus 16 months for low/medium-volume hospitals (*P*=0.017). In a multivariable analysis, a hospital volume of 20 or more annual resections was associated with higher survival after adjustment for period of diagnosis, sex, age, tumour stage and adjuvant chemotherapy (HR=0.70; 95%CI 0.58–0.84; *P*<0.001).

The study, write the authors, has several strengths including the reliability and completeness of the clinical population-based data available from the National Cancer Registry, with information on all patients with cancer, both those who had a resection and those who did not.

"The increase in the proportion of patients having a resection with no increase in mortality is important, because pancreatic resection remains the only curative option for pancreatic cancer," write the authors. Hospital volume, they add, was a significant prognostic factor for utilisation of pancreatoduodenectomy, as has been shown elsewhere with oesophageal and lung cancer surgery.

"Continuing centralization based on minimum volume standards as well as process and outcome criteria, is likely to improve patient outcomes and should be encouraged," conclude the authors, adding that the extent to which further concentration will lead to additional improvements is unclear.

■ G Gooiker, V Lemmens, M Besselink et al. Impact of centralization of pancreatic cancer surgery on resection rates and survival. *Br J Surg* July 2014, 101:1000–05

Caring for one of our own

When you're caring for a patient and friend, who was recently your colleague, working out boundaries and negotiating the particular privileges and pressures of caring for them can be hard. The problem was explored in a Schwartz Center Round* at the Massachusetts General Hospital.

L SCHAPIRA, L S BLASZKOWSKY, B J CASHAVELLY, C Y KIM, J P RILEY, M C WOLD, D P RYAN, A T PENSON

The patient is a 52-year-old male nurse who presented with metastatic pancreatic cancer. Prior to his illness, he was in great physical shape. He had worked in the inpatient cancer unit of Massachusetts General Hospital (MGH) for almost 30 years. He developed hip pain and was ultimately found to have lytic bone lesions. Computed-tomography scans showed a mass in the pancreas with liver metastases and extensive bony involvement. A biopsy confirmed a diagnosis of pancreatic cancer.

Schwartz Center Round

Nurse Director

"After the patient became ill, he was admitted to our unit twice, each time for several weeks. The challenges in his care arose precisely because he was one of our own. We wanted to do the best for him because he was a nurse – and one of our nurses. There were privacy issues related to the delicate balance of independence and involvement. The staff on the unit did a fabulous job figuring out how to set boundaries while providing the best possible care."

The Oncologist®

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FRED VAN DEELEN, WWW.ORGANISART.CO.UK

Primary Oncologist

"Both the patient and his family made it very clear that he wanted a very aggressive approach. He had a difficult time moving because he was in such pain; his performance status was 3 and he was not a good candidate for aggressive chemotherapy. But here was a man only in his mid-50s, and we knew he was in pain because of the cancer and it was the pain that prevented him from being physically active and more mobile. So we decided to give him our most aggressive chemotherapy (5-fluorouracil, oxaliplatin, irinotecan, and leucovorin [FOLFIRINOX]) and palliated his hip pain with radiation, intravenous analgesia, and a bisphosphonate. Even with maximal analgesia, he still had a tough time walking. We were clear and honest with him about his dire prognosis, but he wanted to continue receiving treatment as long as he could tolerate it. Interestingly, the tumour markers plummeted, suggesting response to treatment, but his pain did not get better. We continued chemotherapy in the face of these contradictory findings until it became very clear that treatment was futile and we needed to change the goals of care."

*Schwartz Center Rounds are monthly multidisciplinary meetings where caregivers reflect on important psychosocial issues that they, along with patients and their families, face and gain insight and support from fellow staff members, with the goal of advancing compassionate health care, supporting caregivers, and fostering the connection between a clinician and his or her patients.

Embracing one of our own

Primary Oncology Nurse

"I did not know this man before he was a patient. In order to meet him, I had to squeeze through a crowd of people in scrubs at the door of his hospital room. For me as well as for the nursing staff, the number-one issue was dealing with so many visitors. Everybody had a special reason: "He'll want to see me …" We discussed it with the clinical nurse specialist because it was disrupting the atmosphere of the entire unit. The patient wanted to do everything with everybody, and there were plenty of people willing to join him. This exhausted him and he found some of the visits draining, but he had a tough time saying no. Many times he was on the computer in the room looking up his own laboratories or I'd find him adjusting his intravenous pumps, and I had to talk to him about just being a patient."

Palliative Care Nurse Practitioner

"My sense from this patient is that he felt comfortable being at MGH because this was home for him. He'd been an employee here for decades and did feel well cared for. But I think that just as we struggled to find a balance between professional and patient boundaries, he too struggled with it and how it affected his identity. 'Am I a patient? Am I a nurse?' We asked ourselves if we would want to be hospitalised and cared for in the same hospital where we work. He trusted his caregivers, and as his disease progressed, he started to relinquish the role of nurse."

Nurse Director

"Some nurses elected not to care for him because they felt that they were too close to him personally to care for him in a professional role. There was a sense shared by the staff of wanting to grant him his wishes because the situation was so terrible. A group pulled together and invited a football player from the New England Patriots to visit him. Others made big posters for him and brought in pictures. People really cared about him.

"He worried about his family, especially his 90-year-old mother. He had 10 siblings, all with different opinions. He would often take a passive role in their presence and did not show them that he was aware of how sick he was. Or if he did, they had difficulty hearing it."

Vulnerability

Primary Oncologist

"Caring for this patient was a real challenge. Most of his cancer care occurred in the hospital. I had seen him a few times in the office; he was always accompanied by several people, usually his sister, who is very vocal and assertive. When I visited him in the hospital, he was typically receiving pain medications, and I often wondered if he really understood what was going on. He'd ask me simple questions such as, 'Am I going to make the cancer go away?' I really wasn't sure that he could deal with reality. It was hard to say, 'You are going to die from this cancer' because there were family members on the edges of their seats asking me, 'What are we going to do next?' There was no indication that they ever wanted to stop his treatment. Every once in a while, the patient would say something to the effect of 'Oh, so in a couple of years from now, can I go back to work?' He never asked 'When will I no longer be able to function?' That topic never came up. He always thought he was going to get better."

Audience Comment

"I have a comment about the blurring of boundaries and vulnerability. What strikes me in listening to this is the parallel between what people are saying about the experience of the patient – that he had to allow himself to be truly vulnerable to be a patient at MGH, giving up the autonomy that people hang onto in other settings – and that the professionals who took care of him describe that same vulnerability, and that we feel it now, hearing his story. It's about people having to acknowledge vulnerability; it makes us understand where the source of our compassion originates."

Nurse

"One of the things I found interesting was that the family appeared to think that our Cancer Center owed this patient something. They expected a lot from us. We got a lot of push back from the case managers who

would say, 'This patient is not meeting level of care and should be at a rehabilitation facility or at home.' Typically, the family's response was, 'He worked here for 30 years and now you're pushing him out the door?'"

Primary Oncologist

"I think everybody should be treated with the same respect. The team became very creative in finding ways of meeting the family's requests."

Inpatient Oncology Unit Nurse Director

"The patient had moved in. From the beginning, we received him with the message that we would care for him and set his expectations accordingly. As time went on and we tried to discharge him, he was reluctant to go. He didn't want to go to rehab. He would say, 'What are you talking about? I'm going to stay here.' We felt guilty and conflicted."

Transition

Inpatient Oncology Nurse Practitioner

"During his last hospitalisation, he came to the point of needing to choose suffering through the pain or taking enough medication to make him sedated. And so one Saturday morning, I walked in and talked to him. He said to me he was 'ready' and did not want to be in pain anymore. And, somehow we got to talking about his family members and his discomfort with expressing this wish directly to them. I offered to do this for him. He said, 'I just don't have a backbone with them.'

"I called his family that Saturday. It was a beautiful day and they were sailing on the Charles River. I talked to his mom, who had put me on speakerphone. I told them we were going to focus on comfort and this meant pain medicines only, without any further blood transfusions or other interventions. His mother's response was to ask if we could put off the decision for another day. I responded that our patient had already made his decision and we need to respect that choice. I think he had a really hard time letting go. He remained on our floor but was transferred to Hospice."

Time pressures

Primary Oncologist

"I felt torn and unable to be physically present at the bedside as much as I had hoped. Our schedules revolve around outpatient clinics except for the weeks during which we are the designated Oncology Rounder. I couldn't come up there every day. My colleagues certainly had the expertise to make medical decisions, but I was still paged to attend family meetings. I would attend at least once or twice a week to have discussions."

Physician Moderator

"Did you feel somehow that you were not giving the patient the kind of treatment or care that he requested or that you would like to deliver to your patients?"

Primary Oncologist

"Absolutely. There are days when I look at my job as triaging in a MASH unit [army field hospital]. I look at my list of patients for the day and I say, 'What do I have to get done?' The phone calls that come in, the 200 emails a day I get. During some of this patient's hospitalisations, I had six or seven inpatients in different units. So how do I give enough attention to all of these matters without putting a couch in my office and just forgetting about going home?

"If I know something serious is happening to one of my patients, then I have to find a way to make it there that day, even if it is 9.00 p.m. That may mean I don't see another patient that day, but not because I don't care about that individual.

"I can only imagine how I would feel if I were the patient and I wonder how I would react, because I wouldn't be happy if my doctor wasn't there. My patients are so gracious and they seem to understand it. I don't know how understanding I would be if I were the patient."

Saying good-bye

Palliative Care Nurse Practitioner

"This patient had a really large and very caring family. They had great intentions. They all had very strong opinions and all wanted the best for their sibling. My sense was that, in some ways, the patient had difficulty communicating his prognostic awareness

to his family because of his own anxiety around it. I think he was protecting his family. He knew his family needed to feel that it was advocating for him, and that it had done everything possible. Once the family members were able to acknowledge and recognise his wish, they did not find it difficult to change course."

"I'll never forget the day he died. His family was standing by his side. The nursing staff was trying to keep the room very quiet, but the family spoke very loudly to him, 'We love you. Don't be afraid. We're going to be okay.' And it was a very tender moment. I think it reflected just how much, and how quickly, they were able to come to terms with the fact that he was at peace. So there was this very quick, very rapid transition. After he passed, Father George, the Catholic priest, came and led a beautiful prayer with the family."

Discussion

Caring for a colleague requires thoughtful evaluation of the usual and unique boundaries in optimal care. Caring for a staff member – "one of our own" – intensifies what is at stake and adds a level of complexity. Taking time to reflect and examine the issues, either from principles or particulars, provides an opportunity for informed and compassionate clinical practice.

Cultural changes in medicine

William Osler, deemed by many to be the father of modern medicine, is credited with formalising the detached air cultivated by many physicians in earlier generations[1]. The equanimity that he displayed has frequently been misinterpreted as aloof distance. In recent decades, the image of the master physician has evolved into one of a humane clinician with strong interpersonal skills who practices evidence-based medicine and is engaged in lifelong learning.

In order for young physicians to graduate from their medical training, licensing boards now demand that they demonstrate the following: compassion, integrity, and respect for others; responsiveness to patient needs that supersedes self-interest; respect for patient privacy and autonomy; composure during stressful situations; accountability to patients and society; and sensitivity and responsiveness to a diverse patient population.

Boundaries

Social and professional boundaries exist to help us best serve the patient and to protect our personal integrity by establishing a professional code of behaviour[2]. It is widely accepted that doctors should not care for their own family members because they will not be able to maintain the necessary objectivity and detachment in critical or stressful situations. Decisions may be made for the patient, rather than with the patient. Crossing the boundary into friendship with a patient can create a shift in the power structure that parallels the familiarity of caring for one's own family member. Getting too close can make it more difficult to confront this patient on noncompliance issues or to impart bad news[3]. It is understandable, especially under conditions of time constraints and organisational pressures, that it would be easier to fall into a casual conversation with a 'friend' than to deliver a methodical and comprehensive recommendation.

Sometimes it is hard to know exactly where to draw such boundaries. After all, we celebrate the healing connections between patients and their professional caregivers and promote personal engagement and compassion. 'Getting on the same wavelength' with a patient can be achieved in many different ways: personal disclosure, exploring common ground and shared interests, and sharing empathic responses and rapport-building or humorous exchanges, to name a few. Personal disclosure is a powerful communication tool, when used deliberately and with therapeutic intent. It can also prove risky and lead the patient to imagine the physician is sharing personal information for his or her own benefit or amusement or hinting at a personal and closer relationship when often none is intended.

A study of 1265 patient interviews found that patient satisfaction was affected differently by self-disclosure depending on whether the doctor was a surgeon or a primary care physician

(PCP)[4]. PCP visits including self-disclosure were rated as being significantly less reassuring than those without (42% compared with 55%, respectively; P=0.027), whereas for surgeons, it had the opposite effect (59% vs 47%; P=0.044). Perhaps patients value manifestations of humanity in stressful situations, especially when meeting experts known for their technical skills, but look for signs of competence in those in whom they trust for longitudinal care.

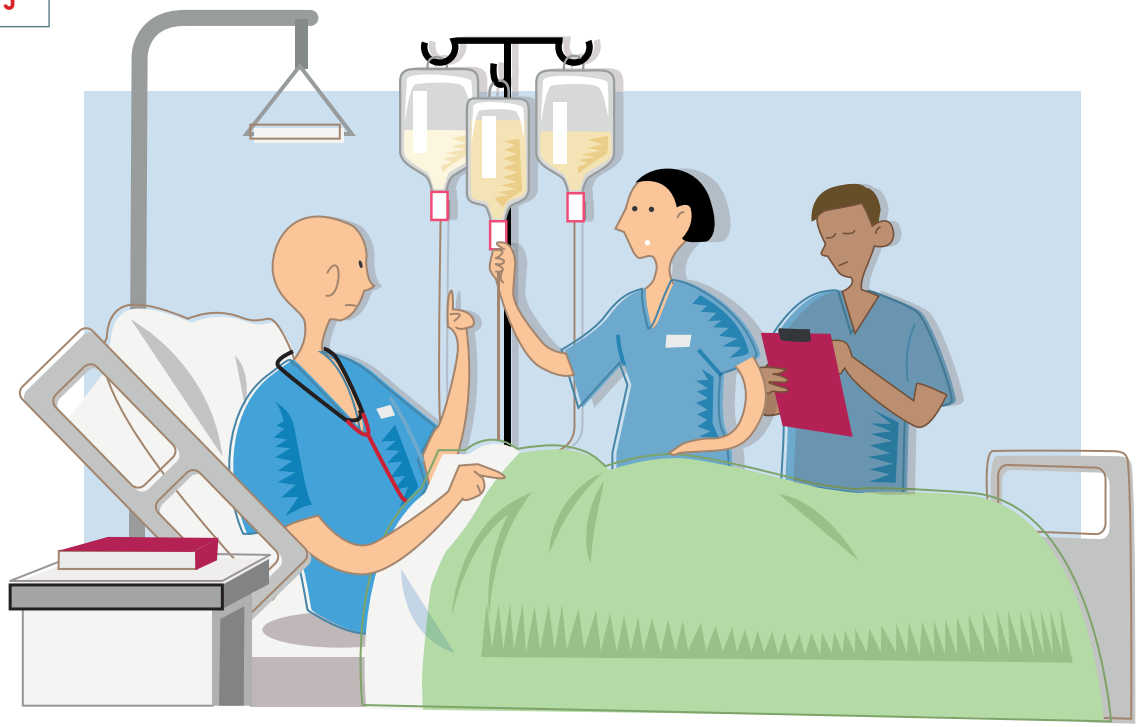
Patients come to clinicians not only bearing a disease, but also with illness in the context of a life. Cancer clinicians are expected, and indeed strive, to provide compassionate care. While clinical situations are often complex, lives also can be complicated to sort out and understand. Clinicians rely on their observation skills, their intuition, and their knowledge of healthy coping mechanisms, and they engage patients in meaningful conversations during which they learn about individual sources of strength, the extent of patients' suffering, and their fears and concerns.

Caring for colleagues is no different from caring for any other fellow human who needs attention and care. Undoubtedly our relationships are multifaceted, and we may be reluctant or only too eager to share personal stories with patients with whom we once worked side by side. Each person and each relationship is unique, and what matters is that we are fully present and engaged, or that we recognise we are unable to provide the necessary care and we step aside and ask for assistance. When caring for a colleague with whom we have a long-standing relationship, there may be an immediate level of empathy; we share the community in which the crisis happens. This relationship has to be developed with patients we are meeting for the first time. The compassion of strangers is created by exploring different pasts and different futures (at least initially) and opening a connection in the present.

Transitions, abandonment and empathy

Patients expect empathic caregivers in cancer care. We connect at an extremely vulnerable time, that requires "human and humane responses to [their] plight," to quote Ken Schwartz. Empathy is showing that we understand the patients' experience and how they feel, respect the gravity of it, and will not abandon them through it. Empathy has recently captured our attention as neuroscientists have mapped out the neuronal circuitry that mediates these complex engagements[5]. Empathy consists of affective, cognitive, and behavioural components, requiring patience, curiosity, and an ability to imagine oneself in the patient's shoes (perspective taking). Halpern wrote that empathic communication makes patients more forthcoming about their concerns, leading to stronger connections with caregivers[6]. Clinical empathy has been described as emotional labour, a powerful metaphor that alerts us to the effort involved in caring[7].

Empathy fluctuates during medical training, with a dramatic drop occurring in the third year of medical school[8]. The empathic 'reservoir' may be depleted as a result of intense experiences, over-reliance on technological aspects



of care, lack of mentorship, and organisational pressures and demands. Empathy appears to be regulated by perspective taking and by cognitive appraisal, and when it is absent, the focus of the interaction is on target organs or test results instead of on the whole patient. This is not simply a moral or philosophical issue, but one that can immediately and significantly impact patient care[5,7]. Empathic physicians take better patient histories and develop trusting and solid relationships with patients. Some studies have also shown that this connection has favourable effects on adherence to treatment, boosts immune function, and improves satisfaction with care, but others have failed to show any favourable effect on hard outcomes[5,9]. However, a recent study of audiotaped encounters between patients and oncologists gives us reason for pause and concern. Pollak and colleagues reported that oncologists only responded empathically to emotional revelations 22% of the time. Empathic responses were more common in younger, and female, oncologists. The authors commented on the "missed opportunities" and the failure to recognise and respond empathetically to emotional patient cues in the setting of a clinic visit[10].

Although we lack hard evidence to quantitate the benefit of healing connections, we hold them dear and aspire to experience them for ourselves and provide them to our patients. Perhaps novel scientific tools will assist us in researching and obtaining quantitative and qualitative data on biomarkers of compassion and empathic engagement that will serve to model clinical skills for future clinicians. Until such time, we rely on cultivating self-awareness, mindfulness, and reflection in our trainees and ourselves and look to role models for clinical guidance.

Conclusion

Caring for a fellow staff member is a wonderful privilege. Being the 'go to' clinician whose opinion is sought out and valued is a huge responsibility. Intrinsic in these roles is a greater responsibility to practice respectfully and professionally. Accomplishing this goal requires emotional intelligence and social dexterity to accommodate the nuances of each patient encounter. Insight and empathy are needed to continuously reassess the strengths and weaknesses of patient-centred clinical relationships. Guarding the trust implicit in those relationships requires more social understanding than most medical trainees anticipate or seasoned practitioners give themselves credit for, but it is vital in meeting the expectations of our profession and our patients. ■

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