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IN EXPERT HANDS
EONS celebrates 30 years of specialist cancer nursing

Marcel Verheij
Revolutionising radiotherapy

Editor
Kathy Redmond
editor@eso.net

Managing Editor
Anna Wagstaff

Editorial Coordinator
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Editorial Advisors
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Contributing Writers
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Publishing Advisor
Gillian Griffith

Art Editor
Jason Harris

Production
HarrisDPI
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Jason Harris

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Direttore responsabile
Alberto Costa

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

Cancerworld

Shaping the future of cancer care

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Marcel Verheij
Revolutionising radiotherapy

SIMON CROMPTON

Could intelligent combinations of drugs and radiation take precision radiotherapy to new levels? Marcel Verheij believes so, but may struggle to prove it without a fairer share of funding.

In the mid-80s, radiotherapy looked doomed. Chemotherapy was in the ascendant, targeted therapies were starting to appear, and in the face of new innovation radiotherapy seemed an increasingly blunt-edged approach to cancer – the equivalent, according to Marcel Verheij, of firing a cannon at an ant. "Frankly, a lot of people thought it was finished."

Then came the digital revolution. Sophisticated imaging, planning and delivery techniques became integrated into radiotherapy so that radiation could be targeted with unprecedented accuracy. Radiation treatment became precise, measurable and lower risk. Today between 50 and 60 per cent of cancer patients receive radiotherapy. Half of those who are cured of cancer have been treated with radiation.

But somehow the world never noticed a revolution had taken place. And Marcel Verheij, Chair of the Department of Radiotherapy at the Netherlands Cancer Institute (NKI) and professor of translational radiotherapy at the VU University Amsterdam, is one of thousands of radiation oncologists today left perplexed. Why do medical oncology and new drugs get all the attention – in the media and even in medical school – when the contribution of radiotherapy to saving lives and improving quality of life is far greater?

We meet at his office at the NKI (known as the Antoni van Leeuwenhoek Hospital) – a comprehensive cancer centre combining hospital and state-of-the art research laboratories in a modern, hotel-like complex in Amsterdam. Verheij has

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just given a talk and tour to visiting science students, and he tells me that every time he meets the students he becomes aware of how "underexposed" his specialty is at universities.

Then he shows them the equipment – software that delineates tumours and compensates for movement, CT scanning and image guidance, 3D representations of tumours and the radiation beams intersecting on them – and he knows that it can hold a special attraction to this technologically-savvy generation. "They are on the edge of their seats," he says.

"I show the differences in what can be achieved with modern technology compared with when I started in the early 1990s, when we would delineate a tumour on a two-dimensional x-ray image with a red pencil. In those days we couldn't envisage the high single doses of radiation we can now give with targeted techniques such as stereotactic ablative radiotherapy. If we continue at that rate of development, there's no limit."

His excitement centres around his own particular interest – innovative uses of radiotherapy in combination with anti-cancer drugs. As the limitations of a monotherapy culture have become increasingly apparent to the cancer world, radiotherapy has found its place in combination with other therapies. First it was chemotherapy. In the late 1980s, it was shown in lung cancer that daily cisplatin was more effective in combination with radiotherapy because it increased the local effect of radiation even when used at low, less toxic, doses. "Today there's almost no solid tumour in a curative setting that doesn't get a combination of chemotherapy and radiotherapy," says Verheij.

Over 20 years, Verheij has been pushing away at the frontiers in this field. His translational research programme at the NKI is today uncovering new ways of using targeted agents at less toxic but biologically active doses to make cancer cells far more vulnerable to radiation treatment.

For example, he is hopeful that the use of synthetic alkylphospholipids in combination with radiotherapy will result in highly effective treatment strategies for patients with non-small-cell lung cancer. His work with synthetic lipids has progressed over 12 years, from cell line studies, through animal studies, into phase I and now phase II studies.

"Combining locally inflicted DNA damage with a drug that interferes with its repair creates a tumour-specific effect"

He's also conducting preclinical studies on the similar use of death receptor ligands, small molecule inhibitors of Bcl-2 and PARP inhibitors in combination with radiation. The latter is particularly exciting: "You create DNA damage only at the site where you want it, namely the tumour and metastases. Combining this locally inflicted DNA damage with a drug that interferes with its repair, such as a PARP inhibitor, creates a tumour-specific effect, allowing an increase in therapeutic ratio. We are evaluating this concept in three different groups of patients."

And yet for all radiotherapy's stellar trajectory, Verheij knows that it could be moving ahead faster. It isn't just the problem of lack of appreciation and profile. It's the challenge of keeping research and innovation going at the same pace as medical oncology – where the research structures are clearer and better resourced.

The fact that there aren't many professors of translational radiotherapy speaks volumes in itself. Verheij took up the professorship in 2004, and became Chair of the Department of Radiotherapy at the NKI in 2007, but long before then – since his residency started in 1993 – it was a principle at the institute to link clinicians with researchers and ensure that both understood the other's language. Today, with Verheij at the helm, there are clearly delineated structures to twin radiotherapy clinicians with researchers, and of the 22 radiation oncologists working at the institute, seven combine their clinical activities with research. "Unless researchers know the relevance of their discoveries for individual patients, what they're doing remains a hobby," he says.

But even in this privileged environment, finding time and resources for radiotherapy research isn't easy. "It is very expensive time, but if you want to do serious radiotherapy translational research, you need to invest in people to allow them to physically go to the lab, have their own desk, be part of lab discussions and not always have the pager on. It's easier said than done."

Another challenge for translational radiotherapy is how long it currently takes to develop new treatments: progress from cell line studies to the clinic currently takes at least ten years. To speed up the move from pre-clinical to clinical, it's been a priority at the NKI to invest in genetically engineered mouse models to mimic human cancers, and develop image-guided radiation techniques specifically for animals. Verheij would also like to see greater emphasis on identifying potent biomarkers, so that new treatments are only tested on those patients who are likely to most benefit from them – so speeding up testing further.

But there is another more surprising problem facing research: lack of interest from the pharmaceutical industry. Historically, companies

have not been particularly interested in their drugs being used in combination with radiotherapy, says Verheij. So getting hold of supplies for trials has been difficult, and opportunities to develop highly effective combination therapies have been lost.

"We depend on pharmaceutical companies making their products available for trials. But the companies are mainly focused on compounds being given to patients for prolonged periods, whereas we only need the drug during relatively short periods of radiotherapy. And unlike medical oncologists, we don't want to use the highest tolerated dose – just a lower, biologically effective dose that makes the cell more sensitive to radiation. So we have to convince both the pharmaceutical companies and medical oncologists that this is a different approach to the one they are used to. From a commercial point of view, adding the drug for a limited period of time is of course less interesting, but the patient benefit may be significant."

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Fortunately, says Verheij, some pharmaceutical companies are beginning to see the light. His discussions with pharmaceutical companies such as Astra Zeneca and Merck Serono have resulted in them creating expert groups on radiotherapy which collaborate with radiation oncologists over possible trials evaluating their compounds as radiosensitisers at an earlier stage in development.

Without such initiatives, warns Verheij, some of the enormous potential of drugs such as PARP inhibitors will be missed. "Companies will test their compounds as single agents – and some of them will fail because of their toxicity. But we would never know whether at a lower dose, and used as a radiosensitiser, it might have been a wonderful drug. Once a drug has been discarded as too toxic, it's almost impossible to get it back on the agenda."

Such lack of understanding about radiotherapy's potential is symptomatic of its generally low public profile compared with medical oncology. "Medical oncologists have tight relationships with the pharmaceutical companies, which they need of course because there is a pipeline of new drugs that need to be tested in the clinic. There are all these agents coming onto the market incredibly fast, which is very exciting for the media. But we, on the other hand, have one main type of treatment machine – linear accelerators (linacs). We use them for 12 years with software upgrades, and there are maybe two or three companies selling them, so the news about radiotherapy is almost by definition less. No matter how hard we try, it isn't easy to interest journalists in new developments. It's much easier for a medical oncologist to say 'We have the silver bullet.'"

He is proud of meeting these challenges locally at the NKI, in particular creating the right infrastructure and staffing structures for

"Opportunities to develop highly effective combination therapies have been lost"

"If you have to make choices in health systems due to limited resources, on what do you base your choice?"

translational research – and he hopes they will have a wider impact, setting a template for others (including medical oncologists) to follow. He is in close contact with other European centres also active in translational radiotherapy, such as the Institut Gustave Roussy in Paris. He is also advising on the creation of the largest comprehensive cancer centre in the Netherlands which, pooling the expertise and resources of the Antoni van Leeuwenhoek Hospital and the oncological departments at the Utrecht Medical Centre, will reflect his unit's multidisciplinary, research-focused approach.

"What I've learned throughout my career is that it's important to invest in people around you. You can't do the job on your own. You've got to motivate others to follow the same trajectory."

None of this innovative work would have happened if three years into his residency, in 1996, Verheij hadn't been awarded a two-year research fellowship from the Dutch Cancer Society at the Memorial Sloan-Kettering Cancer Center in New York. It was there that he researched his PhD on endothelial damage as a driver of radiation injury of the kidney, but its effect was far more profound than that.

"Interest in apoptosis (programmed cell death) was booming, and there was a group led by Zvi Fuks at Memorial doing very exciting research," he says. "I got my chance to do fundamental research into the way the tumour cell dies on radiation, and it gave me insight into how we might exploit that knowledge – could we add agents to influence the sensitivity of cells to undergo that type of cell death? I tried to speak the same language as researchers. This was really very important for the next stage of my career."

On his return to Amsterdam, he submitted a research grant focused in this area, and that's where he has concentrated ever since. The lessons he learned at Memorial about translational research and about how to structure research programmes within a hospital also shaped his plans at the NKI.

If that plotted course of his career sounds neat, Verheij's arrival into radiation oncology in the first place was by no means straightforward. In short, he went from law, to medicine, to the army, to blood, to radiation, to cancer.

He was intellectually intrigued by what made people ill from an early age, but was unable to get into medical school on his first attempt due to a shortage of places (a lottery system decides who gets onto popular courses in the Netherlands). So he studied law for a year, until his number for medical school at Leiden University came up in 1981. The interest in medical ethics and the law has abided – for many years he was involved in the NKI's ethical committees: "I like looking at the big picture: if you have to make choices in health systems due to limited resources, on what do you base your choice?"

He considered ophthalmology as a specialism, but his medical education was interrupted at 19 when he had compulsory military service for a year and a half. Fortunately he found work in the military blood transfusion centre – the only position where military service could be combined with research – studying blood coagulation. It meant, says Verheij, that his years in the army were not wasted. He learned about research and what it was like working in a lab. He took a lot of blood samples, saw a lot of soldiers faint – and he only had to wear a uniform once a week.

What that led to, when his military service was over, was involvement in an NKI study investigating the effect of radiation on blood vessels – they wanted a PhD student with experience in blood coagulation. And as his interest in radiation grew, that led to a job in the radiotherapy department.

Today, Verheij's horizons continue to broaden. As a former board member of the European Society for Therapeutic Radiology and Oncology (ESTRO) he is aware of worrying international differences in radiotherapy quality and

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is determined to push forward ESTRO's work in making variations visible and stimulating improvements. ESTRO's extensive teaching programme is accessible to everyone, and he believes it is fundamental to driving up standards and spreading expertise.

In radiotherapy research, he believes there needs to be more collaboration and expertise-exchange between centres across Europe. "Practice change is hard to achieve as a single centre – you only get real progress if research is done by large consortia, combining expertise of different centres." This needs to happen before trial collaborations, so that (for example) centres specialising in preclinical models can exchange knowledge with those specialising in proteomics or genomics and can draft trial proposals from scratch once relationships are well established. "You need to establish affinity between centres."

For such European collaboration to work, quality assurance within radiotherapy needs to be harmonised – ensuring that each centre is working according to the same protocols and terminology. National professional organisations for radiotherapy in many countries, such as the Netherlands, are already defining quality – but the effort needs to be Europe-wide. "Raising quality is not necessarily a matter of investing in centres – it's making visible the differences," he says.

"Raising quality is not necessarily a matter of investing in centres – it's making visible the differences"

"The more experience radiation oncologists have in treating a specific type of cancer, the better the quality will be"

There are, he acknowledges, massive variations in radiotherapy equipment across Europe. But the greatest international challenge facing the specialty is creating what Verheij calls "critical mass" in radiotherapy departments – ensuring that staff have the experience and expertise to drive up quality. This inevitably involves national centralisation policies, as have been implemented in the Netherlands.

From the late 1990s onwards, a national programme of increasing radiotherapy capacity in the Netherlands has resulted in a national annual growth in equipment and personnel of 3.5–4%, but the number of radiotherapy centres has remained at 21. Verheij's own NKI centre now treats over 5000 new patients each year. It currently has 12 linacs, seven equipped with cone beam CT scanning for image guidance (a system which his unit was instrumental in developing).

"There is a close relationship between volume and quality. In surgery, it has become common that if a hospital falls below a critical level of surgical procedures performed, it should not offer that type of operation – and I think the same has to be true in radiotherapy. The more experience radiation oncologists have in treating a specific type of cancer, the better the quality will be. It will take time to drive up quality by centralising – it has to be planned carefully so that you do not reduce patient access. But ultimately I think our profession cannot do without similar attempts to increase critical mass and demonstrate that there is a relationship between volume and quality."

Verheij is aware that he speaks from a privileged position. When I ask him what his immediate priorities are, he talks about introducing proton beam therapy – a highly-targeted radiotherapy using protons rather than x-rays to treat cancers with a lower risk of damaging surrounding tissue. In a collaboration with the radiotherapy departments of the VU University Medical Centre and Academic Medical Centre in Amsterdam, he is planning the Netherlands' leading proton facility – and he points out the site where it will be built, just outside his office window.

It is a world away from hospital departments struggling to meet demand with one or two ageing linacs – or drawing a red line around a blurry x-ray. But then Verheij's belief is that progress occurs because there are leaders, innovators and centres of excellence providing models for everyone else to follow. If he hadn't had the chance to be inspired by the integrated translational medicine structures at Memorial Sloan-Kettering when he was a junior doctor, he would never have become Chair of his state-of-the-art department in Amsterdam, setting the agenda for others.

"I call it looking in someone else's kitchen," he says. "I encourage all my students to do it. It's a substantial investment in the future." ■

Keeping one step ahead

ANNA WAGSTAFF

Could trials do more for patients with incurable cancers?

Joining a clinical trial can be a lifeline for patients with few options open to them. But are outdated attitudes and practices preventing them from benefiting as much as they could?

The transformation in the nature of cancer trials over the past 20 years has been well documented. Gone are the days when phase I trials were about dying patients sacrificing themselves to test the toxicity of experimental therapies, with only the slightest hopes of deriving benefit themselves. Today, when so much more is known about targets and mechanisms before a drug enters human trials, early-phase trials are much more about learning who benefits, at what stage, at what dose and possibly even in what combinations.

What are the implications for optimal treatment of patients who have an incurable cancer? Should doctors and patients be rethinking the role that joining a phase I trial can play within their overall treatment strategy?

Jean-Charles Soria, who heads the dynamic Department of Drug Development at the Gustave Roussy cancer centre in Paris, believes that large numbers of patients with advanced cancer are missing opportunities to improve and extend their lives because their doctors fail to grasp the possibilities now offered by phase I trials. His message to medical oncologists is: "Don't wait until your patient runs out of options before suggesting a phase I trial". This discussion should be started early in the disease trajectory, he adds, ideally as soon as a patient becomes resistant to first-line therapy.

"I look at the attitude of most clinical oncologists towards phase I and, to be provocative, I would say they consider phase I to be an alternative to going to Lourdes or to Fatima – desperate, extreme cases. They don't tend to consider their patients for phase I early on in the course of their disease, and this is a major problem."

Twenty years ago, he concurs, this would have been a reasonable attitude, because only about 10% of patients derived any benefit, and only 1% showed an objective response (tumour shrinkage), while toxicity was seen as potentially significant. Since the mid 1990s, with the advent of molecularly targeted agents, and more recently with the advent of new immune checkpoints, he points out that the activity level in phase I trials is much higher – "very similar to any standard chemotherapy you would give in the third-line setting to any solid tumour."

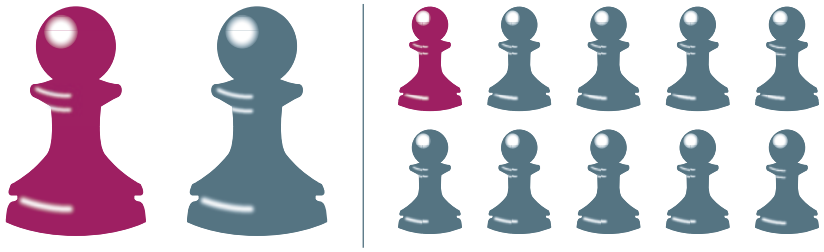
Soria cites a number of studies, including one from his own Gustave Roussy (*Ann Oncol* 2008 19:787–792) and another from the Royal Marsden (*Br J Cancer* 2008, 98:1029–33), that indicate that the objective response rate in phase I trials today is closer to 8–10%, with a further 40% showing stable disease. "Benefit for the patient can be in the range of one out of two, which is much higher than one out of ten." Toxicity is also well managed. "The risk of death in a phase I trial – to take an extreme indicator – is 0.5 %. That is much lower than the risk of death from adjuvant chemotherapy in breast or lung, which is in the range of 1–3%."

Even if this is a convincing argument in favour of joining a phase I trial, why not hold back until all standard lines of therapy have been exhausted? Soria draws an analogy with a game of chess, where you are trying to keep one step ahead of a cancer that can constantly evolve in response to treatment, and every move you make can limit what may be open further down the line. The benefit of not waiting too long before joining a phase I trial is that, whatever the outcome, the option of the standard second- or third-line treatment remains open, says Soria. If you choose the opposite strategy, a place on a phase I trial may not be available when you need it and other options have been exhausted.

He points out that demand for places on a phase I trial is now so high that there are not enough for all the patients who want to join.

"Once you have used up all the standard options, you have no alternatives except a phase I. If there is no slot – that's it. The patient goes to palliative care or whatever. If you start thinking about phase I as soon as you are in the metastatic setting, when the first-line therapy has failed, then if by mischance when you ask for the slot there is none – you get

BENEFIT FROM PHASE I TRIALS – THEN AND NOW



Studies of phase I trials show that up to one in two patients experience disease stabilisation or tumour shrinkage today, compared with only one in ten 25 years ago

"There is a difference between what is evidence based and what is scientifically or medically rational"

multiple chances. You can ask again after the second, or third line." Waiting too long can also damage your chances of being fit enough to join a phase I, adds Soria. "We know that if we give a drug to a patient whose kidney or liver are not functioning well then the risk of toxicity is huge."

It seems highly controversial to suggest that a patient could opt for experimental treatment in preference to an approved evidence-based therapy but Soria responds, "there is a difference between what is evidence based and what is scientifically or medically rational." He gives the example of a patient with advanced melanoma that is not treatable with a BRAF inhibitor, and where ipilimumab has failed as first-line therapy. "What is my standard of care in second line? It is a lousy chemotherapy. What is my option in phase I? It is a PD1 inhibitor [a new class of immunotherapy currently showing great promise in melanoma]. Which do I choose? Anyone with a real mind would choose a PD1 because the likelihood of activity is 40%, while the likelihood of activity of standard chemotherapy is 10%. But that's not evidence based, because the trial has not been done yet."

So if the choice is so obvious, why are medical oncologists not more eager to suggest joining a phase I trial before all standard lines of treatment are exhausted? "Because they don't want to come clean about the fact that we do not know how best to treat them, and they do not know about mechanism of action of all these new drugs in phase I," is Soria's response. Doctors don't like to admit they don't know, "because it's admitting our limitations."

The truth, he adds, is that "In metastatic cancer, with the exception of hormone-dependent tumours or testicular cancer, the only certainty we have is that there is no cure, the patient will die. The question is, how can I delay that from happening while keeping quality of life acceptable? We need to think of all the potential anticancer approaches. Phase I is just one rational possibility. We need at least to discuss it with the patient."

Rapid changes

Denis Lacombe, the headquarters director of the EORTC, Europe's largest cancer clinical trials organisation, believes that access to trials will soon change substantially. The technologies behind next-generation sequencing are evolving so fast that generating detailed molecular data on patients' tumours on a routine basis will soon be feasible and affordable. Medical oncologists will then have to decide what they do with the information. "If you are in a major cancer centre at the forefront of research, that is not a problem. But if you are in a middle-sized hospital in France, the UK, Germany, three or four years down the line, when you have next generation sequencing coming to you, what are you going to do for your patients? Data interpretation services will be critically needed. So there are plenty of changes that I'm sure the average medical oncology community have not anticipated, and they will come very fast."

At the same time, drug development is becoming more targeted, says Lacombe, homing in on subpopulations of patients where the drug is likely to show the sort of major benefit now being demanded by payers – subpopulations like the 40–60% of melanoma patients with the BRAF mutation, or the circa 5% of patients with non-small-cell lung cancer who have a mutated ALK gene. If patients know they may be eligible for a trial that homes in on people like them, they have a huge incentive to join. Once, that might have meant looking for a large phase III; today, however, Lacombe disputes whether the concept of phase I, II and III trials is even meaningful any more, "We believe we should ban this terminology, because there is not such a firewall any longer between phase I, phase II and phase III." The EORTC, he says, now advocates talking in terms of early trials, "designed to learn" and later trials, "designed to conclude".

Early-phase trials now recruit patients in far greater numbers, to enable researchers to explore the drug in sufficient detail to learn who benefits, who is resistant, the best dose and schedule of administration, the most effective disease stage and the impact of combining it with other agents. A case in point is the PD1 inhibitor pembrolizumab, which recently hit the headlines at ASCO – Merck claims

1000 patients were involved in the phase I. Meanwhile, phase III trials are shrinking in size, says Lacombe, because such trials now have to demonstrate larger differences, and therefore require fewer patients to show statistical significance.

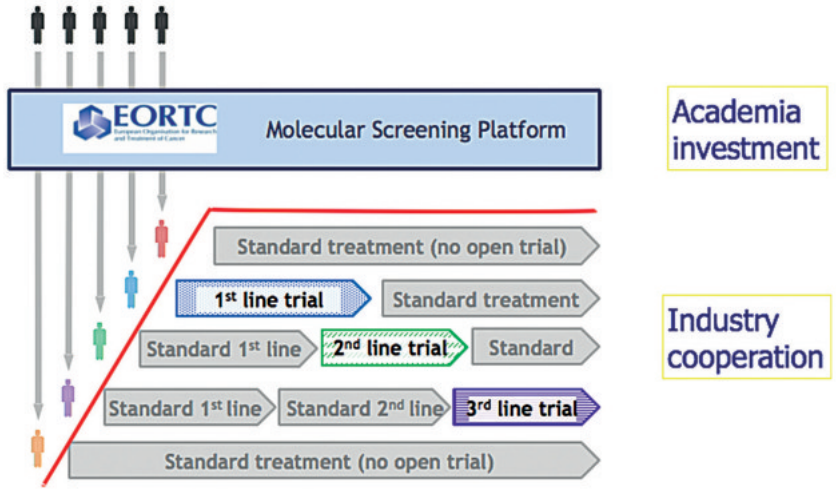
He points out that the early phases of a trial also take longer than they used to – and this is another good reason for patients to seek early access.

The challenge for the cancer research community, says Lacombe, is to ensure that all the data generated from early-phase trials are used to greatest effect to deliver highly effective new drugs and treatment regimens. "The regulators are telling us that it is chaotic out there. You see all these companies developing new agents based on different technologies, even for the same biomarker and the same class of agent." The challenge for patients and their doctors, may be locating relevant trials now that the whole picture is becoming so fragmented.

EORTC hopes that its new SPECTA platform – Screening Patients for Efficient Clinical Trials Access – may contribute to a solution to both problems, helping keep as much data in the public "precompetitive" domain as possible, and helping direct patients in a timely manner towards the most relevant trials. This initiative was outlined in detail by EORTC President Roger Stupp in the May–June 2014 issue of *Cancer World*. The idea is to work with doctors, hospitals and patient advocacy groups to ensure that newly diagnosed patients are asked for biological samples as early as possible, which would be sent to a central lab so their tumour can be subtyped and categorised at a molecular level. If the patient's cancer recurs after standard treatment, they can then be offered a trial for second- or third-line treatment in the event that there is something available that fits their characteristics.

The intention, says Lacombe, is to "take the trial to the patient". He believes it has the potential to transform patient access to relevant clinical trials.

FACILITATING ACCESS TO CLINICAL TRIALS



The EORTC's 'SPECTA' molecular screening platform is designed to help trials of targeted agents find the relevant subpopulation of patients, and help patients find the trials that could help them

Patients' strategies

Not everyone is convinced, however, that channelling patients into earlier trials is necessarily in their best interests – or in the best interest of medical progress. Among the more vocal sceptics is Bettina Ryll, a medical doctor turned researcher with a PhD in molecular biology, whose husband Peter was diagnosed three years ago with an advanced aggressive melanoma, which eventually killed him. Together with other patients and advocates, they founded m-icab – the Melanoma Independent Community Advisory Board – which includes among its aims "aligning industry and investigators' research goals with the best interests of those personally receiving treatment".

Ryll identifies with Soria's chess analogy from her family experience, but questions the rationale for joining a trial of a drug whose benefit may be highly speculative if there are approved potentially effective alternatives. "As

"Patients screened at diagnosis could be offered access to any relevant trial if their cancer recurs"

"If you already have something you know works well, why should you opt for something highly speculative?"

a melanoma patient, what you want is to live, so you are continually optimising your way through the system. Everything can change in an instant, for example with the approval of a new drug, the opening of an expanded access programme or a reimbursement decision. So if, for instance, we already have a PD1 on the market, which has shown unsurpassed overall survival benefit, why should a patient go for something highly speculative instead? After Peter's diagnosis, we took one step at a time, looking each time for the best option available. And once we ran out of that option we started evaluating again. What is the best available therapy now? Then you go further down the line… and at some point there is nothing else out there."

She is not in favour of a blanket message to encourage doctors to think about phase I trials for patients before standard treatment options have been exhausted. "We know that there are good phase I studies and not so good phase I studies. You have some researchers who believe so strongly in their research that they can't wait to test it in patients. But even if there is a good rationale there is no guarantee it will work. And doctors have a lot of clout with patients. So I don't think this is something that we should encourage indiscriminately.

"At the same time, if there is a phase I for a combination therapy, where each component drug is known to work very well, and early trials combining drugs with similar mechanisms have shown impressive results, then the rationale is sound. Joining that phase I might actually be a very good thing to do. There is no 'one size fits all', which is why I think it is dangerous to generalise."

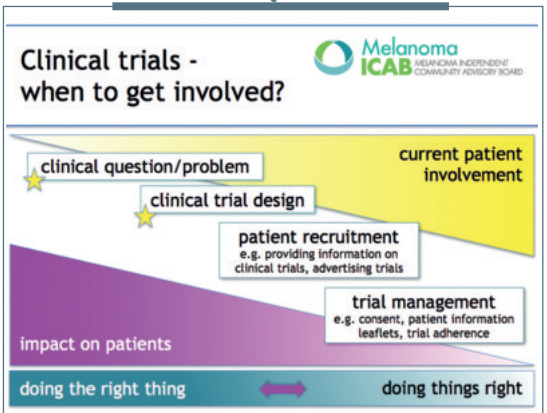
For patients trying to 'optimise their way through the system', the real problem, Ryll believes, is that when the best options are only available on a trial, patients want to join those trials when there is clear evidence of benefit – but to do so they must run the risk that they will be randomised to an arm that is known to be inferior. This she feels is a far more important issue.

While it is essential to learn as much as possible about any new drug and the best way to use it, and to follow results for benefit and toxicity over the longer term and with 'real patients', the question that really matters to patients like Peter is: "Will I do better on this agent than on other available alternatives?" And the answer to that is often known with some confidence at a relatively early stage.

This takes us back to Soria's statement that anyone with advanced melanoma and no BRAF mutation should choose a phase 1 PD1 inhibitor over an approved standard chemotherapy. Yet Merck's PD1 inhibitor pembrolizumab is currently being trialled against a comparator arm consisting of "lousy" dacarbazine or alternative chemotherapies with no greater evidence of benefit (NCT01704287, clinicaltrials.gov). Ryll wants to know, what new knowledge is gained by letting more patients die on dacarbazine. "My pathology textbooks from years ago were already stating that melanoma does not respond to chemotherapy!" she says.

Ryll has some insight into how it feels to be randomised to such a control arm. She and Peter spent one of the worst

GETTING THE QUESTION RIGHT



Patient advocacy groups like the Melanoma Independent Community Advisory Board want researchers to consult patient groups much earlier in the trial process to ensure that the questions they ask are the ones patients need answered and the design of the trial doesn't penalise patients needing access to effective treatments. As trial progression is no longer broken down into discrete phases, patients need to be involved right from the start

Source: Melanoma Independent Community Advisory Board. For more context see www.informed–scientists.org/presentation/the-role-of-patient-groups-in-the-trial-process

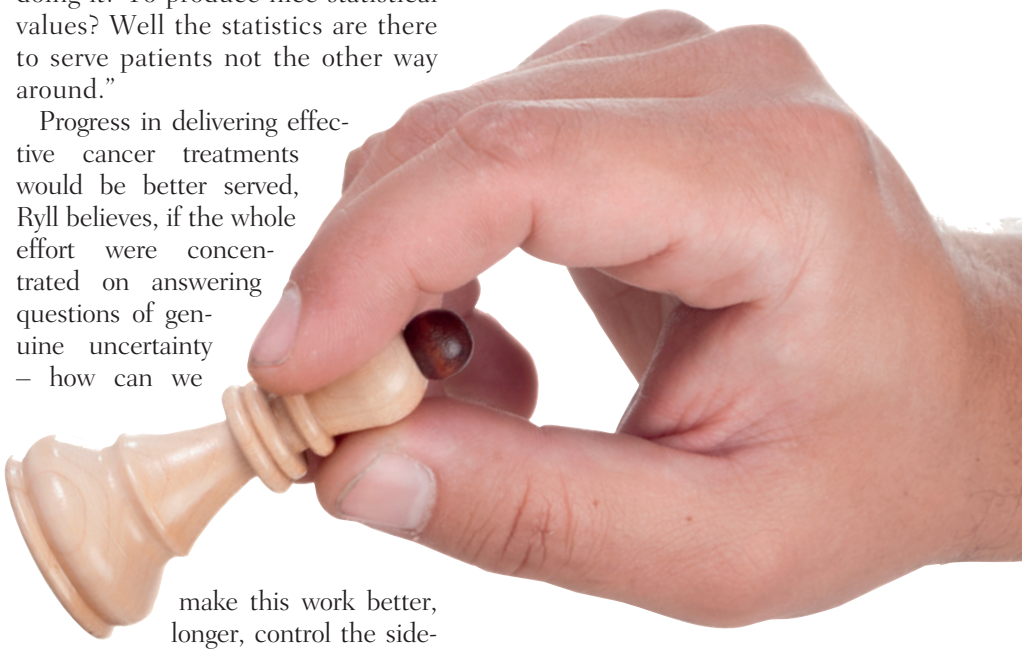
weeks of their life together waiting to hear whether he had been randomised to GSK's novel MEK inhibitor – known today as Teflinar – or to "lousy" dacarbazine after he had met the inclusion criteria for the trial. He hit lucky. Ryll describes the impact of the treatment as "almost miraculous": Before the MEK inhibitor, the tumour that had started under the right arm had already encased his elbow joint, so he could barely use it to feed or dress himself, and the disease was progressing so rapidly they came to dread going to bed at night for fear of the visible change the following morning. And afterwards? Ryll answers by showing a photograph of Peter rowing across a lake with their children after exactly one month on therapy.

The principle of equipoise

At the time that Peter entered the phase III trial, says Ryll, there was not the slightest doubt that the MEK inhibitor worked better than dacarbazine, the 'standard of care'. She believes that clinical trials in which it is known from the outset that one arm is clearly superior to the other are inhumane and unethical as they violate the principle of equipoise – the principle of not knowingly exposing patients to inferior therapies. "In melanoma, clinical trials have effectively become treatment and the best chance for survival, so patients' desperation is used to fill unethical trials – this is no way to do medical research," she says.

Time, resources – and patients' lives – are being wasted merely to increase the certainty with which we already know something, argues Ryll. Worse still, she adds, the questions are always posed in a way that is designed to deliver that proof. "They stack the design in a way that they know there will be a difference coming out. So what's the point of doing it? To produce nice statistical values? Well the statistics are there to serve patients not the other way around."

Progress in delivering effective cancer treatments would be better served, Ryll believes, if the whole effort were concentrated on answering questions of genuine uncertainty – how can we make this work better, longer, control the side-effects? She quotes enthusiastically from a 2009 *Lancet* paper (vol 374, pp 86–89), written by Iain Chalmers of the James Lind initiative and Paul Glaziou of Oxford University's Centre for Evidence-Based Medicine, showing that up to 85% of medical research funding is wasted – much of it because researchers are failing to ask the questions that patients want answered.



Ryll says she has never been able to find anyone who defends these trials. She confronts the pharmaceutical companies, they blame the regulators. She confronts the regulators, they blame the health technology assessment bodies. "But when I question [the HTA bodies], they say 'It's not us. We don't want these trials'. Everywhere I go, everyone points the fingers at the others."

This gives her hope that there may be an opportunity for a new approach, and she points out that companies, regulators and HTA bodies have been discussing more efficient ways of working for many years. Ryll feels that patient advocacy groups like m-icab have an important role to play in making it happen. "We are the ones who are dying, so we are the ones who are motivated to change things and can push for it." ■

"Time, resources – and patients' lives – are being wasted merely to increase the certainty of what is already known"

Stories that give witness, stories that save lives

the special role of health reporters in Africa

SIMON CROMPTON

How can journalists help raise the profile of cancer and get it on the political agenda in countries where infectious diseases get most attention, reliable data are scarce, doctors are reluctant to talk and editors prefer cheery topics? Two award-winning reporters speak of the challenges they face.

In April, Cancer Research UK reported that half of the people diagnosed with cancer today will survive the disease for at least another ten years, compared with a quarter in the early 1970s.

That is in a developed country. Then there is Africa. At Uganda's Cancer Institute, 20,000 of the 22,000 patients attending each year will die within 12 months. In Zimbabwe, there aren't even reliable statistics on how many people have cancer: the government estimates 7000 – even though the population is nearly 14 million. The probable reason: large numbers die even before they have a diagnosis.

Best Cancer Reporter Award winners Busani Bafana and Esther Nakkazi

ESTHER NAKKAZI

Health education the café way. Esther Nakkazi won an award for her article on the emergence in Africa of 'science cafés' like this one, in Entebbe, Uganda, where men are learning about cervical cancer – the threat, the symptoms, how it is transmitted, how it can be prevented – while sipping from a communal bucket of malwa, the local tipple

In such environments, African journalists feel they have a special role to play, revealing deficiencies in services and communicating potentially life-saving health education.

But they live in a different world than the privileged reporters of information-rich Europe. Two recipients of a special award for cancer journalism have spoken of the barriers they face: lack of access to information; official resistance; reluctance of doctors to speak to them; editors adamant that their readers want to hear about more cheerful things than cancer.

Ugandan journalist Esther Nakkazi and Zimbabwe-based journalist Busani Bafana received special merit awards in the 2013 ESO Best Cancer Reporter Award. Through human interest stories and analysis, their articles dramatically illustrate how prevention, diagnosis and treatment are far from simple in their countries.

Based in Bulawayo, Bafana writes investigative pieces on business, the environment and society for the Inter Press Service – an innovative news agency that aims to highlight issues faced by the world's marginalised communities. In a piece titled "Morphine kills pain but its price kills patients", Bafana examined how in Zimbabwe, a country where diagnostic and treatment facilities for cancer are scarce, patients are dying in extreme

"My article sought to capture that burden over the six months that I interviewed and followed patients in my home city"

pain before even receiving an oncology appointment. An effective supply of morphine would at least ease the suffering, but supply is short and the cost prohibitive.

Bafana talked to cancer patients about their experiences. Two daughters worked for two weeks selling enough of their chickens to raise the 18 dollars needed for a two-week supply of morphine for their mother, bedridden with stage 4 cancer of the cervix.

He wrote: "Pain is scrawled all over Ncube's face as she narrates her tale: for six months now she has been on the waiting list to undergo radiotherapy at Mpilo Hospital. The radiotherapy machine has been broken for longer than she has been waiting and a new one is only now being installed. 'The pain is unimaginable,' Ncube told IPS in her home. Pointing to a white plastic bottle filled with paracetamol, a mild painkiller, she added, 'That is all I could get from the hospital.'"

Bafana interviewed officials at the Bulawayo Island Hospice Service, which distributes limited supplies of donated morphine to its 300 patients, but is at risk of closure due to high operating costs and low donor support. He found out that in 2012 Zimbabwe used a total of 3.6 kilogrammes of morphine, despite having an allocation of 11.25 kilogrammes.

And he discovered that the cost of morphine could be brought down significantly if hospitals and pharmacies were allowed to stock morphine powder for making a liquid morphine preparation – which is cheaper and more convenient for severely ill patients to take.

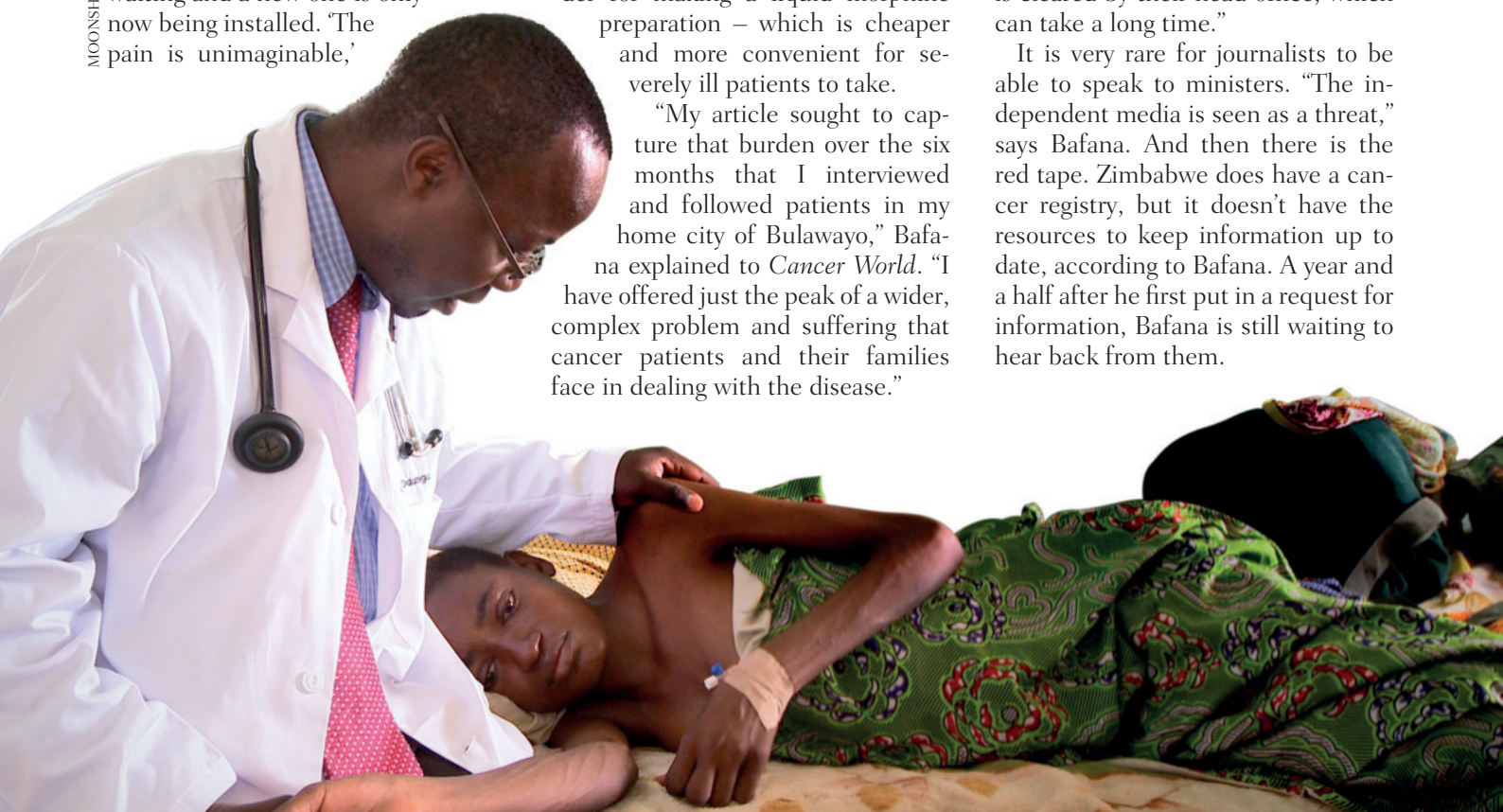
"My article sought to capture that burden over the six months that I interviewed and followed patients in my home city of Bulawayo," Bafana explained to *Cancer World*. "I have offered just the peak of a wider, complex problem and suffering that cancer patients and their families face in dealing with the disease."

It was not an easy story to write. Bafana says that the issue of cancer is easily ignored in Zimbabwe, where HIV/AIDS has dominated the health agenda and traditional beliefs about cancer being part of witchcraft are still strong. Many would rather ignore the subject, even though it poses a serious health burden.

A scarcity of sources

Getting doctors and politicians to even talk about the subject is difficult. "Accessing doctors, especially oncologists, is hard. There are only two oncologists in Bulawayo. If you do manage to interview doctors in Zimbabwe, they usually won't be named – unless everything they say is cleared by their head office, which can take a long time."

It is very rare for journalists to be able to speak to ministers. "The independent media is seen as a threat," says Bafana. And then there is the red tape. Zimbabwe does have a cancer registry, but it doesn't have the resources to keep information up to date, according to Bafana. A year and a half after he first put in a request for information, Bafana is still waiting to hear back from them.



MOONSHINE AGENCY

"Without access to all the information we need, part of the role of journalists is largely to observe."

In Uganda, there is a similar lack of public understanding of cancer. A 2010 *Lancet* study concluded that in Uganda only 13% of people survive any kind of cancer apart from breast cancer. Journalists committed to confronting this face similar problems accessing doctors and policy makers. Esther Nakkazi, a freelance science journalist who reports for a number of regional African news outlets and the Science for Development Network, won her special merit award for an article about African science cafés – an innovative way of communicating health information to very poor communities. But she too depended on observation and obtaining information from non-governmental organisations.

"When it comes to health, getting hold of experts is a real problem," she said. "There are very few around in Uganda, and doctors are always incredibly busy."

She reported that science cafés – normal cafés and meeting places which periodically ask scientists to discuss issues relevant to local people – are gaining popularity in Africa. The initiative began in Nairobi, Kenya, after a public engagement initiative funded by the UK's Wellcome Trust. The subject matter is often health-related, and Esther Nakkazi described an event in a grass-thatched hut in Entebbe, Uganda, where Agnes Bukirwa, a medical officer from the charity Mildmay International, was leading discussion on cervical cancer.

Seven million Ugandan women of reproductive age are at risk of developing cervical cancer, according to WHO estimates. Around 3,600 women receive a diagnosis each year, and 2,500 die of the disease – around double the number of men and women who die in road accidents.

Nakkazi wrote in her piece: "How many people know how cervical cancer is transmitted, Bukirwa asks her audience. Pause. How many know how it is prevented? No answer. 'Back home you have women who may have cervical cancer,' she continues.

"A mobile phone is passed around for members to view an image of the cervix. Men shake their heads. Some laugh nervously. Bukirwa explains what HPV is, and how men can transmit it sexually. She speaks for only 30 minutes; adult learners do not want long talks."

Nakkazi reported how those supporting the Science Café initiative, such as Ugandan scientists and charitable funders, believe that the cafés are an excellent way of spreading basic messages about health and immunisation.

There is a desperate need for such cancer education initiatives, says Nakkazi. "In Africa, the money has followed malaria, TB and HIV/AIDS, so those are the areas that have got coverage. The public know very little about non-communicable diseases such as cancer." The effect can be devastating, she says. "There are many times more deaths from prostate cancer in Uganda than in the United States because public awareness is so poor," she says. "Men are simply getting to the doctor far too late."

It is the job of journalists, she believes, to raise the profile of such public health issues, and give people the information to be able to help themselves. "But there are problems," says Nakkazi, who has her own blog and writes for East African newspapers. "In Uganda, the situation is quite unstable so the appetite is mainly for politics, not health."

"Editors don't make health issues a priority and don't have many journalists covering it. If they do, it's often a matter of reproducing a press release.

The Inter Press Service and SciDev.Net, which published the award winning articles, are very important outlets for serious health and science stories, in a continent that is short of health journalists and wearied by decades of HIV/AIDS stories

"If you do manage to interview doctors in Zimbabwe, they usually won't be named"

"Journalists who want to write serious stories about cancer get batted away, partly because of disease fatigue"

There may be a story on how many doses of HPV vaccine are being sent out, for example, but there will be nothing looking into the effect of the vaccine on girls and families."

Bafana agrees about the need for more awareness about conditions such as prostate cancer, which is three times as common in men of African and Caribbean origin as caucasians. He says that in Zimbabwe it is known as "the politicians' disease" – because it only gets media attention when a major figure such as Robert Mugabe has it. Bafana too encounters lack of interest from editors, but he is also aware that there are all too few health reporters around in Zimbabwe who have the scientific understanding to write authoritatively about cancer.

A gathering of health journalists. Conventions like this one in Kampala, organised by the Health Journalists Network in Uganda, offer important opportunities for networking and learning new skills

Common challenges

The challenges that Nakkazi and Bafana face are common throughout Africa, according to Harry Dugmore, Director of the Discover Centre for Health Journalism at Rhodes University in South Africa. The centre, which opened in 2011, supports African journalists covering health and offers degrees and courses in health journalism.

"People are often surprised by how few media outlets there are in Africa, and even in countries like South Africa, where there are many newspapers and magazines, you don't see much health journalism – apart from of the 'fit and fabulous' variety. I think journalists who want to write serious stories about cancer get batted away, partly because it's a downer and partly because of the disease fatigue caused by HIV/AIDS."

There is an unrealistic burden put on journalists in Africa, he believes, to spread public health messages, because official systems of health education are failing so badly. It has been estimated, he says, that half of the people in South Africa who have HIV or diabetes are unaware of the fact. The need for articles about symptom recognition is clear, but editors can only run so many public service articles. "We're left in the strange situation where journalists are left carrying the can for public health education."

When journalists want to write about health system failures such as long queues and waiting lists, they face a brick wall from officials. "No one denies that the health system in South Africa is in a catastrophic mess – and it's very similar in countries such as Nigeria and Zimbabwe. But this means that hospital staff feel constantly under attack, and nearly always refuse to talk. This kind of journalism now has to be almost completely undercover."

Support for health journalism

What is the way forward? There is increasing awareness, nationally and internationally, of the important role African health journalists have, and an acknowledgement that networking is a good way of providing support and information. The

African Health Journalists Association (www.ahja-news.org) was formed in Nigeria last year, It aims to advance the professional development of journalists who cover health, raise the profile of health stories in the media and promote dialogue between journalists and experts.

Another initiative in Nigeria provides recognition to journalists who highlight important cancer issues. The charity Breast Without Spot, which raises awareness of breast and other cancers, this year launched its Journalist Cancer Control Advocate Award (http://breastwithoutspotng.org/?page_id=382), which aims to reward Nigerian journalists who show commitment in writing about cancer prevention, treatment, control and advocacy.

In Uganda, Esther Nakkazi has been leading attempts to give health journalism a firmer footing. She founded the Health Journalists Network in Uganda (www.hejnu.ug) to improve the quality and visibility of health reporting, broadcasting, writing and editing. It has 70 members. Its journal, *Health Digest*, of which Nakkazi is managing editor, has focused on cancer issues. She is also on the advisory panel of a project based at Makerere University to improve health literacy in Uganda by developing mass media resources for the public and schoolchildren.

So what needs to happen next? Nakkazi is adamant that training journalists to be specialists is the key. She was inspired to try and move Ugandan science journalism forward having completed a Knight Science Journalism Fellowship at MIT (Massachusetts Institute of Technology) in the United States in 2008. All too few can have such experiences, but she believes that professional networks such as the Health Journalists Network in Uganda can help educate and foster committed upcoming journalists. She'd like to see similar organisations being set up and collaborating around Africa.

Health journalists' double role. This issue of *Health Digest*, the magazine of the Ugandan Health Journalists Network (www.hejnu.ug), is an important public health education resource, with information about cancer prevention, screening, care and research

"We've already tried to do some training, but funding is very limited," she says. "The benefit is that if journalists become more active and interested in writing real health stories, with time they may become health editors." That might eventually end the current glut of analysis-free stories about losing weight and looking beautiful.

Busani Bafana agrees that the way forward is giving journalists the means to specialise – but that does involve getting resources. "We need more fellowships, like the MIT scheme," he says. "I personally believe that with more specialist journalists who can reflect medical knowledge and progress, you have the opportunity to do people with cancer a great service." ■

Professional networks can help educate and foster committed upcoming journalists

Survivors demand a fair deal from financial services

MARC BEISHON

Companies should no longer be allowed to deny mortgage or insurance services to cancer survivors without explanation or a transparent risk assessment, say patient advocates. A few hopeful signs show their message may be getting across.

It was in November 2010 that Nicky, a young government worker in Belgium, was diagnosed with lymphoma. It was treated by radiotherapy, and by the start of the New Year in 2011 the therapy was over and the cancer was gone.

"I was only 23 and I tried to move on – but two years later, in June 2013, my boyfriend and I decided to start building a house. We went to the bank and got a loan to finance our building project. Next, we applied to convert my life insurance, which I had taken out before my cancer, to pay off my share of the house loan if necessary. To do this I had to fill in a form with questions about my medical background – but my boyfriend's insurance was accepted and I got a rejection letter.

"I was stunned. I had expected that they would charge extra or that they would put some exceptions in the conditions. I thought that they had made a mistake or did not understand the type of cancer that I had suffered. So I asked for an explanation."

All Nicky received was one sentence stating the disease and treatment and that she was still in 'follow-up' – there was nothing about why she was too big a risk. "I have been trying so hard to learn to live with what happened to me and then an insurance company says they expect that I will die in the next 20 years? It may not be what they said, but it sure is what it feels like. By not granting me insurance they made me feel different – all I have been trying to do since my cancer is to feel normal again."

This is said to be an all too common problem for cancer survivors around Europe. Not only do people have to contend with the denial of insurance that can be vital to carrying on with daily life, but the reasons are often not communicated. In just one sentence, a life or travel insurance company can stop someone from enjoying the security or holiday opportunities that other people take for granted.

More research is needed on just how many are affected, but a recent study in the Netherlands found that life insurance is a particular problem for cancer patients, with a fifth having problems, and of these, more than

60% were rejected (Mols et al. *EJC* 2012 48: 2037–42). Further, cancer patients often encounter other financial difficulties, especially related to employment if they are unable to work at the same level owing to long-term effects.

Asking the company to review her case, Nicky finally got some figures that her own doctor said were incorrect, and asked for advice from the Flemish League against Cancer. So far, however, she has been unable to change the company's position. She does have other options – for example to try for insurance elsewhere, risking further rejection, and appealing to Belgium's Interfederal Centre for Equal Opportunities, which she has now done.

A widespread problem

Ward Rommel, a researcher at the Flemish League Against Cancer, says that insurance is one of the main financial issues facing cancer survivors, particularly the younger ones. "Often they still have to buy a house, start a business or have yet to take out life insurance – so for them it's a real problem. Young men who have had testicular cancer, or those with Hodgkin's lymphoma, are among those more commonly affected." When people are able to obtain insurance it is often only with a high premium, he adds.

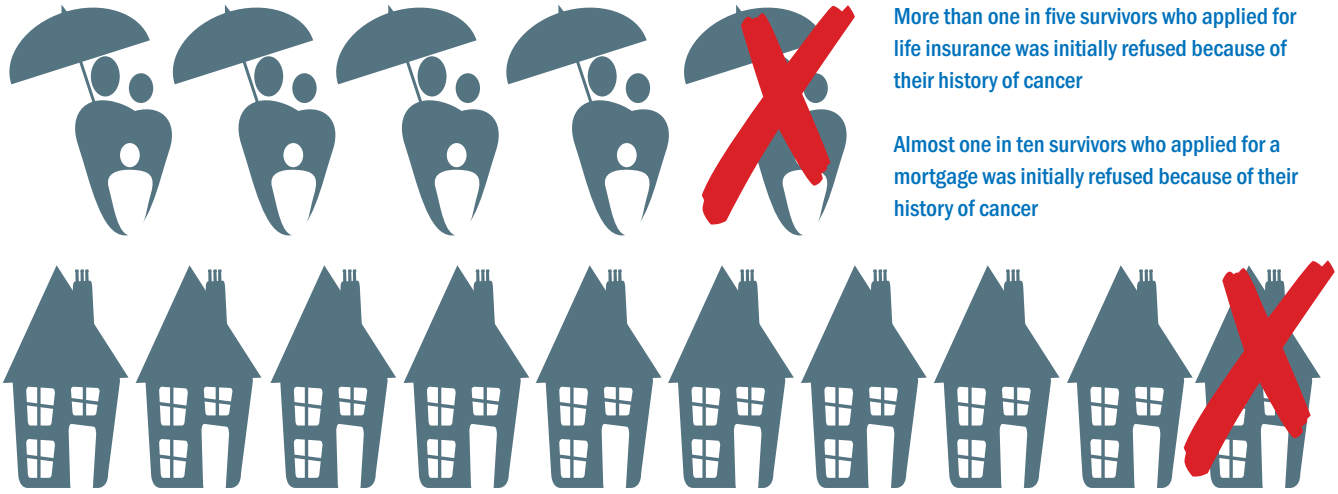
ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

It is important to note that most European countries do have good public insurance programmes for welfare and health, although those relying on extra private health insurance that is outside of government mandates will often run into exclusions for cancer. Even the US has recently ruled out discriminating against pre-existing conditions in obtaining private healthcare insurance in its recent (and controversial) 'Obamacare' reform. "It is the market for other types of private product that is the main problem, such as covering a mortgage with life insurance," says Rommel. "As well as difficulties that cancer patients face in obtaining insurance, they often also complain about the lack of transparency about decisions [as in Nicky's case], and it can be difficult to get information from an insurance company's doctor."

Belgium, in common with many European countries, has an ombudsman for the

"I thought that they had made a mistake or did not understand the type of cancer that I had suffered"

IMPLICATIONS OF A PAST CANCER DIAGNOSIS FOR ACCESS TO FINANCIAL SERVICES



More than one in five survivors who applied for life insurance was initially refused because of their history of cancer

Almost one in ten survivors who applied for a mortgage was initially refused because of their history of cancer

Based on data from a survey of patients diagnosed with colorectal cancer, lymphoma, multiple myeloma or melanoma, recorded in the Eindhoven Cancer Registry, published in Mols et al. *EJC* (2012) 48:2037–42

financial services industry, which adjudicates in disputes between customers and companies. However, it can take considerable time for an ombudsman to reach a decision, especially in more complex cases, which are common in cancer.

The UK's ombudsman takes a minimum of several months for basic cases and it could be a year or more for complex cases, which can be reviewed and appealed several times. All decisions are published on their website. As an example of complexity, one judgement on a refusal to pay out on a critical illness policy for prostate cancer hinged on whether medical evidence indicated that the Gleason score and TNM classification of the complainant's tumour was below the insurer's exclusion criteria (the ombudsman eventually found against the complainant). A payment could depend on whether a cancer is deemed invasive or not – with all that entails in medical judgement.

But there are many complaints that have been upheld about insurance terms being hidden in 'small print', and also being blatantly mis-sold: in the UK there has been a major scandal about mis-sold payment protection policies, resulting in refunds of more than £15 billion. But the position taken by regulators and ombudsmen is that insurers are entitled to sell policies with terms and exclusions they want (although not for illegal reasons such as race), as long as customers are always alerted to the terms and what they mean.

Could insurers do more?

The bigger question is whether insurers could do more for people with pre-existing conditions and those who develop serious illness, as well as being fair and transparent with existing policies. Rommel, who is leading on financial services work for the Association of European Cancer Leagues (ECL), says there has been some attention at European level – notably in 2011 at a survivorship conference at the European Parliament – and a major report, 'Current practices of financial services providers', was prepared by Civic Consulting in 2010 for the European Commission. The report notes that better competition between insurers can serve low-risk people well, as companies target them with lower-

"A woman diagnosed with stage 1 ER-positive breast cancer is actually insurable the next day"

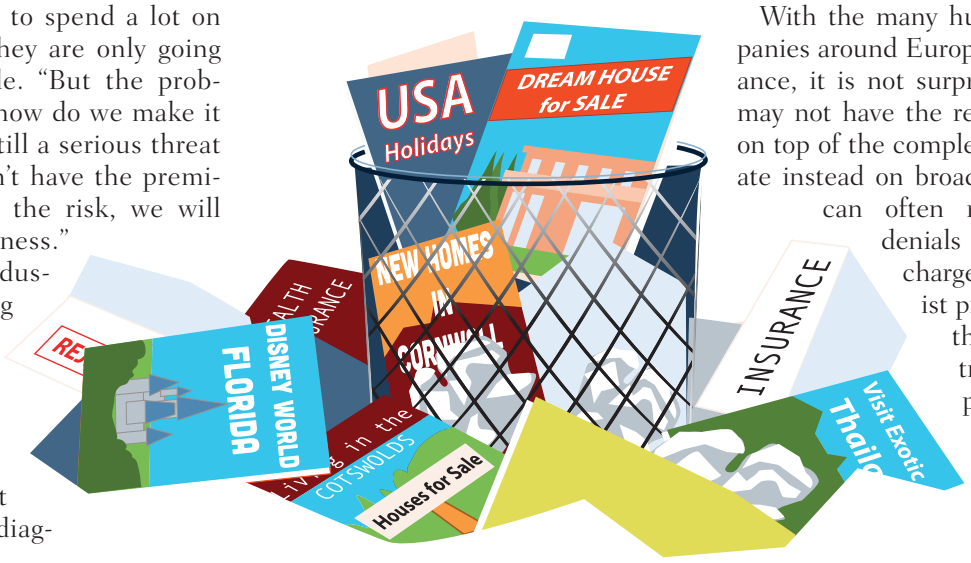
Even specialist providers, such as those that insure travel for cancer patients, say they need much more data

priced products, but high-risk consumers could be priced out of the market or refused insurance.

Insurers put their point of view forward at a recent survivorship summit run by Europe's main cancer trials group EORTC (see also *Cancer World* May–June 2014). John Turner, an underwriter from reinsurer Swiss Re, pointed out that more than €600 million is paid out each year by the European life insurance industry, and cancer is the leading cause, ahead of cardiovascular causes. This is because cancer is more likely to be a disease among the insured and also because insurers are less accurate at predicting risk for cancer than they are for heart problems. "We have few scoring tools for cancer: one is smoking and the other is have you already had cancer, so for survivors that is the single biggest predictor of mortality we have for the risk selection process."

Turner argues that the industry has no incentive to spend a lot on risk analysis if they are only going to decline people. "But the problem we have is: how do we make it insurable? It is still a serious threat to life. If we don't have the premiums that match the risk, we will go out of business." He says the industry is busy feeding in the latest survival data into its calculations, but given how many people die in the first few years after diagnosis, it is unfeasible to take on that risk in many cases. There is a time point, however, depending on the type and stage of cancer, at which people become insurable, at least initially for a higher premium, although a normal premium may be offered when there is a certain duration since diagnosis and for milder forms of cancer.

As an example of rapid progress, he said, a woman diagnosed with stage 1 ER-positive breast cancer is actually insurable the next day – whereas she wasn't in 1995, although she would pay an extra €5 per €1000 insured for three years, which could amount to a lot if the sum insured is large. "But what does the risk mean – because that's the key area where we have miscommunication between the treating physicians and the physicians working for insurers. That 'five per mille' represents a half a per cent of those patients dying – most doctors treating a patient would say that is a low risk. But from an insurance perspective that number is huge because it is a large multiple of the standard risk, which we have to take into account otherwise the whole structure of voluntary insurance falls down."



Overall, Turner said, one of the insurance industry's biggest problems is that for long-term products such as life insurance – which could last 25 years or more – it is hard to set prices based on evidence that will get outdated as five-year survival rates improve, such as in breast cancer. But with cancers such as Hodgkins, for instance, where survivors are almost five times as likely to develop a second cancer in the next ten years compared with the general population – and with cancer causing such a large proportion of claims in critical illness and life insurance – insurers cannot afford to ignore the risk.

With the many hundreds of companies around Europe offering insurance, it is not surprising that many may not have the resources to keep on top of the complexities, and operate instead on broad principles that can often result in blunt denials or massive surcharges. Even specialist providers, such as those that insure travel for cancer patients, say they need much more data, as the EORTC summit heard.

Extending the EU equal treatment directive could improve access to insurance for people with health conditions

A case for regulation?

Naturally, insurers are not supportive of more regulation, but a voluntary system that brings parties together could help more patients obtain insurance, by say explaining a denial and offering more evaluation on the medical position. France has taken a lead, says Rommel, with the AERAS convention (s'Assurer et Emprunter avec un Risque Aggravé de Santé, or 'insuring and borrowing with a higher health risk'), an agreement between the financial services industry, patient groups and government. It allows for speedy acknowledgement of medical progress, several evaluation levels for people denied insurance and capping of high surcharges.

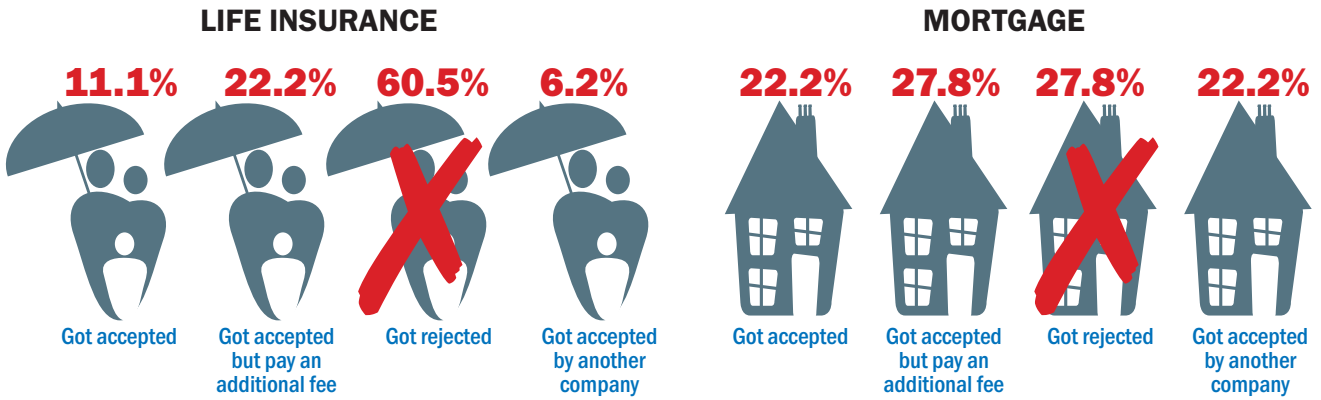
Now Belgium is adding more teeth to this type of arrangement by implementing a law that, from January 2015, should improve access to home loan insurance for people with a higher health risk. The law was first enacted in 2010 but is only being implemented now that opposition from insurers has been overcome.

People in the UK are covered by broader legislation. The country's Equality Act has rules about insurance for people with disabilities ("disability" being a catch-all term that includes illness) that mean companies must use reliable medical information and not refuse to cover cancers that can be well-managed or are curable, but it does not have a special initiative like AERAS or the new Belgian law.

Meanwhile, the EU may extend its equal treatment directive, which could give similar protection to people across Europe. The intention is to tackle discrimination on access to services and goods not already covered by existing European law (such as on gender discrimination), by extending the directive to cover age, sexual orientation, religion and disability. This should help ensure that people with long-term health conditions get more favourable responses from the insurance sector. But it has been stalled for six years due to opposition, notably from Germany. "ECL has been among those lobbying for it, but hopes for progress now lie in the new European Parliament," says Rommel.

Cancer advocates will certainly continue to argue for better services for survivors and patients. In February, a new bill of rights for European cancer patients was launched by the European Cancer Concord, run by the Society of Translational Oncology, but it focuses mainly on care issues and makes no mention of problems such as financial matters. Rommel feels this is an omission and points to a local patients' bill of rights in Flanders, put forward by the Flemish League Against Cancer, where access to insurance is mentioned, and ECL issued similar guidelines for cancer patients' rights in 2004. "A stronger call for broader rights is lacking at European level and we should address this," he concludes. ■

SOME WHO WERE INITIALLY REFUSED FOUND A SOLUTION



Based on data from a survey of patients diagnosed with colorectal cancer, lymphoma, multiple myeloma or melanoma, recorded in the Eindhoven Cancer Registry, published in Mols et al. *EJC* (2012) 48:2037–42

Putting precision pathology on the policy agenda

MARC BEISHON

Will pathology services need a serious overhaul if they are to deliver the accuracy required for precision medicine? Two European initiatives are trying to build the case for change in this least visible of cancer disciplines.

The shift towards personalised medicine has placed a new premium on detailed and accurate pathology reports to inform treatment decisions. But health systems and individual institutions have often been slow to understand the implications and invest in the necessary training, quality assurance and organisational changes to ensure their pathology services are up to the job. This issue was first highlighted because of concerns about the quality of data being used for clinical trials. However, attention is now beginning to focus on the implications of poor quality pathology for everyday clinical decision making.

Recent months have seen two important initiatives to raise standards of cancer pathology across Europe. The first, launched at a meeting at the European Commission this February, is focused on the particular problems associated with rare cancers. The second addresses the pathology challenges of one of the most common cancers, with the launch of the Optimal Pathology Manifesto at the European Breast Cancer Conference in March.

A benchmark for breast pathology

Emiel Rutgers, head of surgery at the Netherlands Cancer Institute, led the launch of the breast pathology manifesto on behalf of the European Breast Cancer Council (see ecco-org.eu/Events/Past-conferences/EBCC9/Manifesto.aspx). He told a large audience that it is not the intention to 'bash' pathologists, but there is a large variation in the quality of pathology around Europe (and the world) that must be addressed if the full range of questions from colleagues about who to treat, and how, can be answered.

Radiologists need correlations between what they and the pathologists see; surgeons need to know whether surgery is needed and the extent of an operation; medical oncologists want information on risks of relapse and suitability for drug treatments; radiotherapists also need local relapse risk data; and geneticists ask for hereditary risks. With breast cancer having such a large heterogeneity in types – and taking patient preferences into account – the implications of misjudging say whether a tumour is associated with a HER2 mutation, or whether breast conserving surgery

SHUTTERSTOCK

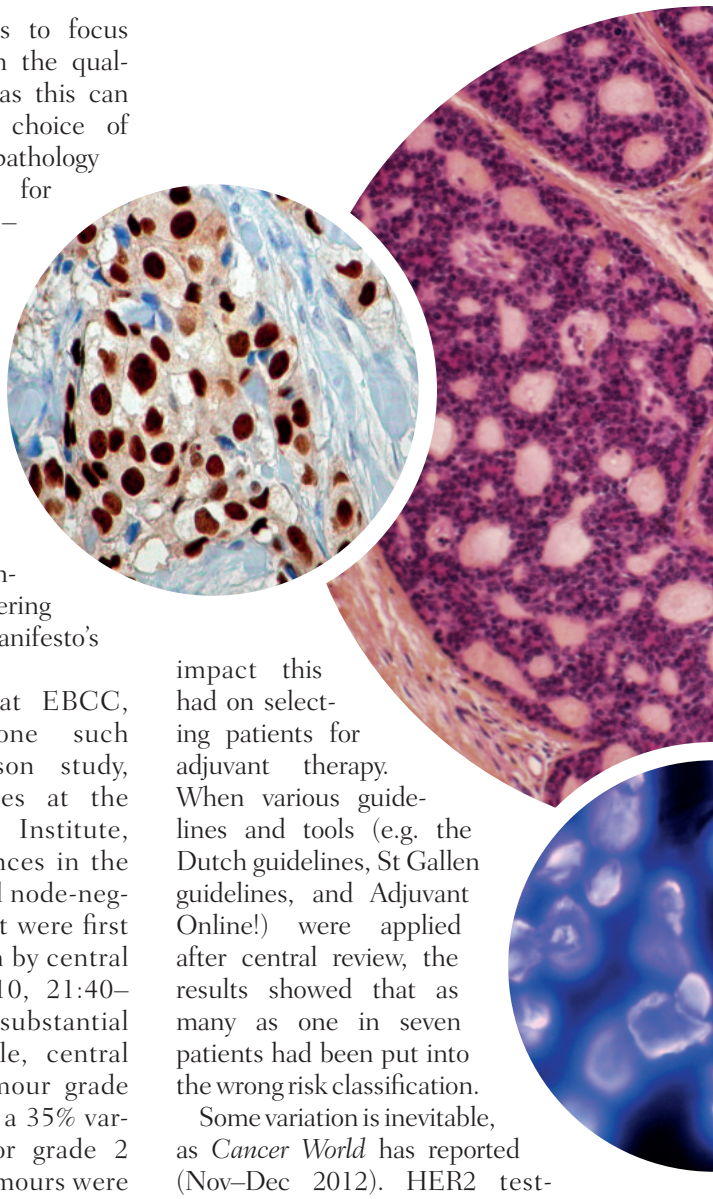
"One aim of the manifesto is to help people become more informed about their own pathology report"

is suitable, can be profound.

The manifesto, which is currently out for consultation, is not a guideline, Rutgers stressed. It sets out in two parts what a breast cancer pathology service should provide, but does not detail the processes as a guideline would. The first part is a list of parameters, which are the usual histological reports on type, grade, size and operative margins, and tests for hormone receptor and HER2 status. Also included are vascular invasion, multifocality/centricity (whether there are multiple tumours in one or several breast quadrants), and Ki67, which is a marker of cell proliferation. In each case, the reason why these parameters are important is noted – one of the aims of the manifesto is to give people information they can use to become more informed about their own or a family member's pathology report.

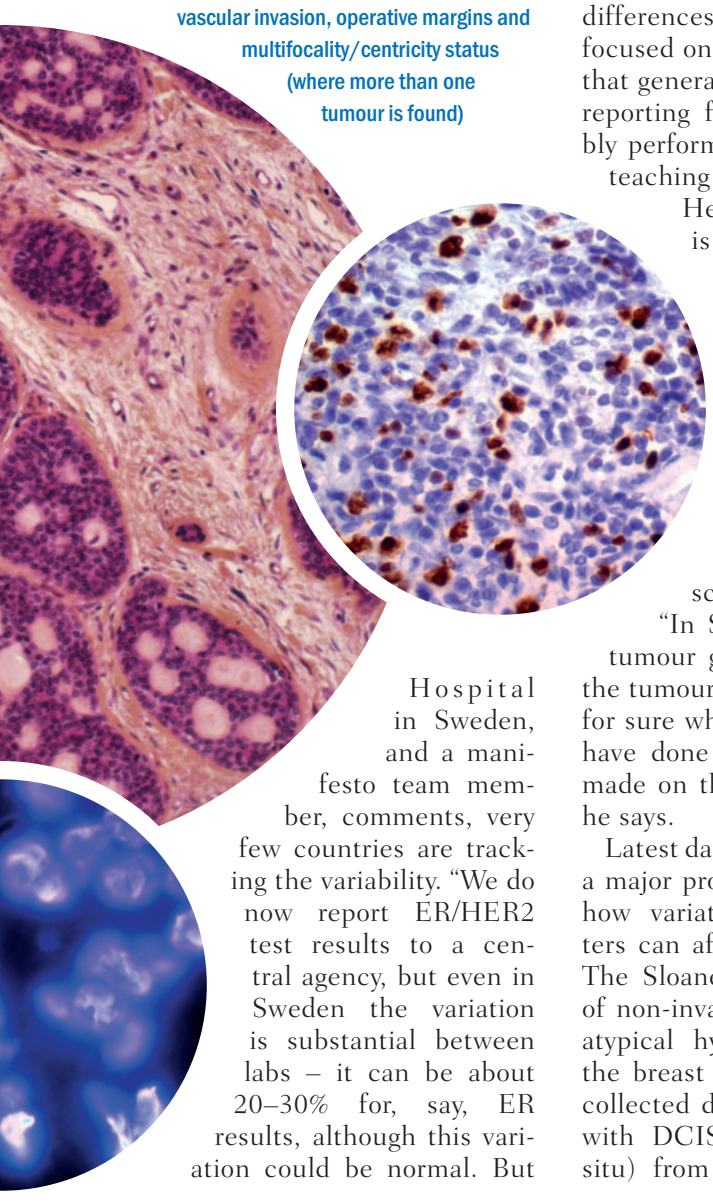
The second part itemises the organisational factors that can deliver an optimal service, divided into what is ideally needed at individual, departmental, hospital and national health system levels. By presenting both technical and organisational factors, the manifesto team hopes that clinicians, policymakers and patient groups will have a benchmark that can help them make judgements about the overall quality and standing of breast cancer pathology, not least from the point of view of the patient and the priority given to the specialty in health services.

The manifesto also aims to focus attention on variability in the quality of pathology reports, as this can impact heavily on the choice of treatments. Poor quality pathology can point to the need for improved organisation – more specialist expertise, or better multidisciplinary working and workforce development. While so-called 'inter-observer' variability has been reported in cancer pathology for many years, there are few large studies about its prevalence and consequences – and gathering more data is one of the manifesto's recommendations.



In his presentation at EBCC, Rutgers mentioned one such inter-observer comparison study, conducted by colleagues at the Netherlands Cancer Institute, which looked at differences in the pathology reports of local node-negative breast tumours that were first assessed locally and then by central review (*Ann Oncol* 2010, 21:40–47). The findings show substantial differences. For example, central review changed the tumour grade in 28% of patients (with a 35% variation in assessment for grade 2 tumours), and 21% of tumours were wrongly classified as HER2-positive. While these results are broadly in line with findings of other reports, this study went beyond documenting inaccuracies to look at the impact this had on selecting patients for adjuvant therapy. When various guidelines and tools (e.g. the Dutch guidelines, St Gallen guidelines, and Adjuvant Online!) were applied after central review, the results showed that as many as one in seven patients had been put into the wrong risk classification.

Some variation is inevitable, as *Cancer World* has reported (Nov–Dec 2012). HER2 testing, for example, is currently not an exact science, and pathologists will vary in assessments of grade and size. But as Tibor Tot, head of laboratory medicine at Falun Central



A demanding job. Accurate and detailed reports are needed on: tumour type and grade, hormonal status (ER/PR), HER-2 status and rate of cell proliferation (Ki-67 index), as well as size, lymph node involvement, peritumoral vascular invasion, operative margins and multifocality/centricity status (where more than one tumour is found)

Hospital in Sweden, and a manifesto team member, comments, very few countries are tracking the variability. "We do now report ER/HER2 test results to a central agency, but even in Sweden the variation is substantial between labs – it can be about 20–30% for, say, ER results, although this variation could be normal. But if you don't monitor it, the variation could be larger and of possible concern." Tot, who is from Serbia and has worked in eastern Europe, says there can be major differences in services that are not focused on breast pathology, noting that general pathology departments reporting few cases cannot possibly perform at the level of a major teaching hospital.

He points out that there is much less comparative data on the basic pathology reporting of type, grade and tumour size than on immunohistochemical and molecular tests for ER and HER2 status, as many laboratories take part in external quality assurance schemes for these tests. "In Sweden we monitor the tumour grade variations but not the tumour size – so we don't know for sure whether all the studies we have done on breast cancer were made on the right sized tumours," he says.

Latest data recently reported from a major project shed more light on how variations in basic parameters can affect patient treatments. The Sloane Project – a UK audit of non-invasive breast cancers and atypical hyperplasias detected in the breast screening programme – collected data from 8,313 patients with DCIS (ductal carcinoma in situ) from 2003 onwards. It has found that many women had a mastectomy for DCIS either as a result of failed breast conservation surgery (799 women, mostly where disease extent had been underestimated) or for tumours that turned out to be smaller than 20 mm in diameter and so should normally have had a lumpectomy (510 women). In total, nearly half of mastectomies were in these two groups (*EJC* online 26 May 2014).

Jeremy Thomas, a consultant breast cancer pathologist at Western General Hospital, Edinburgh, who led the study, says that analysis of the data shows wide variations in mastectomy rates between hospitals. He believes variations in the quality of the pathology are partly to blame. "There are two areas I feel are probably critical in these DCIS cases. One is the quality of the multidisciplinary assessment, in particular between imaging and pathology, where the pathologist is adding crucial information on whether the lesion is indeed DCIS or not, the grade of the lesion and the extent of suspicious calcification. The second is speculation – there are probably differences in zeal among units for carrying out breast-conserving surgery."

Involvement in the team

All cancer pathology depends heavily on rigorous multidisciplinary communication and constant evaluation of how teams are assessing critical parameters such as tumour size and grade, says Thomas. "Above

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"The results showed that as many as one in seven patients had been put into the wrong risk classification"

"It just shouldn't be an option whether to go to the multi-disciplinary meeting – we should always aim to do so"

all, it just shouldn't be an option whether to go to the multidisciplinary meeting – we should always aim to do so," he says. And as Rutgers told the EBCC manifesto session: "It's about precision medicine – no guideline can beat a multidisciplinary board meeting with optimal pathology to hand."

Thomas argues that, even where there are no large teams with specialist consultants, it is possible to organise part-time specialists in tumour types. He adds, however, that small services probably won't have the capacity that larger centres have to hold weekly breast pathology team meetings, where the intricacies of say a rare phyllodes tumour may be discussed, often with trainees in attendance, which in this tumour could have important implications for recommendations on the extent of surgery.

While many pathologists and their services are subject to external assessment and accreditation around Europe, a review this year in the UK is highly critical of the lack of accountability the country's pathology services have to the health system and to patients. The Pathology Quality Assurance Review was prompted by problems with breast cancer tests at an English hospital over several years where a number of women should have received different treatment, and about 80 women were recalled, while some may have died because of the mistakes.

While noting that the UK and the Netherlands were the first European countries to introduce a laboratory accreditation scheme for pathology, the review says the current system "relies almost entirely on professionalism and goodwill." It calls for pathology to be visible to patients and accountable to commissioners, especially given the rapid advances in the field and the variation among services, and for more assurance of the clinical effectiveness of pathology. Many recommendations are made that could also be applicable across Europe, such as for standardisation to cut variations in practice, improving training, sharing of error reporting, and updating accreditation to show clearly which laboratories are doing more than what has been minimally acceptable.

The European breast cancer pathology manifesto also includes generally applicable organisational actions, but notes that such calls need to be realistic given that pathology is currently suffering from a shortage of specialists and huge workloads around Europe.

Attracting more doctors to take up pathology would certainly seem to underpin its future and there is no shortage of exciting issues, in particular the major advances in molecular pathology for which more specialists are urgently needed to both treat cancer and research its treatments. Technology such as digital imaging of specimens and telemedicine can help greatly with the problems of lack of specialised expertise in remote clinics.

Rare cancer pathology

If shortage of specialist pathologists, especially in remote clinics, is a problem in the field of breast cancer, the challenge is considerably greater when it comes to cancers that are much less common.

The particular issues that pathologists face when encountering rare cancers such as sarcomas have been explored in a previous issue of *Cancer World* (May–June 2013). Data from studies show that a large number of diagnoses of sarcoma in Europe are wrong, and that without robust second opinion systems, opportunities to provide the correct treatment can be missed and in some cases irreversible mistakes made.

Not only is sarcoma rare, but it also comprises many different subtypes that only those with expertise and a sufficient volume of cases should diagnose.

A survey carried out by Rare Cancers Europe in 2012 (Pathology in Rare Cancers International Survey, http://tinyurl.com/rare-pathology) found low standards in pathology in eastern and southern Europe in particular, and a need for more education and training. Only two countries (France and Sweden) currently have mandatory referrals to expert centres.

This February, in an effort to draw attention to these worrying findings, and build political support for action, a consensus on rare cancer pathology was launched at a meeting at the European Commission, hosted

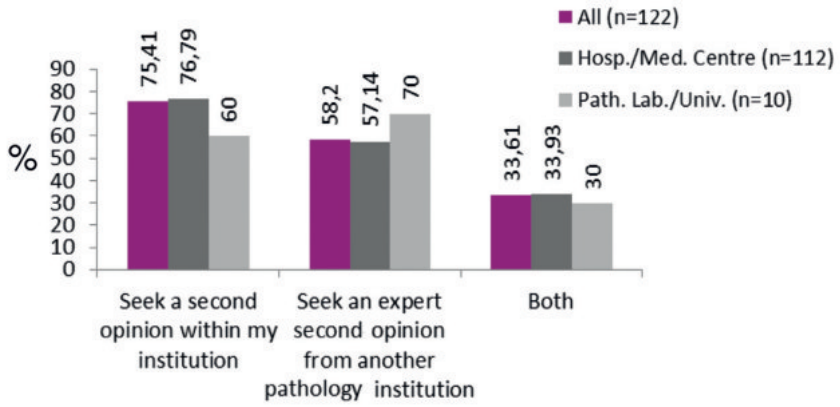
by MEP Zofija Mazej Kukovič. This was a joint initiative between Rare Cancers Europe, ESMO and the European Society of Pathology, and was preceded by an all-day meeting at which each group of rare cancers – sarcomas, rare urological and lung cancers, neuroendocrine tumours and so on – was discussed from a pathology perspective and parameters agreed.

The co-chair, Paolo Casali, a medical oncologist and sarcoma specialist at the Istituto Nazionale dei Tumori in Milan, talked at the launch meeting of the 'tragedy' that 30–40% of diagnoses of rare cancers could be wrong, if sarcoma studies are anything to go by. He pointed to differences in survival of patients with sarcoma across Europe. "The pathological diagnosis may be one of the crucial factors underlying these discrepancies," he said.

Angelo Dei Tos, the group's other co-chair and head of pathology and oncology at the General Hospital in Treviso, Italy, gave a vivid example of a patient who died after being misdiagnosed with GIST, and given escalating doses of Glivec, when in fact she had another type of sarcoma that should have been treated differently.

The overall consensus for rare cancer pathology, said Casali, is on three points: referral to expert pathologists is crucial; there should be networks that arrange referrals; and pathologists should be in multidisciplinary teams where they are challenged to do their best work.

REQUESTS FOR SECOND OPINIONS



In a survey of pathologists conducted by the European Society of Pathology and Rare Cancers Europe, more than one-third of respondents based in hospitals/medical centres did not seek a second opinion from an outside institution in cases of 'suspicious' or 'atypical' samples

Source: Pathology in Rare Cancers: Summary Report, http://tinyurl.com/rare-pathology

Achieving all three, he accepted, is not always easy.

Pathologists with expertise in rare cancers are generally in short supply, and it can be hard to sustain expert multidisciplinary teams without high levels of centralisation. And as Anastassia Negrouk, from the EORTC (European Organisation for Research and Treatment of Cancer), pointed out, there are few reference centres that have the quality controls, open access to data and networking in place that the EORTC would like to see.

Furthermore most patients and doctors have little knowledge of those that do exist, which can lead to delays in referral. While the potential for setting up European reference networks has been enhanced by the cross-border healthcare directive, which came into force in 2013, it was noted that questions remain over how they will be funded.

In the meeting of experts that preceded the Commission event, many complex issues about each family of rare cancers were discussed, which will form the basis for a position paper that presents expert consensus across rare cancer pathology. Getting action around this consensus will, however, require political pressure if rare cancer care is to be better resourced and readily available in more places – not least, a change in attitudes that too often see pathology as a cost centre rather than an essential factor in quality care. ■

"30–40% of diagnoses of rare cancers could be wrong, if sarcoma studies are anything to go by"

All the benefits of expert

When key figures in European cancer nursing gathered at the Royal Marsden to mark 30 years of EONS, they found they had a lot to celebrate – and a lot more work to do.

JANET FRICKER

"All people affected by cancer across Europe will benefit from the care of well-educated, well-informed and highly competent cancer nurses, who will play a central role in providing support, promoting health and improving clinical outcomes." Such is the vision of the European Oncology Nursing Society. Though it remains far from being realised, in many countries the role of specialist nurses in planning, delivering and also researching cancer care has been transformed since EONS was founded in 1984.

To celebrate its first 30 years, and plan how to build on its achievements, EONS held an anniversary event in April. One hundred people were on the invitation list, including 10 past presidents, who between them offered a wonderful insight, through a series of interviews conducted by BBC reporter Nick Owen, into how the fledgling nursing society developed (see page 44).

"EONS has become the voice of cancer nursing," EONS President Erik van Muilekom told the assembled guests. "We should be proud of what we have achieved, but need to continue to improve European cooperation to further the professional development of cancer nurses."

It was particularly apt, he said, that the anniversary event was being held

nursing care

at the Royal Marsden Hospital, London, since it was here that EONS set up its first office when it was founded in 1984 as the Fellowship of European Oncology Nursing Societies.

The idea of forming a society linking cancer nurses working across Europe was first mooted at the 2nd European Conference on Clinical Oncology and Cancer Nursing, held in Amsterdam in November 1983, recalled Rosette Poletti, a Swiss cancer nurse who became EONS' first chairperson in 1984. "At cancer meetings we were never in charge, just invited. In Amsterdam we networked and decided we should take things into our own hands and form a nursing society," she said.

From the outset EONS looked to reposition the role of cancer nurses on the grounds that nurses have the most sustained involvement with the care of patients and should have equal status in multidisciplinary care. It also wanted to provide cancer nurses with a sense of community.

Robert Tiffany, who was appointed the first President of EONS in 1985, is widely acknowledged as a driving force behind the creation of the society. Working at the Royal Marsden in the late 1970s, Tiffany had pioneered the concept of clinical nurse specialists in oncology and helped set up the first oncology nursing courses. He firmly believed that cancer patients had the right to be nursed by a highly qualified skilled work force. "The thing Bob

Robert Tiffany, the first President of EONS (1985–1987), pioneered specialist education for cancer nurses, and understood the need for cancer nurses to collaborate to develop their own speciality and play a central role in planning and delivering patient care as equal members of multiprofessional teams

did was to take nurses internationally and get them to work together in a collaborative way that meant the whole was bigger than the sum of the parts," said Shelley Dolan, the current Chief Nurse at the Royal Marsden. Sadly Tiffany, who was universally acknowledged as the world's leading cancer nurse, died in 1993 aged 50.

Today EONS has matured into a dynamic organisation with 23,000 members from 33 oncology nursing societies spread across 31 different countries, offering a unique platform for national cancer nursing societies to present a united voice. The latest recruit to the EONS family is Palestine, who joined the organisation in February this year.

Realising the vision

For EONS, education has always been the key to developing specialist cancer nurses, and getting recognition for their role and status. The EONS Cancer Nursing Curriculum, now in its 4th edition, has helped to create an international education framework for cancer nurses. The curriculum provides the essential scientific, psychological and

EONS in the words of the presidents

Rosette Poletti: First chairperson

"It all started much earlier than 1984. As oncology nurses, many of us were invited to meetings, but were never in charge. At the 2nd European Conference on Clinical Oncology and Cancer Nursing, held in Amsterdam in November 1983, there were many nurses from different countries who networked and decided to take things into our own hands. We asked for a room, had a meeting and decided to create something that would be a nursing society for oncology nurses. I took charge for a year, then in 1985 I said to Bob Tiffany, 'You're the one who's at the centre, you should be president.' EONS became something that changed the lives of many nurses around the world."

Hansruedi Stoll: President 1991–1993

"The highlight of my presidency was when I signed the European Cancer Societies' curriculum on cancer nursing. Here a group of cancer nurses from EONS produced a curriculum intended to be the standard of teaching cancer nursing throughout Europe. The saddest moment of my presidency was when Bob Tiffany died."

Elisabeth Holter: President 1988–1990

"Robert Tiffany, the first president of EONS, was very inspiring enthusiastic and impressive. He was a celebrity, a star who was known all over the world and had a lot of charisma. In the first few years of EONS all the work was about professional development, and establishing nursing research."

Kathy Redmond: President 1994–1997

"I think EONS inspired cancer nurses. It gave them a vision of how they could contribute to cancer outcomes and be proud of that. The status of nursing across Europe at that time was very diverse. Some nurses were seen as low-level workers whose contribution was not respected. This has changed dramatically – EONS has helped to give nurses confidence that they have a contribution to make.

"As EONS president, I managed to leverage my Irish connection to lobby the then EU Commissioner for Health, Pádraig Flynn, to secure a seat for cancer nurses on the Europe Against Cancer committee. My involvement at European level also helped me recognise that Irish cancer services needed improvement, and I was pleased to be appointed as a nurse to the first Irish National Cancer Forum, which led to fundamental changes in cancer services in Ireland and improved cancer outcomes."

sociological information nurses need to provide care that minimises the trauma of cancer, and maximises outcomes for patients and their families. It is flexible in design so that nurses can adapt the framework for their own country and professional circumstances.

More specific European curricula have also been developed for nurses working with breast cancer, lung cancer and older patients, and for nurses seeking to develop skill and knowledge in the assessment and management of particularly serious or troubling side-effects. The TITAN project, for instance, covers thrombocytopenia, anaemia and neutropenia. An annual Masterclass, run jointly with the European School of Oncology, offers advanced nurses the opportunity to learn alongside clinical oncologists on a week-long full-immersion multiprofessional course. The opportunity the event brings to raise awareness among the doctors of the untapped potential of cancer nurses is an added bonus.

To get the best possible patient benefit from specialist nursing care requires research to develop a strong evidence base, so supporting nurse-led research, is another key plank of EONS' work. EONS research grants allow nurses to carry out significant research projects, while travel grants enable them to spend time in other countries to build collaborations and facilitate research proposals. Cancer nurses can also attend one of the research proposal workshops run by the society to help them develop their confidence and skills in what can be a highly complex and competitive task. Research results are presented at EONS' own scientific conference and at the nursing track of ECCO, the European Cancer Congress, which take place on alternate years.

Perhaps the most important requirement for realising the true potential of specialist cancer nursing, however, is still effecting a change in attitudes within the medical establishment – this is more of an issue in some countries than in others. Advocacy therefore remains an important part of EONS' work. The society's status as a founding member of the Federation of European Cancer Societies, now morphed into ECCO, is important here, as is pressure exerted by its member organisations at a national level.

Looking ahead

Looking to the next phase of the society's development, president-elect Daniel Kelly told the meeting that Europe faces many challenges regarding cancer, including ageing populations, cancer patients with multiple comorbidities, fast-changing treatments and more health-literate patients. In the future, many oncology nurses are likely to find themselves working in community settings away from specialist centres. "EONS is going to have to think

Nora Kearney: President 1997–1999

"I signed the agreement for the first Masterclass with the European School of Oncology, based on the collaboration that Kathy had established. I was the first President Elect, so I was aware what the work would be like. It was very challenging. I remember for two months being in two different countries every week, and having to maintain my hospital work. What made it possible were the people you met on the journey.

The experience of EONS is something that I'd recommend to everyone. It stretches your ability to work at a very high European level politically and professionally. It was an amazing time."

Agnes Glaus: President 1999–2001

"I was involved in teaching on the first European Oncology Masterclasses, which gave us a platform as nurses to teach other health professionals. We used the slogan 'learning to care', which I liked because it encouraged people to be curious and learn together at different levels. The Masterclasses were the start of a new way of professionalism for nurses."

Giel Vaessen: President 2001–2003

"We developed excellent teaching models and workshops. The challenge was to encourage people to go back to their own countries and teach their colleagues."

Yvonne Wengström: President 2005–2007

"At the time of my presidency the use of endocrine treatment in breast cancer was increased from two to five years. We realised that there was a need for new information for patients around treatment and side-effects, which led to more intense collaborations with patient groups across Europe. We developed models to support nurses working in different countries.

"During my presidency the society had undergone a real growth spurt and I was receiving 150 emails a day. When EONS was 20 we realised that we had to build the infrastructure and appointed the first executive director."

Sultan Kav: President 2009–2011

"In my presidency we developed working groups under the CARE strategy involving communication, advocacy, research, and education. The main idea was to engage more with our members."

Sara Faithfull: President 2007–2009

"I identified that men with prostate cancer were a big group who didn't have nursing support. We undertook a survey of around 1000 patients to find out about the areas where patients felt they needed more support, and talked to nurses. We discovered a disconnect. The nurses wanted more technical expertise, while patients were saying they wanted more psychological and symptom management support. We found that when nurses were well informed symptoms were well managed, but if nurses were poorly informed it was worse than having no nursing care at all!

"When UK charity laws changed we had to do work around the membership requirements to put in place a more professional organisation. This was the time that the website was created, and the online learning resources established."

Birgitte Grube: President 2011–2013

"At ECCO 2013 in Amsterdam we celebrated our birthday and invited all the presidents from the other organisations, including ESMO, ESTRO and ESSO, to come to our session. We now hope to collaborate with them in a multiprofessional way to develop educational initiatives at the EU level.

"The whole structure, organisation and administration of EONS works really well now and we're on top of the work. Being president of EONS is the best thing that I have ever done. It is such a huge experience and you learn so much from it, but it uses up all your spare time and more."

about how we manage the growing complexity. We are going to have to consider how we support nurses who are making decisions with patients, rather than for patients," said Kelly.

He highlighted the challenges that remain across Europe in having cancer nursing recognised as a specialty in its own right. "In some countries you need a specialist qualification to become an oncology nurse, whereas in others cancer nurses learn on the job; in some countries there are nurse-led services, whereas in others nurses are expected to carry out specific tasks," he said. EONS aims to give members the confidence to see themselves as valuable members of the multidisciplinary team, he added. "We want to ensure that cancer nursing is recognised throughout Europe as a specialty with its own qualifications and training."

Ultimately, said Kelly, EONS would like to lobby for an equal standard of oncology nursing education across Europe that would deliver parity in terms of certification, and allow nurses to work across European borders.

"As an organisation EONS has always been flexible and innovative," he said. "We need to continue to evolve in order to survive in the changing world of cancer care." ■

Nutritional support for cancer patients

Patients who are receiving adequate nutrition have a better prognosis, respond better to chemotherapy and can tolerate higher doses of anticancer treatments. It is therefore important for oncologists to assess and manage malnutrition.

Malnutrition, which is easily identified during clinical examination by weight loss and hypophagia, is an independent negative prognostic factor for cancer patients. Nutritional health can be considered based on a person's protein status. This is very important because there is no store of protein in the body, yet each protein has a specific function, for example as an enzyme, antibody, or contracting muscle protein or transport protein. The severity of malnutrition is often related to the degree of the protein depletion.

Nutritional health can be defined as having 100% of body protein (see figure overleaf). Depending on the duration of starvation or the cause of malnutrition, protein depletion leads to loss of organ function. This starts with decreased muscle mass (skeletal, cardiac and smooth muscle), followed by decreased visceral proteins, including albumin, transferrin and transport protein. Further protein malnutrition results in impaired

European School of Oncology e-grandround

ESO 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 Federico Bozzetti, from the University of Milan, Italy, reviews malnutrition as an independent negative prognostic factor in cancer, and looks at how to identify which patients are at risk and how to support them. The material is based on a recent review (*Crit Rev Oncol Hematol* 87:172–200). Nada Kozjek, from the Institute of Oncology in Ljubljana, Slovenia, poses questions raised by participants during the live online presentation. Edited by Susan Mayor.

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

immune response, which is compromised with the decrease of lymphocytes and synthesis of antibodies and acute phase proteins. This can be seen in a surgical patient, with impaired wound healing. The next step in protein depletion is impairment of organ function – gut, liver and heart. Finally, further protein depletion leads to a poor adaptation to any minimal biologic stress, which can prove to be fatal. Nitrogen death was defined thirty years ago as when 30% of body nitrogen has been lost. This depletion is incompatible with survival.

So-called secondary malnutrition (the type commonly associated with a serious infectious or neoplastic disease) leads to protein depletion, and differs from pure starvation, such as in anorexia nervosa, where visceral proteins are maintained and remain stable until weight loss is extreme. In cancer or sepsis, where there is an inflammatory status, the decrease of visceral proteins is common.

Several studies have identified malnutrition as an independent negative prognostic factor for survival in patients with a variety of malignancies. We have very extensive evidence to show that malnutrition plays a major role in predicting poor prognosis, based on measuring weight loss,[1] low bioelectric phase angle[2–10] or depletion of body protein or fat with sophisticated laboratory methods.[11,12] On clinical grounds, the Prognostic Nutritional Index[13,14] and the Glasgow Prognostic Score[15] are very effective in identifying patients with a poor prognosis.

Malnutrition not only compromises survival, but also has a major adverse effect on the quality of life. Studies have shown that malnourished cancer patients have:

- higher rates of hospital readmissions and longer hospital stays[16,17]
- increased symptom distress[18]
- reduced quality of life, based on usual questionnaire for cancer patients[19–24]
- reduced muscle strength and functional status[8]

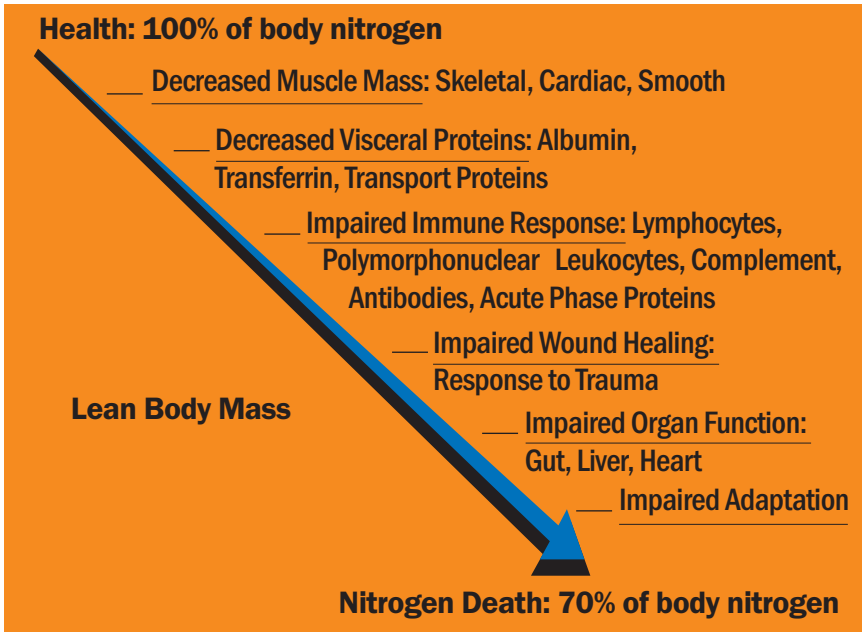
All of these studies have identified malnutrition as an independent factor that adversely affects the quality of life.

Importantly for oncologists, malnutrition increases chemotherapy toxicity. This has been demonstrated for weight loss and hypoalbuminemia[25] and low total body nitrogen as a predictor of neutropenia.[26] It has also been demonstrated for sarcopenia as a significant predictor of toxicity, based on CT scan.[27] It is also true for patients with a body mass index (BMI) lower than 25kg/m².[28] All of these factors have been found to be associated with poor adherence to chemotherapy, and high toxicity.

Malnourished cancer patients also have poorer responses to chemotherapy, both in terms of the percentage of patients responding to chemotherapy and the duration of response to treatment.[29,30] The fact that malnourished patients have a poor prognosis, are more likely to have poor responses to chemotherapy, and have increased toxicity means that it is important for oncologists to assess and manage malnutrition.

Question: *We have so much data, going back more than 40 years, so why are people still trying starvation*

CONSEQUENCES OF VARIOUS DEGREES OF PROTEIN DEPLETION



diets to kill their cancer and why is the awareness of the negative impact of malnutrition still so low among oncologists?

Answer: *When patients die because of cancer there is often a combination of cachectic status due to the inflammatory reaction that we know is a major contributor to the weight loss, metabolic derangement and poor nutrient intake. For oncologists and other clinicians it is not clear whether a cancer patient has died because of tumour progression or starvation. Some patients with a slowly progressing tumour or a tumour not involving vital organs could survive for some months, but they die sooner because they do not eat enough. The problem is related to the fact that it is difficult to separate the morbidity and mortality that is due to the simple deficiency of macronutrients from the alteration of metabolism that is due to inflammation, which is a major cause of cachexia. So many oncologists have a nihilistic approach and do not try to feed cancer patients in an optimal way. In contrast, I suggest that these patients should be supported in the best possible way with nutrition.*

How can we identify cancer patients at nutritional risk?

There are several nutritional screening tools, but the most important and most commonly used in hospitals are shown in the table above. The Malnutrition Screening Tool (MST) relies mainly on unintentional weight loss and appetite, so it is very simple to use this score if a hospital has limited resources. The Nutritional Risk Screening includes more parameters: unintentional weight loss, BMI, severity of disease, age, and impaired general condition, with scores ranging from 0 to 7. An important point about this screening tool, which is commonly used in Europe, is that it was developed to identify not only malnourished patients but also those who may improve with nutritional support.

The Malnutrition Universal Screening Tool (MUST) is widely used in the UK and Europe, and includes unintentional weight loss, BMI, severity of disease and food intake. The Short Nutritional Assessment Questionnaire (SNAQ) asks questions about unintentional weight loss, appetite and use of oral supplements or tube feeding. A very interesting and comprehensive review on screening tools by Marian van Bokhorst[31] found there is no perfect screening tool, and none of the tools are better than the others, but concluded that the important thing is to use a tool to assess patients from a nutritional point of view.

Question: *Which malnutrition risk screening tool would you recommend?*

Answer: *It depends on the situation. I used the Nutritional Risk Screening 2002 tool (NRS-2000) for my studies, and we published at least two studies demonstrating that nutritional risk is correlated to the type and stage of a patient's tumour. In routine clinical practice, if I realise that a patient is anorexic because they say they have no appetite, relatives report that the patient is not eating and the patient has lost weight, this information is enough to consider nutritional support. However, if you want to stratify for trials of nutritional support, I would recommend the NRS-2002, though this is not because it has been demonstrated to be better than the others. Ideally in routine practice a patient's chart should include a space to report their nutritional risk.*

Ways to provide nutritional support to cancer patients

The approach to nutritional support depends on the availability of a working/accessible gastrointestinal (GI) tract. Very simply, we can consider nonsurgical cancer patients identified

COMPARISON OF MALNUTRITION RISK SCREENING TOOLS

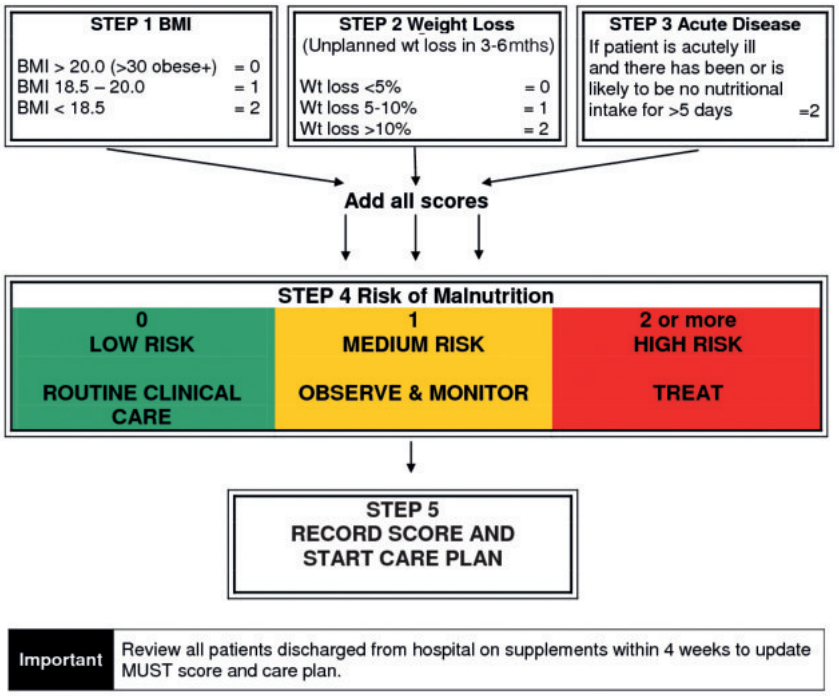
Malnutrition Risk Screening Tools	Description	Parameters Used
Malnutrition Screening Tool (MST)	MST is a simple, quick-to-administer, 2-question tool.	Unintentional weight loss[a] Appetite[a]
Nutritional Risk Screening–2002 (NRS-2002)	Developed by ESPEN, this is a preferred tool to screen for malnutrition in European hospital settings.	Unintentional weight loss[a] BMI[a] Disease severity Age Impaired general condition
Malnutrition Universal Screening Tool (MUST)	Developed for screening in the community, MUST is widely used in the United Kingdom and Europe.	Unintentional weight loss[a] BMI[a] Disease severity Food intake[a]
Short Nutritional Assessment Questionnaire (SNAQ)	A simple, easy-to-administer, 3-question screening tool developed in the Netherlands for hospital screening.	Unintentional weight loss[a] Appetite[a] Use of oral supplement or tube feeding

It is important to screen patients for nutritional status; the choice of screening tool is less important

BMI – body mass index; ESPEN – European Society for Clinical Nutrition and Metabolism

[a] Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition diagnostic characteristic

MUST MALNUTRITION UNIVERSAL SCREENING TOOL



This screening tool, developed by BAPEN, the British Association for Parenteral and Enteral Nutrition, is one of several tools that can be used to assess patients' nutritional status

as malnourished at nutritional risk in three broad groups:

- patients with the whole GI tract working
- patients with the upper GI tract inaccessible
- patients with the whole GI tract inaccessible or not working.

In patients with the whole GI tract working, I think the first approach is oral nutritional intervention with supplements, which are better if enriched with omega-3 or leucine, with or without dietetic counselling and megestrol. However, sometimes we may also consider supplementary intravenous nutrition. In patients who already have a central line it is sometimes easier to give nutritional supplementation by vein than forcing oral intake or using a tube.

What are the effects of oral supplementation?

Dietary counselling alone does not ameliorate quality of life, but dietary counselling plus nutritional supplements improves weight more than dietary counselling alone or usual care.[32–34] Dietary counselling plus nutritional supplements improves quality of life, according to two studies.[35–37] However, oral nutritional intervention has no effect on cancer mortality.

An experimental diet high in protein and enriched with 10% free leucine was found to significantly improve the muscle protein fractional synthesis rate compared to a standard diet.[38] A study giving amino acids rapidly in high quantity (40 g), given as a bolus, increased the mixed muscle fractional synthesis rate in cancer patients undergoing intense chemotherapy.[39] These studies show that giving amino acids as a bolus or an enriched leucine diet can improve muscle synthesis in cancer patients, despite chemotherapy or inflammatory status.

There is some controversy over supplements enriched with omega-3 fatty acids, according to four systematic reviews and two meta-analyses.[40–45] One meta-analysis concluded that omega-3 supplementation increased lean body mass in cancer patients, while the other found no improvement.

Recent non-randomised clinical trials have shown that omega-3 fatty acids increased lean body mass in patients with head and neck cancer[46] and increased the muscle mass, body weight and response to chemotherapy in patients with lung cancer.[47]

Recent randomised controlled trials, not included in the previous meta-analyses, demonstrated improved quality of life in patients with lung cancer,[48] as well as reduced leukopenia in patients on neoadjuvant chemotherapy for oesophageal cancer,[49] and reduced weight loss and higher remission rates in leukaemic patients receiving omega-3 fatty acids.[50]

How can we optimise the use of oral nutritional supplements? An excellent systematic review[51] found greater adherence to higher-energy-density supplements (91% with 2 kcal/ml). Adherence was probably better with liquid oral nutritional supplements. This sort of energy

supplement should be in addition to food, with clinical benefits when the intake was in the range of 300–600 kcal/day for more than five weeks.

Dietary energy density was positively associated with energy balance. Survival was positively associated with energy balance while systemic inflammation had a negative association. The review recommended using omega-3 fatty acids and/or leucine-enriched oral nutritional supplements. When amino acids are used, they should be given as a bolus.

Patients with inaccessible upper GI tract

Options for patients with an inaccessible GI tract are tube feeding using either a nasogastric tube or percutaneous endoscopic gastrostomy, where the tube feeds directly into the patient's stomach, passing through their abdominal wall.

There is a lot of experience in patients with head and neck cancer, during radiation with or without chemotherapy, and many non-randomised trials report better weight maintenance and quality of life, as well as better adherence to therapy and fewer hospital admissions, compared with oral feeding.

A randomised clinical trial comparing percutaneous endoscopic gastrostomy with use of a nasogastric tube found that percutaneous endoscopic gastrostomy was associated with better weight maintenance and a longer duration of enteral nutrition[52,53] as well as a similar[52] or better[53] quality of life. The results are quite limited so we cannot recommend percutaneous endoscopic gastrostomy over nasogastric feeding.

Patients whose whole GI tract is inaccessible or not working

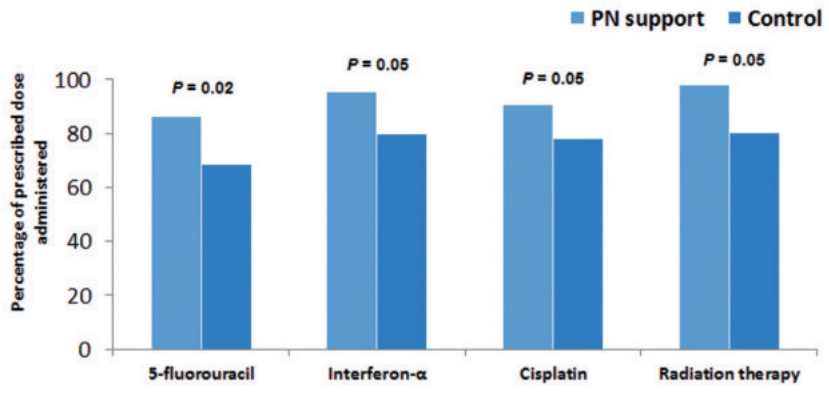
You are obliged to use parenteral (intravenous) nutrition in patients whose GI tract is inaccessible or not working. There is little scientific experience and very few randomised trials, but the approach is very practical and well accepted by those patients who already have a central venous catheter and may not be able to differentiate between therapy and nutritional support. This may be important from a psychological point of view, as the patients do not realise that they are so compromised that they require nutritional support to survive. Small-volume high-density emulsions can cover a large part of the patient's energy requirement, so they can be used easily in home environments.

Supplemental parenteral nutrition can be useful in patients whose GI tract is only partially obstructed or who are partially aphagic (have a reduced ability to swallow), because delivery via a vein may be more comfortable for them and is easier than putting a tube in the stomach or forcing oral nutrition. A randomised study in patients with cancer of the oesophagus showed those fed by parenteral nutrition were able to receive higher doses of chemoradiation therapy (see figure below) without increased toxicity, compared to controls.[54]

A recent Chinese study identified malnourished cancer patients using a nutritional screening tool and treated them with enteral or parenteral nutrition. In comparison with patients who did not receive any nutritional treatment, those who received enteral or parenteral nutrition had a significantly reduced risk of developing adverse events. The authors concluded that undernutrition and nutritional risk are common problems that impact on outcomes of hospitalised cancer patients.[55]

There are few studies on the use of supplemental parenteral nutrition at home, but one study showed giving supplemental parenteral nutrition intravenously in cachectic patients who were not totally aphagic when their oral intake dropped to 21–24 kcal/kg/day was

NUTRITIONAL SUPPORT AFFECTS ANTICANCER THERAPY DOSE



A study of patients with oesophageal cancer showed that parenteral nutrition (PN) increased the dose of chemoradiation therapy patients could receive without suffering increased toxicity

Source: Adapted from SS Sikora et al. (1998) *JPEN* 22:18–21

associated with an increase in energy balance, longer survival and improved maximum exercise capacity.[56] A further study demonstrated an increase in lean body mass in cancer patients receiving supplemental parenteral nutrition.[57]

We conducted a study in 414 incurable cancer patients who were cachectic and almost aphagic using parenteral nutrition at home. Results showed a six-month survival of 28% and a three-month survival of 57%.[58] In contrast, according to the literature, without nutritional support these patients would have survived less than three months.

We were also able to identify some simple biochemical/clinical prognostic factors that predict a higher rate of three-or six-month survival in patients on home total parenteral nutrition. A randomised trial cannot be carried out for ethical reasons, but comparison with evidence in the literature suggests that survival can be prolonged with parenteral nutrition at home. Home parenteral nutrition may therefore prolong survival in selected incurable cancer patients who are cachectic and aphagic, usually with malignant obstruction, and who do not have jaundice or major liver, renal or respiratory insufficiency.

According to the guidelines of both the American Society for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism, the routine use of enteral or parenteral supplementation during chemotherapy is not recommended. However, if patients are malnourished or facing more than a week of starvation, then oral nutritional supplements and/or enteral nutritional support should be considered (grade B recommendation, with supporting evidence in the literature). If this is not feasible, then parenteral nutrition is recommended.

If patients develop GI toxicity from chemotherapy or radiation therapy, short-term parenteral nutrition may be better tolerated (and more efficient) than enteral nutrition to restore intestinal function, prevent nutritional deterioration and allow full adherence with therapy (general consensus statement). ■

The references cited in this article can be accessed online at www.cancerworld.org

To treat or not to treat: who should decide?

HANNEKE WM VAN LAARHOVEN, INGE HENSELMANS AND J (HANNEKE) C DE HAES

Shared decision making is ethically sound and the evidence shows it leads to better outcomes. But if a patient is determined that they want no part in the decision, is it paternalistic to insist?

Mr C was an aristocratic, 79-year-old Surinamese man. He visited my outpatient clinic because of a pT4aN1a colon carcinoma. After surgery, he went to a rehabilitation centre, but he was improving day by day and was determined to get home as soon as possible. Given his high-risk colon carcinoma, he had an indication for adjuvant chemotherapy with capecitabine and oxaliplatin. However, adjuvant chemotherapy could also hamper his rehabilitation process. Together we extensively discussed the pros and cons of adjuvant treatment. Afterward, Mr C seemed quite certain: the increased chances of living without cancer outweighed the risk of side-effects of chemotherapy. Nevertheless, I suggested he think it over and discuss the issue with his relatives. Two weeks later, Mr C came in again, accompanied by his sister. Despite the hesitations of his sister ("Isn't quality of life far more important than quantity of life?"), it seemed as if he was even more determined to start adjuvant treatment. His physical condition had remarkably improved, and, after he had received further oral and written information on the specific treatment regimen from our oncology nurse, we decided to start chemotherapy.

When I saw him after the first course of chemotherapy, he looked quite well. When I asked him about the past three weeks, however, he told me they had been awful. Mr C was in serious doubt: with respect to his chances of survival, he wanted to go for the maximum, but this reduction in quality of life was really not what he wanted. Although I could not pin down the exact toxicity he had experienced, the message was clear: he was not going to complete adjuvant chemotherapy in this way. For

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

a moment, I considered a dose reduction of oxaliplatin, but then decided to propose stopping oxaliplatin altogether. The added benefit of oxaliplatin to capecitabine in patients older than 70 may be limited,[1] and oxaliplatin presumably was the major cause of my patient's feelings of weakness and reduced walking ability. Also, I had the impression that the next course would be 'make or break'. If it did not go well, he would probably completely stop his adjuvant treatment, which would be a pity given his wish to go for the greatest chances of survival. Mr C and his family agreed to continue with capecitabine monotherapy.

I saw Mr C and his sister again four weeks later. In fact, he was one week late; he had accidentally extended his capecitabine-free period by one week. Nevertheless, he told me he felt terrible: he had lost weight and was using his cane to walk. He actively announced he wanted to reconsider chemotherapy. I asked him to step on the scales: 64 kg. This was exactly the same weight as when he started chemotherapy. Why then was Mr C telling me he had lost weight? And why did he complain about walking with a cane? He had been walking with a cane all the time! Again, Mr C reported side-effects of chemotherapy that I could not really confirm. How to continue? A dose reduction of capecitabine might help, but by extending his capecitabine-free period, Mr C had already effectively performed a form of capecitabine dose reduction. Was a further dose reduction going to help him? I did not think so. Wasn't Mr C actually telling me he wanted to stop the treatment? I asked him so. He denied

"Why had I made this decision when I feel so strongly that this kind of decision making should be shared?"

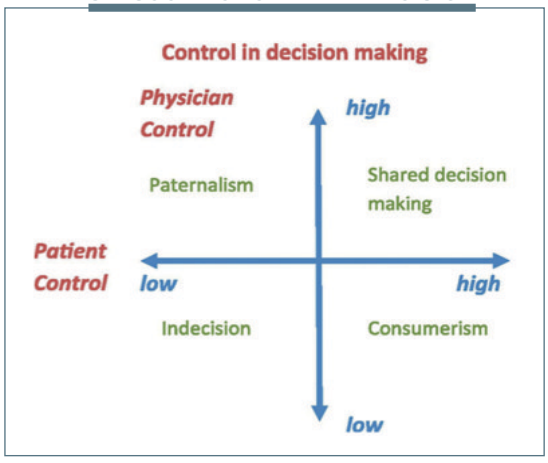
this. Stopping was not really what he himself wanted to suggest. He wanted to know my expert opinion. I explained that in his case the choice to stop or to continue treatment was not just a medical decision but a decision that needed input from his side, too. Technically speaking, I had no formal reasons to stop adjuvant chemotherapy. Mr C was clinically well, laboratory results were within acceptable limits, and there were no grade 2 or higher toxicities, so if Mr C wanted to continue, we could continue. But Mr C insisted, "You are the expert". I paused for a moment. What was going on? Why did Mr C not simply tell me he wanted to stop, rather than insisting on my medical expertise? I decided to change gears and asked him how a decision to stop treatment would make him feel. When he swiftly responded, "Relieved," I simply made the decision to stop.

We talked a couple of minutes more about the logistics of follow-up. Then, Mr C and his sister left the room – relieved.

I stayed behind – confused and irritated. Why had I made this decision when I feel so strongly that this kind of decision making should be shared between a doctor and a patient? Being trained in the age of patient's autonomy and rights, shared decision making is a natural part of my consultation with cancer patients.[2] Across cultures, different decision-making models can be identified,[3] but, as a doctor in the Netherlands, I have a legal obligation to inform my patient adequately about the pros and cons of a treatment, and I cannot start treatment without the patient's explicit consent.[4] Although some decisions concerning starting or stopping oncological treatment are clearly medically preferable (e.g. haematological grade 3 toxicity precludes continuation of chemotherapy), many decisions concern a clinical equipoise (i.e. options are equivalent and all appropriate). At this moment, both continuing and stopping adjuvant treatment could be considered appropriate for Mr C from a medical point of view. In such a case, the only adequate way to reach a decision seems to be through shared decision making. Apart from its ethical impetus, evidence indicates shared decision making improves patient outcomes.[5] So, why then did I not convince Mr C to share in the decision to stop his treatment? Should shared decision making sometimes be replaced by a doctor's decision if the patient chooses not to share in the decision making? Or… could the whole process we went through be called shared decision making after all?

Based on the degree of patient and doctor control, theorists have identified four prototypes (or quadrants) of doctor–patient interaction.[6–8] When doctor control is high and patient control is low, the relationship is characterised by 'paternalism', whereby the doctor controls the consultation agenda, and patients' values and preferences are not taken into account. For a long time, doctor–patient interactions could generally be characterised as paternalistic. If, in contrast, doctor control is low and patient control is high, one speaks of 'consumerism'. The patient sets the agenda and takes sole responsibility for the decision; the doctor's role is primarily one of information provider. In modern times, the societal image of a typical patient reflects such an autonomous, assertive, and well-informed consumer. If both patient and doctor control are low, a dysfunctional scenario of 'indecision or standstill' is at hand, and no decisions or

ONCOLOGIST AND PATIENT STRUGGLING TO MAKE A DECISION



CONTROL AND TYPES OF DECISION MAKING

Patient's initial active agenda setting
Patient (P): So, I've a question for you – whether we can have another think about taking those pills – if I should continue or whether we can maybe do away with them completely, or maybe we can go for just the half – so that I would take 5 once a day instead of twice a day. That's what I'd like to talk to you about. So that's my suggestion.

Patient turning back once a final decision to stop is dawning
Oncologist (O): Well, but if you are so clearly saying "this is not what I want," then we should just stop.
P: Well I'm not actually insisting on that. I'm not pushing for that exactly, but that's why, in consultation with you...
O: Exactly, but that's just it... you're not exactly insisting on this, but that's what I think you're saying between the lines – that that is really what you'd like...
P: Yes, uhm... yes... but you know how these things work, the medical science, and I don't. I'm not medically trained, so you can also give me your evaluation. Apart from what I say – of course your opinion counts as well.

Patient's explicit refusal to make the final decision
O: But do you... you're actually giving even more reasons why we should stop.
P: Yes, but I still feel you should have the final say, because you know more about these matters than I do. You know more about chemical values and the results and the effects and the side-effects. I mean... I rely on your knowledge.

Oncologist changing gears
O: OK, but now I'm going to tell you that we'll stop – but then what I want to know is how you'll feel when you leave here. Will you feel relieved when you go out the door – or maybe secretly a bit sad? How will you feel when you go out of here?
P: Well I can tell you straight away – relieved.
O: Well, then the decision's made – we're going to stop.
P: But that's with your conviction...
Sister: Here we go again...
O: ...with my conviction...

progress can be made. Finally, if both patient and doctor have high control, this represents 'mutuality' or a 'shared' model. The agenda is set jointly, patients are told that there are equivalent options, appropriate information is given based on the doctor's expertise, the patient's values and preferred role in decision making are explored, and eventually both parties are satisfied with the decision-making process and the eventual decision.[5,9] This is the prototype of the doctor–patient input that reflects shared decision making, as currently advocated.[10]

Clearly, in the case of Mr C, 'consumerism' was not an issue. Having the consultation ending in 'indecision' was not an option as, in contrast to palliative treatment, in adjuvant treatment the time frame is stringent. Despite my preferred 'shared and mutual' decision-making style, I felt as if I had ended up in the 'paternalistic' quadrant. Although Mr C had set the agenda to discuss the continuation of chemotherapy, and I had explored his values and preferences, in the end I made the final decision, and the ownership of that decision was shifted to my side. However, paradoxically, in a way, in the case of Mr C, shared decision making would have been paternalistic too, as I would have forced him into taking responsibility for a decision from which he seemed to want to defer.

Why was it so difficult for Mr C to share in the responsibility for the final decision? Several barriers to shared decision making can be identified from the literature that may be categorised into the following: a 'lack of competencies' required to take part in the decision-making process; a 'position of dependency' in the patient–doctor relationship, hampering active involvement in decision making; and the 'inability to cope' with the burden of decision making. The modern focus on patient-centred communication requires a high level of communication competence from the care provider but also from the patient. Patients need competencies enabling them to ask questions, act assertively, and express their concerns and feelings.[11] It was shown that less-educated patients more often prefer a passive role in decision making.[12] Also, an exploratory study showed that lay people's confidence in their understanding of cancer-related jargon was related to their perceived efficacy in participating in treatment decision making with a fictive oncologist.[13] Moreover, patients mention barriers to participation such as simply forgetting questions or not knowing how to interrupt the doctor.[14]

Mr C, however, was a well-educated, eloquent man, and competence may not have been a major issue. Possibly the second barrier – dependency in

"Shared decision making would have been paternalistic too, as I would have forced him into taking responsibility"

the patient–doctor relationship – played a role. A patient is in a vulnerable position and can feel too reliant to act assertively in interactions with oncologists. Often accompanying this feeling is a high motivation to trust the doctor.[15] This is supported by the finding that patients often report the fear of being labeled a difficult patient.[14] Although Mr C was actively invited to put forth his decision and was assured by the oncologist that his opinion was valuable to her, it cannot be excluded that this barrier still played a role, given Mr C's pronounced respect for medical expertise.

Finally, patients may choose not to be involved in communication or decision making to protect themselves.[16] This can be a result of their general style of coping with adversity, for example, by 'blunting' or avoiding confrontation with information about adversity or denial.[17,18] Patients may anticipate and fear feelings of regret in the future and may be afraid to take on responsibility for a possible bad outcome of the decision, so-called anticipated regret.[19] Indeed, a larger role in the decision-making process may be related to anxiety in the two weeks following the decision.[20] Hence, making decisions can be a burden for patients. From an ethical perspective, clinging to the principle of autonomy in a liberal individualistic sense and forcing these patients into shared responsibility for a treatment decision may not be beneficial and thus directly in conflict with the ethical principle of beneficence.[21,22] Alternative ethical notions of autonomy exist in clinical practice, including the idea that the patient is entitled the wish not to participate, which is known as procedural independence or Socratic autonomy.[23]

Shared decision making suggests that in the process of decision making the patient and the doctor are partners who, ultimately, reach a decision for which the responsibility is shared. We advocate that healthcare professionals should do the utmost to lift the patient barrier of incompetence, for example, by avoiding jargon, providing written information, and actively inviting patients to ask questions and express their concerns and feelings, as well as to lift the barrier of dependency, for example, by making explicit that a patient's opinion is valuable in the decision-making process. However, if patients are unable to cope with the burden of the ownership of the final decision, we should be willing to relieve this burden by offering to take on this responsibility. Likewise, to avoid running into paternalism, clarifying the patient's preferred role in decision making as well as exploring the values that would have to be taken into account from the patient's perspective is critical. In fact, by exploring the fears implicated in Mr C's reluctance to share in the decision making and explicitly asking whether he wanted me to make the decision, both the ethical principle of autonomy and the principle of beneficence could have been done justice.

In conclusion, the emphasis of the last decades on patients' autonomy and patients' rights to make decisions regarding their medical treatment may have obfuscated the fact that, for a variety of reasons, patients may not be able to make a decision. We believe that, when striving toward shared decision making, the focus should be put on the steps taken to reach the final decision, rather than on the amount of 'sharedness' in the responsibility for the final decision. In this way, the role the patient wants is respected, and the patient's values and preferences are taken into account. We advocate that an optimal medical decision is one that integrates information about the patient's clinical state and circumstances, the available research evidence, as well as the patient's values and preferences, including the patient's preference regarding his or her role in decision making.[10] ■

The references for this article can be found at www.cancerworld.org

Acknowledgement

Hanneke W.M. van Laarhoven and Inge Henselmans contributed equally as first authors

Author affiliations

Hanneke WM van Laarhoven, Department of Medical Oncology, and Inge Henselmans and J (Hanneke) C de Haes, Department of Medical Psychology, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

newsround

Selected reports edited by Janet Fricker

Health risks continue into middle age for childhood cancer survivors

Journal of Clinical Oncology

Elevated risks for morbidity and mortality among survivors of childhood cancers increase beyond the fourth decade of life. An analysis of the retrospective Childhood Cancer Survivor Study (CCSS) shows survivors of childhood cancers aged 35 years and older are five times more likely to experience new onset of severe, disabling, life-threatening, or fatal health conditions than their same-age, same-sex siblings.

Health outcomes research conducted over the last three decades has established that survivors of childhood cancer are at increased risk for morbidity and mortality during their childhood and young adult years, largely as a result of adverse effects of the therapies that cured their primary malignancies. What has not been clear, however, is whether such adverse health conditions continue as this population ages.

In the current study Gregory Armstrong and colleagues, from St Jude Children's Research Hospital, Memphis, Tennessee, set out to address the risk of future serious health problems for survivors of childhood cancers, and whether survivors who reach their third decade without developing serious conditions still have elevated risks.

Investigators compared the occurrence of, severe, disabling, life threatening and fatal health conditions for 14,359 survivors and 4,301 siblings. The survivors had all been diagnosed before the age of 21 years and were still alive after five years. The data were drawn from the Childhood Cancer Survivor Study, a retrospective cohort study with longitudinal follow-up of the survivors of childhood cancer from 26 institutions in the US and Canada.

Results showed that the cumulative incidence of suffering a severe, disabling, life-threatening, or fatal health condition by the age of 50 years was 53.6% for survivors, versus 19.8% for their siblings. The hazard ratio (HR) for experiencing severe, disabling, life-threatening or fatal events was 6.8 for the 15- to 19-year-old age group, 3.8 for the 20- to 34-year age group and 5.0 for the >35-year age group. Among survivors who reached 35 years of age without a previous grade 3 or 4 condition, 25.9% experienced a subsequent grade 3 to 5 condition within 10 years, compared with 6.0% of siblings ($P<0.001$).

"We now identify that elevated risk for severe, disabling, life-threatening, or fatal health conditions extends across the aging spectrum into the fourth and fifth decades of life, increasing significantly beyond age 35 years versus a sibling comparison population," write the authors, adding that these findings have important implications for cancer screening and prevention.

Exposure to systemic chemotherapy or focal radiotherapy, the authors suggest, may accelerate the aging process. Indeed, mechanisms for aging, such as telomere shortening or free-radical mediated injury, have been hypothesised to occur in cancer survivors. "These data ... highlight the need for longitudinal, risk-based follow-up; and identify the increasing health burden on this population as they age," write the authors.

■ G Armstrong, T Kawashima, W Leisenring et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the Childhood Cancer Survivor Study. *JCO* 20 April 2014, 32:1218–27

CML patients fare better in teaching hospitals

Blood

Patients with chronic myeloid leukaemia (CML) have a better survival if they are treated in teaching hospitals compared with treatment in municipal hospitals or by office-based physicians, the German CML Study Group has reported. The results showed that patients with blast crisis in particular show superior outcomes.

With the introduction of tyrosine kinase inhibitors (TKIs), treatment of patients with CML profoundly changed. Not only have their prognosis and quality of life improved remarkably, but treatment has become less complex. One consequence is that treatment of CML patients has shifted from

teaching hospitals to municipal hospitals and office-based physicians. In the current study Michael Lauseker and colleagues, from the Ludwig-Maximilians University of Munich, Germany, set out to investigate whether healthcare settings have an impact on patient outcomes.

For the study, outcomes were considered for the 1,491 patients enrolled into the German CML Study IV. For the analysis each study centre was classified into one of three categories: teaching hospital, municipal hospital, or office-based physician. Survival times were calculated from the date of diagnosis to the date of last observation, unless the patient had already died. Cox models were estimated to assess the impact of study centre type and experience with CML, with models adjusted for European Treatment and Outcome Study (EUTOS) score prognostic group, calendar year of diagnosis, age at diagnosis, and Karnofsky performance status (KS). Furthermore, the models were stratified according to randomised treatment.

Results showed a significant survival advantage for patients treated at teaching hospitals. When this group of patients was compared with patients treated in municipal hospitals, the HR was 0.633 (95% CI 0.414–0.966; *P*=0.034); and when they were compared with patients treated by office-based physicians, the HR was 0.609 (95%CI 0.363–1.024; *P*=0.060). Survival for the 73 patients who suffered a blast crisis was statistically significantly better for those treated at teaching hospitals. After two years, 47.7% of blast crisis patients treated at a teaching hospital were alive compared with 22.3% of blast crisis patients treated at a municipal hospital (*P*=0.015) and 25% of blast crisis patients treated by an office-based physician (*P*=0.012).

"Our data indicate a survival advantage for CML patients treated initially at a TH [teaching hospital] compared with those that were treated at an MH [municipal hospital] or OBP [office-based physician]," write the authors. Because the differences in the outcomes between the three groups were "not negligible", they add, further research should try to replicate such an analysis in an independent data set and explore potential reasons for the observed differences.

■ M Lauseker, J Hasford, M Pfirrmann et al. The impact of health care settings on survival time of patients with chronic myeloid leukemia. *Blood* 17 April 2014, 123:2494–96

Stereotactic radiosurgery effective for multiple brain metastases

■ Lancet Oncology

Stereotactic radiosurgery without whole brain radiotherapy (WBRT) for patients with five to ten brain metastases was found to be non-inferior in terms of overall survival to that for patients with two to four metastases. The prospective, observational study, funded by the Japan Brain Foundation, also showed that the number of treatment-related adverse events did not differ between the two groups.

The American Society of Radiation Oncology guidelines state that level 1 evidence only supports stereotactic radiosurgery without concurrent WBRT for patients with up to four brain metastases. Debate continues as to how many tumours can or should be treated by stereotactic radiosurgery alone. Stereotactic radiosurgery is considered to have several benefits, including the fact that it can be repeated and done after WBRT, and that it does not prevent radiation therapy to other parts of the body, chemotherapy, or major surgery for another lesion.

In the study Masaaki Yamamoto, from Hospital Moto Gamma House, Ibaraki, Japan, and colleagues from the Japanese Leksell Gamma Knife (JLGK) Society, set out to examine whether stereotactic radiosurgery without WBRT as the initial treatment for patients with five to ten brain metastases was non-inferior in terms of overall survival to that for patients with two to four brain metastases.

Between March 2009 and February 2012, 1,194 patients from 23 facilities in Japan with one to ten newly diagnosed brain metastases were enrolled. The patients, who had all types of original malignant tumours except sarcoma, were split into groups based on the number of tumours observed on initial MRI. The primary endpoint was overall survival defined as the interval between stereotactic radiosurgery and death due to any cause, or the day of last follow-up.

Results showed that the median overall survival after stereotactic radiosurgery was 13.9 months (95%CI 12.0–15.6) in the 455 patients with one tumour; 10.8 months (9.4–12.4) in the 531 patients with two to four tumours; and 10.8 months (9.1–12.7) in the 208 patients with five to ten tumours. Overall survival did not differ between the patients with two to four tumours and those with five to ten tumours (HR 0.97, 95% CI 0.81-1.18, *P*=0.78, and for non-inferiority *P*<0.0001). The proportion of patients who had one or more treatment-related adverse event of any grade was 9% for patients with two to four tumours versus 9% for patients with five to ten tumours (*P*=0.89).

"This result challenges the practice of inconsistent use of stereotactic radiosurgery for patients with five or more brain metastases, in whom most treatment guidelines still strongly recommended WBRT, and provides evidence in favour of offering stereotactic radiosurgery to patients with multiple brain metastases. Existing treatment guidelines for the management of patients with brain metastases might need to be revised in the near future," write the authors.

■ M Yamamoto, T Serizawa, T Shuto et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* April 2014, 15:387–395

Radiotherapy benefits patients with N1–N3 breast cancer

■ The Lancet

For women with breast cancer and one to three lymph nodes testing positive for cancer, radiotherapy is beneficial after mastectomy and axillary dissection, reports a meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).

Prior meta-analyses have shown that post mastectomy radiotherapy (PMRT) reduces the risk of dying of breast cancer and of recurrence in patients with node-positive disease. But whether PMRT benefits patients with only one to three positive nodes has been controversial, with most studies concluding that there is insufficient evidence to make firm recommendations for this group.

In the current study Paul McGale and colleagues, from the EBCTCG group in Oxford, UK, performed a meta-analysis of individual data on 8,135 patients with node-positive disease enrolled in 22 randomised trials between 1964 and 1986. From this larger group, they identified 3,786 women who had undergone mastectomy and axillary lymph node dissection and been randomly assigned to receive radiation to the chest wall and surrounding regions or no radiation.

The women fell into three categories: those with no cancer in the lymph nodes (n=700); those with cancer in one to three lymph nodes (n=1,314); and those with cancer in four or more lymph nodes (n=1,772).

Results showed that for women with axillary dissection and no positive nodes, radiotherapy had no significant effect on locoregional recurrence (two-sided significance level [2p]>0.1), or overall recurrence (2p>0.1), or dying of breast cancer (2p>0.1). For women with axillary dissection and one to three positive nodes, radiotherapy did reduce locoregional recurrence (2p<0.00001), overall recurrence (2p=0.00006), and deaths from breast cancer (2p=0.01). Of these 1,314 women, 1,133 were in trials in which systemic therapy (cyclophosphamide, methotrexate and fluorouracil, or tamoxifen) was given in both trial groups. For this group of patients radiotherapy again reduced locoregional recurrence (2p<0.00001), overall recurrence (2p=0.00009), and deaths from breast cancer (2p=0.01). In women with axillary dissection and four or more positive nodes, radiotherapy was also found to have reduced locoregional recurrence (2p<0.00001), overall recurrence (2p=0.0003), and death from breast cancer (2p=0.04).

In an accompanying commentary Philip Poortmans, from the Institute Verbeeten, in the Netherlands, writes, "The results of this EBCTCG meta-analysis clearly confirm that post mastectomy radiotherapy should be considered equally for patients with one to three involved axillary lymph nodes as it should be for patients with four or more affected axillary lymph nodes. The same considerations concerning regional radiotherapy also seem to be valid for patients treated with breast-conserving therapy."

Since the absolute risks of breast cancer recurrence and dying of breast cancer have been reduced in many countries due to advances in detection and treatment, he adds, the absolute benefits from post mastectomy radiotherapy today are likely to be less than those reported in the study.

■ EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomized trials. *Lancet* published online 19 March 2014, doi:10.1016/S0140-6736(14)60488-8

■ P Poortmans. Postmastectomy radiation in breast cancer with one to three involved lymph noeds: ending the debate. *Lancet* published online 19 March 2014, doi:10.1016/S0140-6736(14)60192-6.

Exercise guidelines unrealistic for cancer survivors

■ British Journal of Cancer

Expecting the majority of sedentary cancer survivors to achieve current exercise guidelines is likely to prove unrealistic, concludes a UK systematic review. The study did, however, show that aerobic exercise tolerance was improved at both eight to twelve weeks and six months follow-up.

Over the last decade exercise interventions for cancer survivors have received increased attention as an effective way to improve health-related quality of life and physical function and to reduce fatigue. Furthermore, an association with a reduced risk of disease recurrence has been suggested. The current exercise guidelines indicate that cancer survivors should achieve 150 minutes per week of aerobic exercise and twice weekly resistance (strength) training (Rock et al., *CA Cancer J Clin* 2012, 62:242–274). However, the Quality Health 2012 survey from the UK Department of Health found only one quarter of cancer survivors achieved such levels.

In the current study Liam Bourke and colleagues, from Queen Mary University of London, UK, set out to systematically review the effects of interventions to improve exercise behaviour in sedentary people living with and beyond cancer. From a review of electronic databases including the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, AMED, CINAHL, PsycINFO, SportDiscus, and PEDro, the authors identified 14 trials (11 for breast, 2 for colorectal and 1 for

prostate cancer) involving a total of 648 participants.

Results showed that none of the trials included in the review reported an adherence of 75% or more for a set prescription that would meet the Rock et al. (2012) aerobic exercise guidelines, and only three trials reported an adherence of 75% or more to a lower aerobic exercise goal. Notably, write the authors, all three of these trials incorporated both a supervised and independent exercise component as part of their interventions.

For the seven trials reporting change in aerobic tolerance as an outcome, a meta-analysis showed that, at eight to twelve weeks, aerobic exercise tolerance was significantly better in the exercise group than the control group (standard mean difference [SMD]=0.73, 95%CI 0.51–0.95), and continued to improve at six months (SMD=0.70, 95%CI 0.45–0.94).

"The review findings indicate that currently there is a lack of convincing evidence to suggest that existing exercise interventions are useful for achieving the Rock et al. (2012) guidelines ... in sedentary cancer cohorts," write the authors.

The study, they add, suggests that interventions combining the supervision of exercise training in tandem with a requirement of independent exercise are likely to promote better adherence.

In an accompanying commentary Clifford Hudis, from Memorial Sloan Kettering Cancer Center, and Lee Jones, from Duke Cancer Institute, write that large clinically meaningful reductions in disease risk can be achieved when moving from the least active (or low fitness) group to a moderately active (fit group). "In other words, only small changes in exercise behaviour may be required in sedentary individuals to produce meaningful reductions in disease recurrence or risk of other chronic diseases," they write.

■ L Bourke, K Homer, M Thaha et al. Interventions to improve exercise behaviour in sedentary people living with and beyond cancer: a systematic review. *Br J Cancer* 18 February 2014, 110:831–841

■ C Hudis, L Jones. Promoting exercise after a cancer diagnosis: easier said than done. *ibid* pp 829–830

Radical prostatectomy shows continued survival benefits

■ NEJM

Extended follow-up of the Scandinavian Prostate Cancer Group-4 trial (SPCG-4) up to 23 years shows men with early prostate cancer undergoing radical prostatectomy have reduced risk of all-cause mortality, prostate cancer-specific mortality, and distant metastases and reduced need for androgen deprivation therapy in comparison to those undergoing 'watchful waiting'. The benefits of surgery with respect to death from prostate cancer were found to be largest in men less than 65 years of age.

In the SPCG-4 study, between 1989 and 1999, Anna Bill-Axelson and Lars Holmberg, of Uppsala University Hospital, Sweden, randomly assigned 695 men from 14 centres in Sweden, Finland and Iceland, with early prostate cancer, to radical prostatectomy (*n*=347) or 'watchful-waiting' (*n*=348). The study, which was funded by the Swedish Cancer Society, was undertaken before the era of PSA (prostate specific antigen) testing.

Results showed that, during 23.2 years of follow-up, 200 of 347 men in the surgery group and 247 of 348 men in the 'watchful waiting' group died. Of the deaths, 63 in the surgery group and 99 in the 'watchful waiting' group were due to prostate cancer (RR 0.56, 95%CI 0.41–0.77; *P*=0.001). Androgen deprivation therapy was used in 145 patients who underwent prostatectomy versus 235 who underwent 'watchful waiting' (RR 0.49, 95%CI 0.39–0.60, *P*<0.0002). Other palliative treatments, such as radiation therapy, were less common in the radical prostatectomy group than in the 'watchful waiting' group (49 vs 63).

The benefit of surgery with respect to death from prostate cancer were most marked in patients younger than 65 years, where 31 deaths occurred in the radical prostatectomy group versus 58 in the 'watchful waiting' group (RR 0.45, 95%CI 0.29–0.69, *P*=0.002); and in those with intermediate-risk prostate cancer, where 24 deaths occurred in the radical prostatectomy group versus 50 in the 'watchful waiting' group (RR 0.38, 95%CI 0.23–0.62, *P*<0.001).

In the interval from 10 to 18 years of follow-up, the number needed to treat to prevent one death decreased from 20 to 8 in the whole cohort, and from eight to four among men younger than 65 years of age. By December 2012, 294 men in the 'watchful waiting' group had not received curative treatments.

"Extended follow-up confirmed a substantial reduction in mortality after radical prostatectomy; the number needed to treat to prevent one death continued to decrease when the treatment was modified according to age at diagnosis and tumor risk," write the authors. However, they add that a large proportion of long-term survivors in the 'watchful-waiting group' have not required any palliative treatment.

"The overall long-term disease burden is also a reminder that factors other than survival should be considered when counselling men with localized prostate cancer; the risk of metastases and ensuing palliative treatments also affect quality of life," write the authors.

■ A Bill-Axelson, L Holmberg, H Garmo et al. Radical prostatectomy or watchful waiting in early prostate cancer. *NEJM* 6 March 2014, 370:932–942