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ARE TUMOUR BOARDS DEFUNCT?

Why can't multidisciplinary decision-making be done in real time?

PASSPORT TO THE FUTURE

Can IT ensure better healthcare for survivors of childhood cancers?

WE'RE LIVING WITH CANCER

Patient advocates spell out what matters most when the disease is advanced

Jean-Charles Soria

Beyond the science

Editor
Kathy Redmond
editor@eso.net

Managing Editor
Anna Wagstaff

Editorial Coordinator
Corinne Hall

Production
HarrisDPI
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Jason Harris

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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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Spending cuts could jeopardise survival gains

KATHY REDMOND EDITOR

The largest study of cancer survival in Europe – EUROCARE 5 – recently reported that cancer survival rates across Europe improved between 1999 and 2007. Moreover, while survival remains poorer in Eastern Europe than other European regions, the gap appears to be narrowing. This welcome progress probably reflects improvements in the quality of cancer services across Europe.

We know that levels of public spending on healthcare is one of many factors that account for disparities in cancer survival across Europe: survival is better in countries that spent more per capita on healthcare than in those that spent less. What implications does this have for the impact of the current cuts in public healthcare spending?

The period covered by the EUROCARE 5 study saw a rapid increase in healthcare spending across Europe. But from 2009 onwards, spending has slowed significantly across all European countries, especially those hit hardest by the economic crisis. This means that there is a risk that we will see a reversal of the progress we have seen in cancer survival rates.

There are growing concerns about the fiscal sustainability of healthcare systems in many European countries, not least because of Europe's increasingly ageing population. Different countries have adopted a variety of approaches to try to control healthcare spending, including reducing benefits and increasing out-of-pocket payments, imposing severe budget constraints on hospitals, controlling spending on drugs, merging services and rebalancing service provision away from expensive inpatient care to outpatient care and day surgery. Only time will tell whether these measures will roll-back the steady progress seen in cancer survival rates throughout the 2000s. The problem is that the true impact of austerity on cancer survival will only become apparent in a few years' time.

In the meantime it is important to encourage governments to continue to provide adequate resources to cancer services and also to focus on policies that can impact on cancer outcomes. Policy makers need to find ways to strengthen the governance of cancer care, the foundation of which is a national cancer control plan. This requires not only setting targets and defining how these targets shall be achieved, but also systematically measuring outcomes and indicators of quality cancer care, to ensure that targets are being met. Benchmarking performance will help ensure that the limited resources that are available for cancer control are used to the greatest effect.

It is likely that cost containment measures to control healthcare spending will continue for the foreseeable future, and it is going to be a challenge to ensure that healthcare reforms do not compromise access to high-quality cancer care for all patients. Countries that are lagging behind in cancer care performance have to think carefully about how to get the best out of their limited resources. Putting a national cancer control plan in place would be a good place to start.

Jean-Charles Soria: Beyond the science

SIMON CROMPTON

Phase I trials now play an essential role in treating patients with metastatic cancer, offering vital "extra moves" in the battle to outplay the disease, says Jean-Charles Soria. He warns, however, that not every patient wants to play every move, at any cost. Getting that bit right is where the real challenge lies.

In 2002, when Jean-Charles Soria was at the beginning of his career in medical oncology, he met a bishop who made a surprising assertion. Soria remembers the words: "Jean-Charles, he said, I wouldn't like to be you on the day of judgement. You have received so many gifts that the judgement is going to be very harsh."

The words have stayed with Soria, a practising Catholic. It wasn't good enough to shine at a clinical oncology conference, or get papers published in prestigious journals, or sit back and enjoy the perks of being a high flyer. His gifts were there to maximise for the good of others.

So he has all the hallmarks of a young man in a hurry. At the age of 42 he was installed this January as Editor in Chief of Europe's prestigious cancer journal, the *Annals of Oncology*. In 2006 he became France's youngest full professor when he was appointed Professor of Medicine and Medical Oncology at South Paris University aged 35. A member of the committee of the American Society for Clinical Oncology since 2006 he has contributed over 350 papers to peer reviewed publications including two original publications, as senior author, in the *New England Journal of Medicine*.

He is considered, he says, "a prototype for the new wave of oncologists carrying out precision medicine focused on the molecular architecture of the tumour" – particularly known for his cutting-edge work in phase I trials, and new models of treatment in lung cancer.

And yet that is not enough. When we meet at his office at the Gustave Roussy Cancer Centre, Paris, where he is full-time cancer specialist and Chair of the Drug Development Department (DITEP), Jean-Charles Soria hurries through

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the state of the art medicine. The impressive career history is mere background. What he really wants to talk about, and what he wants to become a major focus of his work, is something altogether more simple but also more challenging: addressing the real needs of patients.

It isn't that he has lost interest in the potential of new targeted therapies and new molecular knowledge of tumours. On the contrary, they are at the heart of the dilemma.

"Today, our greatest challenge is not to sacrifice humanity to technology," he says. "The risk is greater than ever before because of the power of biotechnologies and bioinformatics. Today, we know a lot about a patient's disease and are extremely well trained at identifying targets, at using new technologies to image and molecularly decipher the tumour, to provide a more sophisticated and individualised approach. But we all get so excited by the science and forget that we are treating a patient with a history, his own challenges, a projection of life that varies very greatly from one to another. It's not easy for doctors to talk about failure and death, and we also find it hard to understand that what may be traumatising bad news for one patient – for example hair loss – may not be bad news for others.

"I am asking oncologists not only to be good clinicians, with a robust biological background, but also to be good empathetic and open human beings. And it's not easy."

The dilemma, says Soria, is that precision medicine is changing everything in oncology but medical oncologists are not keeping up with the implications. They fall back on outdated assumptions, scales and training. What needs changing in particular is the assumption that "efficiency" equates to delaying tumour

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progression – whatever the human cost.

A priority now is to have more of an eye on those costs, whether they be patient anxieties or poorly understood drug toxicities. For example, Soria believes it is time to start using a new language when assessing drug toxicities in phase I trials, because molecular target agents bring new kinds of side effects – often chronic, such as diarrhoea – which are simply not accounted for in old scales established to measure the acute toxicity of cytotoxic compounds. What is currently categorised as "mild" toxicity might be intolerable to a patient over a long period. Soria is looking at the issue as part of the EORTC New Drug Advisory Committee's task force on phase I methodology.

"I'm not asking for oncologists to be some sort of Robocop, efficient but empathetic, trained in bioinformatics and molecular biology, nice to everyone. There are very few of those people and it's impossible to do everything. But I am saying that we must deal with the challenge of how, as a community, we can simultaneously push the frontiers of better biotechnological approaches, better informatic approaches, better drug development approaches, better evaluation of toxicity, while keeping track of a patient at the centre of it all who has their own, possibly tragic, story."

Soria has himself played more than a minor part in changing the cancer game: he speaks of his passion for refining targets and treatment with precision medicine. Born in La Paz, Bolivia, to a Bolivian mother (a bilingual secretary) and a French father (an engineer), Soria studied medicine at the Paris Medical School, winning the silver medal for best student in 1997. Between 1999 and 2001 he took a postdoctoral fellowship at the M D Anderson Cancer Center in Houston, Texas, then gained a PhD at South Paris University in the fundamental basis of oncogenesis in 2001, before starting work as Assistant and Associate Professor of Medicine and Medical Oncology at Gustave Roussy. As head of the hospital's phase I trials unit since 2006, his work has focused on identifying new pharmacodynamic biomarkers to predict disease progression and treatment effectiveness, and early clinical development of targeted therapies for solid tumours.

His thoracic cancer research team has contributed to major advances in the field of molecular medicine, including the role of proteins such as ERCC1 and MSH2 in DNA repair and their use as predictive markers for resistance to chemotherapy in lung cancer. The group is using this knowledge to sensitise tumours to chemotherapy and targeted therapies.

Soria also led research into a new engineered monoclonal antibody with very low toxicity, MPDL3280A for non-small-cell lung cancer, which he described at the European Cancer Congress in September last year as a "game changer" in the field of immunotherapy. Finally, he says, it looks as if immunotherapy will fulfill all its early potential.

What particularly excites Soria, and you can see his glee as he describes it, is that because molecular technologies can be targeted at the patients who will benefit from them most, and

because toxicities are increasingly well-controlled, the entire trials process has been transformed. No longer are phase I drug trials an option of last resort for those who are dying. His own early clinical trials unit, where so many of these new developments have been tested, is bringing immediate hope of a longer good-quality life to the majority of patients.

"Today, I think there is a complete misunderstanding in the oncology community about what phase I trials are, or how much they have changed in the past decade. They used to be the step before palliative care. They involved between 40 and 100 people at two or three centres, testing a new compound to define tolerability or toxicity. Today, it's completely different. Most of the time a phase I trial also offers a new therapeutic option with intrinsic activity: this has been true for imatinib, vemurafenib, crizotinib, and the new PD1/PDL1 immunecheckpoints. Phase I is no longer for a small group of people who are ready to die and are willing to be exposed for toxicity. It is hundreds of patients who will have a response to a therapeutic compound. It is multicentre, it is about activity rather than toxicity. In fact in some cases phase I has almost entirely swallowed up phase II."

A recent analysis of patient data from main phase I centres across Europe, published in the *Journal of Clinical Oncology* (2012, 30:996–1004) found that today half of all patients benefit from their participation, with a risk of death from toxic side-effects lower than that associated with receiving adjuvant chemotherapy. "Today, what we are offering in phase I is as good as any third-line treatment, and you can quote me on that."

Soria acknowledges that in some countries phase I trials are even more crucial to access innovative efficacious drugs. This is notably the case in the UK, for example, because of the drug rationing imposed by the National Institute for Health and Clinical Excellence. In France, the transformation of early trials has been hastened by the recognition of seven comprehensive cancer centres (sites de recherche intégrée sur le cancer, or SIRIC), 16 phase I centres designated by the national cancer institute, INCa (of which the Gustave Roussy is the largest and most active), and the implementation of molecular tumour profiling for personalising treatment at 28 regional centres.

It is the future. And its importance is being shamefully neglected by some academic institutions, believes Soria. "People need to understand that phase I is absolutely mandatory for any academic medicine centre that wants to push precision medicine," he says. "When you tell a patient, come and see me, we will analyse the molecular structure of your tumour –

"We're playing a game of chess with death. We need to anticipate moves, and research gives you extra moves"

and then you have no action to take as a result of that analysis, you are selling them a mirage. If you are an academic centre which cannot do molecular profiling, or cannot offer a large palette of new compounds, you will never do precision medicine, you will never do personalised medicine, you are just blah blah."

That is why the centres that have aggressive precision medicine initiatives are the same centres pushing early drug development, and why the phase I unit in Gustave Roussy, which conducts 57 phase I trials at a time, has become an Integrated Drug Development Department. Its wards currently accommodate 370 patients, but by 2015 it will be able to provide beds for more than 500 patients in phase I trials.

"Today it is clear to me that the survival of a metastatic cancer patient is entangled with their capacity to participate in clinical research, and notably early clinical trials," he says.

Yet many cancer specialists still believe that clinical research is optional, and separate from standard care. It appalls him. "Clinical research always gives you more options," he says. "We're playing a game of chess with death. We need to anticipate moves, and research gives you extra moves." One way forward is to build more bridges between clinicians and basic researchers. He is a supporter of the model put forward by Stephen Friend of SAGE Bionetworks, a non-profit organisation providing tools to conduct collaborative biomedical research, where medical doctors and PhDs are paired up over three years so that they can learn from each other.

Soria talks in passionate terms about the lifesaving mission of oncologists, the need for them to do patients the honour of being open and helping patients to be open. It is partly borne of his experiences talking to patients – several times, he refers to patients with cancer being suicidal and the inability of doctors to spot or deal with this. He talks fondly of a patient who told him that she wanted to leave some money to his department, but no she didn't want to leave it to research: "I don't care about mice," she had said, "I care about that stupid doctor who told me I had sciatica when in fact I had a bone met. I want to donate it to training better doctors."

But it is also a result of his family history. When Soria was 13 his sister received a diagnosis of leukaemia at the age of seven – the family moved from Bolivia to Paris in 1984 so that she could receive treatment there.

It was successful, and she is still alive today. But it has impressed deeply on him the waves of impact cancer can have not only on an individual but on a family. "It has created a sense in me that this is a discipline where the stakes are high," he says. "So there is a huge need for specialists with passion and commitment. I am convinced that if we don't deal appropriately with the human being and his or her own challenges, then we're going to miss out on delivering optimally to the patient."

To achieve this, oncologists will have to meet many challenges. How do you identify those patients who would benefit more from talking about the prospect of death or other anxieties than talking about the size of their tumour? How do you find time for such conversations? How do you provide oncologists with the tools to have difficult conversations? How do you teach empathy?

Implementing methodologies for breaking bad news, such as the American SPIKES six-step protocol, is only part of the solution. Oncologists need training so that they recognise that open communication with patients is at least one third of their job, and so that they don't participate in the "magical thinking" that if you talk about the end, you're going to precipitate the end.

Training is the key, says Soria. He remembers being confronted with his own failings when an

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external consultant visited his department to provide guidance on talking to patients. Like all doctors, his oncologists had sometimes been faced with patients angry that they had been kept waiting a long time. And sometimes, oncologists would feel a sense of injustice at this, especially if they had made special attempts to fit a patient into a busy schedule. "But we forget that for these patients, who are already under great stress because of their disease, the consultant's door is like a door into space – it can bring you to beautiful countryside, or your infancy, or a terrible place. So it is unacceptable that we should try and logically justify why we are late. As the consultant told us, there is only one answer: I am deeply sorry. We do not realise we are saying the wrong things."

Such areas, Soria has resolved, will be a focus for his efforts now. He acknowledges that he has always felt an inner pressure to deliver, and in the past his efforts have been "diffuse".

"My wife recently said to me: 'You have written 350 papers, when are you going to stop? This is insanity.' So now my priorities are to develop an intelligent approach to drug development, push precision medicine initiatives in lung cancer, develop molecular and clinical predictors of drug efficacy and toxicity, and to put

"How do you identify patients who may get more from talking about the prospect of death than the size of their tumour?"

The real deal. Soria's family are a welcome reminder that there are more important things in life than pushing forward the frontiers of medicine

new efforts into training fellows and assistant professors on breaking bad news."

One other focus will be the *Annals of Oncology,* the flagship journal of the European Society for Medical Oncology. Soria has a bond with both ESMO and its journal. He was a member of the ESMO Executive Board between 2008 and 2009, and his first English peer-reviewed original manuscript was published in *Annals* in 1997. When he was appointed Editor in Chief in September last year, Soria put on record his determination to raise the "impact factor" of the journal – a measure reflecting the number of citations to articles published in the journal and used as a proxy for the relative importance of the journal in its field. He also wants to increase the number of high-quality reviews and guidelines and attract more randomised trials including negative ones. "We will solicit articles on cutting-edge topics such as precision medicine and novel immunomodulatory agents, reflecting the new paradigm in oncology," he says.

When I put to him recent criticisms of journals' obsession with impact factor – Nobel Prize winning biologist Randy Schekman has described it as a "toxic" influence because it encourages the publication of articles that are eye-catching rather than good science – Soria is pragmatic. "The flaws and limitations of the impact factor are known to many people, and I'm in line with those criticisms," he says. "I know it can be completely linked to four or five good papers and all the rest can be average. But you can't pretend that impact factor isn't there. I am going to be judged, and impact factor is something measurable that's very clearly defined by the outside world. We need to define goals, and at least I'm totally transparent about my aims."

Soria is aware that as a high-flyer, he needs pulling firmly down to earth sometimes. In this respect, his family – in whom Soria continually says he is "blessed" – have clearly had an important role. He remembers his wife, Isabel, a paediatrician who he married 16 years ago, greeting his excited announcement that he had had a paper accepted by the *New England Journal of Medicine* with the words: "Good, now change your boy's diaper."

Her attitude was right, says Soria. "I used to go home from work thinking, right, I've done my 14 hours, now it's time to enjoy. But Isabel said no, it's time to have kids, forget you exist, raise the kids and make them better human beings." He got more than he bargained for. "I imagined that my maximum tolerated dose was two children, but we had four so my MTD was exceeded by far."

Soria calls his family his "hidden garden" where he can recharge his batteries. He never allows work to intrude at weekends. Along with his strong religious faith, he says, his family are a continual reminder that there are higher goals in life beyond the frontiers of medicine.

He shows me pictures of his children, aged 15, 12, 8 and 5, and tells me that the 12-year-old girl wants to be a doctor. But it is the career thoughts of his eight-year-old boy, who nearly died of a pulmonary malformation in infancy, that have amused and chastened Soria.

"If he is asked what his daddy does, he says he works a lot, doesn't make a lot of money, and is totally useless because every patient dies. He says he does a job to avoid at any price. That's his description." We look at the picture of his mischievous face. "You know what he wants to be when he grows up? A priest." ■

Mothers coping with cancer

Better understanding of the impact that treating pregnant women for cancer has on their unborn child means women in this position have more options open to them, as Ainhoa Iriberri explains in this article, which was first published in *SALUDRevista* – a leading Spanish health magazine – and won her a Best Cancer Reporter runner-up award.

Very few women are diagnosed with breast cancer before the age of 40 – according to available data only 1 in 241 are diagnosed this young. And having breast cancer during pregnancy is even more rare. It is so rare that there are no reliable statistics, although the figure of 2.3 cases in every 100,000 pregnancies has been quoted. Adriana Juez had never in her life heard these figures, though she did of course know about breast cancer – her mother had died from it and her maternal aunt had survived it. So she couldn't help thinking about it when in late October 2011, when she was still only 37 years old, she noticed a lump in her breast. She mentioned it to her gynaecologist, the same one who had helped bring her three children into the world. "It looks like a fibroadenoma (a benign tumour), but given your family history, I think we'll have it analysed," he told her. Adriana was all set to go along with that. But, just as statistics can sometimes throw surprises at us, so circumstances too will sometimes insist on scattering complications in our path. The circumstance that complicated Adriana's life was the so-called 'waiting period', which is the time people joining a private insurance scheme have to wait before they can have certain procedures carried out. Among them, the removal of a benign-looking lump.

Ainhoa Iriberri

That was not the only unusual thing to happen to Adriana before the end of 2011. In December, while the lump was continuing to grow, her birth control method failed, without her knowing it. She missed two periods, but she put this down to her periods getting 'out of sync'. The New Year began without any reduction in the size of the lump in her breast, which just kept on growing. Finally, the insurance waiting

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That was then, this is now. Evidence that pregnant women can safely be treated for cancer was published in 1999, but old assumptions prevail in the public mind – and among some healthcare practitioners – until the mass media spreads the word

SALUD REVISTA.ES

period ended and in February she was able to go back to see her doctor, who put her through tests that thousands of women in Spain go through every year, though few of them as young as Adriana. The results from the lump biopsy were to have been known within a few days, but meanwhile she received some unexpected news: without realising it, Adriana had become 11 weeks pregnant. "I like children, so I was overjoyed," she recalls.

But the joy didn't last long. Just long enough to share the good news with her large family, and of course with her husband César – "a strong character", as Adriana put it – before he received the phone call that he would never have wanted. The lump was not only malignant, it was also very large. So big that the cancer was suspected to be fairly well advanced. In the circumstances, it was felt that Adriana would be better off in a large public hospital, specifically Vall d'Hebron Hospital, whose Breast Cancer Centre in 2006 had introduced a programme for treating the small number of pregnant women who had this disease.

Until 1999, no-one quite knew what to do with patients like this. They were an embarrassment to cancer clinics, which had no idea about what medical advice to give. That's where the myths about breast cancer in pregnant women sprang from,

according to Dr José Manuel Aramendía, medical oncology consultant at Navarra University Hospital.

A popular misconception

How often have we watched films on TV in which, faced with such a diagnosis, there was a choice to be made: the woman or her baby? Both could not be saved. "There is not a great deal of clinical experience in this area to draw upon, but it's what used to happen. In fiction, and among the general public, abortion was spoken of as the solution for dealing with cancer in pregnant women," muses the doctor.

A simple enough approach in theory, but it had proved to be wrong – a fact already known to many cancer specialists as early as 1999. As is often the case in medicine, it was an article in a scientific journal that finally put the record straight. The article in question appeared in the *Journal of Clinical Oncology*, and the lead author, David L Berry, was a perinatologist at the MD Anderson Cancer Center. The centre took it upon itself to dispel all those myths. "It took a series of cases for the treatment to be standardised; until that happened, and for fear of damaging the foetus, pregnant women were routinely excluded from any kind of clinical trial. However, as a research centre it received more cases of pregnant women with breast cancer, and doctors there jumped at the chance to study them, feeling 'if they didn't, no-one else would'," recalls cancer specialist Cristina Saura, the doctor who saved Adriana's life in the multidisciplinary unit at Vall d'Hebron.

The opening sentence of the article set down the popular myths about cancer in pregnant women. "A diagnosis of breast cancer during pregnancy can be absolutely devastating for the patient and her family. Actively treating the malignant tumour and continuing with the pregnancy are generally seen as mutually exclusive options, setting the life of the mother against that of the child," according to the American authors.

Adriana, diagnosed with breast cancer while pregnant, plays with her daughter Valentina, who has just turned six months

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The following seven pages demolished this assertion, point by point, concluding with an unequivocal statement: "Breast cancer can be treated by chemotherapy during the second and third trimester of pregnancy, with minimal complications for the birth."

Needless to say, Adriana knew nothing of this when she checked into the Vall d'Hebron unit with her two items of news. "The last three times when I was pregnant, they wouldn't even let me take a paracetamol tablet, so why would I think that they could give me chemotherapy?" she recalls. I was of course offered the option of terminating my pregnancy. "My husband didn't think the two things could be compatible either, but said he would respect my decision to continue with the pregnancy; I was quite certain in my own mind that I didn't want a termination and he didn't either."

Saura says that all patients admitted to her unit – 25 as of last October – are offered the option of terminating the pregnancy and are guided through the procedure if that's what they decide. "Abortion is a personal choice and, clearly, if the mother does decide to continue with the pregnancy, there are certain risks to be taken on board," the oncologist explains. "They gave me the encouragement I needed, telling me I could have the treatment *and* still have my baby," Adriana recalls.

Dr Aramendía is in absolutely no doubt: "It's not a question of choice at all – the therapeutic benefit to the mother is in no way increased by having a termination." He goes on to

point out that this is not a moral or religious issue (the oncologist practises at Navarra University Hospital, which is opposed to abortion), so much as an issue of scientific evidence and professional ethics. Saura, on the other hand, says that two women from her series of patients did opt for a voluntary termination, one of them on finding out that she already had metastases at the time of the diagnosis.

The possibility of metastases also went through Adriana's mind when she learned she had breast cancer, and this possibility preyed on her mind throughout the remainder of her pregnancy. The diagnostic imaging tests that can be used in such situations are limited, and PET (positron emission tomography), which is used to confirm whether the cancer has spread to different parts of the body, is one of those that is contraindicated.

BREAST CANCER IN PREGNANCY

1. **It is rare to find cancer in pregnant women.** There are some very moving cases – "moving" because they are essentially tragic – but cancer during pregnancy is a rare event and affects one in every 3000 pregnancies at most (though there are no reliable statistics). The incidence is believed to have risen because women are becoming mothers at an ever older age.
2. **Breast cancer is the most common form of cancer in pregnant women.** Breast cancer accounts for around 50% of cancer cases occurring during pregnancy. Next come cervical cancer, lymphomas and melanomas. These cancers have nothing to do with pregnancy as such, but one thing they do have in common is that they affect young women, in particular women of child-bearing age.
3. **It is difficult to diagnose.** When a woman becomes pregnant, her body undergoes many changes. This is why it is difficult to diagnose cancer in its earlier stages – many of the symptoms can be confused with the signs of pregnancy. For example, benign breast lumps are also commonly found in healthy pregnant women.
4. **It can be cured.** What can make the prognosis of breast cancer worse is the patient's age and late diagnosis, not the pregnancy itself. But early diagnosis affects the prognosis, and these women are usually diagnosed late, giving the tumour a chance to grow and spread.
5. **Treatment is delayed.** Chemotherapy should be started in the second or third trimester – starting it in the first trimester is not recommended. As a rule, radiotherapy is not recommended during pregnancy, but surgery is admissible.

Inevitable uncertainty

Adriana could not breathe easy until at least a month after giving birth to Valentina, who is now six and a half months old and blissfully unaware of what her mother was going through while her baby was preparing to enter into the world. For, whilst pregnancy as such does not affect the prognosis of the disease, it does mean that the diagnosis has to be delayed. In the majority of cases, when the cancer is detected it is already long past the earliest stage at which the disease could have been dealt with by removal of the tumour.

"What happens is that the woman puts any physiological changes she detects down to the pregnancy and does not even suspect that it could be cancer. In fact, 80% of those breast lumps are benign – but what about the other 20%?" queries Saura. Dr Aramendía takes the same line, and believes an effort has to be made to detect breast tumours in pregnant women at an earlier stage. Both believe that any lump detected in the breast of a pregnant woman should be investigated, just as it would with any woman who is *not* expecting a child. "This is an idea that needs to be got across to patients as well as doctors," suggests the oncologist at Vall d'Hebron.

So the reality is that the prognosis for a pregnant woman is generally worse than for one who is not expecting a baby. But, as Dr Aramendía is quick to point out, this has nothing to do with the pregnancy itself, but is due to other contributing factors: age, tumour characteristics and, as already mentioned, the delayed diagnosis. "Cancerous tumours that occur in young women are generally more aggressive at a molecular level," the doctor points out.

Of the series of 25 pregnant women treated for breast cancer at Vall d'Hebron, 11 had to undergo chemotherapy. "I found out I was pregnant at 11 weeks, and at 15 weeks I started my chemo. Surgery was not an option

"Women put any physiological changes down to the pregnancy and do not even suspect it could be cancer"

Tests and scans are needed before each treatment session – a good reason for being treated at a multidisciplinary unit

because the tumour was very big," recalls Adriana.

Chemotherapy in pregnancy is safe, but not just at any time. To avoid harming the foetus it is necessary to wait until the second or third trimester. Saura recognises that this is something many patients find hard to take, because they want to start the treatment right away, as it is widely believed that the sooner you start attacking a malignant tumour the sooner it will be gone. However, this apparent delay does not worry the experts too much. "Treatment is by no means immediate even in women who are not pregnant; so, luckily, the fact that diagnosis is usually late means that there is really not that long to wait until the second trimester," says Saura. While chemotherapy may not be a favourite pastime for any patient, it is even less so for someone expecting a baby. "The important thing is to do an analysis of the mother and take a scan of the baby before each treatment session," Saura explains. This involves a whole round of procedures – a good enough reason for being looked after in a multidisciplinary unit like Navarra University Hospital or the Catalan hospital, where they have gynaecologists, oncologists, surgeons and paediatricians. "Spanish doctors are honest people and generally like their patients to be looked after in centres like this," says the oncologist.

Chemotherapy's downside

"Each time I had to go for chemotherapy, there was a whole round of procedures to go through and I was more worried for the baby than for myself," says Adriana, who admits that she "didn't enjoy this pregnancy as much as the last three." Ten sessions is what this kindergarten teacher had to put up with, but she appreciated all the support she got from the family during this time. "My mother-in-law became the mother I no longer had; then my sisters came over from Argentina – where Adriana hails from – and the USA; and my sisters-in-law were a wonderful help to me in everything, especially in looking after my other children," she recalls.

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Despite her ordeal, Adriana manages to see the positive side. "The pregnancy helped me not to be so obsessed with myself and with my illness, that and my other children; you always have to make an effort, for example to put your make-up on." Worst of all was the hair-loss and the fact that Adriana knew she was going to find it difficult to come to terms with this, having lived through it in her family. "And what about the children? Were they aware of what was happening to you?" Adriana was asked. "Well, we never lied to them," she replied. "But neither did we use the word cancer – that was a word they associated with death, as it was the reason for their grandmother no longer being around. But, yes, I did tell them I was ill, that the doctors were going to make me better, but that I was going to be very tired; this enabled me, for example, to stretch out on the sofa if I needed to at some point, only I told them to tell me when ten minutes were up."

The months were passing and Adri-

The medical team at Barcelona's Vall d'Hebron Hospital, who make up the multidisciplinary team treating pregnant women with cancer

ana's luck seemed to be running out again. She had just finished her second round of chemotherapy, when the stubborn tumour decided to grow back to the size it was before. "The doctors saw that there was no sense in going on and decided to induce birth; it was the 34th week and the baby was ready," she said.

What happened to Adriana is, according to Dr Aramendía, one of the major concerns when it comes to breast cancer in pregnant women, once it had been shown that chemotherapy was a safe and effective treatment. "The challenge of reducing the risk of problems with the development of babies born to pregnant women diagnosed with cancer is focused more on achieving term birth, in other words after at least 38 weeks. That's what determines what the after-effects will be, not so much the treatment."

Valentina is born

Happily, Adriana's streak of bad luck finally ended with the birth of a healthy baby girl, Valentina; not that she was able to spend all that much time in the company of adults for the first month of her life, having been born premature. Scarcely a month after giving birth, Adriana was back in the operating theatre, this time for the removal of the tumour diagnosed six months earlier.

It was on that very same operating table that she started receiving some much needed good news. Firstly, she was told that the sentinel node was negative. This is the first point in the lymphatic system to which the breast cancer spreads and, if cancer cells are detected there, generally the entire lymph node chain is removed, something that impacts negatively on recovery and means a worse prognosis. Secondly, the CT scan showed her body to be free of cancer. However, Adriana's recovery still had a long way to go. "They put me on another round of chemotherapy because they discovered that the tumour was due to genetic mutation of the BRCA1 protein and a specific treatment had to be used for this type of cancer." In all, she had about 20 sessions, which ended in December, when Valentina was just coming up to six months old.

What comes next

The process isn't over yet, because her familial cancer needs one final step: removal of her other breast and ovaries – a standard procedure in women with BRCA1 gene mutation, which will significantly reduce the risks of recurrence.

That is the only thing standing in the way of Adriana's getting back to working at the kindergarten, something she is longing to be able to do, while realising that she still gets very tired. Knowing that her journey is about to come to a happy conclusion, Adriana has a strong wish to get her message across to other women in a similar situation. "When I was starting my treatment, my doctor suggested I have a word with two women who had been through the same as me: one whose pregnancy was far more advanced than mine and the other already under long-term monitoring, with a child of two and a half who was amazing," she says.

And Valentina? Does she love her more than her other children? Adriana ponders briefly before answering: "You can't talk about loving more; you don't love one child more than another. But I suppose I do see her a bit like my little angel. I believe in God and I know He was with me throughout the whole process; for me, Valentina is a gift," she concludes. ■

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Are tumour boards defunct?

The advantages of a multidisciplinary approach to managing cancer patients are no longer seriously questioned, and were recently spelt out in a policy document endorsed by professional societies, patient groups and cancer insitutes (*Eur J Cancer* 50:475–480). The complexity of cancer, the risks and benefits associated with alternative treatment options, the care needs of patients, all point to the need for input from specialists in many disciplines. But are regular face-to-face multidisciplinary team meetings the best way to achieve this?

Tim Allen, a pathologist at the University of Texas Medica Branch, thinks not. In an article he co-authored last year (*Nat Rev Clin Oncol* 10:552–554), he argues that tumour boards delay care, provide minimal patient benefit, don't account for psychosocial issues and should be scrapped in favour of real-time decision making using social media. Under this system, suspected cases could be flagged up immediately using "standardised hashtag streams for cancer teams via Twitter", and "all discussion regarding patient care would be integrated online with imaging systems… using protected Facebook-based discussion pages…"

Riccardo Valdagni, a radiation oncologist and leader of the Prostate Programme at the Istituto Nazionali dei Tumori in Milan, takes a different view. First author of a paper published in the *European Journal of Cancer* (2011, 47:1–7) defining the requirements of a specialist Prostate Cancer Unit, Valdagni believes that patients get better care when they are treated by teams that not only meet together but work as a unit, preferably at a single site.

Cancer World's Anna Wagstaff asked Valdagni and Allen to see if they could find any common ground.

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Tim Allen

The idea of tumour boards has served us well but it is time to move on. Several articles have recently documented increasing delays between the diagnosis and the beginning of treatment. Having to make a patient wait a week or two for a tumour board to meet is just one of the things that is wrong with it. Then there is the cost: the direct costs of tumour boards are high, and to hold the meetings requires numerous personnel hours.

A lot of physicians have put the tumour board on a pedestal, and no-one wants to toy with it. But literature shows that it does not meet its own goals, which is to standardise and improve patient care.

The tumour board concept needs to be reshaped – its function shouldn't be lost. Bryan Liang [co-author of the *Nature Reviews Clinical Oncology* article on Introducing Real Time to Oncology Management] and I propose using the internet for real-time communications between the various parties, including not only the clinicians, surgeons if necessary, pathology, and radiology, but also people with knowledge of the social/economic aspects of the patient, so we don't reach a treatment decision that is inappropriate or unfeasible. Also the patients themselves can be integrated into the discussion to ensure their preferences are known and they are well aware of what is happening and why.

The basic idea is to get the patient's diagnosis, correlate it with radiology, determine the stage, figure out the therapy, and institute that therapy as quickly as possible. The goal will be to do this in truly real time, or pretty close. Twitter (e.g. Group Tweet) has been suggested by us. It would have to be an internet vehicle with appropriate security.

Riccardo Valdagni

Social media may respond to the need for rapid exchange of information, but in oncology, with few exceptions, speediness is not the main criterion for quality of care. In the case of prostate cancer, for instance, the decision-making process is complex, and the 'right' amount of time is required to finalise patients' choice.

We do need to find better ways to involve patients in multidisciplinary discussions about their treatment and care – the lack of patient input is one of the pitfalls of traditional tumour boards. However, as MIT Professor Sherry Turkle suggested in her 2012 book, the use of social media should not be confused with real communication. It can be very useful to exchange information, but it is not very likely to support a shared decision-making process and promote the engagement of the patient.

Taking again the example of prostate cancer, patients with localised disease often face the opportunity – and the burden – of choosing between two to four different options (surgery, external radiation therapy, brachytherapy, active surveillance), all equal in preserving their survival, but each with different physical, sexual, emotional and social consequences. The literature highlights that when patients are not involved in the decision-making process they are more likely to regret the decision to undergo a certain treatment and may wish they had chosen a different approach.

So patients need to be given information, but this is only the first step. The information has then to be acquired, understood and assessed from the patient's perspective. To achieve this, discussing with the physician is paramount. A virtual environment may not be the ideal medium to help clinicians to take into account the patient's perspective. We need to find multidisciplinary cost-effective organisational models that promote the patients' engagement and a relationship based on mutual trust.

I agree that speed is not necessarily the most important thing. What we are trying to do is to remove the unnecessary loss of time so that all that is left is the appropriate time spent with patients in a very condensed or close to real-time fashion – less down time.

And there is certainly the issue of digesting the information, and understanding it. That's why the person-to-person contact is so important, and it should continue and probably be expanded. But this real-time online model allows important decisions – the medical/therapeutic ones – to be made with the patient's and family's input, if they wish, along with the team's input. Any personal communication or necessary patient involvement not only can occur, but should occur before during and after this process.

I completely support the concept not only of today's idea of person-to-person engagement, but actually improved personal engagement with patients. It is vitally important for the entirety of the patient care, and should be emphasised even as we progress to the real-time multidisciplinary team approach. I would argue that using social media as a communication tool would actually permit more of that. At the moment patients don't show up at tumour boards, families don't show up at tumour boards, patients sit at home and worry, and that's one of the things that the person-to-person engagement supplemented by a real-time multidisciplinary approach could improve.

In our model, the patient's involvement starts as soon as they walk in the GP's door – before a diagnosis of cancer has been made. Instead of the patient then going on and worrying and being out of the loop, which is often the case, this model portends a world in which the patient and family are involved every step of the way, if they want.

We can't take it for granted that most patients have easy access to the web and adequate digital literacy to interact with physicians by using social media. It's true that patients are increasingly approaching the internet, but interaction with social media platforms may be not as straightforward as with the internet browsers. Could we end up excluding patients even more, rather than including them in the care process?

I'd also question whether the research really does show that tumour boards fail to improve patient care. Weak study design together with improperly identified outcomes and a large number of confounding variables make it impossible to draw clear-cut conclusions on the added value of multidisciplinary tumour board-based cancer management over the mono-disciplinary approach. Also, let's not forget that face-to-face tumour boards probably provide the best context to discuss clinical cases: each physician can contribute with their own expertise and continuous training is achieved. Cross-fertilisation of different specialist cultures is an asset, and a true team is something more than just a number of individuals digitally connected. Virtual communities are more and more common but members require more time to create steady ties based on mutual trust.

Furthermore, I don't think we can just assume that holding 'real-time' discussions on every case, instead of dealing with them at regular scheduled meetings, will necessarily save clinicians any time. Will clinicians be expected to be 'online' all the time? We know from using Blackberries and smartphones that we are expected to be constantly on call – people expect immediate feedback. What is the impact on physicians likely to be? Will it increase the likelihood of clinician burnout? And last but not least, while medical professionals need to act, we also need time for reflection and self-reflection. Will the digital environment support that?

There may be patients who do not want to use social media, or are not comfortable with it. So this model has to take that into account and work with it. But there may also be patients who not only are very comfortable doing things in real time, internet fashion, but who actually demand it. And for some patients the idea of having to get up, drive several miles, and spend half a day hearing the same thing you'll hear in 10 minutes online is not an option.

If you look at the West article that we built on [Practising in partnership with Dr Google, reprinted in *Cancer World* http://is.gd/yo82ZQ], it describes patients who are pushing doctors and researchers to make better use of online internet-based medical communication. Patients are interested in using social media for their healthcare.

I agree there is not much research out there. But recent literature shows tumour boards aren't working, and cutting out the down time would be of value even if they were. I would argue for more research, to assess and quantify the value of a real-time multidisciplinary team that I'm advocating for. We need to know how much time we are saving, not just that we are saving time. We need to hear from patients – are there things that we can alter to make it easier and better for them? Our idea is in its early stages, and it may be that it's done differently in some places versus others, but there's no overcoming the idea that in today's world of telemedicine, taking care of patients in rural areas, the need to save time, the tumour board concept is frankly defunct and we need to utilise these teams that have been built from the tumour board mentality and make them function with an online platform with as much participation as the patient is interested in, so we can get answers quickly, get the patient treated quickly, provide better care and hopefully save money at the same time.

Research and clinical practice show that most patients want to be in charge of their health, but at the same time they want and need to rely on the professional, clinical expertise of physicians. Shared decision making is what we are talking about.

It's true that one of the main pitfalls in traditional tumour boards is the lack of patients' involvement. Patients should get the chance to sit down – face to face – with their GP or with a specialist (depending on how the healthcare system is organised) and discuss screening-related issues (in the case of prostate cancer), the effectiveness of different therapies, and potential treatment side-effects. Part of the discussion could address how far the patient wants to be involved in the decision-making process, and which media could be used to keep them engaged over time. Specific questions should be asked to assess who the patients share health-related decisions with, how self-confident they are at making choices, and whether they are familiar with social media if we want to tweet them information about their care process. You can't just collect patients' medical information and then tweet them therapeutic options. This applies to diagnosis as well as recurrence events.

I can see the potential value of using social media to connect the patients with the care team and connect clinicians among themselves. But before we invest in implementing social-media-based communication, we need to know what patients think about it. We should conduct pilot studies to define the pros and cons, and we should look at cost-related and medico-legal issues, and also address the questions: Does it really save time? Will clinicians be expected to be permanently 'online'? Will it increase the likelihood of burnout?

The bottom line is that changes we make to the way decisions about treatment and care are made must demonstrate that they preserve the patient–physician(s) relationship which is the basis of the care (versus cure) path, and preserve a truly multidisciplinary approach. ■

Living with cancer

Advocates define their priorities for advanced disease

MARC BEISHON

The ABC conference on advanced breast cancer gives centre stage to a group of patients who feel they've been marginalised and their needs ignored for too long.

People who have been treated for early-stage breast cancer have many issues to handle, not least the fear of a recurrence. However, the advocacy and support movement for this large group is strong. That has not been the case for those with metastatic disease, who not only have to cope with an incurable condition, but have faced isolation from the mainstream breast advocacy movement, and also from health professionals and society in general.

A recent survey of women with advanced breast cancer in Europe, presented in a report called 'The Invisible Woman', found that more than half feel they are perceived negatively by society, and only 36% said they had received help from patient groups. Many also said they suffer from psychological, physical or financial problems. A majority want improved access to treatment and better access to, and interactions with, healthcare professionals.

The organisers of the Advanced Breast Cancer (ABC) conference, which held its second meeting in Lisbon in November 2013, are determined to change this picture by including advocates – many of them patients – and also health professionals such as nurses and psycho-oncologists as an integral part of the event. Presentations from them are a part of the main conference, and the opening keynote is from a patient or patient advocate.

ABC is mainly a consensus-setting conference – its primary aim is to produce and update a set of international guidelines for the care and treatment of people with metastatic and locally advanced disease. Advocates also have the opportunity to make the case for changes to the wording and scope of recommendations, and get to vote alongside clinicians.

ABC2 had probably the largest and widest international gathering of metastatic breast cancer advocates so far – some 50 organisations from 25 countries. A special set of meetings, organised by an advocacy committee, was dedicated to their particular concerns. While most advocates were from organisations that represent people with all types of breast cancer, there are now some who have formed groups specifically for those with metastatic disease, and also for people such as young women and those with inflammatory breast cancer. Everyone there recognised that people with advanced

An appeal for equity. In a keynote speech, Doris Fenech, a breast care nurse living with advanced cancer, called for people like her to have the same access to clinical trials and treatments as patients with early disease

JORGE NOGUEIRA

cancer are a special group who need and deserve much more support from the medical community and also society at large.

This is how it is

No one understands this better than Doris Fenech, a breast care nurse and advocate from Malta, who has advanced breast cancer. In a powerful and moving keynote address she talked about what women typically go through when living with advanced disease. "I look well and no one imagines I have metastatic cancer and am receiving chemotherapy, and that the cancer cells will overpower my body," she said, detailing also the series of symptoms and diagnostics she went through after a primary breast cancer recurred more than 10 years later.

In a candid account, she told the audience of the 'advantages' of having the disease – how she has become more assertive and does what she wants, today; how, despite the lack of support for people with advanced disease, she found much help from Europa Donna, the European breast cancer coalition; how crucial this support is, given how hard it can be to talk to family and friends; and how she can prepare for her departure.

"I look well and no one imagines I have metastatic cancer and that the cancer cells will overpower my body"

"It took us ten years to understand the best dose and regimen for paclitaxel in the advanced setting"

Disadvantages she gave as physical pain – a good treatment plan is crucial. She said she thought she could cope with chemotherapy again, as she had with primary cancer. "I was not sick but the fatigue is unbearable. With chemotherapy for early cancer there is fear of the unknown, but hope; with metastatic cancer it is more likely ongoing treatment and something you have to live with."

There is a tendency to withdraw from a supportive family to spare them pain, she added. "This can be counterproductive, as they feel they have done something wrong. My life revolves around what I face – I don't plan for old age, and I regret that I may not see my daughters getting married or see my grandchildren."

For most health professionals the diagnosis is the beginning of the end, she said. "They are often at a loss for what to say. We have different social and emotional needs… and have been isolated and marginalised by the media and the public."

Doris Fenech made a strong appeal for equity in treatment – to be included in clinical trials, and to receive treatments that could give a few months of life and enable her and others to see milestones in family life. "Treatment is our lifeline," she said.

Her talk also covered many other points about day to day living and the emotional rollercoaster people go through. All of these were explored in detail in the advocacy stream, which was packed with not only patients and advocates but also others from the conference.

Towards a chronic disease?

Fatima Cardoso, head of the breast unit at Champalimaud Cancer Centre in Lisbon, and one of ABC's four chairs, gave an update to the advocacy group on progress in the aim of transforming metastatic breast cancer into a chronic disease. There are more women and men now living beyond the usual two- to three-year median survival, she said, but mixed progress in the three main cancer subtypes. True advances have been made in HER2-positive disease, which used to have a poor outlook, but little progress in hormonal (ER-positive) breast cancer since the 1990s, when aromatase inhibitors were introduced. Triple negative disease has also seen little progress in treatments, but is becoming better understood – it is now known to be a group of some seven to ten further subtypes, she said.

Cardoso gave a reminder of the importance of guidelines – how they have improved survival and quality of life in early-stage disease, and could do the same in the advanced setting. Already, the first ABC guidelines, issued in 2012, have been widely presented and implemented in some countries. But research has been painfully slow. "It took us ten years to understand that it's important to give trastuzumab [Herceptin] after progression, and ten years to understand the best dose and regimen for paclitaxel [Taxol] in the metastatic setting. This isn't good enough," Cardoso said. There are many unanswered questions about evaluating new treatments, she added, and it's as much, or even more, important to individualise treatments than for early breast cancer.

Cardoso also summarised other recommendations she feels advocates can lobby for around the world. "Treatment in multidisciplinary teams is obvious, but not always done even in the West," she said, adding that medicine should be evidence based and not 'eminence' based – not in the hands of single oncol-

Meet the experts – the session where advocates hear from leaders in the field, and talk about what can be done to speed progress. From left to right: Ann Partridge, Lesley Fallowfield, Larry Norton, Martine Piccart and Kathy Redmond

JORGE NOGUEIRA

ogists who think they know best. Psychosocial support is needed from the start, clear explanations of the cancer and treatment must be given, including that there is no cure, and patients with advanced disease should always be accompanied to appointments.

Advocates had ample time to develop these themes as a large group and also in regional workshops. Access to treatment and to multidisciplinary teams are at the forefront of concerns – many countries currently do not have such teams, let alone specialist breast units, while the cost and availability of the latest drugs is also a serious barrier to optimal treatment. Lack of resources is not confined to poorer nations, but the problem is on a different scale: it was mentioned that in some countries such as Thailand it can be a struggle even to see an oncologist.

The wide spectrum of resources – from the comprehensive cancer centres of the West to countries where it may be difficult even to administer intravenous drugs – is a big challenge for those drawing up international guidelines. While there are no compromises about recommending optimal treatment, based on evidence, and also passing expert opinion about issues such as the need for multidisciplinary teams and psychosocial support, it is recognised that costs and available resources need to be taken into account.

For example, among the guidelines updated at ABC2 is a recommendation on the importance of patients having access to specialist cancer nurses (preferably breast care nurses) – it is vital to have a 'navigator' for treatment and support. The recommendation has been amended to recognise that the role could be provided by training other health professionals or doctors' assistants.

Markers of best practice

Having representatives from many parts of the world helps to put down markers of best practice – although again it was striking that even the most developed nations reported patchy provision for people with advanced disease, and also much to do on the advocacy front to fully include them in breast cancer work. Yes, there are specialist breast units, and the start of an accreditation system for them in Europe – but are they seeing enough people with advanced cancers, and are they employing an appropriate mix of professionals such as psycho-oncologists and gerontologists? Are breast care nurses tied more to early-stage surgical teams and not being given time to develop supportive skills for people in the advanced stage of cancer? Are patients being given the right information and an honest account throughout? Are advocacy organisations using the right messages and information to connect with people living with advanced cancer?

Even in the largest and most prestigious cancer centres and breast units, some patients with advanced cancer are not discussed at tumour boards.

In Europe, Susan Knox, executive director of Europa Donna, says a key milestone was the publication in 2006 of guidelines for quality assurance in screening and diagnosis. This 400-page document sets out the requirements for specialist breast units, and has been the keystone for lobbying by member organisations that now number 46 countries in and around Europe. Accreditation work for units is ongoing,

Count us in!

- Almost half a million women (and several thousand men) are diagnosed with breast cancer in Europe every year
- In around 30% of cases this will develop into metastatic disease
- Only 5% of cancer research funding is directed towards solutions for metastatic disease
- In all but a few countries, no records are kept of cases of cancer that recur as metastatic disease.
- The ABC conference is the first international guidelines conference to focus on the treatment and care needs of people living with metastatic cancer

"There's nothing chronic about two to three years survival after diagnosis"

and Knox says that a priority for Europa Donna is for people with advanced disease to be treated in breast units, which is not yet widely happening for reasons such as lack of trained staff.

Europa Donna, she adds, has done its own informal survey of member countries, finding that only a third say women with metastatic disease are given enough support at the time of diagnosis, and a large majority agreed that there is a need to advocate for special rights for these women with regard to information, treament and counselling. This could lead to national interest groups being established for people with advanced breast cancer, in a similar way to groups for young women with breast cancer that have appeared recently, says Knox.

As one advocate also commented, messaging is so important for involvement and for destigmatising the illness. "They don't want to hear about diet and exercise – we need to tune our messages to the new 'normal' in their lives, and help with the isolation they feel." It was also noted that the word 'survivor' is not appropriate for those with advanced disease, as it is not how women see their lives of daily coping and ongoing treatment.

Advanced advocates

The US already has advocacy groups for metastatic patients, including MBCN – the volunteer-run Metastatic Breast Cancer Network – whose president Shirley Mertz played an active role at the conference, and METAvivor, also run by volunteers. METAvivor's director of advocacy Dian Corneliussen-James – known to all as 'CJ' – is living with advanced breast cancer herself, and also played a leading role at ABC2 in discussions and presenting a summary of the advocacy sessions to the conference. METAvivor was set up to fund research into metastatic cancer – rather than as a support group – and is fiercely independent in pursuit of its mission, says CJ, who notes that there is only a low percentage of cancer research funds being spent on metastatic disease, in particular in the US.

"The minute you say to someone you have breast cancer, they think you are living longer and longer and the disease is virtually chronic now," says CJ. "There's nothing chronic about two to three years survival after diagnosis, although there are outliers such as myself." The proportion of women who go on to have metastatic breast cancer is 30%, and METAvivor wants to see 30% of cancer research funding dedicated to advanced disease – six times the current estimated average in the western world of around 5%.

Duplication of effort in the advocacy movement is a big concern for CJ, and she agrees that there are too few patients at conferences: "We can speak for ourselves – I was delighted to see Doris Fenech speaking at ABC and it is a dream come true to come to a conference that focuses on our disease" – although as she says, all women would rather be spending time with family or doing their usual work rather than "working round the clock on these issues".

At the other end of the spectrum are well-staffed broad advocacy groups like Breast Cancer Network Australia (BCNA), whose CEO, Maxine Morand, is a former minister for children in the Australian state of Victoria. "We are a member-based organisation and connect to patients through breast care nurses, who register them for our resources, such as the My Journey kit, which present information about clinical and supportive care," she explains.

The network has recently updated a resource for women with advanced cancer with information tailored to the site of the spread. "Information is incredibly important," says Morand, noting that there is also a very active online presence where women can network with others in similar situations. BCNA has also been successful in lobbying for access to drugs such as trastuzumab and is now working on gaining reimbursement for regular bone scans for women taking aromatase inhibitors, she says. Fighting for funds and reimbursement is a common theme.

Advocating on many fronts

An impressively wide range of issues were discussed at ABC – a reflection of the growing awareness that people who are living with advanced breast cancer need a broad set of care and support options – if any one is missing or poorly available, it can have a major impact on their quality of life. It underlined CJ's point about the need to avoid duplication and use advocacy resources wisely.

There were sessions on optimal pain control, psychological support, patient perspectives on symptoms, and global disparities in access to supportive and palliative care.

Changing the parameters for drug research to give quality of life far more attention was a frequently raised issue, not least by psycho-oncologist Lesley Fallowfield, and Musa Mayer, an advocate who runs AdvancedBC.org, both of whom sit on the ABC guidelines consensus panel. Improving the overall research climate for breast cancer was another major topic, but participants stressed that this must not come at the expense of other practical concerns that also need to be addressed. Prominent among them are funds and consistent support from local services for home care and home adaptations, social security payments for those not able to work, a requirement for employers to grant flexible working hours to fit in treatment, and a range of rehabilitation services, which need to cover areas such as sexuality and complementary medicine. Pain and symptom management, and the early introduction of palliative and supportive care, are also crucial and often poorly given.

Underpinning it all is a big frustration for advocates – the lack of information about how many people are living with advanced cancer. Most cancer registries record primary diagnoses and mortality, but not recurrences, so there are only estimates. There have been campaigns to change this. In England, a pilot has been run on collecting data on recurrent and metastatic breast cancer from current mandated sources, and to see how this could be integrated with data flows to cancer registries.

As a report on the pilot puts it bluntly: "The lack of information on recurrence and metastasis of breast cancer means that the effectiveness of treatments for primary cancers cannot be adequately assessed and the care of patients with recurrent and metastatic cancer cannot be fully evaluated." It was advocates who pressed to change this.

In a 'meet the experts' session at ABC2, where advocates were able to put questions to some of the world's top oncologists and other professionals, there were equally blunt comments – not least that advocates should get more angry about the lack of progress. Larry Norton, ABC co-chair based at Sloan-Kettering in New York, said: "We probably know how to cure metastatic breast cancer" – it's a matter of looking better at the data, while Martine Piccart, from Jules Bordet Institute in Brussels, added that research teams are sitting on data for far too long, and women who take part in studies should say it is unacceptable not to share data.

As one advocate said: "Informed patients make better doctors" – and the ABC conference is helping to put more patients in the driving seat. ■

KNOW YOUR GUIDELINES

The Second International Advanced Breast Cancer Consensus Conference was attended by more than 1,000 healthcare professionals and advocates – the latter have established a patient advocacy committee that will issue its own position paper this year. The ABC1 main consensus guidelines, first published in 2012 in *The Breast* (vol 21, pp 242–252) cover:

- General – statements on multidisciplinary teams, psychosocial care, priority of including patients in trials, and more
- Assessment – includes staging, response to therapy, and biomarkers
- Treatment – includes factors to include for treatment choice and specific statements on ER+, HER2+ and chemo- and biological therapies
- Bone and brain metastases – assessment and treatments
- Supportive and palliative care – including priority for expert care, and pain treatment
- Male breast cancer – treatment options.

The ABC1 guidelines will be updated with recently available data and new recommendations will be issued on the following:

Locally advanced inoperable breast cancer

ABC2 agreed that where the disease is very advanced (inoperable) in the breast and in the regional lymph nodes, but there are not yet distant metastases, all patients must be discussed in a multidisciplinary team before any treatment; chemotherapy should be the first treatment, not surgery; most patients become operable with either mastectomy or, in selected cases, breast-conserving surgery; and all patients need radiotherapy.

Other recommendations

ABC2 also made recommendations on:

- treatments for other metastatic tumour sites such as liver, pleura and skin
- managing metastatic breast cancer in men
- advanced disease related to BRCA mutations
- the urgent need for specialist breast oncology nurses, or other trained and specialised healthcare practitioners.

The ABC guidelines are developed jointly by the European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO) and will be published simultaneously this year in *The Breast* and *Annals of Oncology*. The ABC guidelines are also endorsed by the European Society of Mastology (EUSOMA), the Latin American Federation of Mastology (FLAM) and the International Society of Senology (SIS).

Thrombosis and cancer

Thrombosis is the second most common preventable cause of death in patients with cancer, so oncologists need to know how to identify who is at risk, and strategies for prevention and treatment. This overview presents the evidence and raises alerts about the use of oral anticoagulants in the cancer setting.

The bidirectional relationship between cancer and thrombosis has been known about for nearly 150 years, since Armand Trousseau first identified the link. However, despite being the second most common and preventable cause of death in outpatients with cancer, until recently cancer-associated thrombosis (CAT) has been a largely undiagnosed and undertreated condition. Cancer patients have a four- to seven-fold increased risk of venous thromboembolism (VTE) compared to the general population, with the highest risk in the first few months after cancer diagnosis. The incidence is high and increasing, with 20–30% of all first VTEs being cancer related.

It is important to be clear what we're talking about. Studies are still hampered by the lack of standardisation of detection and reporting of VTE. The International Society on Thrombosis and Haemostasis (ISTH) subcommittee on malignancy defines acute cancer-associated thrombosis

European School of Oncology e-grandround

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

In this issue, Annie Young, from the University of Warwick, in Coventry, UK, reviews the impact of cancer-associated thrombosis, key risk factors, the evidence and recommendations for treatment. Astrid Pavlovsky, from the Clinical Research Center, Fundaleu, in Buenos Aires, Argentina, posed 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

as "diagnosis of the index DVT [deep-vein thrombosis] or PE [pulmonary embolism] was made within the past 1 month" (*JTH* 2013; 11:1760–65). DVT needs to be fully defined as to whether it is symptomatic, proximal, which limb is affected, and which blood vessel. Similarly, pulmonary embolism needs to be defined by whether it involves a segmental or more proximal pulmonary artery, with some counting sub-segmental arteries as well. It is also essential to define what we mean by other related terms, including recurrence, extension of the thrombosis and incidental thrombosis.

Clinical presentation

Cancer-associated thrombosis can be quite debilitating for patients. Most thromboses are asymptomatic, but a cancer registry with more than 10,000–15,000 patients shows that most patients with DVT present with extremity oedema (80%), pain (75%) and erythema (26%) (*Haematologica* 2008; 93:273–278). Patients with pulmonary embolism present with shortness of breath (85%) and chest pain (40%). Catheter-associated VTE has similar signs and symptoms, with the addition of catheter dysfunction (*JCO* 2003; 21:3665–75).

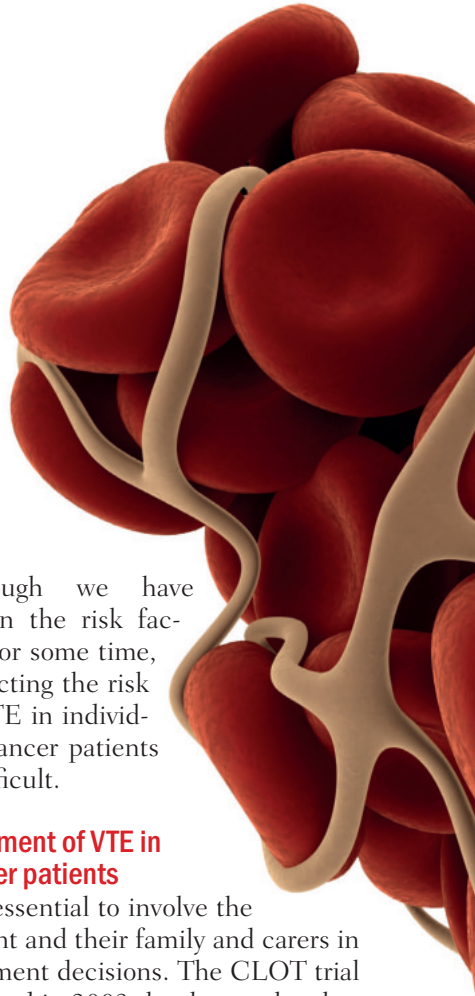
The adverse consequences of cancer-associated thrombosis include: increased risk of early death; compromised quality of life; more frequent hospital visits; need for anti-coagulation, which can cause bleeding complications; increased healthcare costs; increased risk of post-phlebitic syndrome and greatly increased risk of recurrent thrombosis. In addition, patients may have to interrupt potentially life-saving cancer treatment.

Should we screen patients presenting with VTE for cancer? Acute VTE can be the first manifestation of an occult cancer. There have been many small studies looking at using extensive screening, baseline screening or no screening at all. We know that patients with unprovoked VTE are at higher risk of having cancer, but no studies have found screening to be cost effective or to affect patient survival. At the moment in our practice, we do an abdominal ultrasound in patients deemed to be at risk of a malignancy.

Risk factors for VTE in cancer patients

One risk factor for thrombosis in cancer patients is the tumour type. There is a higher incidence in patients with ovarian, stomach and pancreatic cancers, particularly with advanced disease; patients with breast or prostate cancers or melanoma are among those with the lowest risk.

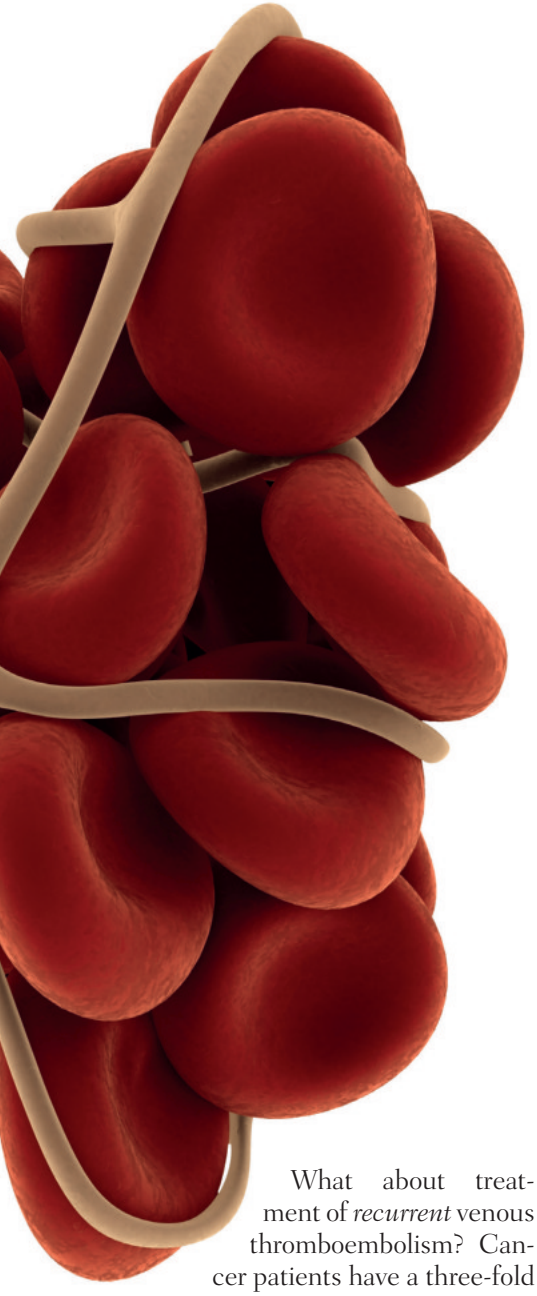
Patient-related risk factors include age (although there have been conflicting reports on this), immobility, previous VTE, and comorbidities. Women have a higher risk of VTE, and some patients have prothrombotic gene mutations. Treatment-related factors also influence VTE risk. Surgeons are generally good at giving prophylactic anticoagulation, sometimes for extended periods, for cancer-related surgery. Some chemotherapies cause increased risk of VTE. Hormone therapies, for example tamoxifen, and some of the new anti-angiogenic agents such as VEGF inhibitors and immunomodulatory agents, are associated with increased risk of arterial thrombosis and a slightly higher risk of venous thrombosis. Lenalidomide and thalidomide in combination with dexamethasone for patients with multiple myeloma also increases VTE risk. More details on risk factors can be found in A Young et al. in *Nature Reviews Clinical Oncology* (9:437–449).



Although we have known the risk factors for some time, predicting the risk of VTE in individual cancer patients is difficult.

Treatment of VTE in cancer patients

It is essential to involve the patient and their family and carers in treatment decisions. The CLOT trial reported in 2003 that low-molecular-weight heparin (LMWH; dalteparin was used in the trial) is superior to warfarin or other vitamin K antagonists (*NEJM* 2003; 349:146–153), but many patients with cancer-associated thrombosis are still treated with warfarin throughout the world. Alternatives include unfractionated heparin (UFH) for patients with renal impairment, and fondaparinux for patients with heparin-induced thrombocytopenia (HIT). The meta-analysis done by Ellie Akl and the Cochrane database shows that this is the treatment we should be giving, and yet many centres do not (*Cochrane Reviews* 2011; 15:CD006650).



SHUTTERSTOCK

Question to the live webcast participants:

Are catheter-related thromboses a frequent problem in your centre ?

Responses: Yes 50%, No: 50%

What about treatment of *recurrent* venous thromboembolism? Cancer patients have a three-fold greater risk of recurrent VTE than the general population (*Blood* 2002; 100:3473–88).

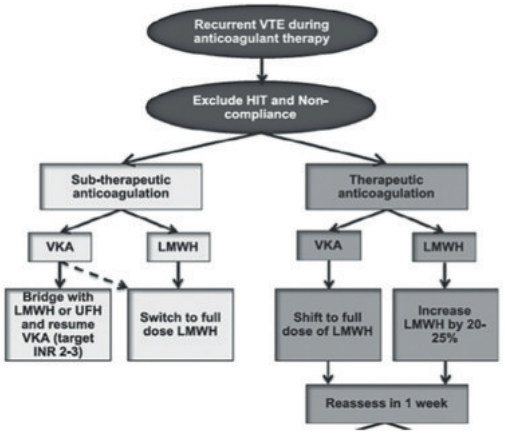
Treating recurrent thrombosis is a real problem in the clinic. Patients on subtherapeutic anticoagulation with warfarin or LMWH can be switched to full-dose LMWH (see figure, *right*). Patients on therapeutic anticoagulation with warfarin should shift to LWMH, and those already on LMWH should have the dose increased by 20–25%, according to expert opinion from the ISTH malignancy subcommittee. Patients should be reassessed after one week. Those showing symptomatic improvement can continue with the increased dose of LMWH. Measure anti-Xa levels in patients without symptomatic improvement to see if you can increase the dose of LMWH.

How long do we treat the patients with a thrombosis? Decisions are based on the balance of bleeding versus thrombosis. Other considerations include the status of the patient's cancer – whether they've got early or advanced disease – type of treatment, impact on quality of life and patient preference. The updated ASCO guidelines for VTE management in cancer patients (2013) recommend considering 12 months anticoagulation when treating symptomatic VTE in patients with advanced or metastatic disease. However, if the increased risk remains, you could consider treatment for the rest of the patient's lifespan. There are no trials clarifying the duration of anticoagulation, but two UK studies have just started looking at duration of treatment in cancer-associated thrombosis. – ALICAT (www.controlled-trials.com/ISRCTN37913976) and select-d (www.controlled-trials.com/ISRCTN86712308).

Prophylaxis of VTE in cancer patients

Are the rates of VTE high enough to warrant prophylaxis? Studies show varying rates of thromboembolism in cancer patients, with control rates of around 15% before 2000 and 5% or less in recent studies. The SAVE-ONCO study published last year compared prophylaxis with the ultra-LMWH semuloparin with placebo (*NEJM*

TREATMENT OF RECURRENT VTE



Cancer patients have a three-fold risk of VTE in comparison with the general population

Source: AY Lee et al. *Blood* (2013) 122:2310–17; P Prandoni et al. *Blood* (2002) 100:3483–88, published with permission from American Society of Hematology

2012; 366:601–609). Results showed a significantly lower rate of VTE with semuloparin (1.2% vs 3.4% with placebo; *P*=0.001), but the FDA decided not to promote this ultra-LMWH, as the results did not clarify which cancer patients would most benefit, given the side-effect of bleeding. Major bleeding occurred at similar rates with placebo (1.1%) and semuloparin (1.2%). We need more trials on VTE prophylaxis, with large numbers of patients at high risk of VTE.

Current guidelines (ESMO, ACCP, NCCN and ASCO) recommend against routine thromboprophylaxis in outpatients with cancer. In patients who have additional risk factors and who are at low risk of bleeding, they suggest prophylactic doses of LMWH or unfractionated heparin. Additional risk factors are: previous VTE, immobilisation, hormone therapy, angiogenesis inhibitors, and treatment with thalidomide and lenalidomide with dexamethasone.

Question: *For patients at high risk, are there any anticancer drugs, other than lenalidomide, that are high risk for thrombosis?*

Answer: *Thalidomide derivatives are high risk. And if we are using erythropoietin-stimulating agents, we give prophylaxis. Apart from these two classes of drugs, I think risk should be assessed on an individual basis.*

Question: *Regarding the cost, would using low-dose aspirin be beneficial?*

Answer: *We don't use low-dose aspirin at all for prophylaxis and treatment of venous thromboembolism. It is cheap but has most benefit for arterial thrombosis. However, clinicians do recommend its use in other parts of the world, especially in Asia.*

Question: *Regarding anti-Xa levels, when you decide to increase the level of LMWH for patients with recurrent VTE, is there any target for the anti-Xa levels you should be trying to reach?*

Answer: *There's great debate in the UK at the moment, each laboratory has a different assay, and you have to go with your own laboratory to determine peak levels. Getting laboratories to do the same assays would be good.*

Risk prediction tools

How do we risk assess the individual patient? Based on consensus, the most recent ASCO guidelines recommend that patients with cancer (outpatients, as well as inpatients) be assessed for their thrombosis risk at the time of starting chemotherapy and periodically after this (*JCO* 2013; 31:2189–2204). Risk should be assessed using a validated risk assessment tool. In the UK, all hospitalised patients – not just cancer patients – undergo a simple, government-mandated, risk assessment for VTE. So we already risk assess all inpatients but not outpatients.

Alok Khorana was the first to develop a risk prediction tool a few years ago, stemming from a neutropenic sepsis study that he was doing that confirmed the risk factors we have previously covered. Patients are scored for their risk factors (see figure below), with a Khorana score of 0 being low risk, a score of 1–2 points being intermediate risk and a score of 3 or more considered higher risk, when you would consider giving prophylaxis. This tool has been validated by studies in two countries – the Austrian Cancer And Thrombosis Studies (CATS) and SENDO (South European New Drugs Office) phase I studies in Italy. The Austrian team added two more risk factors – p-selectin and d-dimer (*Blood* 2010; 116:5377–82), but these have not been validated as yet. We do not currently use the Khorana risk tool in the UK, but only the simple Department of Health generic tool; however, we should, certainly in our centre, as so far it is the best tool we've got.

There is another clinical prediction tool for risk stratification for recurrent VTE in patients with cancer (*Circulation* 2012; 126:448–454) based on two observational studies. High-risk predictors – the sex of the patient,

VTE RISK PREDICTION TOOL (KHORANA)

Patient characteristic (site of cancer)	Risk score*
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynaecological, bladder, testicular)	1
Prechemotherapy platelet count 350×10^9/l or more	1
Haemoglobin level less than 110 g/l or use of red cell growth factors	1
Prechemotherapy leucocyte count more than 11×10^9/l	1
BMI 35 kg/m^2 or more	1

The Khorana risk assessment tool is the best way of assessing risk for VTE in cancer patients.

* 0 points = low risk; 1–2 points = intermediate risk and ≥3 points = high risk

Source: AA Khorana et al. *Blood* (2008) 111:4902–07, published with permission from American Society of Hematology

Question to the live webcast participants:

Are you considering the novel oral anticoagulants for patients with cancer ?

Responses: Yes: 25% No: 75%

the primary tumour site, the stage, and prior VTE – all score +1. Low-risk predictors score negative points – breast cancer scores -1, and stage 1 disease scores -2 points. Scores of <0 are low risk and >1 are high risk, when you would consider anticoagulation. This needs to be validated by other teams. We are starting to risk stratify for the individual patient.

Catheter-related thrombosis

Catheter-related thrombosis is not yet clearly defined: is it a blood clot in the lumina of the catheter, round about the catheter, or a mural thrombus that has gone right across the vein? We have to define what we are talking about, because rates of thrombosis in catheter studies vary widely. In a meta-analysis of warfarin versus control in catheter-related studies we published in 2009 (*Lancet* 373: 567–574), the confidence intervals crossed the line of unity and the difference was not significant. Although early studies showed that warfarin was better, these were tiny studies, and larger studies showed that low-dose warfarin (1 mg) does not reduce the rates of catheter-related thrombosis, with similar findings for LMWH (*JCO* 2005; 23:4063–69). So we do not recommend – and the ASCO guidelines say this as well – prophylaxis for catheter-related thrombosis, certainly not with warfarin and only with LMWH if there are other risk factors.

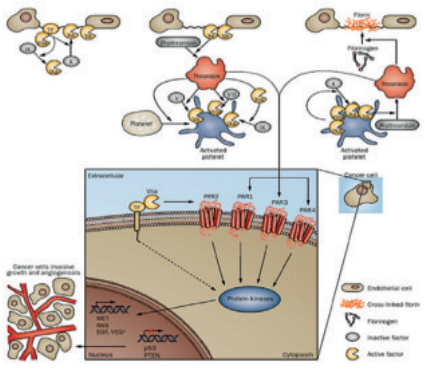
Survival benefit

Since the 1970s we've been looking to see if there is there any survival benefit – do anti-coagulants designed to have an anti-coagulant effect and not an anti-neoplastic effect have any impact on patient survival? A meta-analysis of all relevant studies, published in 2012 – most of them small and therefore underpowered for survival – found no survival benefit of anti-coagulation (*NEJM* 2012; 366:661–662). Some sub-studies and some analyses done *post hoc* showed that specific populations of patients may benefit, but these require further definition. The biological rationale for a heparin effect is emerging.

As well as the clinical predictors and the risk factors for VTE, there are also laboratory biomarkers. These are useful in identifying high-risk patients that may benefit from prophylaxis. These biomarkers encompass: factors that activate at the clotting system, such as d-dimer and p-selectin; factors indicating increase in the inflammatory potential around the milieu of the tumour, such as the leucocyte and platelet count; and initiation of the clotting cascade, which can be tested for by measuring tissue factor expressing microparticles. A recent study showed that TNF-alpha is a candidate gene contributing to VTE pathogenesis in gastrointestinal cancer patients (*Ann Oncol* 2013; 24: 2571–75), so we're now looking at gene studies to see what contributes to VTE pathogenesis.

The figure (*left*) illustrates the close relationship between the molecules responsible for neoplastic transformation and tumour procoagulant activity, which we need to research further. Thrombin generated by the coagulation cascade activates cell surface receptors such as PAR1. The extracellular domain of tissue factor binds to factor VIIa and starts off the clotting pathway. The intracellular domain changes start the signal transduction that modifies and modulates cancerous cells

MOLECULES INVOLVED IN CLOTTING AND CANCER



There is a close relationship between the molecules responsible for neoplastic transformation and those responsible for tumour procoagulant activity, which requires futher research

Source: A Young et al. (2012) *Nat Rev Clin Oncol* 9:437–449, reprinted by permission from Macmillan Publishers Ltd

through many pathways including the protein kinases and the MAP kinase pathway.

How to manage tricky cases of cancer-associated thrombosis

Expert opinion from the ISTH malignancy subcommittee can help with the management of cancer-associated thrombosis in clinical practice (*JTH* 2013; 11:1760–65). However, there are no studies to help with this, as yet.

Symptomatic recurrent VTE

Recommend: If patient is on vitamin K antagonists, switch to LMWHs.
Suggest: If on therapeutic LMWHs, use a higher dose (25%), and assess in 5–7 days.
Suggest: If no symptomatic improvement, use peak anti-Xa level to estimate next dose escalation.

Thrombocytopenia

Recommend: Full therapeutic dose anticoagulation, if the platelet count is ≥50x10^9/l.

Recommend: For acute cancer-associated thrombosis and platelet count <50x10^9/l, full therapeutic dose anticoagulation with platelet transfusion.

Bleeding

Recommend: Careful and thorough assessment of each bleed.
Supportive care with transfusion and surgical intervention to stop bleeding where possible.
Stop anticoagulation.
Suggest: IVC (interior vena cava) retrievable filter in patients with acute or subacute cancer-associated thrombosis with major bleeding.

NOAC INTERACTIONS WITH ANTICANCER THERAPIES BASED ON KNOWN METABOLIC PATHWAYS

Interaction effect*	Dabigatran P-glycoprotein	Rivaroxaban P-glycoprotein CYP3A4	Apixaban P-glycoprotein CYP3A4
Increases NOAC plasma levels†	Cyclosporine	Cyclosporine	Cyclosporine
	Tacrolimus	Tacrolimus	Tacrolimus
	Tamoxifen	Tamoxifen	Tamoxifen
	Lapatinib	Lapatinib	Lapatinib
	Nilotinib	Nilotinib	Nilotinib
	Sunitinib	Sunitinib	Sunitinib
		Imatinib	Imatinib
Reduces NOAC plasma levels‡	Dexamethasone	Dexamethasone	Dexamethasone
	Doxorubicin	Doxorubicin	Doxorubicin
	Vinblastine	Vinblastine	Vinblastine

Novel oral anticoagulants may not be suitable for use in some cancer patients because they share metabolic pathways. Further research is needed to find out more about the impact of the interaction

† Inhibitors of pgp transport and CYP34A pathway; ‡ Inducers – lower NOAC levels

Take home messages

- Cancer-associated thrombosis is an important clinical problem.
- Patients and their families/carers should be informed about venous thromboembolism (VTE) risk and be involved in all decisions.
- All patients should undergo VTE risk assessment and, if appropriate, thromboprophylaxis.
- Tissue factor is a key mediator of clotting, inflammation, tumour progression and angiogenesis.
- More research is needed with novel oral anticoagulants in the cancer setting.

Novel oral anticoagulants (NOACs)

NOACs don't come without their concerns. They are metabolised through the P-glycoprotein pathways and also the cytochrome P450 3A4 (CYP34A) pathway, so we try to avoid their use with anticancer agents metabolised in the same way (see figure above). Some anticancer therapies, for example sunitinib and imatinib, interact with the P-glycoprotein and the CYP3A4 pathways, but we do not know if that translates into any clinical effect, so studies need to be carried out. We are carrying out a pilot study (select-d) comparing the NOAC rivaroxaban with dalteparin in patients with active cancer and VTE at first randomisation, stratifying by risk factors. Patients who are positive for residual vein thrombosis (RVT) at six months (patients with DVT and all PE patients) will then continue treatment, randomised to rivaroxaban or placebo, while those with no evidence of RVT will stop (*JTH* 2012; 10:807–814). ■

Let us convince you!

Enticing medical students into oncology

PETER MCINTYRE

Every summer a group of top oncologists gather in the ancient city of Ioannina to give a select group of motivated medical students a taste of what it's like to work in cancer.

The number of people who develop cancers in greater Europe is expected to grow to 3.4 million a year by 2020, a 20% increase over 2002. Many experts are concerned that the number of cancer specialists will not keep pace.

In 2013, the European Society for Medical Oncology (ESMO) pointed out that less than half of European Union countries have good data about the projected numbers of medical oncologists, while the International Atomic Energy Agency (IAEA) highlighted a shortage of skilled radiotherapy staff.

Career choices by medical students is a factor, and lack of specialised undergraduate training has been long recognised. As long ago as 1998 the Deans of medical schools and oncologists from 17 European countries agreed to improve the undergraduate curricula – but the results were patchy.

Andreas Nearchou, aged 31, and now in the final stages of his first residency at Mälar Hospital, in Eskilstuna, Sweden, puts it like this: "People who have not tried chocolate don't know how it tastes, and if you ask them they may say they are not interested! If medical students are not interested in oncology, I think it is because they don't get enough information."

Andreas developed his taste for oncology at one of the very few courses in Europe that allowed students a glimpse of what could be a rewarding career – an intensive week-long Oncology for Medical Students course at the University of Ioannina in northern Greece. Despite the economic crisis, the course has flourished and this July 2014 starts its second decade, attracting students from Europe, the Middle East and further afield.

Nicholas Pavlidis, Professor of Medical Oncology at the University of Ioannina, and Alberto Costa, Scientific Director of the European School of Oncology (ESO), developed the course after identifying a profound gap in undergraduate training. Pavlidis says: "We found that in most European universities oncology is not at the top of the training. So we said let's put together a programme covering almost all of oncology – surgery, radiotherapy and medical oncology – and attract these guys to oncology."

In 2013 Pavlidis celebrated 10 years at the head of this high-quality faculty with a mission to attract medical students towards the specialism. The €40,000 cost is jointly met by ESO and the ESMO, covering accommodation, registration, meals and books. The student pays only for the travel.

The programme focuses on the common cancers (breast, lung, colorectal, gastric, prostate, head and neck, uterine and ovarian cancer), but also covers "curable tumours" (lymphomas, testicular cancer, paediatric/adolescence oncology and oncogeriatrics).

Each day a faculty member presents a mainstream topic leading to a two-hour discussion on a case study. Each afternoon there is a written one-hour multiple choice exam. At the end of the week, the student who scores highest is offered a month's fellowship at one of the faculty member institutes.

Each year Pavlidis receives 100 applications from fifth- and sixth-year medical students, for just 40 places. Students do not have to pretend to already be converts. "About 60–70% declare they want to become an oncologist when they apply," says Pavlidis. "If they are a good student and dedicated, we are open. As long as they have a good CV, good motivation and a good recommendation from their professor, they are going to get in.

"The ones who come are very ambitious. They try to make some contacts among the faculty members that will guarantee their futures."

Unsurprisingly, the largest number of students – 37 in the first six years – came from Greece, but students have also attended from another 33 European countries, as well as Brazil, Egypt, India, Indonesia, South Africa and Sudan.

Pavlidis said: "Most medical students around the world are aware of this course; it has become very famous. It is amazing to see medical students from Brazil or from India." More recently there has been an increase in students from the Middle East.

Andreas Nearchou came from Cyprus, and attended in 2007, his penultimate year at the University of Ioannina. He had become interested in oncology through helping a colleague with a meta-analysis of osteosarcoma. "I thought it was quite fascinating, but I was not sure 100%. After I attended the course I was more than sure."

He did shifts with Pavlidis and the oncology team in his final year, and also helped out with the subsequent student course. "It is a well-organised course with long days. The lectures are very up to date and the staff are a dream team of oncology in Europe. They really know their areas. It showed me that oncology is not a one man show but you work as part of a multidisciplinary team."

When Nearchou completed his medical degree in 2008, Greece was entering its economic crisis and there were few opportunities in his home country of Cyprus. After an intensive three months studying the language, he applied for a job in Sweden. Much to his surprise – his Swedish was still wobbly – he was awarded a three-month contract,

A lightning tour. Students get introduced to all the most common cancers, and the most curable ones

which has since become permanent.

Now 31 years old, he treats a range of cancers at the Mälar Hospital, 110 kilometres west of Stockholm, while working on a PhD in kidney cancers at Stockholm's Karolinska Institute. He is married to a Greek biologist who also works at the Karolinska, and they intend to stay in Sweden.

Nearchou has recommended the Ioannina course to several Swedish students. "There are only two to three weeks on oncology in the whole degree course, and I think this has to change. In hospitals, 30% of medical treatment cases in are cancer patients."

The University at Ioannina is only 50 years old, but the welcoming address – on the history of cancer medicine – is delivered in the beautiful 18th century Monastery of Agios Georgios of Dourouti. These have covered oncology in Ancient Greece, Egypt, India and the Renaissance, and Darwinian theory and cancer, among other topics.

Last year was the 10th anniversary course, and amongst all the study, the faculty and students found time for a big celebration, with cake, beach volley ball, eating and dancing.

Over 10 years the course has seen a gradual shift from male to female students. Arpine Gevorgyan, an Armenian student at the University of Milan, was on the first course in 2004, and has noted this trend throughout her specialty. "I have seen it happening but I don't know why. About 85% of the young oncologists are women and the older generation are men."

In Ioannina she was especially impressed by the positive attitude towards young doctors. "I knew Pavlidis from his publications and it was really nice to see him organising something for young people who did not even know if they would be oncologists. During the course I became quite sure about my level of preparation and the future."

Gevorgyan said: "It was a great location and the hospitality was really nice. We had a chance to spend time with the local students and to have fun. For young people it cannot only be about being serious. This is a great course and I would recommend it."

Pavlidis is starting to research what career paths the students take afterwards – initial findings suggest something like 60% are engaged in oncology. "I do not know if this was a prior decision or was due to the course. We do not have solid evidence yet but will be sending out questionnaires to find out."

Oncology has not only to attract the brightest, it has to keep them. Gevorgyan, now doing medical research into gastrointestinal cancers at the Istituto Nazionale dei Tumori in Milan and working in public hospitals on solid tumours, feels there is a danger of burn-out. "We are working 18 hours a day and covering Saturday and Sunday. You cannot have your own practice because you are working in a hospital. I will be honest – we are underpaid.

"Oncology is tough because you are constantly working with sick people and you feel you are failing. The research is growing but people still die from cancer, and you cannot do anything about that. You have more failures than successes and it is really depressing, so I am not sure if I will stay in clinical work or go to a pharmaceutical company."

The challenge of retention underlines the need to recruit. And here too, time takes its toll. Pavlidis is due to retire in 2016. "A few years ago I asked some of the faculty members if someone wanted to take over and they all said that this setting was not achievable in any other European city. When I have to retire I am not sure what is next. Probably one of my colleagues will take over. In 2014 it will definitely remain. It would be a pity to stop it now." ■

Dream team faculty

As well as Nicholas Pavlidis (*pictured front*) and Alberto Costa (*not pictured*), the faculty includes (*front to back, left to right*): Rolf Stahel, head of Lung and Thoracic Oncology at the University Hospital of Zürich; Fady Geara, head of Radiation Oncology at the American University of Beirut; Riccardo Audisio, Consultant Surgeon at St Helens & Knowsley Trust, UK; Andrés Cervantes, head of Medical Oncology at the University Hospital Valencia; Jan Vermorken, head of Oncology at Antwerp University; and George Pentheroudakis, a medical oncologist at the University of Ioannina. Jacques Bernier, head of Radio-oncology at the Swiss Genolier Medical Network, Geneva, covered radiation oncology from 2004 to 2011.

Passport to the future

Improving life for survivors of childhood cancer

MARC BEISHON

By the time they reach 40, survivors of childhood cancers are likely to have at least one chronic health problem resulting from their treatment. The search is now on for ways to help people manage their risk and get appropriate care.

Childhood cancer may be rare, but survivors are not. One of the big success stories in oncology has been the steadily increasing proportion of children and young people who survive to adulthood, and who now number in the hundreds of thousands in Europe. The latest EUROCARE-5 study shows an average five-year survival of 79% for children aged 0–14 (five-year survival is currently around 60% in Europe and the US).

Survival in the teenage and young adult age group – 15–24 years old – is also similar to children, although there are differences in outcomes for certain cancers such as leukaemias and central nervous system tumours. There are also differences between eastern and western Europe, but the greatest gains recently have been in the east, where five-year survival has risen from about 65% in 1999–2001 to over 70% in 2005–2007 in the 0–14 age group.

But the mostly good news is offset by problems that are common in adult survivors of childhood cancers, who now greatly outnumber those currently undergoing primary treatment. While there is no definite number of adult survivors of childhood cancers in Europe, experts say it is at least 300,000 and could be as many as 500,000 people, and the current survival statistics translate into about 10,000 a year being added to this growing group. It's a similar picture to the US, where adult survivors (who were diagnosed with cancer aged 20 or under) are estimated to number more than 400,000, and are set to reach half a million by 2020, with an annual incidence of new cases of about 13,500 a year.

According to the authors of a recent paper in *Nature Reviews Cancer* (2014, 14:61–70), this growing population "reflects a highly vulnerable group of individuals who will probably experience adverse health-related and quality of life outcomes during their subsequent lifetimes as a result of their curative cancer treatment." The vast majority, the authors say, will have at least one chronic health condition by the age of 40, and there is a high risk of early death from subsequent cancers and heart and pulmonary conditions. While there can be multiple causes of later ill health, most survivors suffer only because of the late effects of certain treatments for their childhood cancer.

So a priority for healthcare systems

should be to characterise those survivors at highest risk and offer them interventions for late effects, which can be caused by all types of treatment – surgery as well as chemo- and radiotherapy – and also to offer help with psychosocial and quality of life issues. There are many late effects that survivors can suffer from, but most people have little long-term follow-up and guidance after they 'transition' into the world of adult healthcare, where most professionals lack experience of these effects. This means improving the care of survivors is a big challenge.

This challenge is now being tackled by several groups around the world, not least by PanCare, the Pan-European Network for Care of Survivors after Child and Adolescent Cancer. PanCare was set up in 2008 by paediatric oncologists, other medical specialists, epidemiologists, nurses, parents and survivors, to carry out research and develop guidelines on late effects, with the eventual aim of ensuring every child and adolescent survivor receives optimal long-term care.

The survivorship passport

The group has had notable success so far. One advance came when it was asked by the European Society of Paediatric Oncology to develop a survivorship work package in the European Network for Cancer Research in Children and Adolescents project, funded by the EU Framework programme. This package focuses on quality of survivorship, and a key part is the introduction of a survivorship 'passport' – a summary of medical history that could give people much better follow-up treatment as adults.

Riccardo Haupt, one of PanCare's founders and a paediatric oncologist and epidemiologist at the Giannina Gaslini Institute in Genoa, Italy, is the lead on the passport, which he says was lobbied for by parent associations and survivors in the PanCare network. "We know from them that many people lose contact with their cancer centre and do not have documentation on their treatment," he says. "They also often have trouble discussing problems with their GP or with specialists such as cardiologists, who may say, 'You've had cancer – I'm not an expert in this.'"

The passport aims to provide vital data on previous treatment and recommendations on follow-up for late effects for each patient. The first step has been to generate the list of variables that are important for survivors, such as tumour type, risk factors, treatment exposure and so on, which was settled via a Europe-wide ballot. "The second step is to see how complicated it is to complete the passport by inserting the data," says Haupt.

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"Many of us simply don't know our history and who to go to when we have a problem"

Most cancer centres and hospitals do not have records suitable for filling out the passport data fields, and expecting staff to spend an average of more than two hours gathering medical history for each patient is probably not realistic, adds Haupt. A number of data integration methods are therefore being investigated. One advantage of child patients is that the great majority are treated under trial protocols, so data on diagnosis and treatment can be gathered from clinical trials databases.

Sabine Karner, who had cancer when she was young, and who works for Austria's childhood cancer advocacy organisation for parents, has been involved with the passport's development through the International Confederation of Childhood Cancer Parent Organizations, (ICCCPO), which is a member of PanCare, and runs the International Childhood Cancer Survivors Network.

"Paediatric oncologists have listened to the voice of survivors in helping to develop the passport. Many of us simply don't know our history and the long-term effects we could have, and who we should go to when we have a problem," she says. "How, for example, do survivors know if something could be connected with their former treatment? And this is a life-long concern."

Karner points out that some childhood cancer centres, such as the St Anna children's hospital in Vienna, have already produced versions of passports, mostly only as a paper document. The goal now is for everyone to have a standardised one available both online and as a printed document.

"Of course not everyone needs or wants support, but many are simply lost to contact once they are no longer the responsibility of a children's hospital," she says, adding that some countries still have no specialist facilities for older teenagers and young adults with cancer, where the survivorship data could be prepared.

There are though a growing number of survivor groups around Europe, such as a recently established Les Aguerris group in France. Some are dedicated to survivors, while others are set up as subgroups of organisations for parents of those with children with cancer "These groups will raise awareness – and the passport is now very much on the European agenda," says Karner.

So far, a prototype of the passport has been developed by Cineca, Italy's non-profit university computer consortium, with leukaemia patient data from the Italian Association of Paediatric Haematology and Oncology; other groups in Europe are looking at structuring data for neuroblastoma, sarcomas and Wilms' tumour. Decisions about the coding systems for the passport have been complicated, adds Haupt, such as on whether to use the international childhood codes for tumour types, and how best to code complex radiotherapy information, which could also trigger certain recommendations for follow-up.

And there are privacy and data security issues: "For example, who is the owner? Should only the survivor have access or also their GP?" asks Haupt. While the aim is to empower survivors to be responsible for their long-term care, he adds, it is proving hard to translate medical language, for instance about risk factors, into words that people won't find too alarming: "Defining the way the information is disseminated has become a project in itself."

Guidelines for follow-up and care

Feeding into the work on the passport is another initiative dedicated to developing guidelines on clinical practice and how the transition to, and follow up in, adult care can best be implemented. Known as "PanCareSurFup" (PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies), the intention is to incorporate the recommendations from the guidelines developed by this project into the survivorship passport.

Guidelines are particularly needed in the wider medical community – such as GPs, cardiologists, endocrinologists, gynaecologists, and indeed for oncologists outside the paediatric field, says Haupt. "We see the guidelines as the key to making contact with these professionals," he says, adding that this is a global effort from the International Guideline Harmonization Group for Late Effects of Childhood Cancer (www.ighg.org), which was set up in 2010 to bring various groups together, with PanCareSurFup as the guideline development partner. Other core members include the Scottish Intercollegiate Guidelines Network, which published a national guideline on long-term follow-up in 2013, the North American Children's Oncology Group and the Dutch

The passport. Finding ways to ensure data about diagnosis and treatment are recorded in a standardised way for every child and young adult treated for cancer is proving a major challenge

Childhood Oncology Group.

A first clinical guideline has already been published, on recommendations for breast cancer surveillance for girls and young women who were given chest radiation as part of their treatment for cancers such as Hodgkin's lymphoma (*Lancet Oncology* 2013; 14 e621–29). It covers questions such as who needs surveillance, at what age and how frequently. It emphasises how important it is for survivors to be aware of their risk, and makes recommendations for breast cancer surveillance graded according to the amount of radiation that was received. The next topic that will get the guideline harmonisation treatment will be gonadal toxicity.

PanCareSurFup's work packages also include developing risk estimates for cardiac disease, later cancers and radiation dosimetry for various organs, which will inform other guidelines. Underpinning the project is the inclusion of what Haupt says will be the world's largest cohort of long-term survivors, 80,000 in total, who will be followed up by 16 networks and institutes around Europe.

Another PanCare project involves identifying possible genetic risk factors for certain late effects – namely fertility problems and hearing loss – and is coordinated by Mainz University Medical Centre in Germany.

The implementation challenge

The projects are important but Haupt and colleagues face the greatest challenge in embedding survivorship care in national health systems, and getting innovations such as the survivorship passport running as widely as possible. It will be easier in countries with integrated national systems, such as the UK (where aftercare 'pathways' and pilot projects have been underway) and the Netherlands, but less so where there are fragmented regional systems, such as in Italy, says Haupt.

There is also the need to convince health services to cover the added cost associated, for instance, with introducing interventions such as breast surveillance, which in the long run could reap substantial savings by cutting the burden of chronic disease.

Survivors and health professionals such as nurses also need financial support to maintain networking, says Haupt, while research and follow-up cannot stand still, as today's treatments will change or be discontinued in favour of new ones, leading to different patterns of long-term effects.

"There is a lot of expectation now among survivors and their families," says Haupt. "Once it is recognised that this is a population at risk, the recommendations we will be making should be a standard of care in each country." ■

Underpinning the project is the inclusion of the world's largest cohort of long-term survivors, 80,000 in total

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CT screening for lung cancer – do we have an answer?

UGO PASTORINO & NICOLA SVERZELLATI

Concerns still exist regarding the best use of low-dose CT screening for lung cancer and how to select high-risk individuals who will benefit most from participation in screening programmes. Two studies now indicate factors that may reduce the false-positive rate of lung cancer screening with low-dose CT.

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The decision of the US Preventive Services Task Force to recommend low-dose CT screening for all individuals aged 55–79 with ≥30 pack/year smoking history, based on the outcomes from the National Lung Screening Trial (NLST), has not eliminated the scepticism that still affects the scientific community concerning the cost–benefit profile of lung cancer screening. A number of major concerns still exist regarding the best use of low-dose CT for lung cancer screening, including how to identify individuals at high risk of developing lung cancer, the optimal diagnostic algorithm and management of lung nodules, high false-positive rates, and potential harm from overdiagnosis. The recent report on the results of incidence screenings with low-dose CT in the NLST highlights some favourable prospects, and also the current limitations, for lung cancer screening.[1]

Ideally, an effective screening programme should identify all malignant lesions while reducing, as much as possible, the probability of false-positive results. Reducing the number of false-positive results in screening programmes is important because of the risks and costs related to follow-up with low-dose CT scans, and the potential for unnecessary invasive diagnostic and surgical procedures. The NLST is the largest randomised study of lung cancer screening in a high-risk population to date. The NLST enrolled 53,454 current or former smokers between the ages of 55 and 74 years with a smoking history of a minimum of 30 pack-years from 33 sites. Participants were randomly assigned to screening with low-dose CT (n=26,722) or chest radiography (n=26,732). The NLST showed a 20% relative reduction in mortality from lung cancer with three rounds of low-dose CT screening (rounds T0, T1, and T2) compared with radiography.[1] However, in the incidence screenings (T1 and T2) of the NLST the positive predictive value (below 5%) seems far too low to encourage the use of a similar diagnostic protocol for future large-scale screening programmes. As suggested by the authors of the study, the simple increase of the lung nodule size threshold above 6 mm for positive low-dose CT would reduce the false-positive rate by over 50%, with only a minimal loss in lung cancer detection. In agreement with this concept, Henschke et al.[2] have recently suggested that using a nodule size threshold of 7 mm or 8 mm to define positive results in the low-dose CT baseline

round might substantially reduce the frequency of the diagnostic work-up without significantly delaying a diagnosis of lung cancer. Moreover, the decrease in late-stage lung cancers in the low-dose CT group as compared to the chest radiography group at both T1 and T2 reported by Aberle et al.[1] should be perceived as a very promising outcome.

The outcome of a study by McWilliams et al.[3] represents another important step forward in the optimisation of lung cancer screening strategies. In this study, data from two cohorts of participants, which totalled 2,961 individuals undergoing low-dose CT screening, was analysed to identify factors that could predict the probability that lung nodules detected on the first screening low-dose CT scans were malignant or would be confirmed as malignant on follow-up. Using simple predictive tools based on patient and nodule characteristics, a predictive model was developed that accurately distinguished malignant from benign nodules. This type of multiparametric model should be regarded as a reference tool to be validated further and, perhaps, improved by other ongoing trials. The exclusion of forced expiratory volume in one second (FEV_1) from the model developed by McWilliams et al.[3] seems to be in contrast to findings reported by other studies, which showed that decreased FEV_1 is a robust risk factor for lung cancer development, and an easy index to improve the management of nodules detected by low-dose CT.[4,5] It should be noted that the simple visual score of emphysema, as performed in the study by McWilliams et al.,[3] could be an over-simplistic way to measure this factor, and an automated assessment – that is, by using low-dose CT densitometric analysis – might be more appropriate.[6,7]

Since nodule size was the most relevant risk factor in the model tested by McWilliams et al.,[3] any technological development that is able to optimise and standardise measurement of nodules should be adopted in screening programmes. The analyses in both the PanCan and NLST studies were based on the maximum diameter of the nodules, which are associated with major limitations. For example, nodules may grow along an axis different than that of the maximum diameter, and also the minimal diameter variation of small nodules could be difficult to assess.[1,3]

By contrast, a study investigating the use of nodule volume and volume-doubling time as the main criteria for deciding on further action in 7,557 patients in the NELSON (Nederlands-Leuvens Longkanker Screenings Onderzoek) lung cancer screening trial[8] showed that nodule volumetry in the low-dose CT arm obtained a much higher positive predictive value (42.2%) than observed in the NLST, where nodule diameter on low-dose CT gave lower predictive values than chest radiography in the incidence screenings (2.4% vs 4.4% at T1; 5.2% vs 6.7% at T2).[1] Although data comparison needs to be interpreted with caution at this stage, as it depends on the contexts of the specific cohorts undergoing screening, the 3D volumetric measurements of lung nodules have, so far, proven superior to 2D diameter measurements in terms of accuracy – because the whole nodule is analysed, regardless of its irregular shape – and reproducibility.

Incidence screenings ... in the NLST highlights some favourable prospects ... for lung cancer screening

Key points

- Lung nodule size is the strongest predictor of malignancy in low-dose CT screening
- Positive predictive value of low-dose CT can be increased by volumetric assessment and higher cut-off for positive screenings
- Lung cancer risk can be stratified by a multiparametric model

The majority of ongoing European randomised screening trials have adopted volumetric assessment for the management of screen-detected pulmonary nodules, and have selected volume doubling time as the most reliable predictive index to distinguish true-positive screenings (requiring additional diagnostic procedures) from false-positive low-dose CT screening results.

Refinement of volumetric assessment of lung nodules will bring further improvement to future screening strategies. This has been demonstrated by Heuvelmans et al.[9] who, through a retrospective analysis of participants in the NELSON study, demonstrated that optimising the volume doubling time cut-off (≤232 days) reduced the false-positive referrals by 33% at a three-month follow-up.

In the studies by McWilliams et al.[3] and Aberle et al.,[1] neither addressed another fundamental problem of lung cancer screening: optimising the identification of high-risk populations. In an attempt to ensure that individuals at high-risk of developing

lung cancer are selected for screening programmes, the American Association for Thoracic Surgery has recommended low-dose CT screening for individuals from the age of 50 with a 20 pack-year history and a minimum lung cancer risk of 5% over the following 5 years.[10]

However, combining the new screening-generated risk prediction models with measurements of pulmonary damage (as indicated by the FEV_1 levels), and possibly with a few validated blood biomarkers, could identify individuals with a cancer risk greater than 10%, on whom future screening research can be focused.

Until the results of ongoing European randomised trials are available (possibly by the end of 2016), it seems unlikely that European countries will be able to follow the US guidelines. However, in the meantime, all efforts should be made to include volunteers at high risk of developing lung cancer in prospective demonstration studies to improve the efficacy of low-dose CT screening, reduce the burden of false-positive findings and prevent unnecessary surgery for nonmalignant pulmonary nodules. ■

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Author affiliations

Ugo Pastorino, Director of Thoracic Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; Nicola Sverzellati, Department of Surgical Sciences, Section of Radiology, University of Parma, Parma, Italy

newsround

Selected reports edited by Janet Fricker

Study defines optimum exercise level in breast cancer

■ JNCI

Undertaking higher volumes of aerobic exercise or combining aerobic exercise with resistance exercise improves physical functioning and symptoms for breast cancer patients more than standard volumes of exercise, the Canadian CARE trial has found.

For patients undergoing chemotherapy, aerobic and resistance exercise – either separately or in combination – have been shown to improve physical functioning and manage symptoms. Few studies, however, have compared different doses or types of exercise to identify optimal exercise prescriptions for given outcomes.

In the Combined Aerobic and Resistance Exercise (CARE) trial, between April 2008 and September 2011, Kerry Courneya and colleagues, from the University of Alberta, Edmonton, randomised 301 breast cancer patients in a 1:1:1 ratio to thrice-weekly supervised exercise during chemotherapy consisting of either a standard dose of 25–30 minutes aerobic exercise (STAN; *n*=96); a higher dose of 50–60 minutes aerobic exercise (HIGH, *n*=101); or a combined dose of 50–60 minutes of aerobic and resistance exercise (COMB, *n*=104). The strength exercises used were leg extensions, leg curls, leg presses, calf raises, chest presses, seated rows, triceps extensions, biceps curl, and modified curl-ups; while aerobic exercise could be completed on a cycle ergometer, treadmill, elliptical, rowing ergometer, or combination.

The primary outcome was patient-reported physical functioning assessed by the physical functioning subscale of the Medical Outcomes Survey Short Form (SF)-36; with secondary outcomes including physical component subscales of SF-36.

Results show that, for the primary outcome, neither the HIGH nor the COMB regimens proved superior to the STAN regimen (*P*=0.30 and *P*=0.52, respectively). However, for secondary outcomes HIGH was superior to STAN for the SF-36 physical component summary (*P*=0.04), SF-36 bodily pain (*P*=0.02), and endocrine symptoms (*P*=0.02). COMB was superior to STAN for endocrine symptoms (*P*=0.009) and superior to STAN (*P*<0.001) and HIGH (*P*<0.001) for muscular strength. HIGH was superior to COMB for the SF-36 bodily pain (*P*=0.04) and aerobic fitness (P=0.03).

"The CARE Trial did demonstrate that higher doses of aerobic or combined exercise of up to 50 to 60 minutes per session are safe and feasible and do not interfere with chemotherapy completion or exacerbate any symptoms," write the authors.

Moreover, they add, a higher dose of aerobic exercise, curbs some of the negative effects of chemotherapy on aerobic fitness, patient-reported physical functioning, bodily pain, fatigue and endocrine symptoms, while combined exercise improves muscular fitness and partly mitigates worsening of endocrine symptoms.

With regard to the primary SF-36 physical functioning outcome, the authors speculate that the scale may not have been sufficiently sensitive to detect differences in high-functioning young patients.

■ K Courneya, D McKenzie, J Mackey et al. Effects of exercise dose and type during breast cancer chemotherapy: Multicenter randomized trial. *JNCI* 4 December 2013, 105:1821–32

No role for calcium/magnesium in neurotoxicity prevention

■ Journal of Clinical Oncology

The use of calcium/magnesium (CaMg) to protect against oxaliplatin-induced neurotoxicity was not supported by a US randomised trial.

Cumulative neurotoxicity, which commonly consists of cold intolerance, muscle cramps and throat discomfort, represents a prominent toxicity for oxaliplatin-based therapies. The rationale for using CaMg to prevent oxaliplatin-induced neuropathy comes from observations that oxalate is metabolised from oxaliplatin, and that oxalate is known to chelate Ca and Mg elements involved in the function of ion channels in nerve membranes. Therefore it was reasoned that CaMg might prevent or ame-

liorate oxaliplatin-induced neurotoxicity.

Two studies – CONcePT and N04C7 – recently investigated CaMg in the setting of neurotoxicity, but were both stopped early after the CONcePT trial showed patients receiving CaMg had significantly lower response rates than those receiving placebo. Results from the CONcePT study suggest that CaMg does not decrease either acute or chronic oxaliplatin-associated neuropathy; while the results of N04C7 suggest that CaMg decreases the cumulative sensory neurotoxicity seen in the first 100 days of therapy. Additionally, three small published observational studies of the utility of CaMg as a potential neuro-protectant for oxaliplatin proved negative.

Given the early discontinuation of two of the clinical trials, and their divergent results, Charles Loprinzi and colleagues, from the Mayo Clinic, Rochester, Minnesota, set out to undertake a new study to determine the value of CaMg in preventing oxaliplatin-induced neuropathy.

For the study, which took place between June 2010 and June 2012, 353 patients with colon cancer undergoing adjuvant therapy with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) were randomly assigned to intravenous CaMg before and after oxaliplatin (*n*=118), a placebo before and after (*n*=119), or CaMg before and placebo after (*n*=116).

Results using the EORTC Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 tool for patient-reported acute neuropathy data show there were no statistically significant neuropathy differences among the three study arms regarding acute sensitivities to touching cold items (*P*=0.7978); discomfort swallowing cold liquids (*P*=0.4274), throat discomfort (*P*=0.0366) and muscle cramps (*P*=0.5501). Furthermore, no differences were found for clinician-determined measurement of the time to grade 2 neuropathy using the NCI Common Terminology Criteria for Adverse Events scale or an oxaliplatin-specific neuropathy scale.

"Given the more definitive results of this trial and the lack of observed benefit in the CONcePT trial and the other three small, randomized, placebo-controlled trials, the bulk of available data do not support the continued use of intravenous CaMg to prevent oxaliplatin-induced neuropathy," write the authors, who add that results from the current trial may change recommendations for future patients, resulting in savings in both time and expense.

Since CaMg does not appear to provide the solution for oxaliplatin-induced neuropathy, studies are now needed, they suggest, to define patients' risks for developing neuropathy on the basis of genetic factors and to explore the potential for other agents to prevent toxicity.

■ C Loprinzi, R Qin, S Dakhil et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity. *JCO* published online 2 December 2013, doi: 10.1200/JCO.2013.52.0536

Age represents no barrier for pelvic exenteration

■ Gynecologic Oncology

No concerns regarding duration of surgery, blood loss, length of hospital stays or complications rates were revealed for older women undergoing pelvic exenteration procedures, a retrospective US study has found.

Pelvic exenteration is a salvage procedure performed for centrally recurrent gynaecologic cancers that involves, to a greater or lesser degree, en bloc resection of pelvic structures, including the uterus, cervix, vagina, bladder and rectum. Advanced age has been considered a relative contraindication, due to the complexity and significant co-morbidities. Published data, however, suggests that carefully selected elderly patients with gynaecologic cancers can receive treatment without significant morbidity or mortality.

With limited studies exploring the influence of age in patients undergoing exenterative surgery, Pamela Soliman and colleagues, from the MD Anderson Cancer Center, Houston, Texas, set out to determine whether age at the time of the procedure has an independent impact on surgical complications or overall survival.

For the study, all women who underwent pelvic exenteration for any gynaecological indication at the centre between 1993 and 2010 were identified, and stratified into three age groups: young (≤50 years); middle (51 to 64 years) and senior (≥65 years). Altogether 161 patients were included in the analysis – 58 young, 62 in the middle age group and 41 in the senior group.

Results show that operative times were significantly shorter for women in the senior group (8.5 hours) compared with 9.5 hours for women in the middle group and 10.1 hours for women in the young group (*P*=0.0089). The overall incidence of post-operative complications for young, middle and senior age groups was 89.7%, 87.1%, and 87.8% respectively, with no significant differences found between the groups (*P*=0.8863). Overall recurrence rates following exenteration in the young, middle, and senior age groups were 68.4%, 46.7%, and 42% respectively (*P*=0.0165).

Furthermore, overall survival did not differ between age groups (*P*=0.3760). Senior women were more likely to have hypertension (*P*=0.0001) and pulmonary disease (*P*=0.040), but there were no differences between the cohorts for diabetes.

"In conclusion, advanced chronological age should not be considered a contraindication to a potentially curative surgical procedure. When patients are stratified by age, the duration of surgery, blood loss, length of hospital stay, and complication

rates do not increase with increasing age," write the authors.

The study indicates, they add, that pelvic exenteration can be offered to select patients without considerable increase in morbidity due to age alone. Several factors, write the authors, may contribute to higher recurrence rates in young patients, including tumour biology and selection bias.

■ M Huang, D Iglesias, S Westin et al. Pelvic exenteration: Impact of age on surgical and oncologic outcomes. *Gynecol Oncol* January 2014, 132:114–118

Rehabilitation programme improves urinary symptoms in prostate cancer

■ British Journal of Cancer

Multidisciplinary rehabilitation programmes in prostate cancer patients following completion of radiotherapy improved urinary and hormonal symptoms, and quality of life, a Danish study has found.

Occurring in tandem with developments in locally advanced or high-risk prostate cancer treatment – where radiotherapy combined with androgen deprivation therapy (ADT) has increased 10-year survival rates from 60% to 70% – has been recognition of the need to evaluate the impact of treatment on overall quality of life. Clinical attention has focused on how the adverse effects of treatment, such as urinary irritative problems causing frequency, nocturia, urgency or urge incontinence, might be counteracted.

In the current study, Karin Dieperink and colleagues, from Odense University Hospital, Denmark, investigated a multidisciplinary rehabilitation programme comparing usual care against psychosocial support from nurses together with counselling in pelvic floor exercises to reduce urinary irritative problems.

After completion of chemotherapy 161 patients were randomly assigned 1:1 to the intervention group (n=79) or to the usual care control group (n=82).

Patients in the intervention group received two nursing counselling sessions and two sessions with a physical therapist. Physical therapy sessions evaluated the individual patient's need for increased pelvic floor muscle function and general physical activity, and if necessary patients were guided to use biofeedback visual presentations to strengthen their pelvic floors. The self-training home programme consisted of pelvic floor muscle exercises integrated in daily activities, for example, during driving the car, walking, or working in the garden.

The primary outcome was urinary irritative sum score, based on the Expanded Prostate Cancer Index Composite (EPIC-26) using four items regarding pain, bleeding, weak stream, or frequent urination. Secondary outcomes included quality of life arising from the Medical Outcome Study Short-Form-12 (SF-12).

Results show that, in comparison to controls, men in the intervention group demonstrated improvements in the urinary irritative sum score (P=0.011), urinary sum score (P=0.023), hormonal sum score (P=0.018) and SF-12 physical component summary (P=0.002). Furthermore, patients with more severe impairment gained most.

A sub analysis showed that improvements of the urinary sum score were most pronounced in patients living alone (P=0.021), that men with pre-intervention urinary scores indicating moderate to severe problems gained the most (P=0.034), and that pre-intervention urinary irritative sum scores below the study mean value of 68 points predicted a higher effect of intervention (P=0.031).

"Based on the results of this study, it can be recommended that patients treated with radiotherapy of the prostate may be offered a combined nurse–physiotherapist intervention programme, especially patients with impairments within urinary irritative function," write the authors.

Timing, duration, and focus on the empowerment aspects of this intervention, write the authors, require further study.

■ K Dieperink, C Johansen, S Hansen et al. The effects of multidisciplinary rehabilitation: RePCa – a randomised study among primary prostate cancer patients. *Br J Cancer* 10 December 2013, 109:3005–13

Residents trained to include relatives

■ British Journal of Cancer

Training programmes for medical residents that focus on including relatives in the breaking bad news (BBN) consultation improved the communications skills of participants, a Belgian study has found.

Relatives frequently accompany patients to BBN consultations in order to provide support or to serve as the patient's advocate. Their presence, however, often introduces a new level of complexity, since physicians need to deal with two people who have differing needs, knowledge, concerns, distress levels and expectations.

In the current study, Darius Razavi, from the Institut Jules Bordet, Brussels, and colleagues, explored the efficacy of training programmes designed to teach residents the communication skills needed to break bad news to both patients and their relatives.

The study residents, who had a mean age of 28 years, were randomly assigned to undergo a 40-hour dyadic (two way) or triadic (three way) communication skills training programme (n=48) or to be placed on a waiting list (n=47). The investigators utilised the Belgian Interuniversity Curriculum – Communication Skills Training (BIC-CST) consisting of a 17-hour commu-

nication skills training programme focusing on dyadic consultations and a 10-hour programme on triadic consultations.

For each resident, communication skills were evaluated using a simulated BBN triadic consultation consisting of a 20-minute first medical encounter, with an actress playing a 37-year-old woman and an actor playing her 40-year-old husband. During the consultation, residents had to deliver a breast cancer diagnosis and discuss treatment (i.e. surgery, chemotherapy and radiotherapy). Transcripts from the consultation were analysed using content analysis software, with three dictionaries constructed for medical, emotional and social utterance content. For the analysis the consultation was divided into three phases: the pre-delivery phases devoted to preparing the patient and relative for the delivery of bad news by assessing what they know, understand and feel about the current situation; the delivery phase spent delivering the bad news; and the post delivery phase providing emotional support and additional information to both the patient and their relatives.

Results showed that, following training, the duration of the pre-delivery phase was longer for trained residents (RR=3.04; $P<0.001$). Furthermore, the simulated relative's first turn of speech about the bad news came more often during the pre-delivery phase (RR=6.68; $P=0.008$), and was more often initiated by the trained residents (RR=19.17; $P=0.001$). Trained residents also used more assessment (RR=1.83; $P=0.001$) and supportive utterances (RR=1.58; $P=0.001$).

"The results obtained demonstrate that the training programme did have a positive impact on the simulated BBN process, with residents exhibiting improved communication skills, improved inclusion of a simulated relative, and improved expression of the concerns by the simulated patient and relative," write the authors.

While the pre-delivery phase increased from approximately one minute before training to two minutes after training, the increase represented the time required for residents to assess what the patients and relatives felt, knew and understood about their situation.

■ I Merckaert, A Lienard, Y Libert et al. Is it possible to improve the breaking bad news skills of residents when a relative is present? A randomised study. *Br J Cancer* 12 November 2013, 109:2507–14

Wait times influence survival in uterine cancer

■ Journal of Clinical Oncology

Longer wait times from diagnosis of uterine cancer to definitive surgery have a negative impact on patient overall survival, a Canadian retrospective study has found. To the best of their knowledge, the authors state, the investigation represents the first large population-based study to have examined the impact of wait times for uterine cancer surgery on survival.

For patients the wait for surgery is anxiety provoking, with evidence suggesting that long waiting times can have a negative impact on survival, decrease patient satisfaction and result in poorer quality of life. Previous researchers have found longer wait times to be related to shorter survival in breast cancer, rectal cancer, pT2 bladder cancer, and melanoma, although the relationship has been less clear for cancers of the oesophagus, stomach, pancreas, lung, colon, kidney, and cervix.

In the current study Lorraine Elit and colleagues, from Juravinski Cancer Centre, Hamilton, Ontario, Canada, set out to determine whether wait time from the histological diagnosis of uterine cancer to time of definitive surgery by hysterectomy had an impact on all-cause survival.

For the study 14,225 women were identified from the Ontario Cancer Registry who received a diagnosis of uterine cancer between April 2000 and March 2009. Of these 4,808 were excluded because their hysterectomies occurred on the same day as diagnosis or patients did not have a hysterectomy, leaving a final study population of 9,417 women. For the study, wait time was evaluated in a multivariable model after adjusting for other significant factors.

Results show that the five-year survival of women with wait times of 0.1–2 weeks was 71.1%, of 2.1–6 weeks was 81.8%, of 6.1–12 weeks was 79.5% and more than 12 weeks was 71.9%. Compared with patients having wait times of <2.0 weeks, women having wait times of 2.1–6.0 weeks had a hazard ratio (HR) of 0.64 (95%CI 0.55–0.75), those with a wait time of 6.1–12.0 weeks had an HR of 0.65 (95%CI, 0.55–0.77), and those with a wait time of >12 weeks had an HR of 0.80 (95%CI, 0.67–0.97).

"From a regional or provincial perspective, given our data, which demonstrate a strong association between longer wait times and decreased survival, future policies might aim to provide hysterectomies within 6 weeks of diagnosis to optimize survival rates," write the authors, adding that surgery within two weeks of diagnosis is generally believed to be related to acute issues, such as anaemia associated with the need for blood transfusions.

Policies that affect access to hysterectomies for uterine cancer such as access to operating rooms and skilled surgeons, they add, should be examined. "Given that different neoplasms have different degrees of aggressiveness, future research should examine the relationship between wait times and survival for each type of neoplasm to determine appropriate cancer specific wait times," they write.

■ L Elit, E O'Leary, G Pond et al. Impact of wait times on survival for women with uterine cancer. *JCO*, published online 25 November 2013, doi:10.1200/JCO.2013.51.3671

Addressing cancer disparities in Europe

SEAN DUFFY, MIKE RICHARDS, PETER SELBY AND MARK LAWLER

As we learn more about what lies behind the differences in cancer outcomes across Europe, the question becomes: how do we end them?

"Are We Winning the War on Cancer?" was the rather provocative title of the World Oncology Forum in Lugano, Switzerland, at the end of 2012[1]. While significant progress has been made over the last 30 years, with European oncology at the forefront of many advances, a review of cancer outcome data indicates significant disparities between different European countries[2] and indeed sometimes within regions of the same country. A recent publication comparing the United Kingdom's Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) with 18 other comparator nations (the original 15 members of the European Union, Australia, Canada, Norway, and the United States) for the years 1990 and 2010, identified cancer as one of the diseases for which differences in premature mortality could be identified[3]. What are the reasons for these differences? And more importantly, what can we do to close the gap?

Interpreting cancer outcomes

In an attempt to answer this pertinent question, and to use the information to help direct health policy in cancer, the Department of Health in England initiated the International Cancer Benchmarking Partnership (ICBP) in 2009 to study international variations in cancer survival data. The ICBP involves 12 different jurisdictions in six countries: Australia (New South Wales, Victoria), Canada (Alberta, British Columbia, Manitoba, Ontario), Denmark, Norway, Sweden and the United Kingdom (England, Northern Ireland, Wales). Data from population-based cancer registries in the 12 jurisdictions were analysed for 2.4 million adults diagnosed with primary colorectal, lung, breast or ovarian cancer during the period 1995–2007. While the data indicated that relative survival for all four cancers improved during the study period, there were still significant differences between the different countries, with persistently higher survival rates in Australia, Canada and Sweden, contrasting with persistently lower

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survival rates in Denmark and the UK[4]. While the causes for these differences are undoubtedly multifactorial, later stage at diagnosis, particularly for colorectal and lung cancer, and differences in treatment or access to treatment (with survival within stage being lower in the UK than elsewhere, particularly for late-stage disease for breast and ovarian cancer) appear to be playing a role. The ICBP has highlighted the utility of precise comparative investigations of international cancer outcome data and how this approach can help inform changes in cancer policy to address cancer disparities between nations and regions.

The ICBP study also draws attention to the fact that there are differences in survival in patients aged 65 and older when compared with their younger counterparts[4]; this trend has been reported in a number of studies[5]. Increasingly it appears that older patients are being undertreated, and this inequality is resulting in poorer survival in older patients and must be addressed.

Palliative care: a case for earlier intervention?

In caring for patients with advanced cancer, be they young or old, we also need to change our mindset. While traditionally, the use of palliative care has been associated solely with end-of-life-care, increasingly the evidence suggests that palliative care services may not be delivering optimal benefit in this setting. In contrast, a number of recent landmark studies have highlighted that early introduction of palliative care in metastatic disease can yield significant benefit for the advanced cancer patient, with gains seen in improved quality of life and mood, and possibly also in improved survival[6,7].

Getting our message across

While we need to address potential deficits in cancer health systems that lead to disparities in outcomes, we can also approach the problem from the individual's viewpoint, by promoting public awareness campaigns stressing the need for early diagnosis, the availability of cancer

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

screening programmes, and the influence of lifestyle factors such as smoking, alcohol, and obesity on the risk of getting cancer. In the UK, survey data suggest that unprompted public awareness of cancer warning signs is low, except for the classic tumour symptom of lump or swelling, and that barriers to seeking help exist. More recent data also show that 24% of all cancer patients in England present as emergencies, and these patients have poorer outcomes than those being diagnosed through other routes[8]. Public Health England, working in partnership with the Department of Health and National Health Service England, launched the 'Be Clear on Cancer' awareness campaigns to address some of these issues. These campaigns encourage people to contact their community doctor/general practitioner if they experience specific symptoms.

Positive results from pilot programmes have underpinned national cancer awareness campaigns for colorectal and lung cancer and have informed additional local, regional, and national initiatives. The most recent data from the regional lung campaign suggest that it led to the diagnosis of more cases of lung cancer, with statistically significantly more small cell lung cancers (SCLC) staged as 'limited' rather then 'extensive'. The data also suggest a trend toward earlier stage at diagnosis of non-small-cell lung cancer (NSCLC). This was accompanied by a statistically significant increase in surgical resections and a trend toward lower performance status at diagnosis. None of the results were replicated in non-campaign areas[9].

Supporting the needs of the cancer survivor

While efforts in cancer care tend to focus on improving outcomes, the needs of the cancer survivor must also be considered. According to EUROCARE 4, there are nearly 14 million cancer survivors in Europe[10], and there is a significant requirement to incorporate cancer survivorship as a key output of national cancer control programmes, such that survivors can live beyond cancer and return to active life. Programmes such as the UK's National Cancer Survivorship Initiative, launched in 2008 as part of the UK Cancer Reform Strategy[11], the Victoria Cancer Survivorship Program, launched in Australia in 2011[12], and the Livestrong Centers of Cancer Survivorship Excellence in the US, allow a precise evaluation of the needs of the cancer survivor through a comprehensive data gathering and evaluation process. This process thus allows models of care to be put in place to optimise the quality of life for the cancer survivor returning to active living. The use of patient reported outcomes measures (PROMs) can help inform this process[13]. Cancer survivor programmes have also been developed in Italy, the Netherlands, Germany and Scandinavia, and are a significant component of the strategy of the European Cancer Patient Coalition, as they seek to develop an EU cancer survivorship plan[14].

Conclusions

Despite the improvements that have been made over the last 30 years, cancer will soon rival cardiovascular disease as the major cause of premature disease mortality in Europe[15]. Comparator studies have revealed significant differences in outcomes between European countries and regions. These disparities reflect worrying inequalities in access to information, care and support at all stages of the cancer journey. While the reasons for these inequalities are multifactorial, precise enumeration and evaluation of outcome differences in Europe can help underpin the refinement of cancer policies to address these critical issues. We are building the evidence base that helps explain the 'cancer gap' in Europe. What we now need is strong leadership to implement the changes that are required to bridge that gap. ■

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

Author affiliations

Sean Duffy, Medical Directorate National Health Service England, Leeds, UK; Mike Richards, Care Quality Commission, London, UK; Peter Selby, Department of Cancer Medicine, Leeds Institute of Cancer and Pathology, University of Leeds, UK; Mark Lawler, Centre for Cancer Research and Cell Biology, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Northern Ireland