European School of Oncology
Learning to care

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Education & knowledge through people & facts

John Crown

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Join the battle for biomedical research

Kathy Redmond ■ EDITOR

The battle is on to shape the agenda for European research up until 2020. The eighth research framework programme – renamed Horizon 2020 – is currently being discussed at the European Parliament and Council, and it has some good things going for it.

Prompted by pressures to increase public spending to boost growth and jobs, its budget of €80 billion for the period 2014–2020 represents a significant increase over the €55 billion allocated to the current framework programme (FP7). And the Commission has clearly tried to respond to criticisms about how hard it is for researchers to get access to this funding. It has been at pains to highlight changes that have been made to simplify rules and procedures – good news for any researcher who has had to struggle with the red tape associated with applying for an EU research grant.

Not such good news, however, is the decision to cut the slice of the overall cake that is allocated to health research, from its current level of 12% to only 10%. Critics point out that, even in purely economic terms, this is a mistake. Investing in health research not only has the stimulatory effect associated with all public spending, but it can also help cut healthcare costs and reduce the number of people unable to work due to ill health.

Both of these are major considerations. An estimated $47 trillion will be lost globally over the next two decades because of disease and ill health; for Europe the big challenge will be coping with an increasing burden of chronic disease as our population ages. 'Health is wealth' is the new mantra, and giving greater priority to research into the former will help boost the latter.

A campaign has now started to secure a greater slice of the Horizon 2020 funding for health research. Led by the Alliance for Biomedical Research (Biomed Alliance) in Europe, of which ECCO is a founding member, the campaign is also calling for the European biomedical research community to have more of a say in defining research priorities, and for a dedicated infrastructure in the form of a European Council for Health Research.

There is a lot at stake here. A comprehensive strategy involving the entire biomedical community in Europe will be key to addressing the fragmentation of the current research landscape, and to sustaining successful research projects long term and facilitating the translation of innovation into clinical practice. It will also provide opportunities for young researchers whose talents may otherwise be lost to Europe, particularly now that Asian economies are investing so heavily in this area.

Active support from across the cancer community will be crucial. The final package will be agreed at the end of 2013, so we now have a small window of opportunity to influence the outcome. The cancer community urgently needs to make its voice heard at both EU and national levels.

John Crown:

Move aside bureaucrats and let us take a lead

Marc Beishon

Good healthcare managers will always be needed, but decisions on how best to deliver high-quality care should be left to the clinicians who run the services. John Crown, who has long played a leading role in both the clinic and research, is by no means the only oncologist to make this comment. He is one of the few, however, to seek elected office in order to pursue the point more effectively.

Outspoken oncologists, willing to take on 'the powers that be', can often play a very helpful role in galvanising administrators and policy makers and pushing the priorities of clinicians higher up the agenda. There are notable such characters around Europe, but one oncologist has taken a bigger step into the realm of politics by becoming a senator in his parliament – from where he is able to directly challenge politicians and bureaucrats with the protection of parliamentary privilege.

John Crown's day job is consultant medical oncologist at St Vincent's Hospital group in Dublin, a position he took up in 1993; he also holds professorships at two Dublin universities. A breast cancer specialist, he was elected last year to Ireland's senate as one of a caucus of six academics in the upper house. His move into politics follows a long history of confronting the Irish authorities about cancer care and resources, in particular about his specialism, medical oncology, and with good reason.

"When I came back to Ireland after working in the United States, I was just one of four medical oncologists in the whole country, and we were all based in Dublin. We also had no radiation oncology in some areas. Women were routinely getting mastectomies with little adjuvant treatment outside of Dublin and those with metastatic disease were often referred to hospices, not to an oncologist. It was a catastrophic situation."

Much has improved since Crown decided to go public on these issues in the mid-1990s. Not only was he taking on the politicians, but also the 'old school' health professionals who were part of the problem. "It was only when a new minister of

EAMONN FARRELL/PHOTOCALL IRELAND

health, Michael Noonan, came into post and stated that he wouldn't send his relatives to certain hospitals if they had cancer that things really started to change," he says.

Now there are more medical oncologists, better care throughout the country, and Ireland has become a substantial contributor to cancer research, thanks to Crown and colleagues starting up high-quality translational research collaborations and entering a good percentage of patients in trials, especially in breast cancer.

As he points out, there is no reason why a country the size of Ireland should not have a first-rate oncology effort. "We are more than four and half million people, and Dublin is a cosmopolitan city of well over one and half million in its metro area [Greater Dublin]. There are only a few very rare conditions where we should send a patient abroad for treatment. But we tend to have a defeatist attitude that a country that was historically poorly developed shouldn't aspire to have a healthcare system as good as the best.

"And as with many other countries, the politicians put bureaucracy before visionary leadership. It's a fundamental issue that needs to be addressed not only in Ireland but throughout Europe – the leadership role of health professionals is being undermined by the emergence of a managerial class." Crown is passionate about this issue, which he believes is crucial to improving outcomes in cancer and indeed across the health spectrum. Health professionals must be allowed to assume leadership positions as they have the vision to act as true advocates for patients, he says. Professional managers have their place in any institution – but where they set the agenda it is likely to be serving

political edicts to balance budgets and meet targets.

"That often means the welfare of patients comes second, and also – and this may be an old-fashioned view – I do not think that doctors act solely in their own self-interests. We have higher ethical considerations than other professions."

The link between overbearing bureaucracy and poor cancer outcomes can be seen in Ireland and the United Kingdom in particular, he says, pointing to slow access to treatment and drug availability (in the UK especially) as two key factors. Wearing his political hat, he would 'fix' healthcare by reforming health insurance so that the "money follows the patient" and patients are able to choose their providers more easily, and of course that healthcare leadership is passed to medics.

Healthcare cannot exist in isolation from the wider economy and societal trends, of course. Crown is also concerned about how countries such as Ireland that are under severe economic pressure can become more stable. He worries, too, that science and technology are not being prioritised as they should be. While he favours measures such as lowering corporation tax and public sector reform to make it more efficient, he is no advocate of wholesale privatisation of healthcare. "I'm a social democrat at heart with the head of a pragmatist – I believe that no one should be denied care because they can't afford it, but the health system should not be a giant bureaucracy and we need to empower patients with mixed public/private insurance such as in Germany."

ENDA DORAN/EPA

A good deal of Crown's formative years in oncology were spent at one of the world's top cancer centres, Memorial Sloan-Kettering in the US, and his first-hand knowledge of how excellence can be achieved at a not-for-profit institution with great clinical leadership has inspired his work in Ireland. It is a background he shares with most of his colleagues. Of the 33 medical oncologists now in Ireland – itself a gauge of how far the country has come in 15 years or so – 23 were trained at America's top cancer centres such as Memorial, MD Anderson, the NCI, Johns Hopkins and Dana-Farber. "When I was at Memorial I could be in an elevator with more Irish oncologists than there were in Ireland," says Crown. "That's a direct result of our immigration culture."

Crown himself was born in New York to Irish immigrants and as a boy was influenced by the attention cancer was getting in the US, and by healthcare in general, thanks to several nurses in his family. "I knew I wanted to go to medical school and it was in the back of my mind that I wanted to be a cancer specialist." With his family having returned to Ireland, he did his main medical training in Dublin and at Guy's hospital, London, and took the internal medicine path towards cancer, landing an oncology fellowship at Mount Sinai Medical Center in New York. In fact there was only one medical oncologist in Ireland then – the inspirational James Fennelly, who single-handedly brought the specialty to the country – although Crown also encountered other top specialists in London.

"In New York at Mount Sinai I was under Jim Holland – a great oncologist who was a founder of one of the first large cooperative groups, Cancer

"It was easy to get caught up in the excitement about high-dose chemotherapy for breast cancer"

"When I started to speak out against the poor cancer care we had then there were attempts to gag me"

and Leukemia Group B (CALGB). He was an inspiring and methodical clinical researcher. I wanted to work at Memorial Sloan-Kettering as well, and managed to get there later."

He spent six years at Memorial in faculty and staff positions, developing interests in bone marrow transplantation and high-dose chemotherapy, and was recruited by Larry Norton as the first contributor to a new breast group.

Crown says it was easy to get caught up in the excitement about high-dose chemotherapy for breast cancer because early use showed high remission rates, although very high toxicity. Many women, especially in the US, were treated in this way, and at great cost, and it was mandated by some American states. But of course when large randomised trials were carried out, including by Crown after he had moved to Ireland, with British oncologist Bob Leonard, the results were disappointing when compared with conventional chemotherapy.

As he noted in a comment in *The Lancet* in 2004, there is probably "no other treatment in medical history that has had such a meteoric rise or as humiliating fall from grace as high-dose chemotherapy". When one 'positive' trial was found to be fraudulent, there was added notoriety for the approach. "But it was very important to do the negative trials of course," he says.

Other work that Crown did in the US was ultimately more fruitful. "I also worked on paclitaxel (Taxol) and docetaxel (Taxotere) and found my feet as a drug developer, and I spent a year working in the lab with Janice Gabrilove, a great scientist, on approaches using G-CSF and interleukin."

With a post at such an illustrious cancer centre, it was only a rare consultant's position that tempted Crown back to Ireland and, as he now knows, he was competing with several others who went on to become eminent in other places. "But it was a real riches to rags experience," he says. "When I started to speak out against the poor cancer care we had then there were attempts to gag me. I wasn't one of the golf playing, rugby following physicians from a fancy family – the health system was very patriarchal, as it was too in the UK, where there were those who wanted medical oncology stopped in its tracks, and it was terribly sad that patients were being denied treatments that were dismissed by certain senior doctors." He adds that UK medical oncology was set back for years when the brilliant Gordon Hamilton Fairley was murdered by Irish terrorists in London. "That is a source of perpetual embarrassment for me, especially at the time of the ESMO award in his name."

With more public awareness of the issues in Ireland, pressure from advocacy groups and more support from government, additional posts were created for some of the outstanding medical oncologists in the Irish–American diaspora, and Crown says there has long been a solid tranche of excellent, mainly British-trained, cancer surgeons in place. At St Vincent's, as tends to be the case at other Irish hospitals, there is no head of cancer, and the various specialists have enjoyed a good deal of autonomy to work on their own systems of multidisciplinary care, with freedom to order the tests and scans they needed, and early access to drugs such as Herceptin (trastuzumab). "To British colleagues we have seemed more like an American set-up," he says. "But our bureaucrats are catching up with us now."

He is certainly no fan of Britain's NICE (National Institute of Health and Clinical Excellence). "It tends to make a generation of cancer patients suffer before it approves drugs – and the economic tools they use such as quality life years are blunt instruments. NICE has taken a narrow view on several drugs and been proved wrong – such as the four kidney cancer drugs we have now. Before we had nothing to offer these patients and we know the drugs can make huge improvements. You have to factor in the rarity of certain tumours and the availability of other treatments – I doubt that NICE would have approved the drugs used in the MOPP

He supports reorganising services around centres of excellence, but is scathing about the way it is being done

regime for Hodgkin's lymphoma at the time."

As he adds, the cost of funding drugs for a few thousand kidney cancer patients in an economy such the UK is not high, and spending on healthcare is no bad thing, particularly in a recession, given that some economists take the Keynesian viewpoint of stimulating growth. "But obviously we must ensure we do not spend wastefully. The Americans made a colossal mistake in cancer when they allowed oncologists to sell the drugs they were themselves prescribing."

Some government decisions have been easy to make in cancer services, such as cutting out hospitals performing too few breast cancer operations, but there is a constant battle to counter bureaucratic decisions, says Crown. A recent programme to establish centres of excellence for cancer care has met the full force of his pen. On reallocating services, though strongly in favour of the principle, he is scathing about what he sees as arbitrary decisions that ignore evidence of local expertise.

Another part of his armoury is a business masters degree (MBA) he completed in 2000, with a thesis on strategy for European medical oncology, such as proper recognition of the specialism and true multidisciplinary care, much of which has now happened. "One of the first things they teach you on an MBA is the difference between management and leadership," he says, pointing also to hugely critical comments he has made about bailouts of the Irish banks and what that money could have bought in the health service, from hospital funding, to hiring colorectal cancer specialists, extending mammography to the over 65s, cervical cancer vaccination and more. "We could have vaccinated the whole world against cervix cancer for what we spent on our bank bail out." His message was: "don't kill the health service to pay goons" – and now he is in parliament he has become an even more formidable advocate.

Other topics that have received the Crown broadside include complementary therapies ("intellectually dishonest"), local financial mismanagement, and – not least – attempts to gag physicians from speaking out (he himself made headlines when he was dropped from appearing on a television programme alongside health officials).

Like other oncologists returning to 'unfashionable' parts of Europe, it has been research that has helped give Crown this platform. Not only did he set up a clinical trials unit at St Vincent's, but in 1997 he founded, with John Armstrong, the Irish Clinical Oncology Research Group (ICORG), filling a major gap. Until then, Ireland had been the only country in western Europe without a national trials group.

He carried out a great deal of work on conventional chemotherapy while in Ireland, including trials with various international cooperative groups on paclitaxel and docetaxel. For the latter he was one of the senior investigators who presented evidence that it was superior to doxorubicin (Adriamycin) to the US regulatory body, the FDA, leading to its approval. His experience with trial designs for these and other drugs such as cisplatin and carboplatin was especially valuable when he became involved in trastuzumab and the dawn of clinical molecular medicine – but it was, as he admits, a lucky break.

"I got a call from Dennis Slamon, whom I knew only by repute, saying he'd like to bring a group of Irish Americans to Dublin, and we hosted a seminar on HER2. He also said he'd like to include Irish patients in the original pivotal trial of the drug trastuzumab." Slamon of course is the legendary oncology chief at the University of California in Los Angeles (UCLA) who spent years researching HER2 biology and pushing for drug development. "We said we would love to be part of the trial but unfortunately we then spent months arguing with our ethics committee, which said we shouldn't be experimenting on cancer patients, and we only managed to get one person on the trial and so missed out on authorship. But when the next trials

came along we were jointly leading them."

The trastuzumab trials run by Slamon and colleagues were under the BCIRG (Breast Cancer International Research Group), now part of TRIO (Translational Research in Oncology), and Crown says they were well designed, according to 'visionary' questions that Slamon wanted to test, and by a close-knit group of researchers – in contrast to some other trials that he describes as often "dismal".

One international trastuzumab phase III trial led by Slamon, in which Crown was closely involved with the design, was BCIRG-6, a complex multi-arm trial that tested various concurrent chemotherapies, and which he says was also radical in that some patients would not be receiving doxorubicin. "I crossed the Atlantic 13 times during the design phase, and there was much scepticism about it, including from the corporate hosts, who almost undermined it," he says. "There were several other trastuzumab trials taking place that just picked what was thought to be the best chemotherapy and added Herceptin. Our approach was that you couldn't be developing elegant, sophisticated molecular drugs as if they were chemotherapy – itself a by-product of the chemical weapons industry."

He adds that scepticism stemmed mostly from doubt that a consortium of investigators would follow a complex, radical protocol for a large trial, and that a more open, permissive design was necessary to carry out such studies. "I didn't doubt we could do it and neither did my colleagues. And for BCIRG-6 we got 3220 patients signed up – an extraordinarily high rate of trial compliance."

ICORG, which also covers researchers in Northern Ireland, has been a success, says Crown. It now employs 20 people and includes some 100 researchers, and has a full portfolio of patients in trials in most tumour types, and at one point 35% of all breast cancer patients were in studies. "Most pharmaceutical companies have now opened clinical trials offices in Ireland, and we've been able to provide many millions of euros worth of free drugs," he says. In keeping with American links, ICORG was also the first group outside of North America invited to join the National Surgical Adjuvant

ENDA DORAN/EPA

"The HER2 target may be 'low-hanging fruit'. The next generation of drugs may be far harder to develop"

Breast and Bowel Project (NSABP), the major US-based trials group.

Another concern about trials, says Crown, is the lack of effort going into looking for biomarkers in subgroups. "For example, I was involved in a study on sunitinib in breast cancer. It does produce response in some patients but all the randomised controlled trials were negative. The tragedy was there was no tissue collection to look for biomarkers. We are defining eligibility on old techniques and not matching the extraordinary precision of our new therapies with the right diagnostics and prognostics. It cost the drug company many millions of dollars and we may have lost an agent that could benefit some patients. We are determined that most of the trials we join from ICORG should have mandatory tissue collection and a translational component."

Too many companies think that finding biomarkers will restrict market size, he adds – but unless the benefit is clearly evident, there can be no market, such as with bevacizumab (Avastin) in breast cancer, which Crown says he is no longer using except in some existing patients.

"We need to stop thinking about existing phases in drug development and start collecting tissue on day one with every patient, and try and design each stage with meaningful molecular predetermination of eligibility, or if not we should at least collect larger tissue banks at phase II to see if a patient group benefits. We've become conditioned by small benefits. If we'd taken this approach with Herceptin we would have seen excellent benefits at phase I and II, and by the phase III adjuvant stage, instead of requiring four trials of 3000 patients each, I bet we would have had a positive result with one trial of say 400 patients, because the benefit was so big – as we had the right marker and the right molecule."

The story of HER2 biology just keeps expanding, he adds, with a growing family of new molecular treatments. "It's fascinating and there is the possibility that we may be able to cure metastatic breast cancer – I know we did cure some with high-dose chemotherapy but the numbers were not worth the toxicity involved. With trastuzumab, my colleague Giuseppe Gullo at St Vincent's presented a great abstract at ESMO showing we now have many long-term disease-free survivors." One of the most exceptional cases he's seen in Ireland, he adds, was a woman whose liver had deteriorated badly and was given trastuzumab outside of a trial because she couldn't take the chemotherapy as well. "We got permission to give Herceptin to her and within a year her liver had returned to normal and she's never relapsed. We stopped the drug three years ago. I believe we are curing 5–10% of advanced breast cancers we treat with trastuzumab and chemotherapy, and that's unprecedented."

He also mentions a potentially extraordinary finding from a North American trastuzumab adjuvant trial, where about 160 patients who were HER2-negative got on the trial – "But Herceptin seemed to work for them as well. It could be a fluke, or there may be a biological explanation concerning stem cells, or immunology, which is being researched."

Given the increasing complexity of medical oncology, it's no surprise to find that Crown is a strong critic of other specialists, such as surgeons and radiation oncologists, becoming involved with drugs. "Those gynaecologists who deliver babies and treat breast cancer with chemotherapy must be much smarter than me," he says. "Seriously, the discipline of drug therapy in internal medicine is critically important and we are likely to see subdivisions within medical oncology according to molecular subtypes."

Given that there has been no recent breast cancer drug successes on the scale of trastuzumab, Crown says it's possible that the HER2 target is "low-hanging fruit". He notes promising data though on everolimus (Afinitor) for oestrogen-positive disease, but overall "the next generation of

drugs may be much harder to develop". In any case, he reckons Ireland will be in the frontline of molecular selection in drug development in early-stage trials, and reports that there are now "brilliant" researchers in place. "I think you will see a lot from Ireland in translational research in the next few years," he says, mentioning a key enabler, Molecular Therapeutics for Cancer Ireland (MTCI), a 'strategic research cluster' funded by Science Foundation Ireland and set up in 2009.

Crown is the principal investigator for MTCI, which is researching mainly breast cancer targets, such as novel therapies for triple negative disease. MTCI and ICORG are uniting the country's cancer research effort, he says. Ireland has six medical schools – a high proportion for its population, despite having a relatively low number of doctors – and there is now much more cooperation than competition among them and with researchers at other locations.

While Crown's primary interests lie in treatment, he recognises that major advances lie in prevention and early detection. "You can't overlook the benefits of ending hormone replacement therapy and factors such as obesity in breast cancer, while the advances in imaging for detection will be breathtaking." Both his daughters received the cervical cancer vaccine, he revealed publicly – a sensitive topic in Ireland.

Tobacco is an area of prevention where Crown has made a political impact, speaking out in the senate for a ban on smoking in any enclosed space where children may be, such as in cars. He described their exposure to smoke as "a form of child abuse", adding medical details of the different respiratory rate of children. "I used to be a smoker myself and I've heard all the so-called arguments about civil liberties – they are just addiction thinking. I'd like to see the European parliament giving say 10 years' notice that it will be illegal to manufacture and import tobacco products."

Europe presents a possible future avenue for Crown. On the cancer front, he is keen to promote small, fast-moving research groups, as exemplified by BCIRG/TRIO, that can harness diversity but will avoid the 'committeeism' that he feels some cooperative groups have succumbed to. He was among the founders of the campaign to stop the European clinical trials directive, and perhaps he could make a bigger contribution at policy – and political – levels by stepping away from the clinic and further into Irish and European affairs.

"I'm in the Irish senate for five years and I will continue to develop MTCI – and the big question is whether I put more time into politics. I could also aim to combine my medical research experience with my interest in public administration – and we Irish certainly make good bureaucrats."

The trouble he faces is that, as with cancer research, there are just so many political targets to aim at.

Off duty. With his children Katie (left), Mia and Jack

Endotherapy for Barrett's oesophagus with early neoplasia

Unnecessary oesophagectomies continue to be performed in many centres because of a lack of knowledge about the efficacy and safety of more conservative options. Massimo Conio looks at the evidence for two alternatives – endoscopic mucosal resection and radiofrequency ablation – and discusses which patients should be eligible and where the treatments should be carried out.

We can safely and effectively use an endotherapy approach in patients who have Barrett's oesophagus lesions infiltrating to the muscularis mucosae, which means a T1a cancer. The limit of endotherapy treatment is shown clearly in the figure overleaf. Surgery is required for T1b cancers, which involve submucosal invasion of the oesophagus. The most well-known approach for endotherapy is endoscopic mucosal resection (EMR), which enables removal of any malignancy in the mucosa. It also provides an adequate assessment of the histology and enables accurate staging. This approach therefore enables us to decide what to offer patients as radical treatment.

A recent study showed how endoscopic mucosal resection can improve staging, with downstaging of the lesion in 28% of cases and upstaging in 20% (*Am J Gastroenterol* 2010; 105:1276–83). This demonstrates how useful this technique can be.

Retrospective studies comparing endoscopic treatment and surgical treatment of muscosal T1a lesions in Barrett's patients show comparable overall

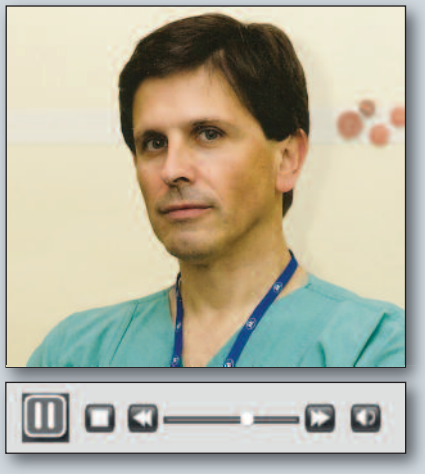
European School of Oncology
e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these is selected for publication in each issue of *Cancer World*.

In this issue, Massimo Conio, of the Department of Gastroenterology, Sanremo Hospital, Sanremo, Italy, provides an update on the latest developments in the use of endoscopic treatment in patients with Barrett's oesophagus complicated by superficial cancer.

Peter Siersema, of the University Medical Centre Utrecht, in the Netherlands, poses questions arising during the e-grandround live presentation.

The presentation is summarised by Susan Mayor.

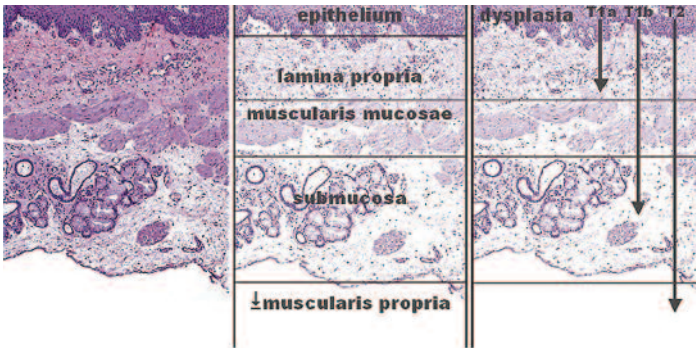


The recorded version of this and other e-grandrounds, is available at www.e-eso.net

survival (*Gastroenterology* 2009, 137:815–823). This means that it is no more effective to send a patient with such a lesion to the surgeon to have their oesophagus removed than to treat with endoscopic resection. The major adverse effect on quality of life means it is always better to avoid surgery where appropriate.

In the past, resection was used to treat only visible, focal lesions. However, the risk with leaving behind a wide surface of neoplasia is that metachronous lesions might be present. At the beginning, endoscopic mucosal resection was considered mainly for patients of advanced age and those with comorbidities. Until a few years ago the gold standard treatment was still, unfortunately, oesophagectomy, which had the advantage of providing not only the entire specimen, but also of removing all lymph nodes. Things are changing today. In patients with segments shorter than 4 cm, it is now possible to consider removal with mucosectomy or similar techniques.

THE LIMIT FOR ENDOTHERAPY TREATMENT



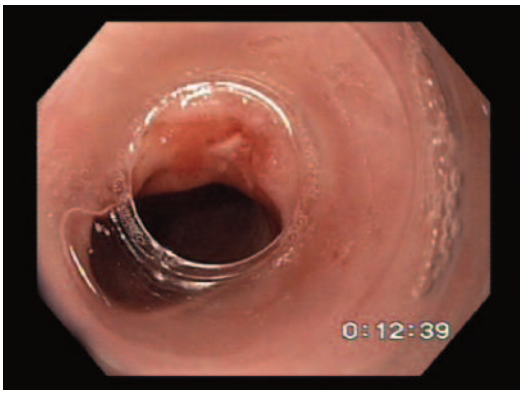
T1a cancers can be managed by endotherapy; for more advanced cancers surgery is required

How is resection performed?

Resection is usually performed by using a plastic cap placed on the tip of an endoscope or using a multiband ligator (MBM). A very simple study showed that the only significant difference between the two approaches was procedure time, which was shorter in the MBM group (*Gastrointest Endosc* 2011, 74:35–43). This technique is also considerably easier than oesophagectomy and can therefore be performed in centres with a lower annual number of patients, although they should nonetheless be sent to referral centres. Unfortunately, the study showed that perforations occurred in three patients undergoing EMR-cap resection and in four patients undergoing MBM, but this rate is unusual, as can be seen in the table on page 18.

Question: *What is your preference between the two techniques for removing tissue from the oesophagus: cap resection or MBM?*

A SMALL EROSION AT THE TOP OF THE OESOPHAGUS



This patient could be treated with a circumferential mucosectomy to completely remove Barrett's oesophagus

Source: Image courtesy of Massimo Conio

Answer: *I started with cap resection so am used to this method and will continue to use it with most of my patients because of the experience gained, but I think the risk of perforation should be lower with MBM.*

A historic paper analysing the result of mucosectomy in patients with low-risk early adenocarcinoma lesions (I, IIa, IIb and IIc), in which histological assessment showed no lymphatic or vein invasion, demonstrated that complete resection was achieved in 96% of cases (*Gut* 2008, 57:1200–06). Endoscopic resection failure occurred in 4% of patients, resulting in their having surgery, and metachronous lesions were seen in 21%. However, the five-year survival rate was very good, at 84%. If you are able to select patients carefully, I think that the five-year survival could be almost 100%.

What about cases where there is minimal infiltration of the submucosa? A very limited study suggests that in the most favourable cases – invasion of only the superficial layer of the submucosa, no infiltration of the lymphatic vessels or veins, a good histological differentiation grade G1 or G2, and macroscopic type I or II – then maybe oesophagectomy should be avoided (*Am J Gastroenterol* 2008, 103:2589–97). However, when there is oesophageal invasion and the patient is fit for surgery, they should be referred to a surgeon.

Question: *This can be quite a difficult diagnosis for a pathologist to make. What kind of pathologist should look at this type of tissue? And can you comment on how tissue should be delivered to the pathologist and how it should be processed in the laboratory?*

Answer: *This is a very interesting question. First of all, after each resection with EMR-cap you can immediately retrieve the specimen, which should be fixed by pinning it on a tablet. If you put it in a bottle it will shrink, making it difficult for the pathologist to make an adequate assessment, particularly of the depth of the lesion. You need to fix it as soon as you can. There are artefacts due to the resection and cauterisation, but in most cases we can achieve quite a deep resection. The pathologist should be trained in this area. There are a lot of problems in differentiating low-grade dysplasia from inflammatory reactions, and so on. It is always good to have a couple of pathologists judging a specimen.*

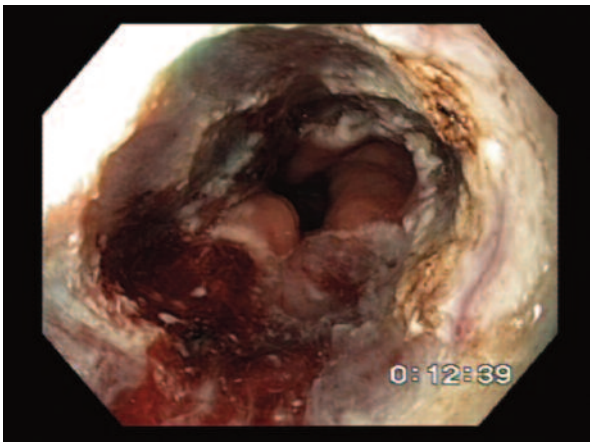
The figure on page 14 (*bottom*) shows a patient with a small erosion at the top of the oesophagus. We decided to completely remove Barrett's oesophagus, performing a circumferential mucosectomy. The figure above shows a patient with metachronous lesions, whom we decided to send to the surgeon. The bad news was that the patient underwent an oesophagectomy, but the good news was that there was no remaining cancer and the lymph nodes were negative.

Metachronous lesions after EMR

There is a 30% risk of developing metachronous lesions after endoscopic mucosal resection. It has therefore been suggested that we should ensure complete eradication of Barrett's oesophagus with stepwise endoscopic mucosal resection or with the new methods of radiofrequency ablation.

A retrospective study of stepwise radical endoscopic resection in 169 patients from four referral centres, with a Barrett's oesophagus length <5 cm and endoscopic mucosal resection performed every four to eight weeks until complete eradication of Barrett's oesophagus, showed eradication of neoplasia was obtained in 98% of patients, but eradication of intestinal metaplasia occurred in only 85% (*Gut* 2010, 59:1169–77). Four perforations occurred acutely during the procedure, and two perforations occurred late during dilation of stenoses. The main drawback of this technique is the onset of stenosis, which can be a real problem. In the study it affected 50% of patients.

METACHRONOUS LESIONS IN THE OESOPHAGUS



This patient could not safely be treated with endoscopic mucosal resection and was referred to surgery for a full oesophagectomy

Source: Image courtesy of Massimo Conio

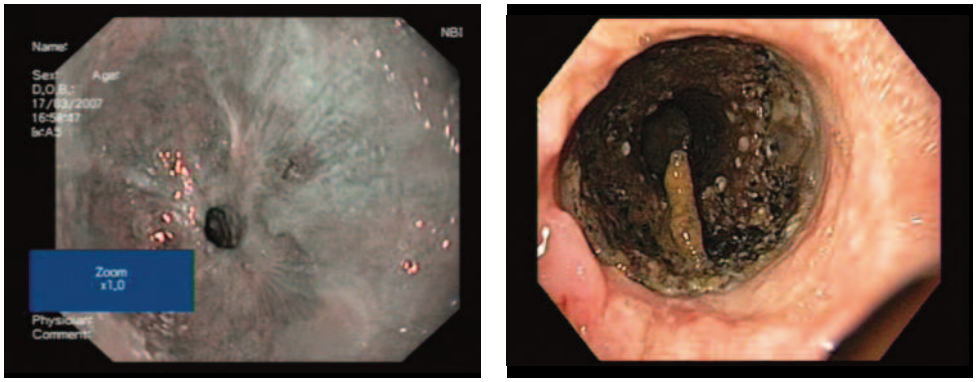
Question: *Does endoscopic mucosal resection become more difficult when you do this in a second procedure or in a third procedure? Is it more difficult to complete the whole resection if you come back a second or third time, because fibrosis could make it more difficult to lift and remove the lesion?*

Answer: *This is a problem, so in selective cases I prefer to carry out complete resection in one session only, and not stepwise, because of the risk that fibrosis due to scarring may prevent an adequate resection of the residual metaplastic tissue in the following endoscopic sessions.*

The figure overleaf shows a significant stenosis occurring two weeks after a procedure (*top left*). In refractory cases we use a removable stent (*top right*), left in place for four to six weeks, which is easy to remove. We do not usually use stents larger than 16 mm. For the future, stents are being developed that will reduce the risk of migration, which can occur in these patients.

The BARRX system can be used to achieve destruction of the oesophageal wall, using radiofrequency ablation with probes of 360° or 90°, until the muscularis submucosa. The stenosis rate with this system seems to be lower. A study by Shaheen published in 2009 (*NEJM* 360:2277–88) randomised 127 patients (64 with low-grade dysplasia, 63 with high-grade dysplasia) to radiofrequency ablation or a sham procedure. Complete eradication of intestinal metaplasia occurred in about 75% of patients with radiofrequency ablation at 12 months (see figure overleaf, *bottom*); eradication of low-grade dysplasia was achieved in about 90% of patients and high-grade dysplasia in 80%. There was a striking difference compared to patients who did not receive this treatment. However, follow-up was relatively short, at only 12 months, and

MANAGING STENOSIS



Stenosis – severe narrowing of the oesophagus – is a complication that may occur in up to 80% of patients treated with a circumferential endoscopic mucosal resection (*left*). In refractory cases it can be treated with a temporary stent (*right*)

there was a problem with subsquamous intestinal metaplasia. The number of strictures was very small, however, at 6%.

Question: *In terms of the complete eradication rate, 75% may represent a good success, but on the other hand it means that 25% of patients have Barrett's oesophagus left behind. This is not good because of the risk of developing malignancy.*

Answer: *I think that many things must be analysed in patients undergoing radiofrequency ablation and we should, of course, achieve higher rates of eradication of intestinal metaplasia. There is always the risk of subsquamous mucosa and patients need to be maintained on a surveillance protocol.*

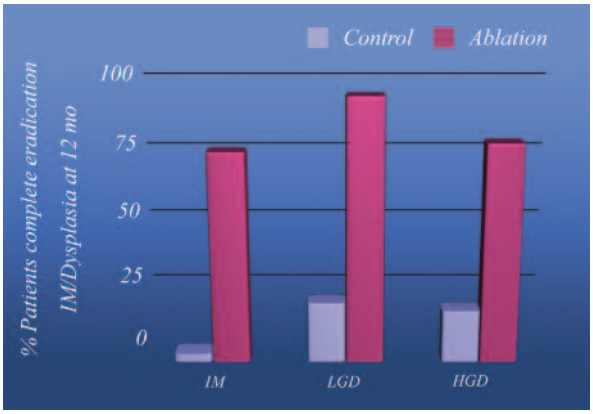
The same group analysed the durability of response to radiofrequency ablation in a group of 106 patients with Barrett's oesophagus with dysplasia. They aimed to evaluate the eradication of neoplasia; the eradication of Barrett's oesophagus; the durability of response; disease progression and adverse events. The results for eradication of neoplasia and Barrett's oesophagus at two years (n=106) were very good – 95% and 93%, respectively – and more or less the same at three years (n=56)– 98% and 91%, respectively (*Gastroenterology* 2011, 141:460–468).

At three years without maintenance, complete eradication of neoplasia occurred in more than 85% of patients and complete eradication of intestinal metaplasia in more than 75%. There is always the risk of persistence of metaplasia. Adverse events were reported in 3.4% of cases; oesophageal strictures accounted for 7.6% of adverse events.

In terms of disease progression, three patients with low-grade dysplasia progressed to high-grade dysplasia, one progressed from high-grade dysplasia to cancer, and one from low-grade dysplasia to adenocarcinoma. This rate means that 4.2% of patients must undergo endoscopic follow-up (one per 73 patient-years). The cost of surveillance of these patients will be maintained, but it still represents a great advance.

In an editorial accompanying the paper by Shaheen and colleagues, Inadomi pointed out that you need four radiofrequency ablation sessions to obtain complete eradication, and then 50% of these patients require further radiofrequency ablation sessions in the second and third year (*Gastroenterology* 2011, 141:417–419). This indicates we should

COMPLETE ERADICATION USING RADIOFREQUENCY ABLATION



At 12 months follow-up a striking difference was seen between the patients in the control arm, who were treated with a sham procedure and those treated with radiofrequency ablation, in the rates of complete eradication of low-grade and high-grade dysplasia (LGD/HGD) as well as intestinal metaplasia (IM)

Source: NJ Shaheen, P Sharma, BF Overholt. *NEJM* 2009; 360:2277–88; © Massachusetts Medical Society, reprinted with permission

use the term 'remission' and not 'complete healing' or 'complete regression', because there is always the risk of subsquamous persistence, even if it is minimal, which means we need to follow up.

A multicentre randomised trial compared stepwise endoscopic mucosal resection (SEMR) against radiofrequency ablation (RFA) with or without endoscopic mucosal resection to look at the recurrence of stricture. It included patients with Barrett's oesophagus length <5 cm who underwent at least four sessions of SEMR or RFA following resection of focally resectable visible lesions (*Gut* 2011, 60:765–773). The study was relatively small, including only 47 patients (25 undergoing SEMR; 22 RFA±EMR). At the end of the follow-up, complete response of neoplasia occurred in 100% of patients in both arms, and complete response for intestinal metaplasia occurred in 20 out of 25 patients undergoing SEMR and in 18 out of 20 treated with RFA±EMR. But we are waiting for more results, because the number of patients is small and follow-up was only three years in the study mentioned previously, so we have to see what will happen in another two or three years before making decisions on treating every Barrett's oesophagus patient with radiofrequency ablation.

What about complications? The most important complications were stenoses: in the SEMR group, stenoses accounted for five of the six severe complications and for 17 of the moderate complications; in the RFA group, three stenoses occurred in patients with moderate complications. Overall, the rate of stenosis was 88% in the group undergoing mucosal resection versus 14% in the radiofrequency ablation group (see table below).

Based on current evidence, radiofrequency ablation should be offered to patients with low-grade and high-grade dysplasia and a long extension of Barrett's oesophagus, because there is a low rate of stenosis and it is very easy to perform. Unfortunately, there is a lack of histological examination and we need to follow up.

COMPLICATIONS: STEPWISE EMR VS RFA

	SEMR	RFA
Severe complications	6 (1 perforation, 5 stenoses)	-
Moderate complications	18 (1 early bleeding, 17 stenoses)	4 (1 late bleeding, 3 stenoses)
Mild complications	5 (bleeding)	3 (2 ac. bleeding, 1 laceration)
Stenoses	22/25 (88%)	3/21(14%)
N dilations	4 (1-15)	3 (1-4)

Stenosis accounted for the majority of severe and moderate complications in this multicentre randomised trial. All six serious complications and the great majority of moderate complications were in the mucosal resection group

Source: FG Van Vilsteren, RE Pow, S Seewald et al. *Gut* 2011; 60:765–773

Personal experience of one-step circumferential EMR-cap resection

I have just submitted for publication my group's experience of one-step circumferential EMR-cap resection of Barrett's oesophagus with early neoplasia. The study includes 47 patients with Barrett's oesophageal length of about 3.0±1.4 cm, all with either high-grade dysplasia or intramucosal carcinoma (Conio et al, submitted 2012). Results showed a stenosis rate of 30% using one-step EMR in this group of patients. This is a significant rate of stenosis, but we should not worry about this if the procedure is performed at a centre where there is an expert and use of stents is routine, and we need to explain this to patients. Complete eradication of neoplasia and metaplasia was achieved in 96% of patients.

Of the 47 patients treated with circumferential endoscopic mucosal resection, only two underwent surgery: one took a personal decision to undergo oesophagectomy and the other underwent superficial adenocarcinoma. During follow-up of the remaining 45, seven (16%) had residual areas of Barrett's oesophagus, which were very small (<5 mm) and were successfully treated with endoscopic ablation using argon plasma coagulation (APC).

Overall, studies of one-step circumferential EMR-cap resection in Barrett's oesophagus with early neoplasia show good outcomes (see table overleaf). The main complication is stenosis, which affects between 2% and 88% of patients in the different studies.

Massimo Conio (MC): *What do you think about risk of stenosis?*

Peter Siersema (PS): *Stenosis is one of the concerns with this technique. On the other hand, as shown clearly in your data, patients undergo a median of only one dilation session, so the majority of these strictures can be managed very easily in one or two dilation sessions. In my experience, stent placement is generally not required for dilation of these restrictions. So risk of stenosis is a cause for concern, but it is a manageable concern that does not affect your patients' quality of life. Bleeding can be a concern, however, if you are not experienced. It seems quite severe and quite dramatic, but in my experience*

RESULTS OF ONE-STEP CIRCUMFERENTIAL CAP-ASSISTED EMR OF BARRETT'S OESOPHAGUS WITH EARLY NEOPLASIA

Author	No. of pts HGD /IMC	BE length median	Techniques	Median no. of sessions	Complications *n* (%)	Outcome
Our study 2011	47	3 (3-12)	EMR-C	1	Bleeding: 3 (6%) Stenoses: 13 (26%)	CEN/CEM 43/47
van Vilsteren 2011	25	4 (2-5)	EMR-C MBM	2 (1-3)	Bleeding: 6 (24%) Perforation: 1 (4%) Stenoses: 22 (88%)	CEN 20/25 CEM 25/25
Pouw 2010	169	3 (2-5)	EMR-C MBM Snare	3 (2-5)	Bleeding: 4 (2%) Perforation: 4 (2%) Stenoses: 84 (50%)	CEN 161/169 CEM 139/169
Lopes 2007	41	4.9 (1-15) mean	Lift&cut	1.5 mean	Bleeding: 8 (19%) Perforation: 2 (5%) Stenoses: 1 (2%)	CEN 36/41 CEM 31/41
Larghi 2007	26	2.5 (1-8)	EMR-C Snare	1	Bleeding: 2 (8%) Stenoses: 3 (12%)	CEM 21/26
Peters 2006	37	4 (3-5)	EMR-C APC	2 (1-3)	Bleeding: 1 (3%) Perforation: 1 (3%) Stenoses: 10 (26%)	CEN 37/37 CEM 36/37
Soehendra 2006	10	4 (2-10)	MBM	3 (2-5)	Bleeding: 3 (30%) Stenoses: -	-
Giovannini 2004	21	3.5 (2-5) mean	Lift&cut Inject&cut	1.5 mean	Bleeding: 4 (33%) Stenoses: 2 (17%)	CEN 18/21 CEM 15/21
Seewald 2003	12	5 (1-10)	Snare	2.5 (1-5)	Bleeding: 4 (33%) Stenoses: 2 (17%)	CEN/CEM 12/12

The nine studies reported to date on the use of one-step circumferential EMR (EMR-C) in patients with Barrett's oesophagus with early neoplasia showed good outcomes, and varying rates of complications, which included stenosis, bleeding and perforation

HGD– high-grade dysplasia; BE – Barrett's oesophagus; MBM – multiband ligator; APC – argon plasma coagulation; CEN – complete eradication of neoplasia; CEM – complete eradication of metaplasia

most of these bleedings can be managed endoscopically very easily with all the devices we have nowadays.

MC: *I agree. When you perform this technique you must be able to cope with any complications. The most feared complication is perforation, which almost never occurs, and bleeding. We can stop the bleeding quite easily and well with new hot biopsy forceps and it is not usually necessary to use clips. I had an experience three months ago in a patient with a long section of Barrett's oesophagus who had torrential bleeding, and I was unable to pass any device through the channel. Because of high outflow of the blood I decided to tamponade by placing a Blakemore–Sengstaken tube, and I left it there for 24 hours. This was a first time for me, but the bleeding stopped after 24 hours.*

I think that this type of treatment should be performed only in referral centres where endoscopy experts are available. You must have every kind of device, and you must have the experience to cope with severe complications.

Managing perforations

The figure opposite (*top*) shows a new method which allows the sealing of gastrointestinal perforation with an over-the-scope clip device (OVESCO). (Details can be found in *Gastrointest Endosc* 2010, 72:881–886, with videos.)

The figure opposite (*bottom*) shows an oesophageal perforation that occurred during radiofrequency ablation (*Endoscopy* 2011, 43:67–69). This corroborates my point that this procedure should only be performed in a centre that has all available instruments. This case was treated with removable plastic stents, but nowadays I think we can afford to use other stents.

In a patient with Barrett's oesophagus, high-grade dysplasia and intramucosal cancer, we perform endoscopic ultrasonography, mainly for the evaluation of the lymph nodes. But if is quite short (C ≤ 4 cm, using the Prague classification) we can probably treat the patient with endoscopic mucosal resection. If it is longer, I would suggest it is better to perform

SEALING A GASTROINTESTINAL PERFORATION WITH AN OVER-THE-SCOPE CLIP DEVICE (OVESCO)

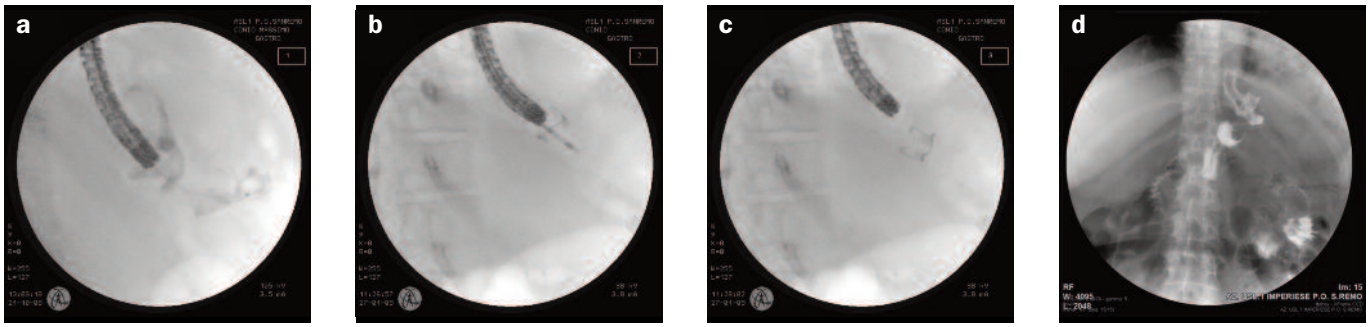


Figure a shows the perforation in a patient with a sleeve gastrectomy. In *figure b*, the tissue is grasped and put inside the cap, with a clip outside. *Figure c* shows the clip as it is being released. *Figure d* shows the contrast medium and closure of the fistula

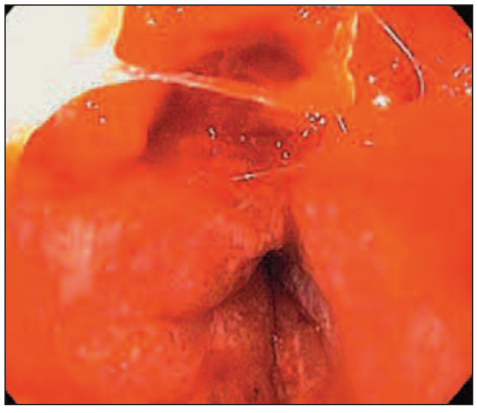
Source: X-ray images with gastrographin, courtesy of Massimo Conio

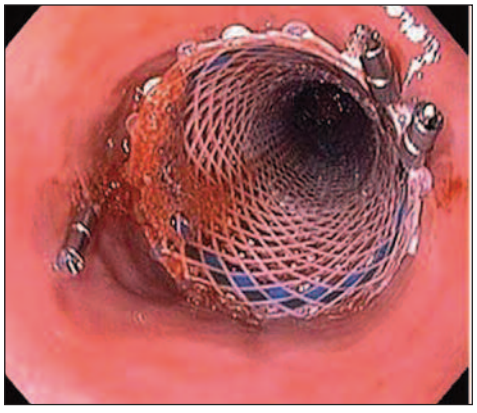
EMR focally plus HALO radiofrequency ablation. The histology will determine the patient's further treatment. If there are no dysplasia or everything is confined above the muscularis mucosa, we can offer surveillance. But surveillance should probably stop after a couple of years if we have removed everything. This approach has not yet been proved for patients with submucosal cancer, and we have to send them to surgery.

Question: *What is the next step of follow-up after EMR in your study?*
Answer: *I have not provided all the data from my studies, but we did not find cancer or dysplastic lesions after two years of follow-up. So we suggest that in patients who had complete resection, follow-up should be carried out every five years rather than two years. There are other issues, such as what happened at the level of the new squamous/columnar juncture, because it has been shown that a lower-grade dysplasia might be found. But I would say that complete resection may allow us to observe these patients every five years after the first year of intense control.*

A study on the risk of progression in patients with non-dysplastic Barrett's oesophagus showed that 96% of patients followed for five years did not develop cancer; after 10 years, 97% of this group had still not developed cancer (*Clin Gastroenterol Hepatol* 2011,

PERFORATION ARISING FROM RADIOFREQUENCY ABLATION





Patients should only be treated in centres that are equipped to deal with any complications that may arise. This perforation was treated with a plastic stent, but improved versions that can reduce the risk of migration will soon be available

Source: B Vahabzadeh, A Rastogi, A Bansal et al. (2011) *Endoscopy* 43:67–69; © Thieme Medical Publishers, reprinted with permission

9:220–227). The risk of progression was very small, and was only in patients with longer extension (0.65% per year in patients with a Barrett's oesophagus measuring ≥6 cm). In my opinion, this means that radiofrequency ablation should be the preferred option in all patients who have a long extension, even if they have no form of dysplasia, because it is very difficult to sample everything.

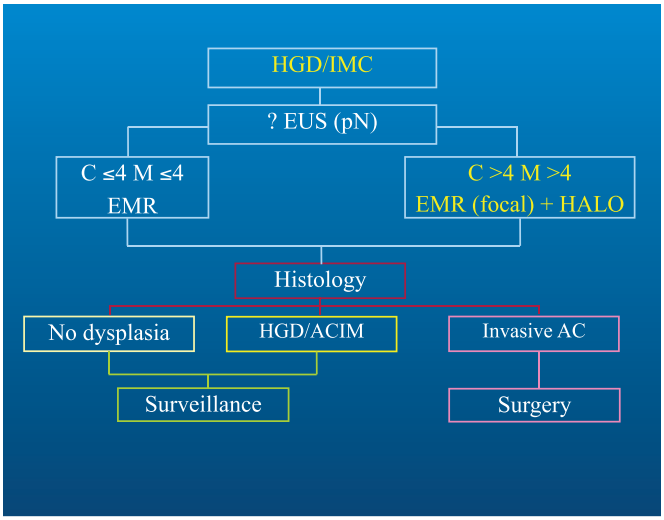
MC: *A Danish study published recently in the New England Journal of Medicine (2011, 365:1375–1383) of more than 11,000 Barrett's patients showed the risk of disease progression was very low. So it is a nonsense to recommend radiofrequency ablation in every patient with Barrett's oesophagus that is not complicated even by low-grade dysplasia. What do you think?*

PS: *I do think that there might be a question for patients with low-grade dysplasia in the long term, especially now we know some more long-term results on this. But there is now a tendency in the US for people to start treating patients without any dysplasia. We know that the risk in that group is very low and there is no justification for treatment with radiofrequency ablation. I think for low-grade dysplasia it is still too early, and in recognised and characterised low-grade dysplasia there might be a case for ablation therapy.*

Question: *Looking at your treatment algorithm for high-grade dysplasia and intramucosal cancer (see above), you performed EMR or EMR+HALO RFA. When histology showed no dysplasia you performed surveillance, and for invasive cancer you performed surgery. I agree, but I do not fully understand what you mean for patients with high-grade dysplasia and early cancer who then undergo surveillance. Is that not something that you need to treat?*

Answer: *If histology detected intraepithelial neoplasia, then the patient should undergo endoscopic follow-up for at least a couple of years. I am talking about patients with radical removal of intestinal metaplasia in Barrett's oesophagus. In the future, we should avoid performing focal mucosal resection because it does not make sense. The risk of metachronous lesions is very high.*

MANAGEMENT ALGORITHM



Management algorithm for patients with high-grade dysplasia or intramucosal cancer

HGD – high-grade dysplasia; IMC – intramucosal cancer; EUS – endoscopic ultrasonography; pN – positive lymph nodes; C, M – Prague criteria for grading extent of Barrett's oesophagus; AC – adenocarcinoma; IM – intramucosal

Summing up

Radiofrequency ablation is a very promising technique, but we are still waiting for long-term results after three years. There is plenty of room for further randomised studies. I would suggest these should ideally be pan-European studies, because this is quite a rare disease and not many centres are able to recruit a large number of these patients. A high level of endoscopic expertise is required and patients should be sent to referral centres that have a wide range of multimodality treatments.

PS: *While chairing a session on Barrett's oesophagus for young gastroenterologists at the recent UEGW (United European Gastroenterology Week), I found that it is sometimes difficult for gastroenterologists to convince their surgeons that patients with early cancers or high-grade dysplasia should undergo endoscopic treatment and not surgical treatment. How would you advise these gastroenterologists to convince their surgeons that it's really worthwhile to consider endoscopic treatment in these patients instead of performing an open resection, which is still being done in quite a few centres all over Europe?*

MC: *The most important evidence is the literature. The data have shown that the results are comparable. In the best centres in the world, the mortality rate for oesophagectomy is 3% and the morbidity rate is about 40%. Surgeons should understand we are not competitors – we have to work together. If there is a patient in whom mucosectomy shows an invasive cancer infiltrating the muscularis mucosa – even the upper layer – surgery should be carried out. But the quality of life with endoscopic treatment versus surgery is very different. Even the first day after endoscopic treatment, the patient feels very well, with no pain, and can go home in 48 hours. In contrast, there are a range of complications with surgery, including anastomosis leakage and impaired ability to eat normally.*

International guidelines offer hope of speeding up progress in advanced breast cancer

Marc Beishon

Groundbreaking international consensus recommendations on managing metastatic breast cancer have been welcomed by patient advocates and professionals alike. When backed by strong political advocacy, they believe the guidelines will raise standards of care, give much-needed structure to clinical research and improve awareness about a group of patients whose needs have been neglected for too long.

At about 1pm on 5 November 2011 – just after the scheduled end of the ABC1 (Advanced Breast Cancer) conference in Lisbon, organised by the European School of Oncology (ESO) – history was made when a large multidisciplinary panel composed of experts from 15 countries completed its voting on the first global recommendations for the treatment and care of women and men with metastatic breast cancer.

For the first time, oncologists caring for patients with advanced disease have a set of evidence-based international consensus recommendations that can guide their decision-making. Patients who want to understand their treatment options and make informed choices have a document they can refer to that represents the optimal management of this disease, and are applicable almost anywhere in the world. And the prospects for improving results for patients with metastatic breast cancer have taken a leap forward now that there is an agreed standard of care providing a benchmark against which alternative management strategies can be compared, introducing some structure to a field of clinical research that has been chaotic for so long.

The panel voted on more than 50 guideline statements that will be edited, confirmed and presented early this year in a special paper in *The Breast*, covering all aspects of advanced breast cancer, from psychosocial care to chemotherapy and targeted agents, to treatment of specific sites of metastases.

Some statements about chemotherapy could not be agreed at the time – and others were far from unanimous – which was expected given the uncertainty and lack of evidence in a number of areas. Indeed, the need for much more research is a theme underpinning the new consensus and was much discussed at the conference. But given that this was the first international meeting of its type, a major goal was achieved with agreement on a wide range of recommendations that will now set a benchmark for a patient community that has long been suffering from inconsistent treatment and lack of support.

Six years in the making

These recommendations, which are summarised on pages 28 and 29, were not the work of a few experts, cooked up over a period of weeks or months. They mark a stage in an inclusive process that

started many years ago. Fatima Cardoso, one of the four senior breast oncologists coordinating ABC1, who heads the breast unit at the Champalimaud Cancer Centre in Lisbon, opened the conference with a look back at the preparatory work that led up to the event, which started with the formation of the international metastatic breast cancer taskforce by ESO in 2005. This taskforce put forward initial recommendations and proposals, which were published in *The Breast* and the *Journal of the National Cancer Institute*, and were put up for discussion in well-attended sessions during the last three European Breast Cancer Conferences. The process culminated in this ABC1 conference, where an international consensus group met to vote on a full, updated set of statements, in a similar way to the St Gallen meeting for early-stage breast cancer.

More than six years since the start of this long process, Cardoso had a very clear message for the assembled delegates: "It's time to change. It's time for treatment of metastatic breast cancer to follow guidelines – an approach that has done so much to improve results in early disease – and it's time to tackle the lack of psychosocial support for women and men.

"The same high-quality principles used in the early-stage setting should

"Patients with metastatic disease often feel unwelcome, representing as they do a feared outcome"

apply," she said, with all women and men with advanced disease seen by a multidisciplinary team in a specialised breast unit, with each subtype of metastatic breast cancer treated differently and according to evidence, with many more patients in high-quality trials. At present, she added, in the majority of oncology departments even in the developed world, patients with advanced cancer are often cared for by individual physicians, outside a multidisciplinary team.

Cardoso's message on the need for urgent change was strongly supported by the results of a survey carried out among the breast cancer community in the run up to ABC1. More than 80% of respondents agreed that advanced breast cancer does not have the high profile of early disease, and they listed the lack of clear and applicable management guidelines and the lack of high-level evidence for treatment options as the main reasons why.

These guidelines are key, says Cardoso, because they not only represent an international consensus based on available evidence, but they also help to provide the setting to raise standards everywhere, with greater consistency in training and care, and to identify areas of research priorities that need more funding and resources to optimise the management of this disease.

ABC1 can claim to offer a strong base for building such an international consensus, she said, because it was led by joint US-European coordinators, and the consensus panel included representatives from nursing, psycho-oncology and patient advocacy alongside top oncologists from several disciplines and a wide variety of countries covering four continents.

Leading it all, alongside Cardoso, were two top American breast medical oncologists, Larry Norton from Memorial Sloan-Kettering and Eric Winer from the Dana-Farber Cancer Institute, together with Alberto Costa, a senior breast surgeon and director of ESO, who helped ensure the presence of many of the world's leading specialists to present the state of the art for research and treatment. And there was no holding back on the highly complex science underlying the huge challenge of improving outcomes.

Guidelines help informed choices

But this conference kept a clear focus on patients, so it was Musa Mayer, a patient advocate who runs AdvancedBC.org, a patient support site, who gave the keynote talk. Mayer spoke of her experience as a survivor of early breast cancer, of how she met many fellow patients who later died from advanced disease, and of how little information and support there had been. "Women and men living with metastatic disease have been largely invisible and unheard – at no time is this more apparent than in October when we in the US are awash with pink ribbons and upbeat messages about early detection and survivorship," she said. "Patients with metastatic disease often feel unwelcome, representing as they do a feared outcome for those with primary breast cancer."

Now there are support groups for those with advanced cancer, she added, noting that several had posters at the conference. As more people are living longer, thanks to new treatments, their day-to-day concerns take on new urgency, said Mayer. How do you manage the effects of treatment and cancer progression, or the impact of treatment failure, and the loss of function and place in the community? "These take a heavy toll," she said, adding that it is difficult to plan and fund services for this group of patients because there are no reliable statistics on how many have advanced cancer and where they are. "We lack an accurate count of this population in the US as distant recurrences are not captured by cancer registries."

It's time for patients with advanced disease to be counted and made a public health priority, said Mayer, who also called for better funding for research on metastases, and a rethink of clinical trials, particularly regarding the choice of endpoints for efficacy, and full integration of quality-of-life measures, for example using patient-reported outcomes.

"If the confusion patients face in

"ABC1 is a crucial first step and patients and advocates are watching and grateful that our time has finally come"

making treatment decisions can be reduced, and meaningful guidelines can be crafted that account for individual differences and respect patient preferences, it will help women and men with metastatic breast cancer manage the anxiety and loss of confidence they feel when a treatment fails," she said, adding, "ABC1 is a crucial first step and patients and advocates are watching and grateful that our time has finally come."

Management of advanced disease

Clinical aspects of advanced breast cancer occupied the majority of the conference, from imaging developments, well summarised by Nehmat Houssami from Sydney, Australia, and pathology challenges, discussed by Giuseppe Viale, from the European Institute of Oncology, Milan, to state-of-the-art treatment of HER2-positive, triple negative and ER-positive subtypes, and treatment approaches for specific sites (bone and brain) and specific populations (older and very young patients). These presentations set out the current evidence from which the majority of the consensus statements have been developed.

HER2+ subtype

On the HER2+ subtype, for example, Cardoso set out the evidence for its management – that it is a well-identified disease and selection of patients is crucial; the targeted drugs trastuzumab and lapatinib work well; there is a good safety profile of the agents; and trastuzumab can be combined with several different chemotherapies. But brain metastases are an important problem, and resistance to therapies inevitably occurs – a topic covered in some detail by George Sledge from Indiana University, and the then ASCO president. Ian Krop from Dana-Farber looked at some of the drugs in the pipeline that might help address some of these issues.

Triple negative disease

In contrast, there are no targeted therapies approved yet for triple negative disease, which causes a disproportionate number of deaths, reported Eric Winer. The conference heard from Andrew Tutt, based at Guy's Hospital breast unit in London, about the latest developments in PARP inhibitors, which have been the subject of much attention but also disappointment in the cancer world, and from Angelo Di Leo, Prato, Italy, on other possible targeted approaches. Despite early hopes, the anti-angiogenesis drug bevacizumab now appears to have no survival value (and indeed the FDA has withdrawn approval in the US for use in advanced breast cancer).

ER+ subtype

The much more common endocrine-responsive (ER+) category – which accounts for 75–80% of cases – was also given a thorough review. A group of top oncologists, including Bella Kaufman (Israel), Olivia Pagani (Switzerland), Nadia Harbeck (Germany) and Cliff Hudis, from Memorial Sloan-Kettering and ASCO president-elect, covered the topics of hormone therapy, the complexity of applying chemotherapy in this group, and the applicability of targeted therapies.

Managing bone and brain metastases

The conference heard too about complex management issues for bone and brain metastases, with contributions from Robert Coleman, of Sheffield, UK, and Nancy Lin of Dana-Farber. In bone, a new antibody drug, denosumab, is showing benefit.

Younger patients, older patients

Particular issues in the management of patients who are very young (below 35 years old) were also discussed. Data on optimal therapy for women aged below 35 are sparse because few develop metastatic disease. Karen Gelmon from the British Columbia Cancer Agency, Canada, said it is not known whether therapies for older women are equally applicable in those under 35 or 40, and she charted possible options, noting that there is a higher proportion of triple negative and HER2+ disease in some younger populations. There are also many social and lifestyle factors to consider with these groups, she said.

Prudence Francis, from the MacCallum Cancer Centre in Melbourne, Australia was among those who travelled furthest to ABC1. She noted the under-representation of older people in clinical trials despite the rising incidence of metastatic disease in an ageing population. She also described how comprehensive geriatric assessment can help meet good quality of life and function, and outlined the treatment strategies – some of which are underused – that are more suitable to older patients.

TREATING PATIENTS IN POORER COUNTRIES

Nagi Saghir, from the Breast Center of Excellence in Beirut, described the growing burden of breast cancer in low- and middle-income countries, where in many it is common for women to be diagnosed with locally advanced or metastatic cancer. Much work is needed on raising awareness, improving access to drugs and to high quality palliative care, and countering the 'brain drain' of health workers through better local training opportunities, he said.

Guidelines for managing patients with advanced breast cancer

General recommendations

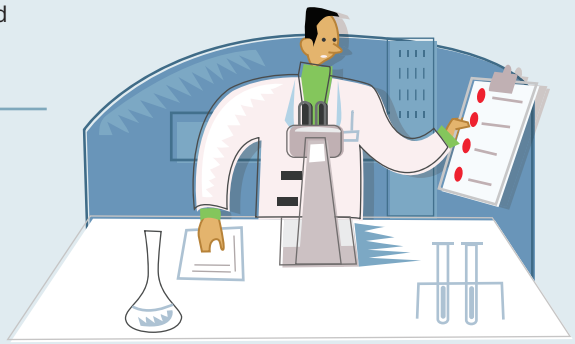
- As management of ABC is complex it is crucial that it is carried out by a multidisciplinary team
- From diagnosis, patients should be offered routine psychosocial and symptom-related care

- The virtually incurable nature of the disease must be explained and discussed, as well as realistic treatment goals
- Patients and their families/caregivers (where appropriate) should be invited to take part in decision making
- As there are few proven standards of care, inclusion in clinical trials must be a priority whenever available
- Balanced decisions about costly treatment should be made, but patient preference, wellbeing and length of life should be the main decision factors
- Validated patient-reported outcomes provide useful information and should be integrated with clinical assessments

Use the guidelines!

If you are responsible for treating patients with advanced breast cancer, or are a patient trying to decide on the best treatment options, these guidelines are for you!

This text is a brief summary. The Guidelines will be published in full in the Breast and online at www.abc-lisbon.org



Assessment

- Minimal staging work-up recommendations; tumour markers can be an aid; a framework for response to therapy; safe biopsies of metastatic lesions at first diagnosis; reassessment of ER and HER2 status at least once
- The panel did not recommend routine brain imaging for HER2+ and triple negative patients

Guidelines facilitate research

Eric Winer stressed how common it is for general oncologists, and not just breast specialists, to take care of patients with advanced disease, adding to the importance of getting international guidelines agreed, disseminated and used. Yet he also argued that guidelines are not an answer in themselves. "I think sometimes people forget the purposes that guidelines serve. They do lead to better care by eliminating some variability, and especially unnecessary care. But what may be more important from my perspective is that guidelines facilitate research."

He described three inputs into research – first, if patients are treated according to guidelines it is much easier to look back and assess how they have done, which will contribute to comparative effectiveness work. Second, a great deal is learned when professionals struggle to come up with a guideline for a given problem, as there is a lot of debate and uncertainty, and that automatically means there is a need for prospective clinical research. And finally, practising according to guidelines helps craft an overall clinical trials agenda. He called for better partnership with basic scientists, improved access to biopsy tissue and an end to the 'intolerable' delays caused by regulations.

Treatment

- Targeted therapies should be considered after a receptor-positive test in either the primary or metastatic tumour, as it is unknown which should be taken into account
- Treatment choice should take into account a wide range of factors (these were detailed)
- Age should not be a reason to withhold therapy
- The small subset of patients who can achieve complete remission should be treated in a specific way
- A range of treatment options and approaches were agreed for disease in these categories: HR+; ER+/HER2-; HER2+ and ER+/HER2+
- Sequential chemotherapy is the preferred choice; combination chemotherapy should be reserved for cases of rapid progression
- Bevacizumab can be considered in highly selected cases but there are currently no predictive factors
- A bone-modifying agent (bisphosphonate, denosumab) should be routinely used for bone metastases; radiological investigation and treatment may be needed for bone pain; spinal cord compression should be investigated according to symptoms
- Two statements were made on brain metastases and appropriate surgery, radiosurgery and whole brain radiation
- The true value of the removal of the primary tumour in stage IV breast cancer patients is currently unknown, but it can be considered in selected patients if technically possible and only if performed optimally. There is ongoing research on this
- Treatment of men with metastatic breast cancer:
  - Endocrine therapy is the preferred option as ER+ comprises the majority of cases, with tamoxifen the endocrine agent of choice
  - An aromatase inhibitor is an option for men progressing or relapsing on tamoxifen, but should be given concomitantly with an LHRH agonist

Palliative/supportive care

- Supportive care should always be part of the treatment plan
- Expert palliative care including pain control should be a priority and patients should have access to effective control of pain including morphine
- End-of-life care discussions should start earlier in the course of metastatic disease

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

The conference discussed many topics of research that may hold the key to progress in treating advanced disease.

The mechanics of metastases

The science of metastases was covered by several speakers. Primary tumours seem predisposed to invade different organs at the metastatic stage, and scientists are homing in on mechanisms and targets for the selection of say bone or lung for cancer spread, exemplified by the work of Roger Gomis from the Institute for Research in Biomedicine, Barcelona. The loss of a metastatic suppressor in certain breast cancers, for example, is one area to target; another is the Src gene that allows cancer cells to develop in the bone in a so-called 'seed pre-selection' mechanism.

Much of this work is made possible by analysing the gene expression signatures and single gene alterations of tumours, and Laura van 't Veer, a pioneer of gene signatures, described how clinicians will be able to make use of new tools to develop personalised approaches for metastatic patients.

The 'seed–soil' mechanism

The way tumour cells are prepared for circulation and seeding was also up for discussion. David Lyden, at Weill

"We have to be very clear about the benefits and harms of the treatment we are recommending"

Cornell Medical College, presented work on exosomes – tiny particles secreted normally by bone marrow, but also by tumours, which contain information that can 'educate' and prepare the environment (in particular the blood vessels) for remote metastasis. Early intervention in this process could be valuable in what is a detailed development of the long-hypothesised 'seed–soil' mechanism.

Larry Norton told the audience about 'self-seeding', where primary cancers are both the source and a recipient of tumour cells – which is very different from the widely held model of one-way spread to distant sites, and has now been confirmed in many experiments.

Guidelines and the quality of life

The focus then returned to the experience of patients, with discussion of issues in palliative care and balancing benefits and harms. Radiation oncologist Alan Rodger discussed the role of radiotherapy in metastatic breast cancer, noting its proven role in palliating bone and brain metastases. Patricia Ganz, from the Jonsson Comprehensive Cancer Center in Los Angeles, looked at endpoints for treatment, arguing that patient preferences must be included, particularly where therapies that have a benefit only on progression-free survival also lead to increased toxicity.

This theme was taken up by Lesley Fallowfield, an outspoken pyscho-oncologist from the UK. "We have to be very clear about the benefits and harms of the treatment we are recommending," she said. "Patients have to make some very difficult decisions."

Fallowfield questioned some of the research suggesting that patients will accept all sorts of toxicities for minimal benefit, arguing that much of it is flawed, and that the veracity of much of the safety and side-effect data from trials is doubtful and often does not tally with patient-reported outcomes. Quality of life experience is often "under-reported, under-recognised and under-treated", she said, and she called for the use of better systems for capturing patient-reported outcomes, which are now available.

Patient advocacy groups will have a crucial role to play in improving the way patient experiences are reported and evaluated, thereby improving the quality of information on which future patients can base their decisions. But, as Stella Kyriakides and Bettina Borisch, past and current presidents of the European Breast Cancer Coalition, Europa Donna, both pointed out, strong patient advocacy will also be essential if the new guidelines are to have the desired impact on improving research, treatment and support. A strong political voice for advocates is needed to raise awareness about the needs of patients with advanced breast cancer, generate support for the resources to meet those needs, and ensure patients get to know about the new guidelines – and their doctors start to use them.

The ABC conference takes place every two years, alternating with the Breast Cancer in Young Women conference. ABC2 is scheduled for 7–9 November 2013, in Lisbon

MANAGING COSTS

The issue of cost was tackled head on by David Cameron – not the British Prime Minister but an oncologist based in Edinburgh. More money is lost to economies through cancer than other diseases, he said, so there is a case for spending more on cancer to help the financial situation. Drugs are often put forward as the major expense but are only about a fifth of cancer spend at present in countries such as France, he noted, so it is also important to look at optimising the other 80% of spend. In the US, the fastest rising costs are in imaging.

"Could we also save money in how we organise healthcare?" he asked, suggesting that more people could be treated as outpatients, which may be more convenient to them, if not to health professionals. Drug costs are rising too of course, although much spend is on conventional chemotherapy as the cancer population rises and more older people receive treatment as 'ageism' disappears.

Cameron weighed up the debate on using cost-effectiveness bodies such as England's NICE to determine often tough decisions about what will be paid for. "We have to understand health economics so we can drive the agenda on behalf of our patients," he said.

Living with the timebomb of a childhood cancer

Award for article on a mother confronting her worst nightmare

Don't bury your head in the sand – being alert to early signs of cancer gives the best chance of survival. This is the message the mother of one very young cancer patient wanted to pass on. **Silja Paavle**, reporter on the Estonian daily *Õhtuleht*, helped her do so in this article, which won her a Best Cancer Reporter merit award.

"One shouldn't walk through life with one's eyes closed and, when you hear about terrible things, think that they cannot happen to you. Even the most terrible things happen somewhere. You simply have to learn to live with them." So says the mother of a girl who has been diagnosed twice with a brain tumour.

Karin, the mother of the eight-year-old Karmen (the names have been changed), admits that, somewhere in her subconscious, the awareness of a brain tumour ticks away like a timebomb. When the time approaches to call the doctor for an appointment, she gets very nervous. Her family certainly don't miss the nerve-wracking days they went through during the treatment of their little girl's twice-diagnosed brain tumour.

Karmen was an ordinary, lively little girl from Tallinn who could walk and talk by the time she was around a year old. She was not prone to illness until one morning, when she had a seizure. "We went straight to the hospital, where she was given treatment and examined. A head scan showed that she had a brain tumour. According to the initial assessment, it was the size of a baseball." This is how Karin describes the news, which came as a major shock to the girl's parents. "I cried for days," she admits.

The doctors' hopes that the tumour was benign was some consolation – malignant tumours usually announce themselves beforehand through some ailment or general poor health.

Having gone to the hospital due to a seizure, Karmen was not allowed to go home. A week later, she underwent brain surgery, and afterwards the doctor told the girl's mother that the tumour was suspicious. "I was terribly shocked – how can anyone say something like this to a mother until they are absolutely certain? But I suppose doctors have experience," sighs Karin. It did give her time to get used to the bad news – the tumour was larger than the doctors had at first thought, and it turned out to be malignant as well.

When Karmen's doctor, Karin Orgulas, informed her, Karin decided it was time to fight and move on. "I understood that it was not the worst type of brain tumour, but it could grow extremely fast," she says.

The child received chemotherapy and, fortunately, coped well.

Silja Paavle

Õhtuleht

When it comes to childhood cancers, coverage in the popular press tends to score higher on quantity than quality. This particular story gave readers important information as well as an unsentimental insight into the stresses, hopes and fears associated with having your child diagnosed with cancer


TERVIS

100

Ajukasvaja küüsis vaevelnud tüdruku ema: teadmine vähist tiksub nagu viitsütikuga pomm

Kõik ajukasvajad on pahaloomulised

Kalli ravi eest maksab toetusfond

This was a difficult time for the whole family: Karin had just started a job, but now she had to take her daughter to the doctor every 10 days. During the day, when Karin was at work, Karmen's grandmother stayed in hospital with her. In the evenings and at nights, Karin took over.

Karmen would only eat food prepared by her grandmother, which she cooked after returning home from the hospital. "If my mother had not helped us, it would have been extremely difficult," says Karin gratefully.

The first period of treatment lasted a year, after which Karmen, as with all cancer patients, remained under observation; she had to be examined every three months. When the family returned for her head scan, several unfortunate incidents occurred – one time the machine was out of order, another time the doctor was on holiday.

When the procedure was finally carried out, it became evident that the malignant tumour had returned to the three-year-old's brain.

"I was horrified to think what might have happened if we had succeeded in getting the scan at the first attempt. Since the tumour grew very fast, it might have gone unnoticed the first time, and early discovery is essential for success," says Karin.

This time the doctors considered surgery too dangerous, so radiation and chemotherapy had to be used to fight the tumour. First, Karmen received 30 sessions of radiotherapy.

"In five weeks, she was under anaesthesia 30 times in all. During radiotherapy, she had to lie completely still and flat on her stomach under a machine – without a full anaesthetic. This is difficult for small children," says her mother.

The chemotherapy lasted a year. The family spent their days going to the Children's Hospital, then to the Oncology Clinic in Hiiu, and then back to the Children's Hospital.

There were times when the whole family was at the hospital – Karmen's little brother suffered from laryngitis, and it was not rare for the mother to be in the

"During radiotherapy, she had to lie completely still and flat on her stomach. This is difficult for small children"

"Once Karmen shouted at a grown-up: What are you staring at? Never seen anyone like me before?"

oncology ward with their daughter, while the father was in the infectious diseases ward a few floors below with their son.

Karmen experienced no serious side-effects from chemo- and radiotherapy, though Karin spits three times over her shoulder for luck when she says so. "She coped with the treatment very well."

Between each period of treatment, Karmen had to be taken to hospital for blood tests. During breaks between the chemotherapy sessions, the family had to visit the hospital a couple of times – Karmen suffered terribly from vomiting.

Due to the hormone treatment accompanying radiotherapy, Karmen's appetite and weight increased. "This was awful – in the end, she even had difficulty walking. A child that young cannot understand why she is not allowed to eat. She only feels hungry and cries about it," sighs Karin, adding that they no longer have problems with excess weight.

Karmen is now eight years old and there is nothing to show that she has suffered a serious illness. She takes her disease with childlike levity and knows that, however bad it is, doctors can help.

Karmen now has to have a brain scan at regular intervals; she also has to be injected with growth hormones, as the radiotherapy interfered with her growth. "At first, we feared that growth hormones would make the cancer grow again, but the endocrinologist reassured us, telling us that the body usually produces its own growth hormones and therefore they will not cause the tumour to grow back," says the mother.

Karmen must also avoid being hit on the head; having lost her hair during chemotherapy, she is used to wearing a hat.

Karin remembers that when the four-year-old Karmen lost all her hair and was unusually chubby due to hormone therapy, people would often stare at her. "Once Karmen shouted at a grown-up: what are you staring at? Never seen anyone like me before?" she laughs.

Karin says that, although Karmen's difficult disease, which took up so much of their energy, did put a strain on relationships within the family, they coped relatively well. Throughout the course of treatment Karmen was utterly positive and responded well. "However, there were several children with cancer at the hospital who never recovered. Each of these stories was very sad," sighs Karin.

Whenever she heard sad news, she told herself that every tumour is different and each child's disease is different.

Karin is very grateful to her GP as well as to the doctors and nurses at the Children's Hospital, who are highly committed to their work and answer all the parents' questions, in spite of the difficulties.

When things get tough, they are always there for their patients – even at night.

ALL BRAIN TUMOURS ARE DANGEROUS

"In essence, all brain tumours are malignant, but their speed of growth and level of malignancy differ," says Karin Orgulas, a doctor in the oncology ward of the Tallinn Children's Hospital. She was also Karmen's doctor.

Like the principal character in the recently published book '*Regina: Mu imekaunis võitlejanna*' ('*Regina: My beautiful fighter*'), Karmen was diagnosed with a primitive tumour in the upper part of the brain, which always develops very rapidly. Orgulas adds that brain tumours can occur in all parts of the brain.

In Estonia, around 8–10 children undergo brain tumour surgery every year, and brain tumours make up one-third of all childhood malignant tumours. While all other malignant tumours also require medical treatment, i.e. chemotherapy, only a quarter of the most malignant brain tumours receive this treatment. "With brain tumours, the important question is whether the tumour can be entirely removed or if this is impossible because of its location and extent," says Orgulas. On average, three children a year need chemotherapy.

Early diagnosis is of the utmost importance in brain tumours. Orgulas advises that parents should consult a doctor at once if their child is experiencing headaches, vomiting and problems with balance.

A brain tumour diagnosis is extremely serious and, in the early stages of the disease, it is very difficult to say whether the child will recover or not, because so many different factors are involved. In some cases, children may have to remain under observation for the rest of their lives and live with the knowledge that the disease could return at any time.

This article was first published in *Õhtuleht*, on 31 August 2010, under the title 'The mother of a girl suffering from a brain tumour: awareness of cancer ticks away like a time-bomb'. It is reprinted here with permission.

A world-class centre arises from the French ground-zero

Anna Wagstaff

A chemical explosion in Toulouse 10 days after the twin-towers attacks in the USA traumatised the French city. But from this disaster arises an innovative hospital with unique links to research and industry. Jean-Pierre Armand has seen his dream cancer centre at the Toulouse 'oncopole' through to completion. Now a new chief executive must bring the dream to life.

ANDER GILLENEA, C.PICCI

"If only we could start from scratch." This thought has no doubt crossed the minds of many senior figures in cancer as they try to reshape slow-changing systems and processes to keep up with developments.

Whether integrating biobanking into surgical pathology, convincing smaller hospitals not to treat patients where they lack the necessary experience and expertise, or facilitating cooperation between hospital-based researchers and basic scientists, the option of starting from scratch seems very enticing.

Following a decade-old tragedy, just such an opportunity will soon be bearing fruit in the south of France, with the completion of the Toulouse 'oncopole', a public–private partnership which "aims to become the European leader in the field over the next ten years" and will be "dedicated to winning the fight against cancer".

The brand new campus, covering more than two square kilometres, will be home to a new University Cancer Hospital, attached to a large public–private research facility, geared to collaborating with the hospital in translational research projects. A group of small biotechs using university lab facilities on the oncopole site will link with basic researchers at the city's highly-rated University of Science and Medicine, and will look for opportunities to develop and market innovations, specialising in selected fields such as the application of nanotechnology in cancer therapies. Completing the oncopole line up will be Pierre Fabre laboratories, which brought the cytotoxic drug vinorelbine to market, and has a particular interest in cancer immunotherapy, and Sanofi, one of France's biggest pharmaceutical companies.

Like a phoenix from the ashes. The Toulouse oncopole is built on land left devastated by a catastrophic explosion at a chemical works in 2001. The University Cancer Hospital – the curved building in the centre – will open in early 2013

It all began with a catastrophic event. On 21 September 2001 – 10 days after the 9/11 attacks in the USA – an explosion ripped through an area in the southern part of Toulouse, generating a shock equivalent to an earthquake measuring 3.3 on the Richter scale, or 100 tons of TNT. It was not a terrorist attack, as many initially assumed, but an industrial accident at a large chemical complex. It left 30 people dead and 2500 severely injured, with many school children numbered among the casualties; 40,000 people found themselves temporarily homeless.

It was in response to this disaster that the proposal for the Toulouse oncopole arose. The city needed investment to repair the physical damage and replace jobs. But it also needed something positive on a human level to help heal the wounds and pull the community through a period of shock, mourning and recrimination. Using the devastated industrial wasteland to create a top-class centre focused on the fight against cancer fitted the bill perfectly, and played to the city's strengths and history. Toulouse is home to one of the earliest centres of radium therapy – the Claudius Regaud Institute, named in 1923 after Marie Curie's closest clinical collaborator. The city is also very strong in both science and innovation, being home to some of the country's top-ranking universities, as well as France's prestigious aerospace industry.

The Toulouse oncopole truly is an opportunity to 'start from scratch', says Jean-Pierre Armand, who, to his great delight, was drafted in from the prestigious Gustave Roussy Institute in Paris to oversee the development of the new University Cancer Hospital. In doing so he has helped to create a 'promised land' for his successors, although he himself is returning to Paris.

But he has high aims for those who will follow. "The aim is not to improve or update. It is to use the expertise and experience we have in high-quality cancer care to invent new jobs and develop more effective research, discovery of new types of drugs and a better connection between this central hospital and the network of clinics serving three million people in the Midi-Pyrénées region."

Centred on the hospital

Armand has been an outspoken critic of what he sees as a damaging dislocation between university-based academic medicine and the oncology clinicians who carry out the majority of treatments. He believes the new set up in Toulouse provides an opportunity to get this relationship right, which accounts for his great hopes and infectious enthusiasm. Key to its success, he argues, is having a real cancer hospital at its heart. "This is not the type of place where you just do experiments and get experience. This hospital will be treating cancer patients from the region, just like any other cancer hospital, with real doctors tackling the same treatment dilemmas and attending to the same care needs as in any other hospital."

Armand expects two major benefits to flow from this. The 30 or so research teams attached to the hospital will be more likely to focus on resolving problems that are a priority for patients and doctors, and more likely to focus on solutions that will be of value and practical to implement in the real world. They will also have access to a very rich source of information emanating from cancer treatment centres throughout the Midi-Pyrénées region. These clinics will routinely feed information back to the new hospital via a custom-built IT system supporting what Armand describes as a 'living biobank', designed to capture patients' clinical and biological information over the course of their disease.

Bridging the gap between bench and bedside. Jean-Pierre Armand stands in the concourse that connects the University Cancer Hospital to the associated research centre

This patient-driven approach should feed through to the work of the biotechs, which will be looking to pick up potentially marketable results. To ensure the relationship between patients and research works to the benefit of both sides, safety mechanisms have been built into the system. One seat on the board of the hospital is reserved for someone with responsibility for the whole of the Midi-Pyrénées, whose function will include ensuring access to clinical trials even for patients located at the furthest periphery of this very large region. An ethics committee will oversee the work of the biotechs and protect the interests of the patients.

Both Sanofi and Pierre Fabre laboratories have long had a presence in Toulouse, but their move to the oncopole is expected to herald a much greater degree of interaction between these pharmaceutical giants and the rest of the research and clinical community in Toulouse. A Sanofi spokesperson talks of the oncopole as "an ecosystem" that "allows liaisons between the research teams, clinicians and patients". The Sanofi team in Toulouse specialises in early innovation, including in the field of tumour microenvironment, and will, for instance, welcome to its site teams from INSERM – the National Institute for Health and Medical Research.

Bursting with innovation

This collaborative, synergistic approach extends well beyond the confines of cancer science. The aeroplane manufacturer Airbus has been invited to put two representatives onto the board to boost the culture of innovation. And a shared interest has been identified with the aerospace industry in terms of access to a massive and expensive piece of equipment. It turns out that the sort of particle accelerator that is used to fire protons, carbon ions and other large particles for use in a particular variant of radiation therapy (hadron therapy) is the same as that required to test the ability of space materials to withstand exposure to neutrinos. Collaborating to develop such a facility at the oncopole site will give patients from the region access to hadron therapy, while allowing the aerospace industry to test their materials locally rather than sending them to northern Europe.

This is not only about the benefits for Toulouse. Armand and his team are well aware of how rare it was, even before the financial crisis, to get government investment of €300 mn for a project like this, and it comes with a responsibility to the rest of the country and beyond. The 'living' biobank is one precious resource that will be made available to the wider research community. There will also be a comprehensive education programme for all the oncology specialisms, including post-doctoral education covering all the jobs to do with oncology, research, industry, medicine.

There is also a unique solution borrowed from the aero industry about what to do with the existing Claudius Regaud Hospital in the centre of Toulouse. Instead of closing it down, it will become a training environment where medical students will learn in a setting as close as you can get to a working cancer hospital. The Claudius Regaud, complete with operating theatres, radiation bunkers, labs, wards, bathrooms and toilets, will become a simulator hospital where students can learn about the different pathways and approaches to all aspects of caring for cancer patients – radiotherapy, chemotherapy, surgery, nursing, psycho-oncology and pathology. Armand is enthusiastic: "We will adopt the technique used by Airbus. When they build a new plane they don't train pilots first on the real plane, but in a simulator."

Innovatory approaches to communications is another area Armand is thrilled about. The new IT system now linking the cancer hospital with all the cancer clinics throughout the Midi-Pyrénées does far more than facilitate the 'living biobank'. It is a crucial component that allows them to deliver on a commitment to care for patients as close to their homes as is safely possible, and will also

The old hospital – its operating theatres, wards, labs and radiation bunkers – will be used as a simulator hospital

make it possible for local clinics to participate in clinical trials.

An equally innovative and perhaps recognisably French approach is being taken to ensure fruitful interaction between the clinical staff and the academic researchers who share the same place of work: good food. Some of the communications budget has been used to upgrade catering facilities to the level of a Michelin one-star restaurant, where staff will want to spend time. "That will be a place where the real doctors with their own real problems will discuss with real scientists. Sometimes they have different interests, but they will listen to each other and they will exchange. This is one of the advantages you can have when you work on one site."

But it is a new thoroughly low-tech approach to communication with patients that Armand is probably most proud of. This innovation has already attracted attention from cancer centres throughout France and beyond. "In my hospital we have discovered that today a patient spends 15 minutes with the doctor in the day, but two hours with the people cleaning the ward. And so we have developed a very thorough communications training for the people cleaning the room."

Cleaning and other ancillary staff are in a good position to communicate with patients, says Armand, precisely because they are not highly educated. Patients feel relaxed talking to them about how lousy they feel, their hopes and fears for the future, or perhaps just the fortunes of le Téfécé, Toulouse's premier league football club. "It works fantastically, and now people are contacting us from elsewhere, asking us to come and train their staff or accept them on courses down here."

Armand feels that this sort of patient-centred approach, when combined with the critical mass of scientific, technical and industry know-how on site, gives the Toulouse oncopole the potential to make an important contribution to the global fight against cancer.

Now he has set up the dream factory, it is for others to make those dreams come true. Armand has overseen every stage of the planning of the new hospital, but it is time for him to pack his bags and head home to Paris. The actual move from the current Claudius Regaud hospital to the new site will take place in 2013 under a new director. In the ten years that have passed since the explosion that started it all, cancer survival has continued its maddeningly slow progress, while the financial crisis now threatens public spending on both health and research. But as Armand points out, the crisis has also mobilised many young people who are impatient for change – les indignés, los indignatos – and this is the spirit he feels in needed to get the most out of the wonderful facilities in Toulouse. "We've built the hospital, we have very strong support from patients and families, but we also need determined men and women," he says. "We have a lot of doctors now who just accept the bad results we have in cancer and are not really fighting to improve them. We now need many of these younger indignés to enter the game."

COULD YOU BE THE FIRST CEO?

The University Cancer Institute of Toulouse Midi-Pyrénées, Oncopole (http://www.oncopole-toulouse.com), is looking for a committed, innovative chief executive officer. Could that be you? The CEO will run the University Cancer Institute, including the hospital and the research centre; direct orientations for research and care; work with stakeholders; and implement the project. Main responsibilities include:

- Drawing up medical and scientific programmes, budgets and reports;
- Establishing new clinical and research labs at the UCI;
- Promoting the UCI on an international level as one of the world's top cancer centres;
- Advancing UCI findings; and
- Developing strategic partnerships with industry groups and innovative enterprises to stimulate technology transfer.

The CEO must be a MD and PhD and have a successful record managing a hospital, a translational research lab or a national health or research organisation. International health and science management, fundraising and diplomatic skills are highly valued.

The CEO will start no later than January 1, 2013.

Candidates should email their CV + letter of application + list of publications + letters of recommendation to: The President of the University of Toulouse 3, Pr. Gilles FOURTANIER (iuc.recrutement@univ-tlse3.fr)

For more information, contact the Toulouse UCI search firm, Your Voice: desk@your-voice.fr

IMPACTFACTOR

nature REVIEWS CLINICAL ONCOLOGY

The importance of local control in pancreatic cancer

Edgar Ben-Josef and Theodore S. Lawrence

The ECOG E4201 study adds another piece of information to a growing body of evidence pointing strongly to the importance of local control and the role of radiotherapy in unresectable pancreatic cancer. Based on this evidence, we believe radiotherapy should be used routinely in this setting.

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The role of radiotherapy in unresectable adenocarcinoma of the pancreas has been in question for the past three decades. Radiotherapy can palliate common symptoms such as pain, duodenal ulceration and bleeding but its impact on survival has not been clear. Whereas older trials were inconclusive, the recent phase III trial reported by Loehrer et al.[1] has shown that radiotherapy improves overall survival when added to gemcitabine. Patients with non-metastatic unresectable adenocarcinoma of the pancreas were randomly assigned to receive gemcitabine alone (1000 mg/m^2 per week for 6 weeks, followed by 1 week rest, then five more cycles of 1000 mg/m^2 for 3 out of 4 weeks) or gemcitabine (600 mg/m^2 per week) concurrently with three-dimensional conformal radiotherapy (50.4 Gy in 28 fractions) followed by additional gemcitabine (five cycles of 1000 mg/m^2 for 3 out of 4 weeks). The study was closed early owing to poor accrual but, in the 74 patients enrolled, median survival improved from 9.2 months to 11.1 months (P=0.017). This came at a cost of increased frequency of grade 4 toxic effects (although combined grade 3 or 4 toxic effects were the same in each arm). These results lend support to the notion that radiation therapy improves the survival of patients with unresectable pancreatic cancer through intensification of local therapy, given that uncontrolled local growth is the cause of death in 30% of patients with this malignancy.[2]

The trial conducted by Loehrer et al.[1] is one of two trials conducted in this decade addressing the question of whether radiotherapy can be of benefit in unresectable adenocarcinoma of the pancreas. The other study, the Fédération Francophone de Cancérologie Digestive and Société Française de Radiothérapie Oncologique (FFCD–SFRO) trial[3] showed a worse survival (8.6 months vs 13 months; P=0.03) when chemoradiotherapy was added to gemcitabine. However, the chemoradiotherapy regimen tested in that trial (60 Gy in 30 fractions in 6 weeks concomitant with a 5-fluorouracil infusion [300 mg/m^2 per day] days 1–5 for

6 weeks and cisplatin [20 mg/m^2 per day] days 1–5 on weeks 1 and 5) was highly toxic (65.5% grade 3 or 4 toxic effects) and, no doubt, contributed to the worse outcome.

Unfortunately, radiotherapy has been used suboptimally in this disease. The sensitivity of the organs to radiotherapy in the upper abdomen has limited the radiation dose to ineffective levels, and attempts to increase the radiation dose have been unsuccessful, resulting in high morbidity and mortality.[4]

An alternative strategy is to use radiosensitising drugs that enhance the effect of radiation preferentially within the tumour. The two drugs that are used most commonly with radiation in the treatment of pancreatic cancer, gemcitabine and 5-FU, both appear to decrease the ability of cancer cells to repair radiation-induced DNA damage.[5] At the University of Michigan we have carried out a series of trials using full therapeutic doses of gemcitabine – a potent radiosensitiser[6] – and concurrent three-dimensional conformal radiotherapy to maximise systemic and local control. However, toxicity has prevented the escalation of the radiation dose beyond 36 Gy in 2.4 Gy fractions even when only the tumour was targeted and clinically negative lymph nodes were excluded.[7]

> **"The question now is not whether radiotherapy is of benefit in this disease but rather how to make it more effective"**

An option that might allow delivering an increased radiation dose to the pancreas without exposing the dose-limiting organs to toxic levels of radiation is intensity-modulated radiotherapy (IMRT).[8] For example, we recently completed a trial in which we used IMRT to simultaneously reduce the dose to the stomach and intestines and increase the dose in the tumour in patients with unresectable pancreatic cancer. We have established that high-dose radiotherapy (55 Gy in 25 fractions) can be delivered safely with concurrent full-dose gemcitabine, with the use of IMRT delivered during breath hold. The rate of severe toxicity (24%) observed when using this chemoradiotherapy dose[9] compares favourably with toxic effects reported with other contemporaneous regimens. In addition, there are encouraging signals of efficacy; the median overall survival and two-year overall survival in this trial[9] (14.8 months and 30%, respectively) are significantly better (hazard ratio = 0.63, log-rank P=0.028) than historical controls (11.2 months and 13%, respectively).[10] These results also compare favourably with other contemporary phase II and phase III trials in this patient population, with either 5-FU-based or gemcitabine-based chemotherapy. High-dose radiotherapy also improved the two-year local control from 38% (historical controls)[10] to 59%.[9] Most importantly, 12 of 50 patients (24%) receiving high-dose radiotherapy were able to undergo resection with good outcomes; 10 patients (83%) had R0 resection and five patients (42%) had a major pathological response. The median survival in these patients who had undergone resection was 32 months.[9]

Thus, the results from the Eastern Cooperative Oncology Group (ECOG) trial[1] coupled with the finding that a significant proportion of patients with pancreatic cancer die of complications of uncontrolled growth,[2] and results showing improved local control and survival in patients receiving high-dose radiotherapy, suggest a new paradigm. The question now is not whether radiotherapy is of benefit in this disease but rather how to make it more effective and how to combine it optimally with systemic therapies.

A number of strategies can be explored to further intensify local therapy. Firstly, improvements in radiotherapy planning and delivery: we need to improve targeting of the tumour while avoiding the critical normal tissues and to incorporate individual susceptibilities to radiation toxicity into treatment planning. Secondly, we have to explore the use of novel tumour-specific radiosensitisers: with so many targeted agents in the pipeline, this strategy is more promising than ever. Potential candidates include CHK1 inhibitors, nab-paclitaxel, PARP inhibitors, MEK inhibitors, and many others. Thirdly, we have to carefully study the potential role of surgery in selected patients.

Finally, potential progress can be made by individualising therapy. One such effort underway is an attempt to use the status of SMAD4 (also known as DPC4) to select patients for intensive local therapy versus intensive systemic therapy. Loss of DPC4 is associated with a widely metastatic phenotype, while patients with intact DPC4 are more likely to die of local complications.[2] Thus, in a currently planned national trial, DPC4 status will be determined upfront by cytology. Patients with

Practice point

Radiation therapy with gemcitabine improves the survival of patients with non-metastatic unresectable pancreatic cancer compared with gemcitabine alone. Therefore, gemcitabine combined with radiation can be considered a standard of care for these patients.

intact DPC4 will be randomly assigned to receive an intensive or a standard chemoradiotherapy regimen (following 12 weeks of gemcitabine) whereas patients with DPC4 loss will be randomly assigned to receive FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) versus gemcitabine (followed by standard chemoradiotherapy) for two weeks.

In summary, the current ECOG trial adds one more piece of information to a growing body of evidence pointing strongly to an important role of radiotherapy in local control for unresectable pancreatic cancer. Future advances could come from better selection of patients for intensive local therapy using molecular biomarkers.

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Time for another rethink on prostate cancer screening

➜ Andrew J. Vickers and Hans Lilja

Screening for prostate cancer using PSA is a careful balance of benefits and harms. But current US practice involves testing older men who have little to gain and aggressively treating low-risk cancers. Debates about whether to test need to be replaced by debates on how to test better.

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The US Preventive Services Task Force (USPSTF) recently issued a recommendation against the use of prostate-specific antigen (PSA) testing for prostate cancer screening.[1] They concluded that "there is moderate or high certainty that [prostate cancer screening] has no net benefit or that the harms outweigh the benefits." In this article, we review the USPSTF report and make three simple points. First, the USPSTF report is riddled with errors, so much so that we would be sympathetic to accusations that the task force was biased. Second, if the USPSTF were indeed biased against PSA screening, this would be entirely understandable: urologists, radiation oncologists and others have made such a mess out of PSA screening that it is easy to see why a group of family practitioners, obstetricians and paediatricians would like to write the whole thing off. Third, PSA screening can be done in different ways, and the ratio of benefit to harm will depend on choices regarding how PSA tests are used. As mid-life levels of PSA are strongly predictive of long-term risk of prostate cancer morbidity,[2,3] we would argue for risk-stratified approaches, to minimise harms for men unlikely to benefit from screening and ensure careful follow up of those at the highest risk of unfavourable outcome.

Regarding our first point, the USPSTF report is riddled with errors of fact, interpretation and statistics. Some of these errors might be considered understandable. Take, for example, the claim that in the interim report from the European randomised screening trial (ERSPC) after a median follow up of 9 years,[4] "48 men received treatment for every prostate cancer-specific death prevented." The number of 48 patients was obtained by dividing the between-group difference in prostate cancer diagnoses with the between-group difference in cancer deaths. As not all men diagnosed with prostate cancer in this study were treated — some were placed on

active surveillance — the USPSTF statement is incorrect. It is also highly misleading, as the ratio of diagnoses to deaths that are avoided is time dependent; consider that this ratio is infinity at early follow up because screening does not prevent death in a man diagnosed with advanced-stage cancer at his first PSA test. The empirical estimate from the Göteborg arm of ERSPC, which has longer follow up (14 years) is that 12 men need to be diagnosed to prevent one death from prostate cancer.[5] Still, the ERSPC report[4] used the phrase "number-needed-to-treat" and cited the number 48, so perhaps the USPSTF error is understandable.

The principal flaw of the USPSTF might also be seen as an understandable mistake. Specifically, the USPSTF draws definitive conclusions of "moderate or high certainty of no benefit" on the basis of interim data: the largest randomised trial of prostate cancer screening – the European ERSPC trial – has not yet reported on the main endpoint of cancer-related mortality at its prespecified primary timepoint, data were only reported because the difference between groups crossed a prespecified significance boundary at interim analysis. It seems bizarre to be certain of "no benefit" when a major trial is yet to report in full.

What is less understandable is that the USPSTF make unsupportable claims that seem designed to emphasise that screening is harmful and that there should be less of it. For example, the USPSTF cites a perioperative mortality rate from radical prostatectomy of 0.5%, far higher than most contemporary estimates, such as 0.1%.[6] This is because they used a study of Medicare patients to draw their conclusions, that is, the oldest patients at highest risk for perioperative death. In addition, it is hard to understand the biological mechanism behind the claim that because "the [negative US] trial evaluated a shorter screening interval [than the positive European trial] ... more conservative screening and treatment strategies might be more effective than more aggressive ones."[1] Less regular screening may well decrease the harms of screening, but there is simply no mechanism by which it could be more effective.

Our second point is that contemporary PSA screening and treatment is a farrago and so if the members of the USPSTF were indeed prejudiced against PSA screening, it is not hard to see why. There is a lot to dislike about how prostate cancer is detected and managed in the US. For example, PSA screening is routinely used in men who have nothing to gain from it, with testing applied to one-third of men aged over 70 years who have a greater than 50% risk of death within five years.[7] In addition, digital rectal examination is widely used even though it is not informative in a screening setting.[8] Urologists are then extremely quick to biopsy, with current guidelines recommending biopsy for almost any indication: a raised PSA, a lowered ratio of free-to-total PSA, a high PSA velocity or a positive digital rectal examination. Worst of all, radiotherapy or surgical treatment is almost universally recommended: empirical studies show that fewer than 10% of men with low-risk disease are offered active surveillance.[9] Couple this with apparent conflicts of interest, such as groups of urologists purchasing radiation equipment and then self-referring patients, and it is not hard to see why those outside of the prostate cancer field see PSA testing as nothing more than a scam.

> **"...current PSA testing as it is commonly practised in the US is indefensible"**

Prostate cancer screening is not a single intervention, such as a certain dose of a specific drug; it can be implemented in numerous different ways. Starting PSA screening at, say, 70 years, using a very low PSA threshold for biopsy and then aggressively treating all cancers will lead to enormous amounts of overdiagnosis and overtreatment and will have little effect on mortality. Conversely, focusing on younger men, only biopsying those meeting stringent criteria, and managing low-risk cancers by active surveillance will lead to a better balance of harms and benefits. Indeed, given the diversity of approaches to PSA screening and subsequent management of PSA-detected tumours, it is hard to know whether it is even coherent to make statements such as "PSA screening is associated with a 42% rate of overdiagnosis" or "48 men need to be diagnosed after a PSA test to save one life".[1]

We would argue that the interim analysis of ERSPC and prespecified analysis from the Göteborg randomised trial in Europe demonstrates that PSA-based screening can reduce cancer-specific mortality and, as such, our question should really be how to make it work better. A key method will clearly be risk stratification: focusing PSA screening on the men at highest risk of prostate cancer morbidity and mortality will improve the ratio of benefit to harms. As it turns out, the most powerful risk factor is PSA itself.[2,3] Indeed, re-analyses of the European ERSPC trial suggest that

Practice points

The outcomes of PSA screening could be dramatically improved by:

- Avoiding screening in older men (age ≥70 years)
- Use of active surveillance to manage low-risk disease

if men with a low baseline PSA level were exempted from further screening, there would be a dramatic reduction in the number of men screened, biopsied, diagnosed and treated per prostate cancer death avoided.[10]

In summary, the question is should we abandon PSA testing? One answer might be that yes, we should: current PSA testing as it is commonly practised in the US is indefensible. However, we should avoid throwing out the baby with the bathwater and instead grasp the opportunity to implement a more-rational, risk-stratified approach to PSA screening, which avoids testing of men with little to benefit and uses active surveillance to manage low-risk prostate cancer. Such a strategy has the best chance to reduce prostate cancer mortality while minimising overdiagnosis and overtreatment.

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Competing interests statement

Hans Lilja is an inventor and owner of patents WO 0227323, US 2002123616, WO 0193861, WO 9201936, WO 9626442, EP 0635575, and DE 9117047. Andrew J Vickers declares no competing interests

NEWSROUND

Selected reports edited by Janet Fricker

Everolimus plus octreotide improves progression-free survival in advanced NET

→ The Lancet

The addition of everolimus to octreotide improved progression-free survival in patients with advanced neuroendocrine tumours (NETs) associated with carcinoid syndrome, the phase III RADIANT-2 study has concluded.

Advanced NET remains a clinical challenge due to the lack of effective treatment options. Generally, chemotherapeutic drugs are not active in advanced non-pancreatic NET patients, and they have furthermore been associated with substantial toxic effects. Currently there are no treatments for NET tumours outside the pancreas that are approved by the US regulator the FDA.

Everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR), has recently shown antitumour activity in patients with advanced pancreatic NETs. The role of everolimus in NETs of other primary sites or in combination with other drugs, however, has not been explored. In the current study, James Yao, from MD Anderson Cancer Center, Houston, Texas, and colleagues, set out to assess the combination of everolimus plus octreotide long-acting repeatable (LAR) in patients with low-grade or intermediate-grade NETs. The long-acting formulation of octreotide, a somatostatin analogue known to improve hormone-related symptoms associated with NETs, has been shown to prolong time to disease progression in patients with certain types of NETs.

Between January 2007 and April 2010, 429 patients with unresectable locally advanced or distant metastatic NETs were randomised in a 1:1 ratio to receive either everolimus plus octreotide (n=216) or placebo plus octreotide (n=213). Patients were recruited from Australia, Belgium, Canada, Czech Republic, Finland, France, Germany, Greece, Israel, Italy, Netherlands, Slovakia, Spain, Sweden, Turkey and the USA.

Results show that the median progression-free survival was 16.4 months in the everolimus plus octreotide LAR group (based on 103 events) versus 11.3 months in the placebo plus octreotide group (based on 120 events) (HR 0.77, 95%CI 0.59–1.00; P=0.026).

Adverse effects were higher but manageable in the combination arm, including stomatitis (62% vs 14%), fatigue (31% vs 23%), and diarrhoea (27% vs 16%).

"No approved antitumour drugs are available for treating progressive disease in patients with gastrointestinal or lung neuroendocrine tumours, consequently affecting the survival of patients. Therefore, our findings that show the efficacy of the mTOR inhibitor everolimus plus octreotide LAR in advanced neuroendocrine tumours are important," write the authors. "These data support the efficacy of everolimus for the treatment of patients with a broad spectrum of advanced neuroendocrine tumours," they conclude.

In an accompanying editorial, Guido Rindi, from the Università Cattolica-Policlinico A. Gemelli (Rome, Italy), and Martyn Caplin, from the Royal Free Hospital (London, UK), write that while everolimus is undoubtedly an important advance in the management of carcinoid tumours, the toxic effects are "not insignificant" and the survival benefit is unknown. Questions remain, they add, around whether everolimus should be used alone or in combination, before or after other drugs, and for how long. Additional issues include whether the agent has any role in the adjuvant setting and what effect it has on overall survival and quality of life.

■ M Pavel, J D Hainsworth, E Baudin et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 10 December 2011, 378:2005–12

■ G Rindi and M Caplin. mTOR inhibitor therapy for patients with carcinoid. *ibid* pp1978–80

Study supports dual blockade of HER2 growth factor

→ New England Journal of Medicine

The addition of pertuzumab to standard chemotherapy (trastuzumab plus docetaxel) results in an additional six months of progression-free survival in patients with HER2-positive metastatic breast cancer, the CLEOPATRA study has found. The study was presented at the 2011 San Antonio Breast Cancer Conference and simultaneously published online.

Pertuzumab is designed to work in combination with trastuzumab as a dual blockade of the HER2 growth factor, which fuels around one-third of all breast tumours. Both drugs are monoclonal antibodies that bind to the HER2 receptor protein in different locations. Pertuzumab plays an additional role as a 'dimerisation inhibitor' that prevents the HER2 receptor from linking to HER3 and thereby forming a dimer that further signals tumour growth.

In the Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study, José Baselga and colleagues, from the Harvard Medical School and the Massachusetts General Hospital Cancer Center (Boston, Massachusetts), randomised 808 women with HER2-positive metastatic breast cancer in a 1:1 ratio to receive a placebo plus the standard therapy of trastuzumab plus docetaxel (*n*=406), or pertuzumab plus the standard therapy (*n*=402).

Results showed median progression-free survival was 12.4 months in the control group versus 18.5 months in the pertuzumab group (HR for progression or death = 0.62, 95%CI 0.51–0.75; *P*<0.001).

The interim analysis of overall survival, performed after 165 events (43% of the prespecified total number for the final analysis) showed a strong trend in favour of the combination of pertuzumab plus trastuzumab plus docetaxel. No increased rates of symptomatic or asymptomatic cardiac dysfunction were observed in the pertuzumab group compared with the control group. Diarrhoea, rash, mucosal inflammation, febrile neutropenia, and dry skin, however, were reported more frequently in the pertuzumab group, although most of these effects were grade 1 or 2 and occurred during the period of concomitant docetaxel administration.

"Our findings suggest that targeting HER2-positive tumors with two anti-HER2 monoclonal antibodies that have complementary mechanisms of action results in a more comprehensive blockade of HER2," write the authors.

Enrolment is already underway in a new double-blind, randomised clinical trial (APHINITY), they add, testing use of pertuzumab and trastuzumab as adjuvant therapy in patients with newly diagnosed HER2-positive breast cancer.

In an accompanying commentary, William Gradishar, from the Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, writes, "For patients with metastatic breast cancer who have progressive disease, there may be numerous anti-HER2 agents available that could be used in combination or in sequence. In patients with early-stage breast cancer, more effective anti-HER2 agents as adjuvant therapies may translate into metastatic disease developing in fewer patients."

■ J Baselga, J Cortés, S Kim et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *NEJM* 12 January 2012, 366:109–119

■ WJ Gradishar. HER2 therapy – an abundance of riches. *ibid* pp 176–178

Androgen deprivation alone inadequate for high-risk prostate cancer

→ The Lancet

Combining radiation therapy (RT) with androgen deprivation therapy (ADT) reduced overall mortality and disease-specific mortality in men with locally advanced prostate cancer compared to ADT treatment alone, a joint UK, US and Canadian study has found. The study, which was funded by the American NCI, the Canadian Cancer Society Research Institute, and the UK Medical Research Council, reported an interim analysis, planned for publication when two-thirds of final analysis events had taken place.

Until now the question of whether the addition of radiation therapy improved overall survival in men with locally advanced prostate cancer managed with ADT has been unclear.

Between March 1995 and August 2005, investigators from the Princess Margaret Hospital in Toronto, Ontario, Canada, the MRC Clinical Trials Unit in London, UK, and Cardiff University School of Medicine in Wales, randomly assigned 1205 prostate cancer patients to receive either a combination of ADT and radiotherapy (*n*=603) , or ADT alone (*n*=602). Of all patients in the study, 1057 had locally advanced T3 or T4 prostate cancer, while 119 had a T2 tumour with PSA concentrations >40 ng/ml and 25 had T2 with Gleason scores of 8 or higher.

After a follow-up period of six years, 320 of the patients had died. Of these, 175 were in the ADT-only group and 145 were in the combined ADT and radiotherapy group. Altogether at seven years, 74% of patients in the combined ADT and radiotherapy group were alive compared with only 66% in the ADT group (HR 0.77, 95%CI 0.61–0.98; *P*=0.033).

The addition of radiation therapy slightly increased toxicity and reduced health-related quality of life, the investigators found, but few patients suffered serious side-effects as a result of either treatment strategy.

"Our findings suggest that the benefits of the combination of ADT and RT should be discussed with all patients considering a curative treatment approach," write the authors.

The 65–69 Gy dose of radiation therapy used in the trial, they add, while low by modern standards, represented the standard of care when the trial was initiated in the 1990s. "The improvement in survival with the addition of RT to ADT recorded in this trial could be increased again with modern RT dose fractionation," they write.

In an accompanying commentary, Matthew Cooperberg, from the University of California in San Francisco, writes, "This study has provided the strongest evidence to date that androgen deprivation therapy alone for men with high-risk prostate cancer is not adequate. These

patients require an aggressive, multimodal approach incorporating prostate-directed local therapy. However, the crucial question – whether the optimum initial strategy should include radiation combined with androgen deprivation therapy, or surgery followed by selective radiation on the basis of pathological findings and early biochemical outcomes – is still open." The definitive answer, he adds, will come through trials randomising men with high-risk disease to receive surgery or radiation as an initial treatment.

■ P Warde, M Mason, K Ding et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised phase 3 trial. *Lancet* 17 December 2011, 378:2104–11

■ MR Cooperberg. High-risk prostate cancer: treat the prostate [commentary]. *ibid* pp 2056–57

Uncertainty over denosumab's effects on bone metastasis in prostate cancer

➜ The Lancet

Targeting the bone microenvironment with denosumab delays bone metastasis by 4.2 months in men with non-metastatic castration-resistant prostate cancer, the authors of a phase III study have concluded. The author of the accompanying editorial, however, took issue over this interpretation.

Bone metastases are a major cause of morbidity and mortality in men with prostate cancer. Preclinical studies have suggested that osteoclast inhibition might prevent bone metastases, and that one approach might be via a molecular pathway involving the signalling molecule RANKL. Denosumab is a fully human monoclonal antibody that specifically targets, binds and inactivates RANKL.

In the current study, Matthew Smith, from the Massachusetts General Hospital Cancer Center, Boston, and colleagues, set out to evaluate the effects of denosumab on bone-metastasis-free survival in men with castration-resistant prostate cancer with no evidence of bone metastases at baseline, but a high risk of progression based on raised PSA or short PSA doubling times.

Between February 2006 and July 2008, 1432 men, enrolled at 319 centres in 30 countries, were randomly assigned in a 1:1 ratio to receive subcutaneous denosumab 120 mg (n=716) or subcutaneous placebo (n=716) every four weeks until a study event, defined as bone metastasis or death, occurred. Participants underwent bone scans every four months to detect bone metastases.

Results showed that the time to development of bone metastases was 29.5 months for men receiving denosumab versus 25.2 months for men receiving placebo (HR 0.85; P=0.028). However, overall survival was not found to differ between the two groups (HR 1.01; P=0.91).

Rates of adverse events and serious adverse events were similar in both groups, except for osteonecrosis of the jaw, which developed in 5% of patients taking denosumab versus none taking placebo.

"Our finding that denosumab increases bone-metastasis-free survival provides clinical evidence for the important role of the bone microenvironment and RANKL signalling in development of bone metastases in men with prostate cancer," conclude the authors.

In an accompanying commentary, Christopher Logothetis from the MD Anderson Cancer Center, in Houston, Texas, pointed out that the delay in the time to metastases found with denosumab in the study of 4.2 months, was similar to the delay in time to skeletal-related events reported in earlier studies comparing denosumab and zoledronic acid in men with metastatic castration-resistant prostate cancer. It is possible, he adds, that Smith and colleagues might have included patients with undetected metastases in their study.

"If clinically undetected metastases were present at study entry, the investigators did not study the so-called metastasis prevention properties of denosumab, but rather explored the drug's effect on the biological continuum of metastases," he writes.

While the study supports the use of denosumab as an alternative to zoledronic acid, argues Logothetis, it fails to support its broad use as a preventive agent for bone metastases.

■ MR Smith, F Saad, R Coleman et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet* 7 January 2012, 379:39–46

■ CJ Logothetis. Treatment of prostate cancer metastases: more than semantics. *ibid* pp 4–6

Hodgkin's lymphoma: chemotherapy alone delivers greater long-term survival

➜ New England Journal of Medicine

Standard chemotherapy alone is more effective than radiation in keeping patients with limited-stage nonbulky Hodgkin's lymphoma alive long-term, the latest results of the Hodgkin's Disease 6 (HD6) trial has found.

In 1994, Ralph Meyer and colleagues from the NCIC Clinical Trials Group and Eastern Cooperative Oncology Group initiated the HD6 trial to investigate whether ABVD chemotherapy alone (doxorubicin [Adriamycin], bleomycin [Blenoxane], vinblastine [Velbe], and dacarbazine) in patients with nonbulky stage IA or IIA Hodgkin's lymphoma resulted in similar disease control to that achieved with radiation-based therapy, but with fewer deaths from late treatment effects.

Altogether in the study 405 patients were randomly assigned to receive ABVD chemotherapy alone or subtotal nodal radiation at a dose of 35 Gy in 20 daily fractions. Patients in the radiation group with favourable risk profiles received radiation alone, while those with unfavourable risks received two cycles of ABVD followed by radiation therapy.

In an earlier publication, after a median follow-up of 4.2 years the investigators

reported that the rate of freedom from disease progression was higher among patients assigned to radiation therapy than ABVD therapy alone, and that no differences in survival were detected.

In the current publication, investigators report that the latest results show that, at 12 years, 94% of patients who had received ABVD chemotherapy were alive, compared with 87% of patients who were given subtotal nodal radiation with or without chemotherapy (HR for death = 0.50; *P*=0.04).

The difference, say the authors, was due to the number of deaths from causes other than Hodgkin's lymphoma, including second cancers and cardiovascular events. Among the patients randomly assigned to ABVD, six died from Hodgkin's lymphoma or an early treatment complication, while 12 died from other causes; whereas among patients who underwent radiation therapy, four died from Hodgkin's lymphoma or early treatment complications, while 20 died from other causes. Event-free survival was similar – 80% with radiation therapy and 85% with ABVD (HR 0.88; *P*=0.60).

"Our results show that improving long-term survival is less dependent than previously assumed on further reducing deaths due to progressive Hodgkin's lymphoma and instead emphasize a need for treatments that will not lead to deaths from late treatment effects," write the authors. Trial endpoints, the add, should be redefined so that the importance of deaths from causes other than Hodgkin's lymphoma is captured.

In an accompanying commentary David Straus, from Memorial Sloan-Kettering Cancer Center, New York, writes, "Although radiation therapy remains a useful tool for the treatment of some patients with Hodgkin's lymphoma, the challenge is to define the subgroup of patients for whom the benefits outweigh the increased risk of late complications."

Limiting the use of radiation therapy to the fraction of patients who require it, he adds, would make an important contribution to the ultimate goal of maximising the long-term cure rate while minimising late morbidity and mortality.

■ RM Meyer, MK Gospodarowicz, JM Connors et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *NEJM* published online 11 December 2011, doi:10.1056/NEJMoa1111961.

■ DJ Straus. Chemotherapy alone for early-stage Hodgkin's lymphoma. *ibid* published online 11 December 2011, doi:10.1056/NEJMe1113291

Serial FDG-PET/CT predicts chemotherapy outcomes in mCRC

➜ Annals of Oncology

Metabolic response measured by FDG–PET/CT can be used to identify patients with metastatic colorectal cancer (mCRC) who will not benefit from chemotherapy after a single course of treatment, a study has shown.

The fact that tumour shrinkage is known to be the final step in a complex cascade of chemotherapy-induced alterations, suggests that earlier changes in cellular metabolism might be used to predict treatment response. Alain Hendlisz and colleagues, from the Institut Jules Bordet (Brussels, Belgium), reasoned that FDG-PET/CT might be used as a surrogate marker of tumour glycolytic activity, allowing the assessment of tumour response to treatment after just one or two cycles. "The aim of identifying patients with non-responding metastatic disease early is to quickly stop ineffective treatments. This can avoid unnecessary toxic effects and possibly allow alternative more effective therapies," write the authors.

Between November 2005 and October 2009, FDG–PET/CT scans were undertaken on 41 patients with unresectable metastatic colorectal cancer undergoing treatment with a biweekly regimen of chemotherapy (29 patients received chemotherapy as first-line therapy and 11 as second line) both at baseline and on day 14. For the study, metabolic non-response was defined by <15% decrease in FDG uptake in the patient's lesions, or if a lesion was found to be metabolically progressive. The PET-based response was then correlated with the primary endpoint of radiological Response Evaluation Criteria in Solid Tumours (RECIST) and the secondary endpoints of progression-free survival and overall survival.

Results show that the RECIST response rate in metabolically responding patients was 43% (10 of 23) compared with 0% (0 of 17) in non-responding patients (*P*=0.002). Comparing metabolically responding versus non-responding patients, the HR for overall survival was 0.28 (95%CI 0.10–0.76) and for progression-free survival it was 0.57 (95%CI 0.27–1.21).

The authors add that 68% of participants displayed a mixed metabolic response, i.e. both responsive and non-responsive PET lesions coexisted within the same patient, and sometimes even within the same organ.

Patients with exclusively metabolic non-responding lesions or at least one metabolically progressive lesion showed the worst outcomes, with the overall survival of these 10 patients being significantly worse than the remaining 30 patients (HR 4.78; *P*=0.001), as was progression-free survival (HR 2.30; *P*=0.043).

The target sample size of 45 patients was not achieved, write the authors, due to slow study accrual and replacement of the FDG-PET/CT scanner used for the study.

"Early FDG-PET/CT metabolic reassessment after one chemotherapy cycle in patients with nonresectable mCRC is able to discriminate, with a high NPV [negative predictive value], tumors unlikely to respond to treatment," write the authors. If independently validated, they add, the results could have a significant impact on future treatment strategies and design of clinical trials.

■ A Hendlisz, V.Golfinopoulos,C. Garcia, et al. Serial FDG–PET/CT for early outcome prediction in patients with metastatic colorectal cancer undergoing chemotherapy. Published online 23 November 2011, *Ann Oncol* doi:10.1093/annonc/mdr554

How are we doing?

The question that could help drive up standards across Europe's cancer services

Janet Fricker

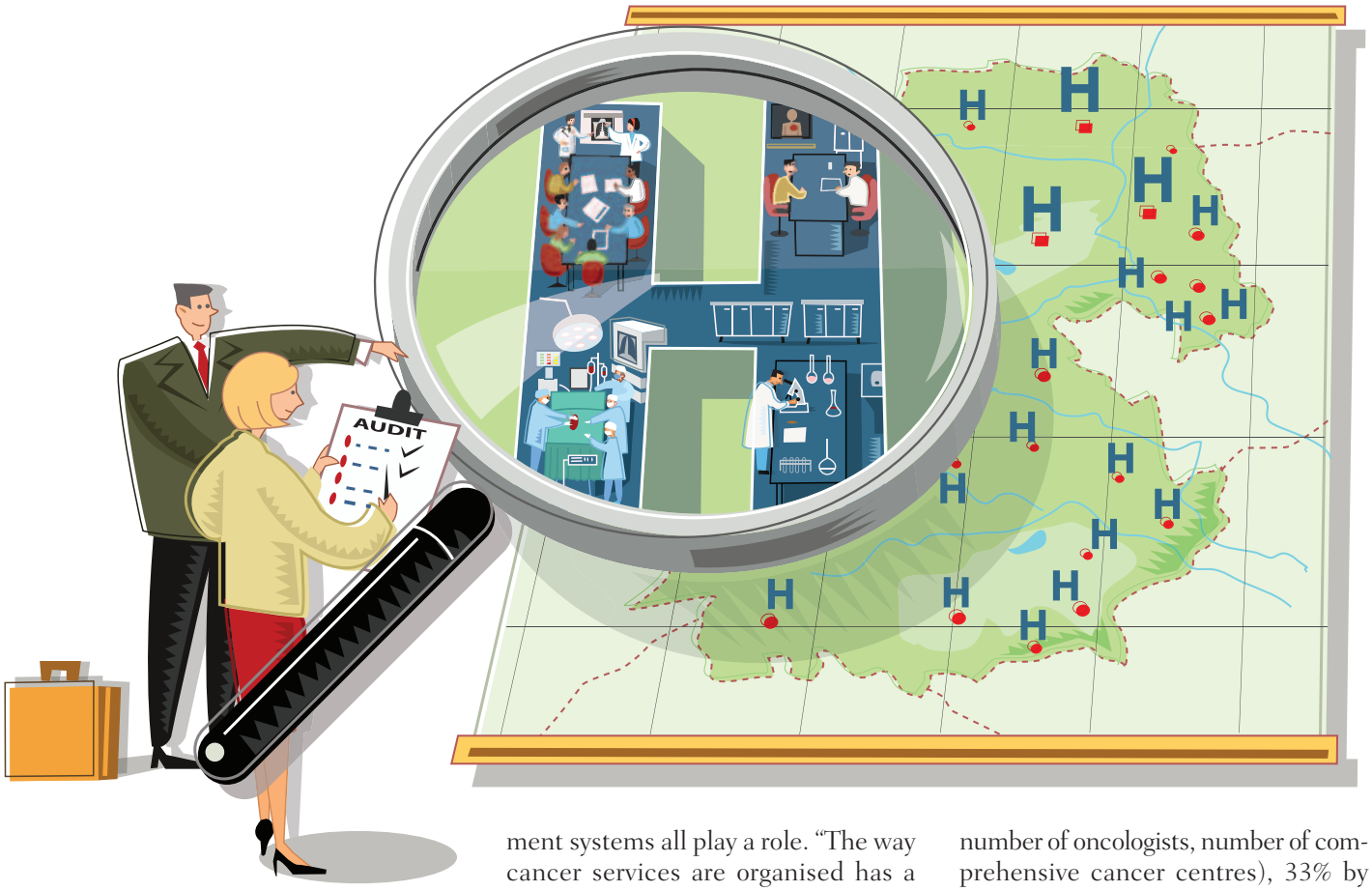
Information on how the performance of individual clinicians, teams and hospitals compares with the best is key to driving up standards in cancer care. In the absence of any lead from national or regional health authorities, ECCO is designing and implementing an audit framework named EURECCA. But could patients' interests suffer to protect professional reputations?

Improving the quality of cancer care through performance feedback to hospitals and healthcare professionals is a topic of growing interest for policy makers and cancer professionals alike. Well-performing health systems make the best possible use of finite health budgets. Monitoring performance across hospitals, health regions and countries also helps identify and spread best practice and can potentially save patients from being treated in places and by professionals who are not up to scratch.

But how can such monitoring be organised in something as complex as cancer care, and who should be responsible? These were two of the questions that were addressed at the 'oncopolicy' session on Inequalities in Cancer Care, organised at the ECCO conference in Stockholm last September.

Chairing the session, ESMO president David Kerr emphasised the need for effective audit systems. "In the bid to improve clinical standards it's really important to develop systems which capture clinical outcomes and make them readily available to citizens," he said.

The urgent need to harmonise cancer care throughout Europe, he added, is underlined by the results of successive EUROCARE epidemiological studies, which reveal persistent differences in cancer mortality between countries. Despite improvements in survival in eastern European countries due to better cancer care and screening, the east–west gap in Europe still continues. The EUROCARE-4 study, which was published in the *European Journal of Cancer* in 2009, covering 42 types of cancer in 23 European countries, showed that five-year relative survival for all cancers ranged from 58% in Sweden to 39% in Poland. Marked survival differences also exist among western countries, with survival in the UK and Denmark for several cancers being relatively low. Other publications on social inequalities and cancer have revealed large differences within western countries in both cancer incidence and mortality. In a study on educational inequalities in cancer incidence done in Turin, Italy, and published in the *European Journal of Cancer Prevention* in 2009, a low level of education was associated with higher risks of upper aero-digestive tract (UADT), stomach, lung, liver, rectal, bladder, central nervous system and ill-defined cancers in men, and with stomach, liver and cervical cancers in women.



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The roots of inequity

In the key note presentation, Kathy Redmond, editor of *Cancer World*, took a closer look at some of the factors that contribute to such variations in incidence and outcomes. Differences in the level of public investment in health care (total health expenditure as a share of the country's GDP), the technology available (such as number of MRI machines), access to specialist doctors and nurses, the number of hospital beds available and reimbursement systems all play a role. "The way cancer services are organised has a huge influence on patient outcomes and has the power to determine whether people live or die," she said.

Redmond referred to the OECD's draft report *'What Explains Differences in Cancer Survival Rates?'* which was published in 2011. Based on extensive data gathering and analysis, together with questionnaires and interviews covering many cancers and countries, the OECD report concluded that around 50% of differences in survival rates can be explained by financial resources (such as access to drugs, number of oncologists, number of comprehensive cancer centres), 33% by process quality (i.e. whether populations have access to services such as cancer prevention, early detection and evidence-based cancer care) and 17% by governance – ensuring the whole system functions as well as possible. Drawing up national cancer control plans, introducing cancer-specific targets with timeframes, developing networks for service delivery, setting in place quality assurance mechanisms and monitoring progress, said Redmond, are all essential aspects of good governance.

"The way cancer services are organised has the power to determine whether people live or die"

"Health professionals and policy makers can use the audit results to identify trends and plan improvements"

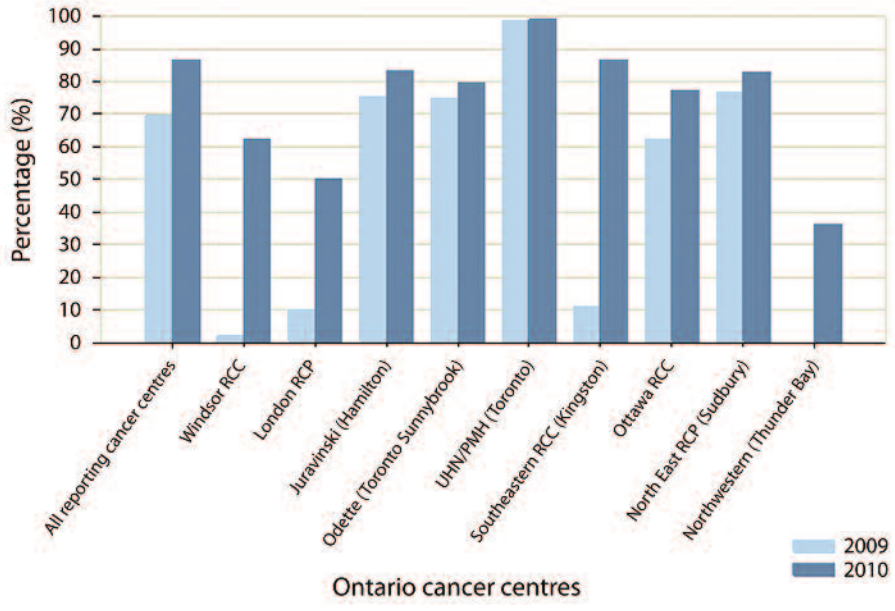
The Ontario example

The Cancer System Quality Index (CSQI) developed and used in Ontario, Canada, offers a prime example of how good governance initiatives can improve service delivery by setting standards for care and measuring their implementation, said Redmond. Launched in 2005 by the Cancer Quality Council of Ontario (CQCO) – a quasi-independent body with a mandate to monitor and report publicly on cancer system performance – in partnership with Cancer Care Ontario (CCO) – a public (provincial) agency responsible for continually improving cancer services – CSQI now undertakes an annual audit reviewing the province's progress against cancer.

The audit reports on 36 evidence-based quality measures covering every aspect of cancer care from prevention to end-of-life issues. Measurements include the percentage of liver and pancreatic cancer patients whose surgery is done at designated referral centres, the percentage of patients who have their care discussed at multidisciplinary case conferences, and the percentage of patients undergoing a radical course of radiotherapy who receive the gold standard intensity modulated radiation therapy. Other aspects covered by the audit include waiting times between cancer surgery and adjuvant chemotherapy, the percentage of patients treated according to guidelines, and patient satisfaction with care, including their satisfaction with the emotional support offered by healthcare professionals, continuity of care and respect for their preferences.

Health professionals, cancer organisations, planners and policy makers can use the web-based CSQI audit results to identify cancer trends and plan improvements to the service. A significant rise in the proportion of lung cancer patients being screened for symptoms using the Edmonton Symptom Assessment System (a screening tool rating the severity of nine symptoms commonly experienced by cancer patients) is one example of an improvement that has been directly attributed to the CSQI. In 2008, when CSQI first began reporting on the use of ESAS, 43% of lung cancer patients were screened using the tool, but two years later this had climbed to almost 60%, with some cancer centres reporting that over 85% of patients had been screened. "The CSQI process helped highlight the value that patients place on the ESAS screening tool as a crucial component of their care," explained a representative of CSQI later to *Cancer World*.

USE OF INTENSITY-MODULATED RADIOTHERAPY



Patients in Ontario view performance data telling them how safe, effective, accessible, responsive, efficient, equitable and integrated their cancer services are (www.csqi.on.ca/ click on 'Quality Dimensions'). Many of these are available on a hospital by hospital basis. The example here shows what percentage of head and neck cancer patients treated with a radical course of radiotherapy have access to the gold standard intensity-modulated radiotherapy (IMRT) at each cancer centre

The variability of cancer incidence and mortality within and across European countries shows there is an urgent need for governments on this side of the Atlantic to follow the Ontario example, and establish clearly defined standards of care for cancer patients and then monitor and improve their delivery, Redmond argued.

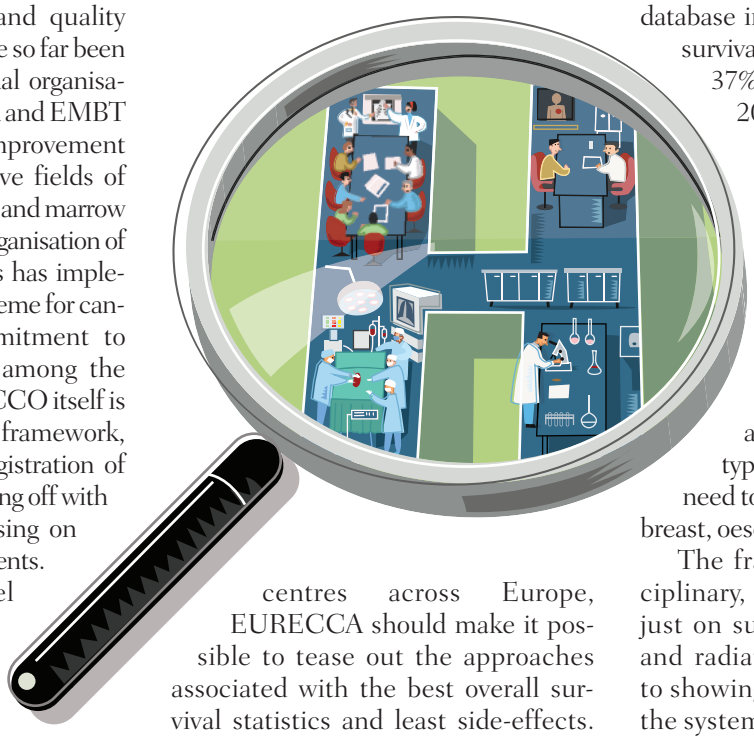
EURECCA – A NEW QUALITY FRAMEWORK

In the absence of the sort of public initiatives represented by the CSQI audit in Ontario, issues of audit and quality improvement in Europe have so far been largely left up to professional organisations. Bodies like EUSOMA and EMBT have introduced quality improvement initiatives in their respective fields of breast cancer care and blood and marrow transplantation, while the Organisation of European Cancer Institutes has implemented an accreditation scheme for cancer centres, with a commitment to continuous improvement among the assessment criteria. Now ECCO itself is introducing a new quality framework, EURECCA (European Registration of Cancer Care), which is kicking off with some core countries, focusing on care of colorectal cancer patients.

Speaking in the panel discussion, Cornelius van de Velde, president of ECCO, and a cancer surgeon at Leiden University Medical Centre, in the Netherlands, described how EURECCA will work, and outlined ECCO's plans to develop it into an infrastructure where every cancer treatment centre across Europe can upload information about tumour characteristics, treatments, and patient outcomes onto a single site.

"The aim is to first identify best practice, and then use this information to shape guidelines that can spread the word throughout Europe. The approach can also provide performance feedback to individual centres," explained van de Velde, speaking later to *Cancer World*.

By inputting data on the treatment and outcomes of multiple patients from



centres across Europe, EURECCA should make it possible to tease out the approaches associated with the best overall survival statistics and least side-effects. Data from large numbers of patients would allow comparisons of 'like with like'. "It's only then that you can establish that the differences observed are due to treatments or techniques rather than confounding factors such as the age, gender or comorbidities of patients," said van de Velde.

Nine independently founded, up and running, national colorectal audit registers have already committed to participating in EURECCA (see table).

A TRACK RECORD OF IMPROVEMENTS

These established systems offer an insight into the enormous gains that can be achieved through audit. Take the example of Denmark – after the introduction of a national colorectal cancer database in 1994, the five-year overall survival for rectal cancer rose from 37% of patients in 1994 to 51% in 2006. A similar story emerges with the Norwegian colorectal cancer registry, where five-year survival for colorectal cancer patients increased after its launch in 1993, from 55% to 71%.

If EURECCA is to succeed in its aim to roll out the audit framework to address other solid tumour types, additional registries will need to be developed for instance in breast, oesophageal and gastric cancers.

The framework will be multidisciplinary, including information not just on surgery but also on medical and radiation oncology. In addition to showing overall survival statistics, the system could also flag up specific complications of surgery or side-effects associated with drug treatments. "Cancer is like a war situation – not only do many people die from the disease, but survivors experience enormous suffering. All these data

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

"Established systems offer an insight into the enormous gains that can be achieved through audit"

"If patients are to participate in the decision-making process, there is a need for full transparency"

could be represented in the analysis, creating the possibility for identifying strategies that prevent problems," says van de Velde.

Patient's views on treatments and the approach of health staff may also eventually be incorporated into the mix. "The system could identify reasons why patients perceive one centre to be better than other, and indicate changes that could be implemented to make services more user friendly."

EURECCA offers the potential to transform the development of cancer guidelines and allow them to represent 'real world' patient situations. "Traditionally guidelines have been based on the beliefs of charismatic leaders backed up by clinical trials," explains van de Velde. "Incorporating the EURECCA data would allow guidelines to become much more evidence based and include data on patients who are normally excluded from clinical trials, either because they're too old or have comorbidities."

Ultimately, he adds, the hope is that EURECCA will offer an online system giving individual cancer centres access to their own confidential data, which would also allow them to compare their performance with other anonymised centres across Europe. "The approach is like giving health professionals a mirror. It allows them to take a good look at themselves and identify how things might be improved."

Where centres are found to be underperforming, mechanisms will need to be introduced to help improve practice, and also identify health professionals who need retraining. But key to the success of the initiative, van de Velde insists, is that there should be no public naming, blaming and shaming of individuals or institutions.

A patient's right to know

The EURECCA initiative was given a very enthusiastic reception at the meeting, but many felt that clinicians and hospitals do need to be held accountable for performances.

"With people's lives at stake, professional sensitivities need to be put to one side," said Redmond. If patients are to actively participate in the decision-making process, added Regine Hagmann, from the German Cancer Information Service, there is a need for full transparency. How can they make informed decisions about where to go and who to trust if outcome information is all anonymised? Survival statistics are the ones patients need most of all, commented Stella Kyriakides, chair of the ECCO Patient Advisory Committee, and these should be publicly available.

Redmond offered an example from Italy to show that making quality-related information publicly available does help pull up standards. A leading Italian daily paper, the *Corriere della Sera* now publishes data for every hospital in the country, showing the number of cancer patients that they treat annually, broken down by cancer type. The figures are collected by the health authorities, but it is the newspaper that presents them on their own website (www.corriere.it/salute/sportello_cancro/), in a way that is easy to search – you just click the relevant body part to identify the cancer of interest, and then click a region on a map of Italy for details on every hospital in the region. The initiative led to patients identifying the centres that performed only a few procedures annually and 'voting with their feet' to avoid them.

The natural competitive instincts of countries, healthcare regions and individual clinicians can all be leveraged to the patient's advantage, said Kerr. When the EUROCARE survey identified the UK as a country with poor national cancer survival figures, it shamed the former Prime Minister, Tony Blair, into launching the National Cancer Plan.

In the UK the process could soon be taken one step further. The White Paper 'Equity and Excellence: Liberating the NHS,' published in October 2010 by the Department of Health, is looking to create a system that will allow clinical teams to see meaningful, risk-adjusted assessments of their performance against their peers. The Paper plans for the information to be placed in the public domain, allowing patients to check on the care results of individual doctors before choosing their provider.

Recording the five-year survival rates of individual clinicians, said Kerr, is likely to result in the creation of league tables in the UK. "The professional pride of clinicians finding themselves at the bottom of such tables would doubtless be responsible for improving care, which would drive up standards," he said.