European School of Oncology
Learning to care

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Education & knowledge through people & facts

Mahasti Saghatchian

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Framing the argument over futile care

Kathy Redmond ■ EDITOR

We "overdiagnose, overtreat and overpromise". This was the claim made by numerous newspaper headlines in response to the *Lancet Oncology* report last September on delivering affordable cancer care. While we do need open and frank discussions about how to curb the spiralling costs of cancer care, it was unfortunate that the media focused so heavily on the cost of futile treatment in the last weeks of life, blaming it all on a culture of excess. This sparked reports that patients would be denied potentially life-prolonging treatments purely on the basis of cost and generated fears that patients might be abandoned in their final months.

There is no doubt that we do overtreat and overpromise in the advanced cancer setting. We know, for instance, that many patients receive cancer treatments in the last weeks of their life, and that some of these treatments have no reasonable chance of helping the patient and are associated with severe side-effects that can lead to hospitalisation and even death. We also know that receiving chemotherapy is associated with a delay in referral to palliative care. But blaming this on a culture of excess is too simplistic.

Making the right decisions in later stages of advanced cancer is difficult for doctors and patients alike. It is often impossible to predict how long a patient will live, and while we have an increasing number of therapies to choose from, we don't yet know enough about who stands to benefit and by how much. There can be a huge disconnect between the expectations of patients and families and those of clinicians, adding to the difficulty of conducting honest conversations with patients about their prognosis, treatment options and end-of-life preferences.

There are no easy answers. But could we be making things harder for ourselves by posing options in terms of a choice between either fighting cancer or optimising quality of life? An emerging body of evidence shows that integrating palliative care into the mainstream care of cancer patients not only improves their quality of life, but might even help them live longer. Early involvement of palliative care specialists has also been shown to cut down on futile medical interventions and help families cope better with their loss of a loved one.

ASCO is now recommending that patients should be offered concurrent palliative care and standard cancer treatments early in the course of their advanced cancer journey. This is in line with efforts to stimulate meaningful interaction between mainstream oncology and palliative care specialists that ESMO and other European professional bodies have been pursuing for some time. However, progress so far has been infuriatingly slow.

Greater integration of palliative care requires changes in the way we organise care and train clinicians. We need to get on with this as a matter of urgency. If we fail to take a lead in addressing shortcomings in the way we care for patients with advanced cancer, the simplistic arguments about a wasteful culture of excess could win, and patients will be the losers.

Mahasti Saghatchian:

pioneering a quality mark for Europe's cancer centres

Marc Beishon

She's an internationalist, she believes in quality control and she's not afraid of a bit of friction. Who better, then, to lead the project to define standards for Europe's cancer centres and sort the centres that meet them from those that need to do better?

In Europe, if a hospital chooses to call itself a comprehensive cancer centre – either as a standalone oncology facility or a department within a general hospital – it is free to do so in most countries. Like other terms that convey quality and authority, such as 'university hospital' or 'institute', the public might assume that rigorous standards are applied by authorities to guarantee that status. But while there will almost certainly be many general hospital regulations about issues such as infection control, waste management and radiation exposure, patients would be hard pushed to find out just how good their cancer care is, or how much a centre is contributing to education and research.

"It's not enough for a cancer hospital simply to say they are one of the top centres – they need to show they are," says Mahasti Saghatchian, chair of the accreditation and designation group at the Organisation of European Cancer Institutes (OECI). "Just because a centre has many top oncologists does not automatically mean that patients are always getting the best treatments, or that they are participating as well as they could be in research programmes. Among the key aims of the OECI accreditation project is for centres to benchmark themselves against others and address weaknesses, and also to recognise where they can work together in research by building trust in their capabilities. And not least we hope it will also be a sign of trust for funders."

As Saghatchian acknowledges, the accreditation tool for cancer centres was some time in gestation – it was six years in preparation before launching in 2008, and the first round of centres finally received accreditation in 2010. A further aim – that of designation – has been added to categorise locations as a unit, centre, research centre or comprehensive centre.

Founded in 1979, the OECI has been around a long time, but it had mainly been a relatively informal networking group for cancer centre directors in western and eastern Europe, says Saghatchian. "That changed when, in 2000, Ulrik Ringborg of the Karolinska in Stockholm, and Thomas Tursz, then director of the Institut Gustave Roussy in Villejuif, Paris, became OECI presidents and developed a vision for comprehensive cancer centres in Europe, in particular to integrate research with care and develop translational research networks."

The accreditation project is part of this vision, which is similar to the comprehensive cancer centre structure in the US, but with more of a focus on all

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aspects of cancer management rather than a research network. But, as with any new measure, it has taken a lot of 'selling', particularly as there is a substantial commitment in time and fees. "It's certainly been one of the most controversial projects I've been involved with in oncology," says Saghatchian. And the OECI has had to find the initial resources to develop the standard, recruit auditors and so on, before fees from centres can make the programme self-funding.

"What has really helped get it off the ground is its incorporation as a work package in the Eurocan-Platform, the EC-funded 7th Framework Programme project that aims to unite 28 European institutes in a translational research effort," says Saghatchian. "It's one of the commission's networks of excellence for research and we managed to get accreditation in, very much as a cherry on the cake – and all the participating centres will also have to undergo the audit to take part in Eurocan."

Not all the participants in Eurocan are hospitals – some are research institutes – but three of the first six OECI accredited centres are Eurocan members, namely the Netherlands Cancer Institute (NKI), the Christie in Manchester, and Valencia's cancer centre (the other three are the Portuguese oncology institutes in Lisbon, Porto and Coimbra). Other centres are in peer review, and applications are pending for a major expansion, including heavyweights such as the Institut Gustave Roussy (IGR) (Saghatchian's own employer), King's Health Partners in London, Cambridge Cancer Centre, Institut Curie in Paris and the German Cancer Research Centre (DKFZ) in Heidelberg.

But what could mark a major breakthrough is a decision by Italy's ministry of health to fund all ten of the country's comprehensive cancer centres to go through accreditation. "We are starting to see governments and health ministries interested in the project. If they want to accredit their oncology effort, say as part of a national cancer plan, the

Clinical care and infrastructure have as much weighting as research in the standard

OECI is the only international organisation able to do it," says Saghatchian.

As she adds, the OECI and EurocanPlatform are also now partners in the second European Forum on Oncology, taking place in May in Berlin, where a key aim is to discuss the 'bottom up' structural reforms that the OECI is promoting in European oncology, including a workshop on 'organisational concepts for comprehensive cancer centres'.

Although much of the initial impetus for the accreditation is coming from the translational research side, Saghatchian stresses that the role of cancer centres in all aspects of health improvement through oncology is very much part of the vision. Clinical care and infrastructure have as much weighting as research in the standard, which itself is not set in stone – it is currently being revised to focus on factors that can really differentiate practice. In any case, as Saghatchian adds, accreditation only lasts four years, after which any centre must go through the process again.

There are now moves to extend the project as an 'umbrella' to include accreditation for specific cancer centre departments such as breast units (where there is progress on a pan-European scheme for certification from EUSOMA and other parties), and also prostate cancer care, where there is currently very little to speak of in comparative tools. "We are discussing the idea of adding prostate units as an annexe to the OECI tool, which would take probably an extra day in the review process to carry out," she says. "But it's important to note that we are not going to duplicate professional guidelines, such as how to carry out surgery or apply systemic therapy. We are taking a global view of a centre and its activities, resources and outcomes."

The accreditation work is one part of Saghatchian's role at IGR, where she carries out two jobs: executive in charge of international and European affairs, and a medical oncologist in the breast cancer unit. It's more or less an equal split between the two roles, and an unusual arrangement in European oncology, especially for someone in mid-career. But such portfolio positions are likely to become more prevalent in cancer centres precisely because of the need to have specialists and not administrators in the frontline of networking and benchmarking work, to improve research collaboration and care outcomes.

Saghatchian was born in Iran before the Islamic revolution, and although her parents were not involved in politics they chose to leave for France with their two daughters when it became apparent that opportunities for girls under the new regime after 1979 would be limited. "I chose to study medicine partly because I had important family figures who had been in medicine – my grandmother was one of the first Iranian women physicians – and also because I wanted a profession I could do anywhere in the world."

Her sights were set firmly on entering a specialty with a

In the genes. Saghatchian's grandmother, Maliheh Dadgaran-Pessian, took a lead in driving through changes in Iran's medical profession when she became one of the country's first women physicians

Clearing the hurdles – the Christie experience

The Christie in Manchester, UK, one of Europe's largest cancer centres, was among the first to receive OECI accreditation as 'comprehensive'. Chris Harrison, medical director, says the attraction of taking part is the wide benchmark it offers to compare against others in Europe. "We have a national peer review programme for cancer, which focuses on care quality, but the OECI review covers not just clinical care but also our teaching and research, and the degree to which they are integrated – that being the hallmark of a comprehensive cancer centre.

"We had to assemble a portfolio of information for the OECI audit team, which comprised people such as another cancer centre director and a specialist nurse, and they visited us for two days, meeting our executive team, doctors and staff, and they went into real depth on a number of areas. They identified several things we need to move further with, such as a fully electronic patient record system, and a better ability to publish outcomes of care. We also had to explain why we don't have direct responsibility for screening and prevention, which we do though support through our regional network. As a large, mostly single-site centre, including basic science, and with links to a local academic system, we were able to give the reviewers a good account of our teaching and research structure."

Harrison adds that, given the UK's relatively worse outcomes, which are thought to result from later presentation, the OECI's move to gather more comparative data on outcomes across European centres will be particularly valuable, and could help develop the role of centres in prevention and early detection.

He is also a co-opted member of the OECI board, and notes that a centre such as the Christie needs to be involved at a European level, given the increasing movement of patients and staff across borders, the impact of European legislation and the need to reach a critical mass for research through programmes such as the EurocanPlatform. "I have also chaired two reviews myself, at Jules Bordet in Brussels and the NKI in Amsterdam, and made other visits on behalf of Mahasti Saghatchian, to Estonia, for example. It is apparent that the OECI accreditation is a catalyst for centres that want to improve their care." Saghatchian, he adds, has been the driving force to getting the accreditation group established.

strong and growing research component, and she quickly rejected fields such as cardiology in favour first of immunology, and then oncology, but she candidly admits that, even relatively recently, she found medical oncology lacked much research promise, comprising as it does mainly chemotherapy. "If I'm honest, really the most gains have been in surgery and radiotherapy in my field of breast cancer – it is only lately that we have personalised molecular therapies and I think medical oncology's time is very much to come in breast cancer. In our tumour board meetings at IGR we have a lot of discussion about surgery and radiation choices, but it's always the same adjuvant therapies – there has not been much change, apart from Herceptin."

A case in point for the future is her own research for a PhD. "I have been looking at breast cancer patients who relapse late – half of the 30% who relapse do so after five years, but all trial work is on short-term rates, up to five years – no one is looking at how to prevent late relapses, as we don't understand them and can't select those patients and treat them accordingly. I've been doing microarray profiles to see if we can find predictive markers for relapse and targets for treatment. It's almost finished – we have identified a set of 214 genes that predict late recurrences and a gene that is overexpressed."

Saghatchian's PhD supervisor is Laura van 't Veer, the pioneer in gene expression profiling, and the work is exactly the kind of translational research that demands more cooperation among European centres, she says. It is why advocates of TRANSBIG's MINDACT adjuvant therapy profiling trial are so enthusiastic – not about the primary question so much, but the 'goldmine' of frozen tissue samples from 6000 patients and the collection of expression data from 44,000 arrays. "It's why we participate in MINDACT at IGR, but it has been the other main controversial area for me, along with the accreditation tool. There is almost a religious divide between those who believe in the Mammaprint gene profile and those who don't, but for me it's not about belief but about science. Every day we use markers that have not met full approval in an evidence base – but that shouldn't prevent us from going on with the research."

Saghatchian spent five years as a medical oncology fellow at IGR, before moving to an academic general hospital in Paris, the Georges Pompidou

"There is little information for patients about where the best care and specialists are"

European Hospital, where she looked after lung cancer patients, among other roles, for two years. "I found that oncology away from cancer centres can be a really different job. There can be a fear of cancer patients and a misunderstanding of what's possible in the emergency unit, for example. In day-to-day care we didn't have palliative care teams or pain specialists, and no molecular profiling – that had to be sent elsewhere – and it is impossible to do research when you don't have enough patients. My own expertise suffered because I didn't see rare cases, and if I did I might not have known how to treat them well."

It is highly unlikely that such hospitals could meet OECI criteria, but Saghatchian says that publicity for centres that do become accredited may help patients and primary care doctors make more informed referral decisions. "There is little information for patients about where the best care and specialists are. This isn't just true for oncology of course but for all specialisms – you often go to where you are told to go or where your friends went." In hospitals that have a cancer department there is a tendency also for surgeons to refer patients there rather than to external cancer centres, which is part of the long-standing discussion about the primacy of organ-based practitioners versus multidisciplinary oncology.

Many large general hospitals do have comprehensive cancer centres, and Saghatchian acknowledges the extra resources that can be brought to bear from other specialists. She is keen to stress that any hospital with a cancer centre is free to seek accreditation, but concedes that some smaller ones will be content with national systems, and are not seeking international recognition. Unicancer, the French programme, and other national initiatives are beginning to apply rigorous audit – the NHS in England, for example, has started local audit of colorectal, lung, oesophago-gastric and head and neck cancers, in some cases at the level of individual units.

"But it is also the case that national systems such as ours in France are applying only basic minimum standards for oncology in most smaller hospitals, such as the number of breast operations that need to be done. It's why cancer plans tend to fail in my view – politicians often won't make the tough decisions to close oncology departments that do not meet higher standards."

Saghatchian returned to IGR in 2003, but asked director Thomas Tursz for a position that would not be a full time clinical post. "It was partly because oncology was a bit dull and also tough with so many dying patients – I didn't want to suffer from burn out – but it was also about my personal history as a foreigner. Even at medical school I had run a small society for foreign students and had the feeling that international exchange work was a great way to keep yourself fresh and learn more. Thomas wanted someone to develop international affairs and he created the job for me."

As she points out, it is perhaps surprising that more cancer centres do not have similar roles. "None of the other centres in France has someone like me I believe, but it is very important for IGR to have a unit to attract funds for research programmes and be a voice for the centre."

Her half-time post relates directly to the aims of the OECI accreditation project, which is why she has been so keen to champion it in Europe, although there is an element of competition. "At IGR we were finding it hard to get funding for academic research, but now we are much more organised about the way we respond to 'calls' for

"Politicians often won't make the tough decisions to close oncology units that do not meet higher standards"

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European framework projects, for example. In the 7th Framework Programme we are involved in more than 20 calls that are now a major source of income. Before it was just an ad hoc effort by a few staff who knew what to do."

That may be competing with other centres to some extent, but Saghatchian adds that new partnerships are forged within programmes such as TRANSBIG and CHEMORES. "In the CHEMORES lung cancer and melanoma FP6 project, for example, we didn't know some of the other partners well at all. Now it's finished, a lung project has emerged that's independent and wouldn't have happened without the original programme. Basic scientists tend to know each other around the world, but in translational research, clinicians often don't know who best to work with and who has the best infrastructure."

Saghatchian considers that IGR now pretty much meets the OECI criteria for a true comprehensive cancer centre, but it's taken a lot of work, driven especially by previous director Tursz. "We have national quality assessment and benchmarking of French centres through Unicancer, which checks aspects such as multidisciplinary care. Five years ago, only 70% of breast cancer patients were discussed by multidisciplinary teams – now it's 100%. Thomas also changed department heads who weren't doing well, made IGR attractive for young people to do PhDs and to work abroad, and not least we had a major interior refurbishment six years ago – although the outside is still rather grim." Lex Eggermont, the current director, was a brave appointment, she adds, as he is Dutch, but has made an impact with excellent financial management and has further boosted IGR's international standing.

The experience so far with OECI accreditation, says Saghatchian, is that standards of care – such as the percentage of patients seen by multidisciplinary teams – are relatively straightforward to compare among centres. "It's harder to look at research and education programmes, and also the integration of research with care. The cultural and organisational differences between countries are also big challenges of course, and we have no plans to work in any language other than English."

Establishing definitions and questions for collecting data that avoid misunderstandings and compare like with like has taken a lot of effort, even with seemingly simple factors such as the number of patients treated, and the resources and infrastructure in place.

"And one of the main issues that the project has revealed is just how difficult it is for centres to collect data about themselves – we've realised that senior management often do not have a clear picture of

"We've realised that senior management often do not have clear picture of what exactly is going on"

THE ACCREDITATION PROCESS

The accreditation component of the OECI's programme is a quality standard for cancer centres, and was developed in two rounds of pilots before the first version was launched in 2008. Apart from membership of the OECI, cancer centres are asked to make a considerable commitment to the programme, including a fee of €30,000 for the larger organisations. Accreditation lasts four years.

The accreditation process involves completing a self-assessment questionnaire and attaching a long list of supporting information, before the audit team conducts its review.

The designation part of the programme is a spin-off designed to help organisations of similar standing form networks with each other, and was also piloted and validated. The four categories are: cancer unit, clinical cancer centre, cancer research centre and comprehensive cancer centre (an accreditation package for the third category, research centres, is yet to be developed).

The quality standards and a user manual, as well as newsletters and other information, are available at oeci.selfassessment.nu

Party time. With nine-year-old son Olivier, all dressed up and ready to dance the night away, Dubai, New Year's Eve 2011

what exactly is going on in their organisations. One very tough question is, 'What is your research budget?' But the data are often not centralised and you do wonder how they manage without crucial information like this. And the bigger the institution, the more difficult it can get."

A case in point is King's Health Partners in London, which is currently in progress with its OECI application. "It's definitely harder for centres such as King's to collect data because it has multiple sites, where people may not be measuring the same things, or in the same way." Meanwhile an example she cites where reviewers found research and clinical care integration is not as strong as it could be is at Helsinki University Hospital. "They did not find a specific organisation for translational cancer research. But we are finding that centres welcome the review process because it does help them to highlight areas that need development and gives them evidence to ask for more resources."

For the time being, a country that will be notable for its absence in the OECI accreditation programme is Germany, except for DKFZ in Heidelberg, which is a EurocanPlatform member. Saghatchian explains that is mainly because of Germany's history of treating cancer by organ specialists, with all the controversy that has created. "The German Cancer Society has its own certification strategy and organisation, OnkoZert, for progressively addressing the issues rather than tackling them head on. The German problem is specific to the country and we won't do much there in next few years except for a pilot."

In fact, following a move to establish second opinion services for testicular cancer, an increasing number of prostate cancer units have been certified in Germany – as many as 68 by last year. This experience is feeding into work by ESO and OECI on establishing a prostate unit standard (see also Systems & Services, p 58). "There is certainly a huge need. Even at IGR we don't have a formal prostate unit and we would welcome guidelines and care pathways for prostate cancer."

"I'm an oncologist, I work with patients who have breast cancer"
"Ah, that must be hard."
"No, no, no, people should know the truth! No it's not hard, it's incredible! We need to open a window onto these amazing lives that I mix with every day"

Extract from the catalogue to an exhibition of paintings of women touched by breast cancer, 'La Vie en Plus', which was a collaboration between artist Thierry Dussac and Mahasti Saghatchian with the Institut Gustave Roussy. This is the portrait of Mahasti

In the current revision of the accreditation, Saghatchian says some basic standards will be removed because they are common to all. 'We are fine-tuning the quantitative data to develop indicators that show differences. For example, one of the ambitious indicators we want is to compare survivorship between centres – the outcome data. That means collecting the same data on patients at the same time for their disease, including follow-up. At present we can only look at country registry data across Europe – but that doesn't show where a patient was treated."

Saghatchian feels the OECI has taken a lead in driving forward the benchmarks for improving outcomes in Europe, and she has certainly brought a great deal of passion to her European work. She expresses frustration that other organisations do not seem to have the same focus. She would like to see the EORTC, which organises international cancer trials, continue its modernisation towards translational research; ECCO, she says, needs to articulate its vision better; and advocacy groups should be pushing much harder for breaking down regulatory barriers, such as in tumour collection. "We are trying to launch a neo-adjuvant trial where we want to collect samples before and after giving Herceptin – but as there is no immediate benefit we can't do it. It's one reason why progress in personalised medicine is slow." She would also like to see the research community become much more imaginative in using the talents in other fields, such as mathematics.

Another factor slowing progress, she adds, is a chronic under-use of IT – "I'm amazed we don't do more with tools such as iPhones and email. Sometimes I get the feeling people are happy to slow down the pace of work because of fear of overload." That applies at IGR as elsewhere – and the use of modern IT is one of the OECI standards – but otherwise her centre is now doing better than ever, she says, with its recent refurbishment and improved efficiency leading to more funding. "The French health system though is slipping in quality and access and we are facing even more pressure from the pharmaceutical industry. We've had some drug scandals, such as with a diabetes pill, which is causing mistrust towards doctors."

Some less pressurised aspects of her work at IGR included helping to produce a book of paintings of breast cancer patients, and a study on the impact of using beauty treatments on self-image and depression, carried out with l'Oréal. And she has not forgotten her roots, setting up a link between IGR and MAHAK, an organisation in Iran that helps children in the country receive cancer treatment.

Above all, the theme that best sums up her approach is networking and movement. "I love the European work – you learn so much when you move around and people should definitely aim to work in other countries."

Perhaps the OECI accreditation process will introduce a measure of foreign personnel and movers in future.

Recent trials in osteosarcoma
and their implications for future studies

Osteosarcoma is a rare cancer and most oncologists will not come across it very often. In this overview a sarcoma specialist presents current evidence on the best way to manage osteosarcoma patients, and looks at what has to be done to improve prognosis in this disease, where survival rates have not changed since the early 1980s.

Osteosarcoma is a malignant mesenchymal tumour producing osteoid. It is a rare type of cancer, with an incidence of only 2–3 per million per year, occurring mostly in adolescence and affecting more males than females (in a ratio of 1.4:1). In adolescence it usually occurs in the metaphyses of long bones, usually around the knee. The problem we face is with metastases, which occur in about 90% of patients. Both primary and later metastases usually occur in the lungs and sometimes in bones, but rarely elsewhere.

In terms of imaging methods, the osseous compartment it still best visualised by conventional X-ray. This is the method of choice for bony alterations. MRI is also needed to look at the primary tumour, showing the amount of marrow involvement, the soft tissues, and the relationship to vessels and nerves, providing essentially all the information the surgeon needs. Imaging for systemic spread depends on location: X-ray for the chest and bone scans for bones. But the most valuable imaging method is a CT scan of the chest.

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, Stefan Bielack, from Stuttgart's Olgahospital, in Germany, provides an update on recent clinical trials in osteosarcoma and the implications of the findings for future studies. Bruce Morland, from the Birmingham Children's Hospital in the UK, poses questions arising during the e-grandround live presentation.

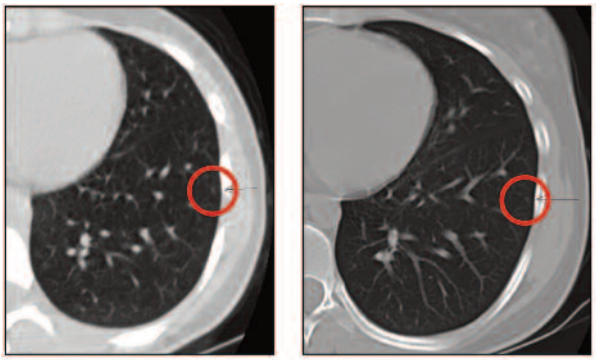
The presentation was summarised by Susan Mayor.

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

This CT scan shows initial staging in a patient who has a very tiny lesion; it is the only lesion and the rest of the CT scan is normal. At the end of chemotherapy, there was no change. How should we treat this patient? We will come back to this later.

The table below shows results of surgery in several series of patients with primary metastatic osteosarcoma, comparing those who achieved surgical remission with those who did not. In most series, patients who did not achieve a surgical remission, or whose metastases were not removed, did not usually survive for five years. The situation is similar at recurrence. Patients who do not achieve a surgical remission rarely become long-term survivors; patients who do achieve a surgical remission have a reasonable chance of long-term survival. Complete surgery is necessary for long-term survival.

TREATING A PATIENT WITH A SMALL LESION



Initial staging | End of chemo

A single small lesion in the chest visible on CT scan before chemotherapy was still there after the treatment ended. What now?

Source: Slides courtesy of Prof P Winkler, Olgahospital Stuttgart, Prof I Arlat, Katharinenthospital, Stuttgart and Dr M Schilling, Radiologische Praxis, Stuttgart-Bad Canstatt

Identifying metastases

How well can CT tell us whether metastases are present? A very interesting joint Italian–Scandinavian study looked at 51 osteosarcoma patients with suspected metastases on CT scan. At surgery it was found that 39 had metastases while 22 did not (*Ann Oncol* 2001; 12:1601–04).

How can we tell whether small nodules might be metastases? Radiologists always tell us that small nodules that do not change after chemotherapy cannot be metastases, or that if they disappear they are not metastases. What the Italian–Scandinavian study found was that changes in nodule number and size during chemotherapy did not indicate whether patients really had metastases. The only factor that was significant was that a lesion smaller than 5 mm was less likely to be a metastasis than larger lesions (P=0.035). But ten of 25 patients with nodules <5 mm had metastases. So if a patient has a small nodule on CT scan, even if it is only one, and even if it does not change during therapy, it can be a metastasis.

Another study from New York looked at 28 patients who underwent 54 thoracotomies. Preoperative CT scans in all the patients showed 183 suspected nodules. At surgery, the surgeons found 329 nodules, 209 of which were osteosarcoma. This means that a CT scan had underestimated the number of lesions in 19 of the 54 patients who were referred for scanning – about one third (*J Pediatr Surg* 2006; 41:200–206).

My take home message for lung metastases, both primary and secondary, is that there is no perfect imaging methodology. CT is the best, but it is not perfect. You will often find more lesions than expected and should look bilaterally, even if a CT scan has shown metastases only on one side. It is essential to remove all metastases or the patient will not survive.

Surgery is usually open thoracotomy. Video-assisted thoracoscopic surgery (VATS) is not recommended because surgeons should palpate the lungs. We do a CT scan after thoracotomy and we send patients back to the thoracic surgeon if there are still metastases. I would even send them back a third time if there were still no remission.

SURVIVAL OF PATIENTS WITH VS WITHOUT REMISSION AFTER SURGERY

		Yes	No	*p*
Primary				
Meyers et al. 1993	surg. remission	20%	0%	<0.001
Kager et al. 2003	surg. remission	40% ca.	0%	<0.001
Tsuchiya et al. 2002	surg. resection	31%	5%	<0.0001
Daw et al. 2006	surg. remission	40%	6%	0.001
Recurrence				
Tsuchiya et al. 2002	early	10%	5%	<0.0001
	late	48%	8%	<0.0001
Kempf-Bielack et al. 2005		38%	0%	<0.0001
Ferrari et al. 2003		39%	0%	<0.0001

These five-year results show that complete resection is a prerequisite for survival

Yes – remission; No – no remission

Going back to our discussion of the patient with the very tiny lesion that did not change during chemotherapy (figure opposite): when she underwent thoracotomy the lesion was found to be a metastasis and she had three more that were not evident on CT scan.

Question: *Could you give some indication of the potential role of adjuvant chemotherapy in patients with recurrent metastatic disease in the lungs? You have clearly outlined the role for surgery. What is the role of chemotherapy?*

Answer: *There are two situations. One is when lung metastases are inoperable and you cannot remove them by surgery. The largest series in inoperable metastases all have the same message: if you give chemotherapy, you can prolong survival by several months but you will not cure the patient. As a group, patients who receive chemotherapy live a few months longer.*

The second situation is where you do achieve surgical remission. Here the role of second-line adjuvant chemotherapy is not as clear. The two largest series are from Italy, and from our German/Austrian/Swiss group. The Italians did not find any benefit from second-line adjuvant chemotherapy. We found that freedom from second recurrence was increased by about 5–6%, which was statistically significant but not a tremendous improvement. In a patient with pulmonary metastases at recurrence, I would discuss and offer adjuvant chemotherapy, but I would never try to convince someone against their will.

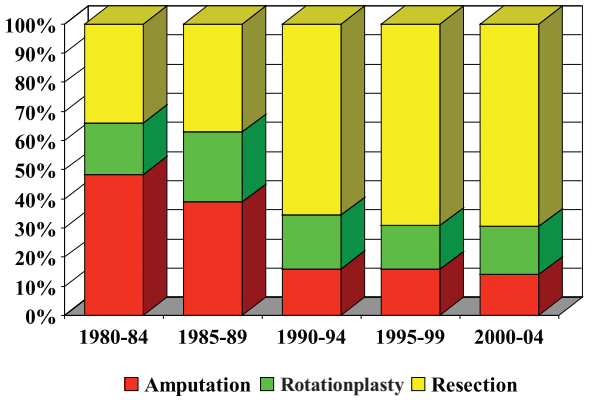
Question: *Does PET have a role in defining metastatic disease?*

Answer: *No, there is currently no role for PET in defining metastatic disease in osteosarcoma. PET will not usually pick up lung metastases that are too small to be seen by CT. Even larger lung metastases – up to about 1 cm in diameter – are sometimes not picked up by PET. Bone metastases are rather infrequent as primary metastases. You usually see them by bone scan and there are no data that indicate PET would be more sensitive. Where PET may have role is in following the osteosarcoma during preoperative chemotherapy, predicting response to preoperative chemo.*

Question: *What is the role of radiotherapy in lung metastases?*

Answer: *We have a very old study with whole-lung adjuvant chemotherapy – a randomised trial from the EORTC. This study, performed in the late 1970s, showed that if you do not give chemotherapy, then adjuvant radiotherapy to the lungs will reduce the risk of recurrence by a small amount. Adding adjuvant radiotherapy to effective chemotherapy will not add anything significant. The only role that I see for radiotherapy of lung metastases is for a limited lesion that you cannot resect. I would discuss with the radiotherapist whether it could be irradiated.*

TYPES OF SURGERY FOR OSTEOSARCOMA



This study of data from 2000 patients with osteosarcoma of the extremities, taken from the COSS (Cooperative Osteosarcoma Study Group) registry, shows that the use of limb sparing surgery has increased significantly since 1980, while amputation is used far less frequently

Source: S Bielack, H Jürgens, G Jundt et al. (2009) Osteosarcoma: the COSS experience. *Cancer Treat Res* 152:289–308, reprinted with kind permission. © Springer Verlag 2009

Surgery after primary tumour

The bar chart below shows the types of surgery used in a large multicentre study by five-year intervals for 2000 extremity osteosarcomas. In the 1980s, limb salvage (shown in yellow) was used in about one-third of patients, and the other two-thirds had either amputation or rotationplasty. The proportion of amputations has since dropped dramatically. Most patients with extremity osteosarcomas treated since 2000 went on to have limb salvage (*Cancer Treat Res* 2009; 152:289–308).

Local recurrence

Our group looked at recurrence in 1702 osteosarcoma patients; 576 developed recurrences and 75 of these had local recurrence. Forty-four had local recurrence only and their five-year survival was 26%; 31 had local recurrence combined with metastases and their five-year survival rate was only 7% (*JCO* 2005; 23:559–568). The results show the importance of avoiding local recurrence.

A study conducted by our group using data from the COSS (Cooperative Osteosarcoma Study Group) registry (*Ann Oncol* 2011; 22:1228–35) shows there are three predictive factors for local recurrence.

Tumour response to chemotherapy. The local recurrence rate for patients who had poor response to chemotherapy was 10% while the local recurrence rate for patients who had a good response (less than 10% viability of the tumour) was only 3%. So, chemotherapy clearly has a role in local control.

PREDICTORS OF LOCAL RECURRENCE

	n	Limb salvage	*P*	% LR (at 5 yrs)	*P*
Response					
Good	826	67%	0.045	3.1%	<0.0001
Poor	515	62%		10.2%	
Limb salvage surgery					
Yes	885	100%	-	7.5%	0.001
No	470	0%		2.8%	
Centre performing biopsy & surgery					
Same	882	66%	0.572	4.2%	0.001
Different	406	64%		10.1%	
Centre volume (</> 1/year)					
Large	1034	70%	<0.0001	6.1%	0.761
Small	321	51%		5.4%	

The results of this study of data on local recurrence (LR) rates among 1820 patients with osteosarcoma of the extremities, taken from the COSS registry, shows four factors predicting for local recurrence, three of them significant

Source: Adapted from D Andreou et al. (2011) *Ann Oncol* 22:1228–35

Limb salvage surgery. There was a slightly higher local recurrence rate for patients who had limb salvage. In our experience, the local recurrence rate was 2.8% in 470 patients who had amputations and 7.5% in 885 patients having limb salvage. So, there is a higher local recurrence rate for those patients having limb salvage.

Location for the biopsy and the surgery. Patients who had to move from the centre that did the biopsy to another for surgery had significantly higher local failure rates. This may be because often the biopsy was not performed in a manner conducive to definitive surgery and may have contaminated the wound more than desired.

Surgical volumes. I would have expected that patients who had surgery at a centre doing more surgery would have a lower local recurrence rate than small centres not doing as many operations, but in our series they had identical local recurrence rates, so surgical volume is not a predictive factor. However, our figures did show that the large centres did limb salvage in 70% of patients, while the small centres did this in only 50% of patients. So, while the local recurrence rates are the same at large and small centres, there is a higher rate of amputation if the surgeon is not very familiar with sarcoma surgery.

Local therapy for inoperable sites

Inoperable sites include many axial osteosarcomas and metastases that can't be reached by surgery. It is usually said that radiotherapy does not work for osteosarcoma. Is that really true? There are a couple of interesting publications on this. DeLaney and colleagues from the US looked at 41 patients with osteosarcoma and inoperable lesions: 27 primaries, 10 local recurrences and four metastases. They were given radiation and some chemotherapy. The local control rate was 68% at five years, with relatively high doses of radiation (median 66 Gy). It was 78% for patients who had gross or subtotal resection together with radiotherapy and 40% for those who had biopsy only (*Int J Radiat Oncol Biol Phys* 2005; 61:492–498).

We did a retrospective analysis of the COSS registry data for 100 patients with 66 primary tumours, 11 local recurrences and 23 metastases. Radiation doses were also relatively high (median 56 Gy) and all patients had chemotherapy. The local control rate was 30% at five years in this highly heterogeneous multicentre cohort: 48% for surgery plus radiotherapy, 22% for radiotherapy alone, 40% for primary tumours, 17% for local recurrences and 0% for metastases (*Cancer Treat Res* 2009; 152:147–164).

The information we can take out of this is that radiotherapy can work for selected osteosarcoma lesions that are not operable. The finding that it works better if you take out large parts of the tumour – debulking – is interesting, as is the finding that it works better for primary tumours than for recurrences or metastases. I think this is because radiotherapy works best if you give it together with effective chemotherapy, and we have effective chemotherapy for primary osteosarcoma but not for recurrences.

The take home message for local therapy is: operate, operate, operate. Surgery is the most important local therapy. You need a good surgeon who knows how to achieve adequate margins. Limb salvage is often feasible. The risk of local recurrence can be reduced by getting four things right:

- good imaging, because the surgeon needs to know where to cut
- smart planning between all disciplines
- good chemotherapy to devitalise the tumour as much as possible, and
- good surgery.

Radiotherapy may be an option for

selected inoperable lesions. There are some studies with proton or heavy ion radiotherapy that may help to define whether these innovative radiation techniques can be more effective than conventional radiotherapy.

Question: *What do you do if you have a residual disease following surgery? What is the role for amputation in the modern era?*
Answer: *If you do not achieve adequate margins with limb salvage, then you should amputate. I think you also need to think about limb amputation and particularly rotationplasty for tumours in very small children, because growing endoprostheses are tedious for young children in their lives.*

Chemotherapy

Chemotherapy for osteosarcoma was started and evaluated in the 1970s with three drugs: high-dose methotrexate, doxorubicin, and cisplatin. Ifosfamide was added in the 1980s. These drugs are still being used today. Adjuvant combination regimens were introduced in the late 1970s and early 1980s and preoperative (neo-adjuvant) chemotherapy has been used since the early 1980s.

Timing of chemotherapy in relation to surgery

We all think that you have to give preoperative chemotherapy, but is this true? Results of a randomised study by the Pediatric Oncology Group in 100 patients (*JCO* 2003; 21:1574–80) did not show a significant difference in five-year event-free survival between patients who had immediate surgery and those who had their surgery after a course of preoperative chemotherapy (69% vs 61%). Similarly our experience for the COSS group, looked at retrospectively but with larger patient numbers, shows that patients who had delayed surgery after preoperative chemotherapy had the same prognosis (54.4%) as those who had surgery first and chemotherapy after (59.9%) (*JCO* 2002; 20:776–790). We can conclude that, if you give the same total amount of chemotherapy, it probably does not matter much when you perform surgery in terms of survival.

For preoperative chemotherapy, we confirmed that histologic response of the primary tumour is related to five-year survival based on treating 1320 osteosarcomas of the extremities with or without primary metastases. Histologic responses to chemotherapy were graded as either good (>90% destroyed) or poor (<90% destroyed; >10% viable). Results (see table below) showed a significant difference in five-year survival and event-free survival across a six-grade histologic response system used in German-speaking countries, ranging from five-year survival of 84.5% in grade 1 (very good response) to 40.5% in grade 6 (very poor response), with a gradual decline in prognosis along the scale (*JCO* 2002; 20:776–790). If you put histologic response to preoperative chemotherapy into a multivariate model of overall survival it beats even primary metastases as a prognostic factor, so chemotherapy response is very important.

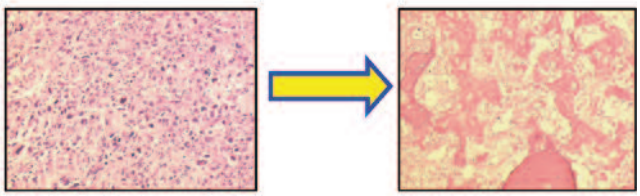
A summary of osteosarcoma trials from the early 1980s to the late 1990s (see table overleaf) shows that everybody uses essentially the same drugs. A randomised trial of chemotherapy versus no chemotherapy, the MIOS trial, showed that chemotherapy is efficacious (*NEJM* 1986; 314:1600–06). Quite a few trials have tried to use modified postoperative chemotherapy in poor responders but none have shown it works.

RESPONSE TO PREOPERATIVE CHEMOTHERAPY PREDICTS SURVIVAL

Response	*n*	5-year survival	5-year EFS	
Good	734	77.8%	67.6%	*P*<0.0001
Poor	586	55.5%	38.6%	
Grade 1	184	84.5 %	79.2%	
Grade 2	236	82.5 %	68.4%	
Grade 3	296	70.9 %	60.1%	
Grade 4	283	59.7 %	44.7%	
Grade 5	237	53.7%	34.3%	
Grade 6	40	40.5%	25.7%	

Multivariate Cox model of overall survival

Variable	Risk ratio	(95% CI)	*P*
Macroscopic residual tumour	4.01	2.66–6.04	0.0001
Poor response	2.44	1.98–3.01	0.0001
Primary metastases	1.88	1.33–2.65	0.0003
Axial site	1.87	1.25–1.80	0.002
Age >40 years	1.41	0.70–2.85	0.340



This study of the data from 1320 patients with osteosarcoma of the extremities, taken from the COSS registry, shows that response to preoperative chemotherapy is more important even than primary metastases in predicting survival

EFS – event-free survival

Source: Adapted from S Bielack et al. (2002) *JCO* 20:776–790

Prospective trials, which usually include only patients with localised osteosarcomas of the extremities, may tell only part of the story. The prognosis is much poorer for patients who present with primary metastases or tumours of the axial skeleton than for those with localised limb tumours (see figure opposite, *top*).

The bar chart opposite (*bottom*) illustrates the progress in Europe and in North America in the last 20 years in terms of five-year survival: basically, there is none. The survival rates have been stable since 1980, which is not really surprising, as we have been using the same drugs since then.

The take home messages for osteosarcoma chemotherapy are:

- Giving chemotherapy is much better than not; multicentre groups can achieve similar results to single centres; and patients with localised extremity osteosarcomas do better than those with other tumours.
- Almost everyone uses preoperative chemotherapy; however, survival outcomes are similar when you operate immediately.
- Poor response to preoperative chemotherapy is a very bad thing. People try to improve results in poor responders by adding drugs and increasing intensity postoperatively, but we do not know whether this works.
- Almost everyone uses the same drugs (two to four of: high-dose methotrexate, doxorubicin, cisplatin, ifosfamide).
- Nothing much has changed over the years in terms of five-year survival.

OSTEOSARCOMA TRIALS WITH CHEMOTHERAPY

Protocol		Drugs	*n*	EFS	(years)
COSS-80	(Winkler et al 1984)	DOX, MTX, (DDP or BCD), +/- IFO	116	68%	(2.5)
MIOS	(Link et al 1986)	MTX, DOX, DDP, BCD vs. no chemo	18+59 18+18	66% & 69% 17% & 9%	(2)
COSS-82	(Winkler et al 1988)	preop all MTX, DOX, DDP; postop GR: MTX, DOX, DDP; PR: DDP, IFO, CYC, ActoD vs. preop all MTX, BCD; postop GR: MTX, BCD; PR: DOX, DDP	59 60	68% 45%	(5)
IOR/OS-1	(Bacci et al 1990)	MTX (HD), DOX, DDP, BCD vs. MTX (ID), DOX, DDP, BCD	127	58% 42%	(5)
SSG-T10	(Sæter et al 1991)	preop MTX; postop GR: MTX, BCD; PR: MTX, DOX, DDP, BCD	97	54%	(5)
EOI-80831	(Bramwell et al 1992)	DOX, DDP vs. MTX, DOX, DDP	99 99	57% 41%	(5)
MSKCC T4-T12	(Meyers et al 1992)	MTX, DOX, DDP, BCD	279	65%	(5)
EOI-80861	(Souhami 1997)	DOX, DDP vs. MTX, DOX, DDP, IFO, BCD, VCR	199 192	44% 44%	(5)
CCG-782	(Provisor et al 1997)	preop all MTX, BCD; postop GR: MTX, DOX; PR: DOX, DDP, BCD	268	53%	(8)
COSS-86	(Fuchs et al 1998)	MTX, DOX, DDP i.a. vs i.v., IFO	171	66%	(10)
IOR/OS-2	(Bacci et al 2000)	MTX, DOX, DDP; postop GR: MTX, DOX, DDP; PR: MTX, DOX, DDP, IFO (HD), ETO	164	63%;58%	(5;10)
IOR/OS-4	(Bacci et al 2001)	MTX, DOX, DDP, IFO	133	56%	(5)
IOR/SSG PILOT	(Bacci et al 2002)	DOX, MTX, DDP, IFO (HD)	70	73%	(5)

EFS – event-free survival; DOX – doxorubicin; MTX – methotrexate; DDP – cisplatin; BCD – bleomycin, cyclophosphamide, actinomycin D; IFO – ifosfamide; GR – good histologic response to preoperative chemotherapy; PR – poor response; Cyc – cyclophosphamide; ActoD – actinomycin D; VCR – vincristine; ETO – etoposide

Chemotherapy dose intensity

A retrospective analysis from Italy suggested that patients who had chemotherapy given at a high dose intensity had a much better prognosis than patients who received less than their allotted amount of chemotherapy over time (*Oncol Rep* 2001; 8:883–888). There were two other retrospective analyses, one from the European Osteosarcoma Intergroup, which looked at doxorubicin and cisplatin (*JCO* 2000; 18:4028–37) and one from our group, which looked at methotrexate, doxorubicin, cisplatin and ifosfamide combinations (*Pediatr Blood Cancer* 2006; 47:42–50). Neither showed that patients who had higher dose intensity chemotherapy had better outcomes.

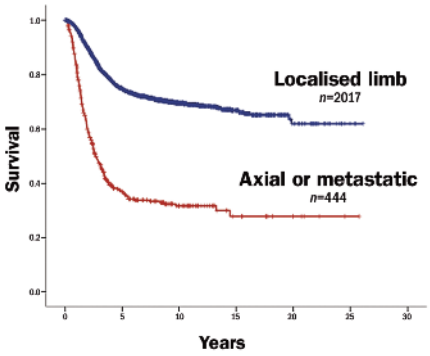
The question of dose intensity was looked at in a randomised trial by a British/Dutch/Belgian/Danish group. Patients were randomised to conventional chemotherapy (cisplatin plus doxorubicin, two cycles preoperatively and four postoperatively) or an intensified arm where G-CSF was added as support, and dosing intervals were compressed from three to two weeks, which meant that three cycles were given before surgery and three cycles after surgery. The response rate was higher for the compressed arm (50% vs 36%). But five-year progression-free survival rates were identical for the compressed and the conventional arms (41% vs 39%) (*JNCI* 2007; 99:112–128).

Retrospective and prospective analysis of high-dose chemotherapy with stem cell rescue – the ultimate dose intensification – did not show improved prognosis, so the take home message is that we are not likely to improve results by dose intensification.

The question we need to ask is whether we can improve outcomes for poor responders, because their long-term survival rates are well below 50%. To look at this we would need to randomise approximately 700 patients, which means that we need about 1400 patients who are willing to be randomised after having received 10 weeks of preoperative chemo, which means we need far more than 2000 patients to go into such a trial. With a disease that occurs in only about two per million people per year, no country can do that by itself, so you need an international group collaboration.

That is what we did in the EURAMOS trial, which recruited 2260 patients from 326 institutions in 17 countries from 2005 to 2011. Figures presented by Katja Zils and colleagues at SIOP 2011 (SIOP abstracts, *Pediatr Blood Cancer* 57:779) showed that complex infrastructures spanning many institutions, countries and even continents, are needed for such a large trial, but that it can be done (see also Cutting Edge p 24).

PROSPECTIVE TRIALS MAY TELL ONLY PART OF THE STORY



Patients with primary metastases or tumours of the axial skeleton have a much worse prognosis than those with localised limb tumours

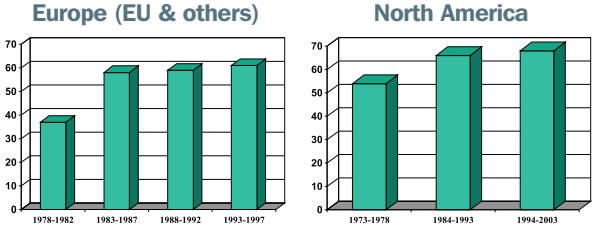
Source: S Bielack, H Jürgens, G Jundt et al. (2009) Osteosarcoma: the COSS experience. *Cancer Treat Res* 152:289–308, reprinted with kind permission. © Springer Verlag 2009

What else can improve prognosis?

Having seen no improvement in prognosis resulting from modifications to chemotherapy we might need to do something else. One possibility may be liposomal muramyl-triphosphate-ethanolamine (L-MTP-PE), a macrophage activator derived from mycobacterial cell wall. Preclinical testing was carried out more than 20 years ago in dogs, and in humans macrophage infiltration into osteosarcoma lung metastases was observed with this drug. It was not clear whether patients survived better, but toxicity was manageable, with mainly fever and chills (*JCO* 1992; 13:1310–16).

This drug was taken forward into a prospective trial in the US – the INT0133 trial. However, at the time the trial was designed, people thought that asking a question only about MTP would be too simple, so there was a second randomisation of ifosfamide versus no ifosfamide. This was added to cisplatin postoperatively, but in the preoperative phase patients had either

FIVE-YEAR SURVIVAL RATES



Progress in survival for patients with osteosarcoma has been minimal since the early 1980s

European data: Stiller et al. (2006) *Eur J Cancer* 42:2124–35, *North American data:* Mirabello et al. (2009) *Cancer* 115:1531–43

ifosfamide or cisplatin. In the end, there were four arms: one with ifosfamide and MTP, one with only ifosfamide, one with only MTP and one with neither. MTP was given 48 times.

The results for 667 patients published in 2005 (*JCO* 2005; 23:2004–11) showed that the addition of ifosfamide to standard chemotherapy did not enhance event-free survival. The three-year event-free survival rate was 68% for patients receiving MTP but no ifosfamide, compared to 71% for patients who received no ifosfamide and no MTP. Overall, adding ifosfamide to standard chemotherapy did not improve event-free survival. The authors suggested that adding MTP to chemotherapy might improve event-free survival, but there was interaction between the two randomisations to ifosfamide and MTP, precluding definitive statements.

A second publication showed six-year event-free survival of 64% for patients treated with neither ifosfamide nor MTP and 63% for those given additional MTP but still no ifosfamide (*JCO* 2008; 26:633–638), so there was no difference favouring MTP observed in patients not treated with ifosfamide. Patients seemed to do better with ifosfamide plus MTP (71%) compared to ifosfamide with no MTP (58%). Combining arms showed the six-year event-free survival was 61% for non-MTP arms and 67% for MTP arms, which was not significant. However, overall survival for the combined MTP arms was statistically better than for the combined non-MTP arms (78% vs 70%, P=0.03). The authors said they could not prove interaction, so concluded there was no interaction.

L-MTP-PE (mifamurtide) is now licensed in Europe, but a license was refused in the US because the FDA considered there was not sufficient evidence of a survival advantage. In a letter to the *JCO*, several leaders of international osteosarcoma groups said they considered it was an interesting agent, but that additional clinical evaluations are required before it can be considered for routine use (*JCO* 2008; 26:3102–03). I think that the information is not sufficient to use this agent as a part of routine treatment today, but we should continue to study it, preferably in a randomised prospective trial. An international group that met in London in 2010 concluded that an MTP trial should be performed, comparing chemotherapy with and without MTP.

Other options for trials include: optimising chemotherapy schedules; inhaled GM-CSF to enhance immune response to osteosarcoma cells (but this was tried and failed; *Clin Cancer Res* 2010; 16:4024–30); IGF-1R inhibitors, which showed positive in vitro results, but no positive phase II data so far in osteosarcoma; mTOR antagonists, with (somewhat) positive phase II data in bone tumours (*JCO* 2012; 30:78–84); bisphosphonates, which are being tried in various trials; and a rank ligand inhibitor, denosumab. Most of these, apart from bisphosphonates, are not yet advanced enough to go into phase III trials.

In summary

The take home messages are:

- Exact staging for osteosarcoma is mandatory.
- Cure requires good surgery and good chemotherapy, which should include several of the four standard agents, which are doxorubicin, cisplatin, methotrexate and ifosfamide. We do not know the value of additional drugs.
- Intergroup collaboration is helpful to get to results and is also feasible, although not easy. For the future, we need biology-driven questions and we must work to ensure that intergroup studies come up with biology results that can lead to biology questions for future trials.

Question: *What is the current standard of care for osteosarcoma now that the EURAMOS trial is closed? This relates particularly to patients who have a poor histological response to three-drug chemotherapy with cisplatin, doxorubicin and methotrexate. There is always a temptation to give patients different chemotherapy postoperatively if they have had a poor histological response, but would you say that the standard of care should still be three-drug chemotherapy in this subset?*
Answer: *Yes. I think that whatever well-chosen chemotherapy you give preoperatively should be the standard for postoperative treatment as well. Nobody has been able to prove that changing chemotherapy by making it more aggressive will ultimately alter the disease course. We will have to wait a while to see whether intensification with ifosfamide and etoposide will result in a higher cure rate.*
Question: *Is there a role at all for high-dose chemotherapy and stem cell support for osteosarcomas in an inoperable site.*
Answer: *No!*
Question: *Regarding MTP, do you think we would be having the same degree of soul searching about its use if it was less expensive?*
Answer: *Cost is one thing. But there are two other issues that concern me. One is the additional burden for the patient. They will have to go to the hospital 48 additional times for their infusions – this is 48 days of their lives, which is a lot for patients who are living their last days. I would rather they do other things than sit in a hospital being treated with a drug that may not work. The other issue is toxicities, which we need to consider when planning future trials with biologic agents. It will be more difficult to add them to a standard regimen that includes MTP than to one that does not. If we add MTP to the standard regimen we should be quite sure that it is a drug that really benefits the patient, otherwise it will be more difficult to move forward.*

Can the Reverend Bayes help deliver proven therapies for patients with rare cancers?

Anna Wagstaff

Conducting clinical trials in people with rare cancers is not easy when the numbers in a small trial do not add up to convincing evidence. Now some researchers are pressing for a new approach – using Bayesian trial designs to make the most of available knowledge.

When you are diagnosed with cancer, the last thing you want to hear is that medical experts have few treatment options to choose from and not much evidence on which to make that choice. Yet this remains the reality for many of the four million cancer patients in the EU-27 who are living with a 'rare cancer'.

There are 186 of these rare cancers (using the recently proposed definition of a cancer diagnosed in fewer than 6 in every 100,000 people per year), with the seemingly contradictory result that almost one in four cancer patients has a rare cancer.

The consequences can be seen in their markedly poorer prognosis. Five-year survival figures – which broadly speaking reflect the efficacy of treatment – show patients with rare cancers do significantly worse, with fewer than half surviving for five years (47%), compared with almost two-thirds for patients with more common cancers (65%). While this may in part reflect the inherent nature of these particular cancers, it is also probably a result of the comparative difficulty of learning about how to treat rare cancers.

How to advance the cause of this disparate group of patients, and unblock progress in improving treatment strategies and developing new therapies, is a question that is commanding the attention of an increasingly coherent community specialising in rare cancers. In early February, around 50 of them – clinicians, researchers, patient advocates, statisticians, epidemiologists, pathologists and representatives from cooperative trials groups and pharmaceutical companies – spent two days trying to find common ground on how to conduct clinical research where patient populations are small.

Organised by ESMO and Rare Cancers Europe, the conference had two aims: to bring everyone involved in rare cancers behind a research strategy that could significantly speed up the development of an evidence base, and to build a united front that can be used to seek agreement on how regulators and payers can better meet the needs of this group of patients, for whom traditional standards of evidence are difficult to achieve.

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

A QUESTION OF NUMBERS

Paolo Bruzzi, clinical epidemiologist at the National Cancer Institute in Genova, Italy, explained the nub of the problem. According to the traditional rules of medical evidence nothing counts but the numbers – which is exactly what rare cancers don't have.

To demonstrate the value of a new treatment or treatment strategy, you have to show beyond doubt that it benefits the intended group of patients – better survival, better quality of life – more than a comparator, which is usually the standard of care. Using the traditional 'frequentist' approach, this involves treating enough patients to show that the difference in outcome between the trial arms is big enough for it not to have come about by chance – the all-important *P*-value.

The standard *P*-value required by regulators – and payers – is $P \leq 0.05$, which means the odds of the demonstrated difference having come about by mere chance is less than 1 in 20. As chance will always play a larger role in the outcome where numbers are small (throwing a six two times out of four is much more likely than throwing a six 20 times out of 40), proving a difference is not just chance requires large numbers of patients: the smaller the difference, the larger the number of patients required.

Where there are too few patients to prove that an observed difference could not have come about by chance, the study is said to be 'underpowered'. As a general rule of thumb, said Bruzzi, trials of therapies for patients with early-stage disease require 500–5000 patients, while in advanced disease the numbers are a bit lower, at 300–1000.

As a consequence, groups of patients who cannot muster this level of participation in a clinical trial risk being excluded from the world of evidence-based medicine: no research, no 'standard of care', no guidelines, no access to approved therapies.

"As a rule of thumb trials of therapies for patients with early-stage disease require 500–5000 patients"

The Bayesian alternative

Prompted by the need to develop an evidence base for treating these smaller groups of patients, doctors, researchers and drug developers have begun to turn to an alternative methodology. Originating from a theorem developed by an English priest and mathematician, the Reverend Thomas Bayes, and first published in 1763, the Bayesian approach to modelling probability has one great advantage over frequentist approaches: it enables all types of relevant information to be fed into the probability model.

Using a frequentist approach, you may have a well-designed and rigorously executed randomised controlled trial that comes up with impressive results, yet fails the test of significance because too few patients were spread across the trial arms to demonstrate that the result could not have come about by chance. End of story.

Using a Bayesian approach, however, the results of that same trial could be looked at taking into account the strength of 'prior' evidence – relevant information that could have been gathered from any number of sources: biological and preclinical studies, case reports, uncontrolled studies, studies with surrogate endpoints, studies on other similar cancers, or studies on the same cancer in different stages.

The advantages of this approach when working with small groups of patients is clear. The disadvantage is that the process of defining the strength of prior evidence is open to subjectivity and therefore to potential bias, which is why it has been regarded with scepticism by the scientific and medical establishment, and has never yet formed the basis for approval of a new therapy by the regulators or indeed reimbursement. One of the tasks this conference set itself, therefore, was to start building agreement around rules for defining prior probabilities that can command confidence.

The proposal put to the conference suggested a scoring system for rating studies for their validity and pertinence, "so that the assumptions of all calculations are explicit and can be criticised". A study in an identical patient population would score higher on pertinence than one with the same cancer but at an earlier stage; a well-designed trial with a control arm would score better on validity than a study that had used historic controls (results from an earlier sequence of patients) or none at all.

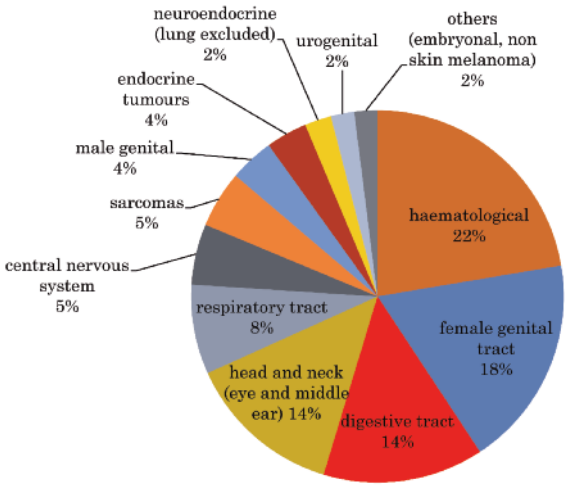
The proposal suggests using a transparent and open consensus process to generate the scores, so as to minimise the risk of bias. The credibility of the result can be further tested by subjecting the model to a sensitivity analysis: controversial values can be changed, or part of the evidence can even be erased to see what impact more (or indeed less) sceptical assumptions would have on the final probability distribution.

Pathological pathways and prior probabilities

Building a consensus around the use of Bayesian approaches to clinical studies could be key to giving patients with rarer cancers access to a whole range of new biological therapies, the conference was told.

This is because biologicals that target mutational pathways, or combinations of pathways, are rarely specific to a single cancer, which means that there is a probability that a therapy developed and

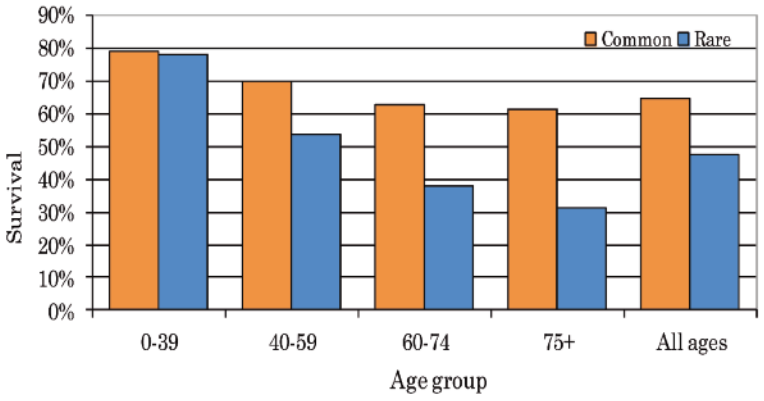
FAMILIES OF RARE CANCERS



Almost 200 types of cancer are each diagnosed in fewer than 6 out of every 100,000 people, every year, and thus fit the recently proposed definition of a rare cancer – some of these are exceptionally rare

Source: RARECARE project on surveillance of rare cancers in Europe (www.rarecare.eu). Slides courtesy of Annalisa Trama, Istituto Nazionale dei Tumori, Milan

SURVIVAL IS POORER FOR RARER CANCERS



Speeding up development of new therapies for rarer cancers will be essential to closing the stark survival gap
Source: RARECARE project on surveillance of rare cancers in Europe (www.rarecare.eu). Slides courtesy of Annalisa Trama, Istituto Nazionale dei Tumori, Milan

approved to treat patients with one of these cancers could also be of benefit to patients with cancers that share the same mutated pathways. Bayesian methodologies allow drug developers to take into account knowledge gained in trials in one indication when investigating the same drug used against the same pathways but in a different indication. If regulators, and indeed payers, are prepared to accept rigorous well-designed Bayesian studies as a basis for approving access to the market and reimbursement, this could substantially reduce the number of patients needed to provide the necessary evidence. This in turn would make it commercially more feasible to develop the drug even where the potential market is small, and would also cut the time taken for patients to get access to the drug.

This new paradigm for developing drugs across tumour types that share a mutational pathway has a number of advantages, comments Andras Fehervary, head of Market Access for Novartis Europe. "By predicting response, it reduces the number of patients needed in clinical trials; by determining response as early as possible, it means trials can be concluded faster; and by predicting not only activity but also adverse events it provides the basis for 'companion diagnostics' that can be used in routine clinical practice to see which patients would benefit most, and which might suffer the greatest toxic effects. It would also accelerate development of new drugs and reduce attrition."

It's a win–win scenario, says Fehervary, which aims at getting the right therapy at the right dose for the right patient at the right time – a goal shared by the industry, health authorities, physicians and patients and their associations alike.

"For this to happen in a sustainable way, we do need to cooperate to create a more efficient system, which must be a patient centric, and patient outcomes centric, system," he adds. "And this calls for new models of collaboration between industry and its partners on important steps."

Fehervary would like to see incremental changes to the current system that would make it easy to conduct trials of targeted drugs in patients with cancers where the targeted pathway is known to play a role, particularly when that drug has already been approved in one indication, and where the disease is serious and there are few or no therapeutic options. Such a system, he suggests, could be based on numerous, fairly small, investigator-initiated trials; an effective way of identifying eligible patients; and agreement from both regulators and payers on allowing information gathered both before and after the trials to form part of the overall evaluation of the efficacy and value of the drug in that setting.

He paints this scenario:

"Assume we are working within INCa [the French cancer research network], and assume a patient has not been accurately diagnosed, but is clearly suffering cancer-related symptoms. The patient is sent to the Institut Gustave Roussy, and is comprehensively screened against a range of biomarkers. That patient is identified as potentially suffering from a rare cancer, and there is a clinical trial running in one of the 21 centres linked to INCa specifically for that form of cancer. The patient is very quickly moved into that trial, and is matched [confirmed to have the relevant diagnosis for the trial]. The trial is set up to run on Bayesian principles.

"Assume the patient responds well to the treatment, and that these results contribute to the overall clinical trial

Building a consensus around Bayesian approaches could be key to giving patients access to new biological therapies

results that show the drug is an active molecule and effective in that setting. In principle, assume there are 30 patients in that group, we should be able to go to EMA [the European regulators] and say: 'We have an active molecule that should be made available to patients, but hasn't gone through the full safety tests that come through the larger trials. However, the risk profile of a patient suffering from a rare cancer is different, because of the poorer outlook for rare cancers, and patients want access.' Hypothetically this could lead to approval."

Fehervary also mentions the need for greater involvement of patients groups in clinical trial design and execution, a stronger focus on patient adherence to their prescribed treatment, better management of side-effects, and a more equitable access to drugs and to optimal standards of treatment as important areas for improvement.

Bigger is 'not always better'

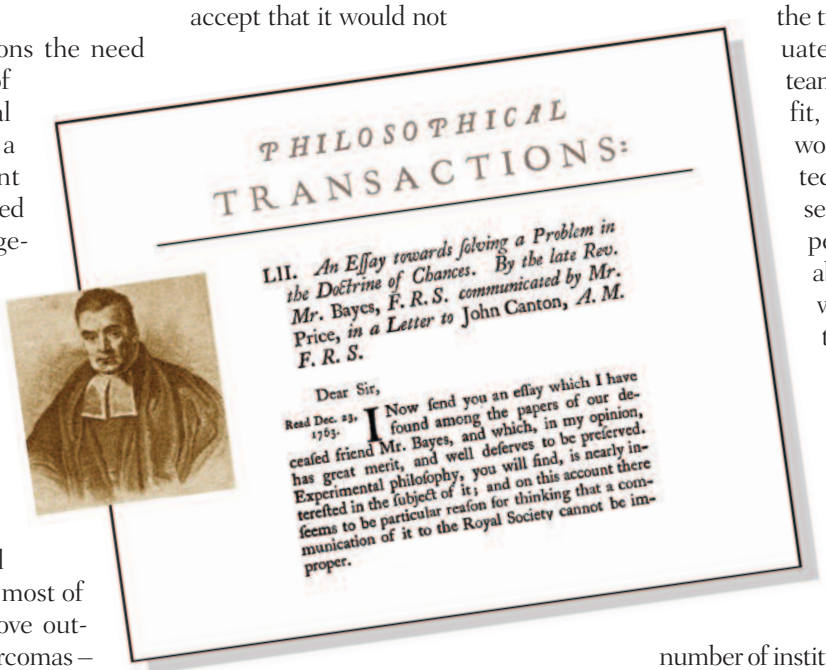
Paolo Casali is a medical oncologist who has spent most of his career trying to improve outcomes for patients with sarcomas – rare cancers now thought to consist of more than 50 (even more rare) subtypes. One of the key organisers of the conference, he is an avowed Bayesian enthusiast, and insists that just because a trial is small this does not mean it has to be either methodologically unsound or inconclusive. He does accept, however, that the smaller the trial the more important is a rigorous methodology: transparent, pre-agreed, open to sensitivity testing. And that is exactly why it is so important to build a consensus around how this can be achieved.

Casali points out that, over the years, more than a few drugs have been approved for small populations on the back of a fairly poor evidence base – for instance trials that had no control arm, or that provide data only on tumour shrinkage. In these cases, where the regulators accept that it would not be possible to run a fully powered phase III randomised controlled trial, pharmaceutical companies (or other sponsors of new drugs) are always uncertain about how much evidence regulators will demand to back up the application for approval, and this may deter them from developing drugs for rare indications.

How much better would it be to have trials designed according to agreed Bayesian principles from the outset, argues Casali. Instead of bringing in additional information at the end of the trial, to be assessed, evaluated and applied by the team of regulators as they see fit, that same information would have to be submitted in advance, with a consensus over its validity and pertinence, transparency about how that consensus was reached, and a sensitivity analysis on more uncertain assumptions.

Casali also questions the received wisdom that bigger trials are always necessarily better. "In rare cancers in particular, large collaborations inevitably lead to involving a large number of institutions whose skills in the disease are limited, which has implications for the quality of care within these studies," he says.

Standard quality control measures used in large trials, such as central pathology review and central review of scans, are useful but introduce their own problems, and will never cover all aspects of good-quality care says Casali.



PHILOSOPHICAL TRANSACTIONS:

LII. *An Essay towards solving a Problem in the Doctrine of Chances. By the late Rev. Mr. Bayes, F. R. S. communicated by Mr. Price, in a Letter to* John Canton, *A. M. F. R. S.*

Dear Sir,

Read Dec. 23, 1763. I Now send you an essay which I have found among the papers of our deceased friend Mr. Bayes, and which, in my opinion, has great merit, and well deserves to be preserved. Experimental philosophy, you will find, is nearly interested in the subject of it; and on this account there seems to be particular reason for thinking that a communication of it to the Royal Society cannot be improper.

The Reverend Bayes and his theorem. The potential for using our knowledge of cancer biology to speed up the evaluation of new therapies and treatment strategies is prompting renewed interest in a theorem that was first published almost 250 years ago in *Philosophical Transactions* under the title 'An Essay Towards Solving a Problem in the Doctrine of Chances' (*Phil Trans* 1763; 53:370)

"Large collaborations inevitably lead to involving institutions whose skills in the disease are limited"

"We need to be ambitious; we can achieve randomised controlled trials in an international setting"

"Every clinician knows that tumour response assessment involves complex clinical reasoning, as does every clinical decision. Clinically speaking, by definition, 'blind' central reviews, which skip clinical data, will lead to a worse tumour response assessment, not a better one."

"There has to be some trade-off between the methodological requirements and clinical quality, otherwise, clinicians will not believe in their own studies," argues Casali, adding that this is precisely what has happened with several adjuvant randomised trials and "basically all" randomised trials comparing adriamycin against adriamycin and ifosfamide in soft tissue sarcomas. "In fact, many sarcoma experts currently rely on small uncontrolled studies for their everyday decisions on medical therapy more than on large randomised trials, even though these are in fact available."

Bayesian is 'second best'

Denis Lacombe, director of the headquarters of Europe's largest clinical trials organiser, the EORTC, is distinctly cautious about the use of Bayesian methodologies for getting new drugs approved or extending their use to new indications, on the basis of results from small trials.

"While alternative designs should be investigated to allow therapeutic progress for these patients [with rare indications], academia has first a role to work together to assess the feasibility of conclusive trials using the most robust methodology... Research groups should avoid applying whenever possible what can possibly be more debatable methodology," he told the conference.

Where patient numbers are small, says Lacombe, the answer is to seek international collaboration, if necessary between collaborative groups. One such collaboration, which answered several questions about the best use of temozolomide in patients with the aggressive brain tumour glioblastoma, involved three major North American groups – RTOG, the NCCTG and the Canadian NCI – in addition to the EORTC. Lacombe does not deny the challenges posed by these sorts of collaborations – a lot can go wrong without meticulous planning and unrelenting efforts to keep everyone in step every step along the way. But this should not be an excuse for not trying, he insisted, and he cautioned against any recommendations that could be interpreted as a green light to do "local, small and inconclusive initiatives."

Matt Seymour, director of the UK's National Cancer Research Network (NCRN), and a specialist in gastrointestinal cancers, took a similar line, but added that there would be a lot less need for huge international collaborations if more countries made more consistent and concerted efforts to increase the proportion of cancer patients treated within trials,

The UK tried it, he said, and as a result "over the last 10 years the number of cancer patients enrolled in trials has increased five fold, to one in every six cancer patients – matching the trial population of the whole of North America." One consequence of this, he says, is that the NCRN was able to recruit sufficient patients from the UK alone to run large randomised controlled trials in some very rare cancers, including one demonstrating efficacy of palliative chemotherapy in glandular carcinoma and another in anal cancer demonstrating the efficacy of chemoradiation.

International collaboration will still be essential particularly for very rare cancers, added Seymour, and indeed he was instrumental in launching the International Rare Cancer Initiative last year as a partnership between Cancer Research UK, the EORTC, the UK's NCRN and the US National Cancer Institute. This group focuses principally on trials in cancer indications with no more than 3 new cases annually per 100,000. Examples include trials in the adjuvant and advanced setting comparing treatment strategies for patients with small bowel adenocarcimona – a cancer with only around 6 new cases diagnosed per 1,000,000 each year.

"We need to be ambitious; we can achieve randomised controlled trials in an

He cautions against allowing Bayesian designs to be used "as an excuse for underpowering"

"We need to start to use Bayesian techniques today in rare tumours so we can assess what issues it raises"

international setting. Where protocols are well designed, well written and very clear, you can achieve high quality even for rare cancers where centres are putting smaller numbers of patients."

Seymour accepts, however, that some cancers are so rare that, even with international cooperation, it is simply not possible to recruit enough patients to answer a trial question within a reasonable length of time using the traditional frequentist methods and significance levels.

It is only in these situations that he would consider turning to Bayesian methodologies, and even then, only where some "genuinely credible" prior evidence is available, and only where all prior evidence is agreed by everyone before the trial starts. Like Lacombe, he cautions against allowing Bayesian designs and prior probabilities to be used "as an excuse for underpowering".

Where next?

The challenge in the coming months will be to amend the draft recommendation to reach a consensus on the way forward for methods for clinical research into rare cancers that satisfies the needs expressed by Casali, while addressing the concerns expressed by Lacombe and Seymour. The hope is to publish a consensus document in the Autumn.

Roger Wilson, who is currently in treatment for recurrent myxofibrosarcoma, and is a former chair of the UK's National Cancer Research Institute Consumer Liaison Group (and former NCRI board member), says it will be a question of striking the right balance.

"What I as a rare cancer patient need is for my scientists to recognise that there are benefits in both approaches and that they need to find the balance which delivers patient benefit. The scientist who drives through a 10-year study in a rare cancer to deliver a result that has been overtaken by a clinical development which he knew nothing about when he designed the study is not a bad scientist, just a brave and unlucky one. The scientist who used a Bayesian approach and was able to adapt his study to account for the new development and then delivered a result which is more relevant clinically at the time it is completed is not just a lucky scientist – he made his luck."

Doing nothing is not an option, he insists. "We need our researchers and scientists to start to use Bayesian techniques today in rare tumours so we can assess what issues it raises, if any." Casali agrees, and he told the conference that during the course of this year, together with colleagues from the worldwide sarcoma community, he will be starting some Bayesian designed studies on new agents in sarcomas.

TARGETING PATHWAYS NOT LOCATIONS

Glivec (imatinib), the first tyrosine kinase inhibitor, blocks the activity of abl, c-Kit and the platelet-derived growth factor receptor PDGFR. It was initially approved to treat patients with chronic myeloid leukaemia. Later this was extended to patients with Kit-positive GIST, and then in 2006 Novartis submitted a single study for approval in five other rare indications. The company is now pursuing a similar strategy with its mTor inhibitor everolimus (Afinitor/Votubia), which has been approved for renal cell carcinoma and subependymal giant-cell astrocytoma on both sides of the Atlantic, and additionally for pancreatic NET in the US. The drug is currently in phase II trials for four additional rare cancers.

Xalkori (crizotinib) inhibits the tyrosine kinases ALK, ROS1 and c-Met, and was recently approved in the US for treating patients with non-small-cell lung cancer with the ALK mutation. Pfizer is currently running trials of the drug in anaplastic large-cell lymphoma and neuroblastoma. In Europe, crizotinib is also being investigated in the EORTC CREATE trial for use in anaplastic large-cell lymphoma, inflammatory myofibroblastic tumour, papillary renal cell carcinoma type 1, alveolar soft part sarcoma, clear cell sarcoma, and alveolar rhabdomyosarcoma – all of them rare cancers.

GlaxoSmithKline is now taking this paradigm one step further by proposing to study its own investigational BRAF inhibitor with an investigational MEK inhibitor in patients who express relevant mutations, regardless of the location of their tumour. According to an article by Michael McCaughan (Elsevier Business Intelligence, November 16, 2011), the expectation seems to be that the US regulators, the FDA, would not oppose this approach in principle in the case of applications for approval across multiple rare cancers, but would be less open to the same approach across more common cancers.

Fixing the holes in the opioid supply lines

Simon Crompton

Patients are still dying in agony despite concerted efforts over many years to change attitudes towards the use and control of opiates. Could a new initiative, which works with NGOs, governments and policy makers to address practical problems, finally hit the spot?

When his cancer pain grew so great he could see no other means of escape, former police officer Bernard Ng from Singapore considered killing himself. But that changed when a hospice provided him with effective pain relief.

"I once gave up living," he says, fighting back the emotion during an interview for the feature film 'Life Before Death', released worldwide this February. "I once told my wife, and myself, 'I don't have quality of life – what is the use of living?' But today I see it the other way. I want to go on living. With medication and the doctor's help I'm okay."

"I'm not asking for a lot. I just want to live a normal life without pain. And if possible I can do all the basic things like take a bath, change my own clothes, you know, without bothering my wife."

According to the Union for International Cancer Control (UICC), more than 3.3 million people with cancer are dying in pain, sometimes in agony, each year. Altogether, tens of millions of people are needlessly suffering pain, and a WHO estimate says that 600 million are going to suffer from

untreated pain in their lifetime. The reason is simple: lack of access to basic, cheap and highly effective drugs, notably morphine. Around 70% of cancer deaths occur in low and middle-income countries, where just 6% of the opioid analgesics are consumed.

Behind that bald fact lies a complex tale of global over-regulation, corporate indifference, burdensome red tape, professional fear and pervasive misunderstanding. Drugs aren't getting to people, not because they are expensive or hard to administer but because systems are failing.

Now an initiative from the Union for International Cancer Control (UICC) and the American Cancer Society (ACS) aims to end this needless suffering. The Global Access to Pain Relief Initiative (GAPRI), launched in 2010, is spearheading a range of actions to make effective pain relief a global reality by 2020. It aims to improve the market for pain medicines, empower governments to expand pain relief, strengthen health systems and mainstream the issue of pain treatment in the global health agenda.

The invisible problem

According to Meg O'Brien, GAPRI director, untreated pain has long been the invisible world health problem, always falling between the cracks of other initiatives. It is common even in countries like the US and UK, but the problem is most dramatic in sub-Saharan Africa, which has 20% of painful deaths in the world, and just 1% of the morphine.

GAPRI has identified the main barriers to people accessing pain relief as legal and regulatory restrictions, weak health systems, and concerns about drug diversion and addiction. All of these interact. But Meg O'Brien says that if she could wave a wand to change one thing, it would be to fix clinicians' attitudes to morphine.

"There are so many myths and misunderstandings about the drugs," she says. "The reality is that, in many countries, even if we were to fix regulations that restrict access to the drugs, we'd see the drugs expire on the shelves because they were under-used."

"The reason is partly historical. When, in the past, pain relief was not easily available and physicians had nothing to give patients, they had to provide a story to explain it. That story was that drugs like morphine are dangerous and addictive. And that story has continued to this day. Some clinicians find it easier to build a wall between themselves and the patient, saying they can't do anything for the pain. They breed an acceptance that HIV hurts, or cancer hurts."

MORGANA WINGARD

Practical solutions. Resolving an acute morphine shortage in Uganda came down to ensuring that a hospice with the knowhow also had a licence and an incentive to supply the health service

MOONSHINE AGENCY

This is the experience in Zimbabwe, where fear and ignorance about morphine conspire with highly restrictive drug control legislation to make good pain control a rarity. According to Dickson Chifamba, executive director at the Island Hospice Service, only 30% of people who need pain relief get it in Zimbabwe. "A doctor has to report to the Secretary of Health any patient who has been on morphine for more than four months," he says. "So because of the bureaucracy a number of doctors do not want be bothered with prescribing morphine." Resistance is particularly great from older doctors, who have not been trained in palliative care.

"There are also the usual fears of addiction and respiratory depression, which means that both doctors and patients see morphine as a medicine of very last resort. They hold off until the patient is in agonising pain." Chifamba recalls recently visiting a cancer patient who was screaming in agony. He was alarmed because on his last visit the patient's pain had been well controlled. When he asked the relatives what had happened, they said they had not collected the morphine doses because they believed it was slowly killing the patient. Many families, he says, believe that morphine should not be given continuously – only when pain is extreme.

Supply-side issues

There are supply problems with morphine too. Chifamba points out that UN conventions designed to control the illegal use of drugs have ingrained highly restrictive systems. Supply problems are exacerbated by the fact that the big players in the pharmaceutical industry show little interest in producing morphine because profits come from patented medicines. That leaves it to small companies, with more limited capacity, to supply middle- and lower-income countries.

David Lee, an expert on opiates and senior strategic advisor for Endo Pharmaceuticals, acknowledges that

"Because of the bureaucracy a number of doctors do not want be bothered with prescribing morphine"

If there were more profit in morphine the global dynamics of supply and demand would be different

if there were more profit in morphine the global dynamics of supply and demand would be very different. "It's certainly a low margin business for the pharmaceutical industry. But I don't think you can say the whole situation is their fault."

"In rich countries, there are many types of opiates, but for many low- to middle-income countries morphine is the only option for severe pain," says Lee, who is CEO of the LAMB Pain Foundation and leads a project managed by the Foundation for Hospices in Sub-Saharan Africa and the African Palliative Care Association to educate hospital administrators and healthcare workers in good pain management and treatment. "It's cheap in principle, and the process to convert the raw material is relatively easy. But movement of it is heavily controlled by international and national laws."

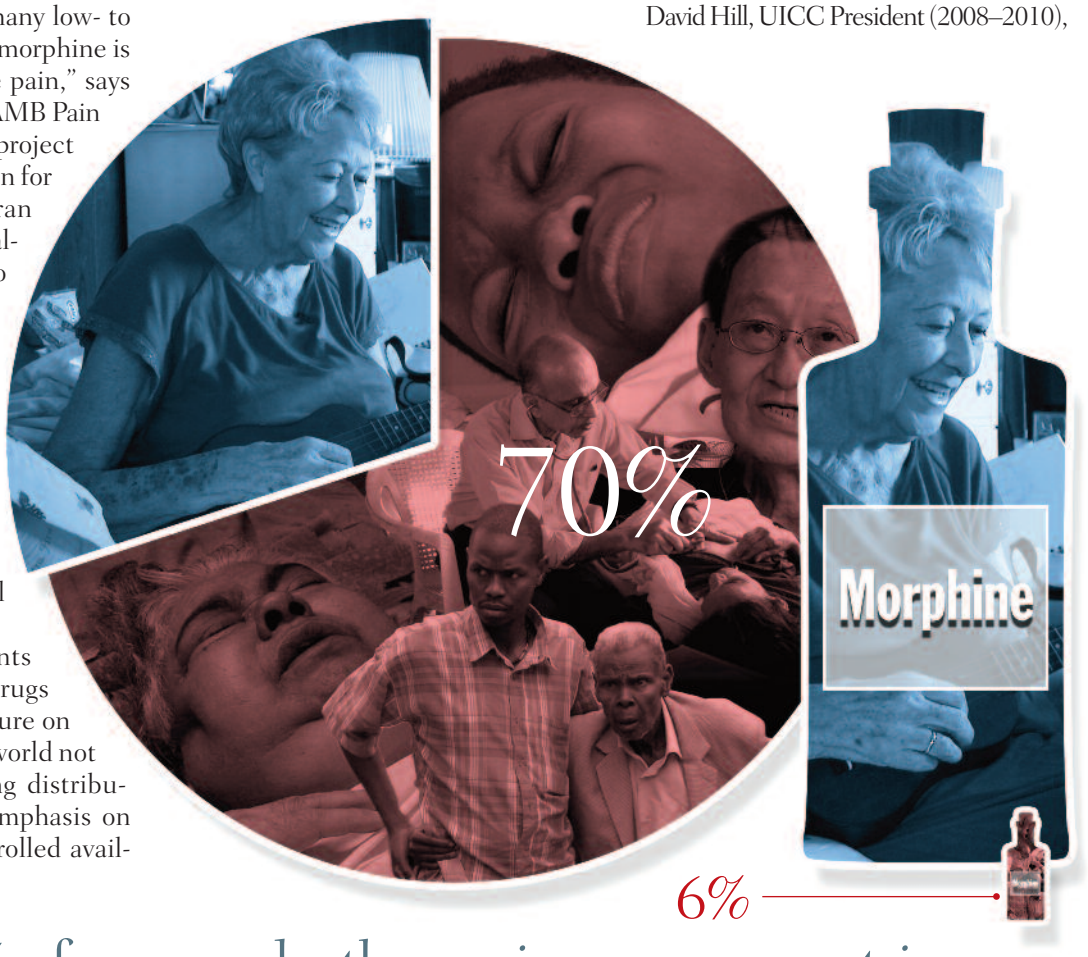
Influential governments waging wars on illegal drugs are putting political pressure on governments around the world not to loosen laws controlling distribution. "There is a lot of emphasis on control, and less on controlled availability," says Lee.

On top of this, national or local legal frameworks to get morphine where it is needed are either non-existent or so cumbersome that health professionals are not prepared to take them on. "There's a reluctance to prescribe because of fear of legal sanction," says Lee.

A NEW DETERMINATION

But if the global obstructions to good pain management are intricate and deep-rooted, there are at least now signs of a growing international determination to overcome them.

First and foremost was the establishment of GAPRI itself – the brainchild of David Hill, UICC President (2008–2010),



IMAGES FROM MOONSHINE AGENCY

Around 70% of cancer deaths are in poorer countries, where just 6% of the opioid analgesics are consumed

"It now needs people who have the ability to do something, to do something"

who pushed the idea ahead in the light of increasing concerns about pain control in the international cancer community. GAPRI has taken shape alongside another project which has helped give voice, images and publicity to its campaign – a feature film called 'Life Before Death' about the global crisis in pain, produced and directed by David Hill's son, Mike. The award-winning documentary, filmed in 11 countries and released this year, interviews health professionals battling the pain epidemic and patients who have experienced extreme pain, and argues for effective pain treatment as a basic human right (www.lifebeforedeath.com).

Both initiatives have taken place in the context of new expressions of a global will to address palliative care issues. Last year's UN General Assembly political declaration on non-communicable disease stated that national policies should improve access to palliative care and foster partnerships between government and civil society to support palliative care services.

The World Cancer Declaration, drawn up by UICC in 2008, is more specific. One of its targets for 2020 is that effective pain control measures will be available universally to all cancer patients in pain. The declaration calls for action where over-regulation hinders good pain control, and stipulates that governments and international organisations should not allow global implementation of the UN's international drug control conventions to interfere with legitimate efforts to advance access to pain medicines.

A hard-hitting report from the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries has highlighted the fact that "pain control, an issue for all cancers and many other diseases, offers the most distressing and insidious example of the cancer divide."

MOONSHINE AGENCY

The Drugs Control Office, Kerala, India. Doctors often choose not to prescribe morphine because they can't face filling out all the permissions forms. This particular state recently overhauled its procedures, but elsewhere in India, as in most countries across the globe, the bureaucracy remains prohibitive

From words to outcomes

David Lee welcomes the new political will to act. But what will turn words into actions, and actions into outcomes?

"All this high-level, professional noise is helpful because there's a reference point, an anchor," he says. "It now needs people who have the ability to do something, to do something. There are a lot of well-intentioned people wanting to change things, but one of the frustrations of the not-for-profit sector is that sometimes people work against each other, rather than working together. There are signs now that it's beginning to happen. I think that the GAPRI initiative is particularly important in this respect, because of the way it interacts with so many different NGOs, governments and other bodies."

Meg O'Brien too believes that GAPRI is getting things moving. "It's a bit like a leaky pipe – you have to fix all the holes at the same time, or else the water starts coming out somewhere else," she says. Issues of availability and training of health professionals in pain control have to be addressed simultaneously. GAPRI is doing this by developing good-practice models that will prove what can be done and will spread knowhow.

The pain-free hospital initiative, for example, is a one-year programme to change clinical practices at key hospitals worldwide during 2012. It provides training for physicians and nurses to evaluate and treat pain, using targeted advocacy campaigns within the hospital to increase awareness of treatable pain. Simultaneously, it works with government officials to ensure that essential

pain medicines are available at all times. GAPRI has launched the project in three hospitals in India, and is working to find funding for similar projects in Vietnam, Haiti, Tanzania, Ethiopia, Turkey and Egypt.

"We make films with patient stories, have teeshirts for patients to wear, and the idea is that everyone gets a feeling that pain can be controlled," says O'Brien, who before starting full-time at GAPRI in 2010 had been involved with pain management initiatives as part of the Clinton Foundation. "Once we can show how pain scores are dropping without addiction, we have a good demonstrative model that can spread through the whole health system."

GAPRI is addressing the problems of global supply head-on, and will be creating a new analysis of morphine supply and demand to take direct to pharmaceutical companies to show them where the potential markets can be found.

With the aid of this, says O'Brien, GAPRI will be able to facilitate "bundled negotiations" with pharmaceutical companies on behalf of several governments. "We'll act as the middle man," she says.

Recently, GAPRI has been working to improve pain relief in Uganda, where morphine shortages resulted in rationing and many people in pain turning up at health centres literally begging for the drug.

"I went there with colleagues for four days, because I couldn't get a good understanding of what the problem was by email. We went from place to place, meeting 25 different people and organisations, mapped out the problem and put together a plan." Three months later, morphine was easily available to all who needed it. Not only that, but the Ugandan government was saving 40% on what it had previously had to pay for morphine.

"It wasn't rocket science to sort out," says O'Brien. The problem was getting existing stores of morphine powder turned into liquid. So O'Brien negotiated new arrangements whereby a local hospice that already manufactured liquid morphine was licensed to sell to government. The hospice benefits by making a profit, and the supply chain is safe.

"In Uganda, we did the contracting, pricing and forecasting – we even found a plastics manufacturer for the morphine bottles. Finding the time and personnel for those sorts of jobs isn't always easy." GAPRI is recognising this by running a fellowship programme, placing people in health ministries for three years to try and prevent pain management falling between the policy cracks.

With the GAPRI initiative, there's finally the hope that good intentions are being turned into practical measures and good outcomes. It's a matter of actually demonstrating what change can achieve, and then encouraging good practice to spread. "A lot of campaigns stop at raising awareness, but sometimes people need more help than that," says O'Brien.

HOST A SCREENING EVENT

Filmed in 11 countries across North America, Europe, Asia, and Africa, the documentary film 'Life Before Death' tells the stories of the health professionals battling the sweeping epidemic of pain that threatens to condemn one in every ten people to an agonising and shameful death.

It shows how their struggle pits them against indifferent governments, dysfunctional bureaucracies, over-zealous law enforcement agencies and, above all, the deep-seated attitudes of those around them. Their mission is to change the culture of medicine to become more focused on care, rather than exclusively on cure.

Through the eyes of patients and their families the film reveals the humanity that empowers people to care for those beyond cure. It uncovers hard truths about the torture occurring every day in hospitals around the world but also of the immense hope that comes from healthcare pioneers who accompany terminal patients on their journeys to dignified end-of-life experiences. It is a film about living well and dying better, making the most of every moment in life before death.

Health professionals and advocacy groups around the world have organised public screenings of this film to raise awareness of the issue and galvanise support for change. If you are interested in hosting such a screening, copies of the film are available from GAPRI, together with promotional materials and ideas for preparing discussions and further action.

For details on this and other ways you can help, go to http://www.treatthepain.com/do-something

GAPRI is running a fellowship programme, placing people in health ministries for three years

IMPACTFACTOR

nature REVIEWS CLINICAL ONCOLOGY

Localised non-bulky Hodgkin lymphoma – future questions

Bertrand Coiffier and Olivier Casasnovas

Late toxicities from radiation therapy are frequent in patients with Hodgkin lymphoma and can hamper survival. These late toxicities should decrease with modern radiation therapy, but results are not mature and so the importance of this decrease is still unknown. Hence, all studies in Hodgkin lymphoma must report long-term outcome.

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In a recent publication, Meyer et al.[1] presented a 12-year follow-up of patients with localised non-bulky Hodgkin lymphoma included in a study that compared chemotherapy to a radiation-based treatment.[1] Inclusion criteria in this study – previously published with a short follow-up period[2] – were not-too-low risk patients (stage IA with one involved node and erythrocyte sedimentation rate [ESR] <50 mm were excluded) but not-too-high risk (patients with tumour diameter >9 cm, a tumour larger than one-third of the chest wall diameter or with intra-abdominal disease were excluded).[2] The study design was quite complicated and divided the patients into a chemotherapy arm and a radiation arm. After randomisation, patients in the chemotherapy arm received doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD); patients with a complete remission or unconfirmed complete remission after two cycles received four cycles in total, and the remaining patients received six cycles in total. Patients assigned to the radiation arm with at least one unfavourable risk factor (>39 years old, ESR >49 mm, more than three disease sites, or mixed cellularity or lymphocyte-depleted histology) received two cycles of ABVD before radiotherapy, whereas those patients with no risk factor received only radiotherapy (subtotal nodal radiation therapy). The study was opened to enrolment in January 1994 and terminated in April 2002, but only 405 of the 450 patients had completed enrolment. The decision to terminate enrolment was taken by the Data and Safety Monitoring Board because by that time the radiation protocol was outdated. This trial was a complicated study with too many possible biases and difficult-to-interpret results that would likely have had little effect on the existing pool of Hodgkin lymphoma trial data. The first results with a 4.2-year median follow-up period showed a significantly better progression-free survival (PFS; or freedom-from-disease progression as it was called in the study) for patients randomised to the radiation arm, with a similar overall survival in both arms but a slight increase of death from causes other than Hodgkin lymphoma in the radiation arm.[2]

This study was saved by the late analysis, even though 14% of the

patients were lost to follow up;[1] late results (median follow-up period 11.3 years) showed a lower 12-year PFS (87% vs 92%; hazard ratio [HR] 1.91; *P*=0.05) but an improved 12-year overall survival rate (94% vs 87%; HR 0.50; *P*=0.04) for the patients in the chemotherapy arm compared with the radiotherapy arm. This longer overall survival was related to a lower number of patients dying from causes other than Hodgkin lymphoma (12 deaths in the ABVD arm versus 24 in the radiation arm). These numbers will likely continue to increase because the number of secondary cancers is much higher in the radiation-based arm than the chemotherapy arm (23 vs 10). These results raise several questions: first, what is a good balance between chemotherapy and radiotherapy in patients with localised Hodgkin lymphoma? Second, is it possible to reduce the intensity of therapy in some patients? Third, when can results from a randomised study be considered definitive in patients with Hodgkin lymphoma? Finally, what is the best endpoint for future studies in patients with Hodgkin lymphoma?

The current treatment for localised Hodgkin lymphoma – a short course of chemotherapy plus low-dose involved-field radiotherapy – cures over 90% of patients.[3,4] To increase this cure rate, deaths after relapse or from other causes need to be decreased or avoided. The treatment of relapsed patients has improved recently with the use of high-dose therapy with stem-cell transplants and new drugs. The ABVD regimen was associated with few severe late complications; secondary myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) are rare and the dose of doxorubicin is usually too low to induce cardiac failure.[5] By contrast, MDS and AML are more frequent with combined therapy, and secondary solid tumours increase over time after radiotherapy.[6] The 30-year incidence of secondary cancers with mantle radiation therapy is around 30% but decreases by 60% to 12% with involved-field radiation therapy. The long term follow-up of another trial – EORTC/GELA H10 – will give insights on the risk of a secondary cancer after involved-node radiation therapy. Cardiovascular complications are also more frequent after radiotherapy, even though they are less common now with the standard use of involved-field radiation therapy.[7]

Is it possible to reduce the use of radiotherapy or to reserve it for a subgroup of patients with localised Hodgkin lymphoma? To date, two studies comparing results of chemotherapy alone versus the combined modality have been reported with a short follow-up period; these studies demonstrated either no PFS benefit[8] or a marginally better PFS[9] for the combined modality and the same overall survival for both treatment modalities.[8,9] To a certain extent, the Meyer et al.[1,2] study also compared both modalities, as 73% of the patients included in the radiation arm received a combination of chemotherapy plus radiation. However, long-term outcome favours the chemotherapy arm, the extended radiation arm being hampered by an excess of death due to late toxic effects.[1]

On the basis of these three studies,[1,2,8,9] there is no clear evidence that we can safely omit a modern radiotherapy treatment in all patients with localised non-bulky Hodgkin lymphoma because PFS results are controversial and data on long-term overall survival with current combined treatments are unavailable.

Recently, response-adapted therapy has emerged as a new concept that is supported by the development of functional imaging. In this therapy design, patients achieving complete remission as determined by ^{18}FDG PET assessment after two chemotherapy cycles will not receive radiotherapy, but those without a complete remission will. To generalise this idea, randomised studies must show that these patients with early complete remission will not have a shorter survival than those receiving radiotherapy. Preliminary results of PET relevance to identify patients eligible for radiotherapy are in favour of this hypothesis, at least in advanced-stage Hodgkin lymphoma.[10] However, the majority of these studies are ongoing and definitive results have not yet been published. Involved-field radiation therapy remains the standard treatment for these patients until such results demonstrate that radiotherapy is not necessary in early responders. Furthermore, an additional issue to address is establishing suitable rules for interpreting interim PET scan results.

The trial published by Meyer et al.[1,2] is also remarkable because results were modified from the early[2] to the later[1] report. Although PFS results did not change, overall survival changed from the same in both arms to being better in the chemotherapy arm, because of late toxic events in the radiotherapy arm. Clearly, for diseases in which overall survival is very good, such as localised Hodgkin lymphoma,

Practice points

- Radiotherapy is associated with late toxic effects
- Long-term follow up (>10 years) should be mandatory in Hodgkin lymphoma trials
- Chemotherapy alone might be sufficient treatment for selected patients

results must not be reported early on and a minimum of 10 years is necessary to allow the analysis of the late effects and deaths caused by late toxic effects.

It is too frequently the case that study reports from trials in patients with Hodgkin lymphoma or non-Hodgkin lymphomas are published with less than five years of follow up. These early results are important, particularly if there is a difference in overall survival, or if a potential change for clinical practice is reported, but they must be called 'preliminary' and followed by the publication of mature results.

This recommendation for the publication of mature results leads to the evaluation of endpoints of studies that assess the first-line treatment of treatment-naive patients. Assessment of PFS allows the evaluation of the efficacy of the tested therapy, but not late toxicity. When there is a large difference between the two arms (larger than 20%), the early results are usually confirmed by late results; however, when the difference is small (less than 10%) results must be called preliminary and need to be confirmed by other studies and/or by mature results.

In summary, our first goal is to cure patients with cancer, but when long-term survival is over 90%, we need to look at the possible toxic effects of treatment on survival. All randomised studies showing a benefit in the experimental arm must be reported with a median follow-up longer than 10 years to allow this assessment to be completed.

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First-line bevacizumab for ovarian cancer – new standard of care?

➜ Susana Banerjee and Stan Kaye

Demonstration of the clinically significant activity of bevacizumab in advanced-stage ovarian cancer has attracted a great deal of interest. Here, we summarize the two positive phase III trials that led to EMA approval of bevacizumab as first-line therapy and discuss the optimum use of the drug in this disease.

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In December 2011, two positive phase III trials[1,2] that assessed bevacizumab in patients with ovarian cancer were reported in the *New England Journal of Medicine*; these results led to the EMA approval of the drug as first-line treatment in combination with carboplatin and paclitaxel for this disease.[3] Bevacizumab is currently the most widely tested antiangiogenic agent for the treatment of cancer. Bevacizumab is a monoclonal antibody that targets the VEGF pathway, which has a critical role in ovarian function as well as in the spread of ovarian cancer.[4] Therefore, positive results from clinical trials assessing bevacizumab in this notoriously difficult-to-treat disease have been eagerly anticipated.

The first study (GOG-0218) was reported by Burger et al.[1] and was a double-blind, three-arm, placebo-controlled study in 1873 patients with newly diagnosed stage III (incompletely resected with residual disease >1 cm) or stage IV epithelial ovarian cancer. Patients were randomly assigned to one of three treatments: combination chemotherapy (carboplatin–paclitaxel), carboplatin–paclitaxel chemotherapy plus concurrent bevacizumab, or carboplatin–paclitaxel

chemotherapy plus concurrent and maintenance bevacizumab. The bevacizumab dose was 15 mg/kg for up to 22 cycles (15 months total). After a protocol amendment, stage III patients with macroscopic residual disease of ≤1 cm were also included. Nevertheless, all patients enrolled had advanced-stage disease and their overall outlook was worse than those patients assessed in the second study, ICON7.[2]

Perren et al.[2] published the results from the ICON7 study. The trial randomly assigned patients to one of two arms: 1528 patients received carboplatin–paclitaxel chemotherapy with or without concurrent and maintenance bevacizumab. Bevacizumab was given at 7.5 mg/kg (half the dose used in GOG-0218) for a total of 18 cycles (12 months total). In this trial, 9% of patients had high-risk, early-stage disease (FIGO stage I or IIA, clear cell or grade 3 histology) whereas 30% were at the highest risk for progression (FIGO stage IV, or stage III and >1 cm residual disease).

The primary endpoint in both trials was progression-free survival (PFS), which was evaluated using RECIST and Gynecologic Cancer Intergroup (GCIG) CA125 criteria in GOG-0218; only RECIST criteria were included in the assessment in ICON7. Despite key differences, for both studies the primary endpoint was met for concurrent and maintenance bevacizumab. In GOG-0218, median PFS was extended by 3.8 months (14.1 months vs 10.3 months; $P<0.001$).[1] In the ICON7 trial, the median PFS was 17.3 months in the chemotherapy-alone arm compared to 19.0 months with the addition of bevacizumab (HR 0.81; $P=0.004$).[2]

In GOG-0218, an additional analysis was carried out that did not take account of CA125 progression (that is, only interpreting the response based on RECIST criteria); in this analysis, the median PFS was six months longer in the group receiving bevacizumab (concurrent and as maintenance) compared to the chemotherapy-alone control arm (12 months vs 18 months; HR 0.645; $P<0.001$).[1] However, this analysis, which was required by the regulatory agencies, has been criticised owing to the bias associated with unequal censoring in the two arms.

In ICON7, the magnitude of PFS improvement is relatively modest (1.7 months);[2] however, a preplanned analysis demonstrated that the benefit of bevacizumab is greater in patients defined to be at the highest risk of progression. The 3.6-month improvement in PFS seen in this subgroup using restricted means analysis (restricted means 14.5 months vs 18.1 months; HR 0.73; $P=0.002$) is similar to the difference in PFS reported in GOG-0218 for the equivalent arms (3.8 months).

For the assessment of the effects of bevacizumab treatment on overall survival, final mature data are awaited. However, in ICON7, an improvement in overall survival with bevacizumab in the high-risk group was particularly noteworthy (28.8 months vs 36.6 months; HR 0.64, 95%CI 0.48–0.85; $P=0.002$).[2] The demonstration of a survival benefit of almost eight months in patients with a poor prognosis is very encouraging.

Toxic effects were as expected, with hypertension grade ≥2 being common (23% of patients in the GOG-0218 study; 18% of patients in the ICON7 study) but generally well controlled. Overall, bevacizumab treatment was well tolerated. Although bowel perforations had been reported in earlier bevacizumab trials,[5] these perforations were rare events in GOG-0218 (<3% of the patients) and ICON7 (1% of the patients). However, the incidence was higher with bevacizumab therapy compared to control arms.

Based on these new trial results, is it possible to say that bevacizumab is the new standard of care? To answer this, several questions need to be addressed. First, which patients should be offered bevacizumab? Although both studies met their primary endpoints for the whole trial population, it could be argued that given the overall survival benefit seen in high-risk patients in ICON7,[2] women with stage IV or stage III >1 cm residual disease should be considered for first-line treatment. The OCEANS study,[6] in which patients with recurrent platinum-sensitive disease were treated with bevacizumab in combination with chemotherapy (carboplatin with gemcitabine), provides a new dimension to this issue. This study reported a significant improvement in PFS with the addition of bevacizumab (8.4 months vs 12.4 months; HR 0.48; $P<0.0001$) and strongly suggests a role for bevacizumab in this setting of recurrent disease.[5] Therefore, a reasonable proposal for patients optimally debulked and thus at a lower risk of early relapse would be to reserve bevacizumab until first recurrence.

The second question is what is the optimal dose of bevacizumab? The licensed dose of bevacizumab, based on the PFS data of GOG-0218, is 15 mg/kg.[3] However, when comparing PFS improvement in a similar patient population (high-risk) in ICON7, there is no difference in PFS improvement between the groups receiving 15 mg/kg and 7.5 mg/kg. The 7.5 mg/kg dose is likely to be more cost-effective and, so far, this is the dose which is associated with an overall survival benefit.

Based on the available data, should bevacizumab maintenance be extended

Practice points

The addition of bevacizumab given concurrently with chemotherapy and continued as maintenance treatment significantly increases progression-free survival as first-line therapy for ovarian cancer, in particular for those patients at high risk of progression.

until disease progression? The maximal treatment effect, as indicated by the greatest separation of PFS curves in GOG-0218 and ICON7, coincided with the end of planned bevacizumab treatment. When bevacizumab is discontinued, the impression is that the disease returns promptly and this is in keeping with observations in other cancers.[7] Results from the OCEANS study,[6] seemingly superior to the GOG-0218 and ICON7 results, were achieved when bevacizumab was continued until disease progression. Taken together, these findings suggest that bevacizumab therapy until disease progression is warranted.

A fourth question is: should bevacizumab be given in combination with chemotherapy (in addition to maintenance) for first-line therapy? The lack of PFS difference between the chemotherapy-alone control arm and the concurrent bevacizumab arm in GOG-0218 would suggest that the main impact of bevacizumab is as maintenance treatment post chemotherapy. However, the significantly increased response rates (48% vs 67%; $P<0.0001$) in the subset of patients with measurable disease following debulking surgery in the bevacizumab arm of the ICON7 trial, and in the OCEANS study (57% vs 79%; $P<0.0001$), indicates clearly that bevacizumab enhances chemosensitivity, and its omission from concurrent treatment may be unwise.

Finally, does the extent of benefit reported so far justify the cost? For those patients with the worst initial outlook, a PFS improvement of four months translates into almost double the time without chemotherapy before the first recurrence. This improvement does represent an important clinical benefit and patient selection is therefore paramount. The identification of a group of patients likely to benefit most from bevacizumab treatment could tip the balance towards a cost-effective therapy.

These important studies by Burger et al.[1] and Perren et al.[2] demonstrate that the anti-VEGF strategy has real potential in ovarian cancer. In addition to bevacizumab, other agents targeting this pathway are in active development[4] and future trials will undoubtedly clarify the best strategy to use all these approaches for the benefit of our patients.

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

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Stan Kaye declares an association with Roche. See the article online for full details of the relationship. Susana Banerjee declares no competing interests

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NEWSROUND

Selected reports edited by Janet Fricker

Complications from robotic prostatectomy no better than conventional surgery

→ Journal of Clinical Oncology

Problems with continence and sexual function are common following both robot-assisted laparoscopic radical prostatectomy (RALRP) and open retropubic radical prostatectomy (ORRP), a US study has found.

Conventional wisdom holds that men undergoing the robotic procedure experience less post-surgical urinary incontinence and erectile dysfunction compared to those undergoing the traditional surgical approach. In the current study Michael Barry and colleagues, from Massachusetts General Hospital, Boston, compared the continence and sexual function of Medicare enrolees following treatment with either ORRP or RALRP. Investigators used a population-based random sample drawn from 20% of Medicare prostatectomy claims filed between August and December 2008. At a median of 14 months following surgery, participants were asked to complete a mailed survey that included self-ratings of problems with urinary continence and sexual function.

Completed surveys were obtained from 685 participants, with 406 reporting having undergone RALRP and 220 ORRP. When results were "dichotomized" 27.1% of men who had undergone ORRP reported a moderate or big problem with continence compared with 33.3% who had undergone RALRP (P=0.113). For sexual function, 89% of men who underwent ORRP reported a moderate or big problem compared with 87.5% who had undergone RALRP (P=0.57).

"Our findings demonstrate the risks patients actually face with these two procedures in the contemporary national surgical experience in Medicare. Low case volumes likely contribute to the high risk of adverse effects with both procedures in the general population," write the authors. Whether the risk of adverse effects will be lower over time with RALRP, they add, remains to be seen, but in the interim, there is a question about value for money.

"The apparent lack of better outcomes associated with RALRP also calls into question whether Medicare should pay more for this procedure until prospective large-scale outcome studies from the typical sites performing these procedures demonstrate better results in terms of adverse effects and cancer control," they conclude.

In an accompanying commentary, Matthew Cooperberg and colleagues, from the University of California, San Francisco, write, "Although methodologically much more sound than an earlier analysis that tried to determine health-related quality-of-life outcomes on the basis of claims data alone, the study… still has significant limitations."

These limitation, the say, include the fact that all the subjects were aged 65 or older, which means there are no data to show whether results might have differed in younger patients. As baseline function was not measured, it is not possible to say whether these were the same for the two study groups. Furthermore, the survey instrument assessed only "bother" and not function. They also point out that all the operations were performed in 2008, when many surgeons may have still been "learning" the robot-assisted technique.

"Although the exact learning curve for robot-assisted surgery remains unclear, it has been estimated that high proficiency in this technique may require that more than 200 surgeries be performed," they write.

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Semuloparin reduces thromboembolic events during chemotherapy

→ New England Journal of Medicine

Semuloparin – the ultra-low molecular weight heparin – reduces the incidence of thromboembolic events in cancer patients undergoing chemotherapy, the SAVE-ONCO study has concluded.

It is well known that cancer patients receiving chemotherapy are at increased risk of venous thromboembolism, with complications including otherwise unnecessary hospitalisations, interruptions of chemotherapy and anticoagulant treatments or insertions of a vena cava filter. Current guidelines recommend antithrombotic prophylaxis for patients with cancer admitted to hospital for medical illness (administered for the duration of their hospital stay) and for patients undergoing surgery for cancer, but not for routine use in ambulatory chemotherapy patients.

In the double-blind multicentre trial, Giancarlo Agnelli, from the University of Perugia, Italy, and international colleagues, randomised 3212 patients with a wide range of metastatic or locally advanced solid tumours to receive subcutaneous semuloparin 20 mg once daily, or placebo, until there was a change of chemotherapy. Patients in the study, who had just commenced a number of different chemotherapy regimens, were recruited from 395 centres in 47 countries.

Results show that, at a median treatment duration of 3.5 months, venous thromboembolism occurred in 1.2% of patients receiving semuloparin, compared with 3.4% receiving placebo (HR 0.36, 95%CI 0.21–0.60; $P<0.001$). The incidence of clinically relevant bleeding was 2.8% in the semuloparin group versus 2.0% in the placebo group (HR 1.40, 95%CI 0.89–2.21), with major bleeding occurring in 1.2% receiving semuloparin versus 1.1 % receiving placebo (HR 1.05, 95%CI 0.55–1.99). The incidence of other adverse events was similar in the two treatment arms.

"The results of this study show that thromboprophylaxis with the ultra-low-molecular-weight heparin semuloparin, as compared with placebo, reduces the risk of venous thromboembolism among patients receiving chemotherapy for cancer, with no apparent increase in the incidence of major bleeding," conclude the authors.

Several criteria have been proposed to identify cancer patients at high risk for venous thromboembolism, they add, including specific cancer types, chemotherapy regimens, levels of serum tissue-factor microparticles or P-selectin and predictive scores for chemotherapy-related thrombosis. They suggest that stratification for the risk of venous thromboembolism among patients with cancer might be clinically useful.

In the accompanying commentary, Elie Akl and Holger Schünemann, from the State University of New York, undertake a new pooled analysis of low molecular weight heparin use in cancer patients including data from their earlier Cochrane review of nine trials, the SAVE-ONCO trial and a recent third study including 503 patients. When these studies are combined, the relative risk for symptomatic venous thromboembolism is 0.57 and for death 0.94.

"The key questions that are not answered conclusively relate to the effect of treatment with low-molecular-weight heparin on quality of life and whether such treatment affects tumor growth or dissemination," write the authors. At time of publication, they add, at least six additional low molecular weight heparin trials in cancer patients, aiming to enrol around 3500 patients in total, are ongoing.

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BRCA1/2 mutations predict ovarian cancer survival

➜ JAMA

Among women with invasive epithelial ovarian cancer, mutations in the BRCA1 or BRCA2 genes are associated with improved five-year survival in comparison to women who do not carry the mutations. The UK study revealing that BRCA2 carriers show the best prognosis represents the largest BRCA-associated ovarian cancer outcomes study reported to date.

Approximately 10% of women with invasive epithelial ovarian cancer carry deleterious germline mutations in BRCA1 or BRCA2. The goal of the study by Paul Pharoah and colleagues, from the University of Cambridge, UK, was to gain a better understanding of the effect on survival of BRCA1/2 mutations compared to wild-type BRCA1/2 from a multiple case series of epithelial ovarian cancer.

In the pooled analysis, participants were drawn from 26 international studies that had enrolled participants between 1987 and 2010 (10 studies from the US, six from Europe, two from Israel, one from Hong Kong, one from Canada, one from Australia and five from the UK). Altogether data were obtained from 3879 women with ovarian cancer – 909 with pathogenic germline mutations in BRCA1, 304 with germline mutations in BRCA2 and 2666 who did not carry BRCA1 or BRCA2 mutations.

Results show that the five-year overall survival was 36% (95%CI 34%–38%) for non-carriers, 44% (95% CI 40%–48%) for BRCA1 carriers, and 52% (95%CI 46%–58%) for BRCA2 carriers.

The study also showed that the clinical characteristics of epithelial ovarian cancer among BRCA1/2 carriers differed from that of non-carriers. Tumours with serous histology, high grade and advanced stage were all more likely among carriers of both mutations.

In a secondary analysis, the investigators found that the survival advantage conferred by BRCA1 mutations was partially mitigated as the mutation site moved from the 5' to 3' end. This suggests, they write, that the site of the BRCA1 mutation may be of individual prognostic importance.

"*BRCA1* and *BRCA2* carriers with EOC [epithelial ovarian cancer] respond better than non carriers to platinum-based chemotherapies and have improved survival despite the fact that the disease is generally diagnosed at a later stage and higher grade," write the authors. The findings, they add, could be used by healthcare professionals for patient counselling regarding expected survival.

"Given the important prognostic information provided by *BRCA1* and *BRCA2* status and the potential for personalized treatment in carriers, the routine testing of women presenting with high grade serous EOC may now be warranted," they write.

In an accompanying commentary, David Hyman and David Spriggs, from Memorial Sloan-Kettering Cancer Center, New York, write that the findings represent the latest evidence that ovarian cancer is a much more genetically and biologically heterogeneous disease than previously appreciated. "Further studies in similarly large data sets are needed to better understand the effects of somatic and epigenetic alterations in *BRCA* gene function as well as

complex interactions with other inherited alleles. The accelerating availability of detailed somatic and germline genetic information will challenge all physicians who stand at the bedside of patients with cancer and struggle to deliver compassionate, individualized care."

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Adjuvant chemotherapy improves outcomes following D2 gastrectomy

→ The Lancet

Adjuvant chemotherapy should be considered as a treatment option after curative D2 gastrectomy, the phase 3 CLASSIC study has concluded.

In Eastern Asian countries (especially Japan and Korea) D2 lymph node dissection (defined as dissection of group 1 and 2 lymph nodes) is regularly performed as a standard procedure for gastric cancer over D1 lymph node dissection (dissection of group 1 lymph nodes only). In western countries, D2 dissection has been associated with higher morbidity and mortality, although recent studies demonstrate that western surgeons can be trained to perform D2 gastrectomy for selected patients with low morbidity and mortality.

With guidelines now advocating D2 dissection in centres with specialist expertise, increased acceptance of D2 gastrectomy raises questions about the optimum adjuvant therapy for patients with operable gastric cancer. The Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) study, was designed to compare the effect of adjuvant capecitabine plus oxaliplatin after D2 gastrectomy with surgery alone on disease-free survival in patients with stage II or III gastric cancer.

In the study, led by Yung-Jue Bang from Seoul National University College of Medicine, in Jongno-gu, Seoul, 1035 patients with stage II or III gastric cancer were randomly assigned in a 1:1 ratio to adjuvant chemotherapy (n=520) or surgery alone (n=515). The study was undertaken in 37 centres in South Korea, China and Taiwan.

Results show that the three-year disease-free survival was 74% in the chemotherapy and surgery group versus 69% in the surgery alone group (HR 0.56, 95%CI 0.44–0.72; P<0.0001). Grade 3 or 4 adverse events were reported in 56% of patients in the chemotherapy and surgery group versus 6% in the surgery only group.

"This study shows that a 6 month course of chemotherapy after D2 gastrectomy improves 3-year disease-free survival compared with surgery only," conclude the authors.

Although overall survival data from the CLASSIC trial are not yet mature, the results suggest an improvement with chemotherapy compared with surgery alone. "An analysis after a median follow-up of 5 years is planned to conclusively establish the overall survival benefit of capecitabine and oxaliplatin in this setting," write the authors. A key question for the trial, (as with any trial undertaken in one geographical region), they add, is whether findings can be generalised to other regions where disease management practices might differ.

In an accompanying commentary, Toshirou Nishida, from Osaka Police Hospital, Japan, raises the issue of adherence and safety. With more than half of patients in the CLASSIC study who were treated with chemotherapy experiencing grade 3 or 4 adverse events, nearly 10% withdrawing due to adverse events and 20% refusing treatment, he writes, non-adherence could be considered a risk of compromising disease outcomes.

"Identification of higher-risk patients and prediction of drug efficacy by biomarkers, and introduction of targeted agents such as trastuzumab, should be considered for adjuvant therapy of gastric cancer in the future," writes Nishida.

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■ T Nishida. Adjuvant therapy for gastric cancer after D2 gastrectomy. *ibid*, pp 291–292

Everolimus overcomes resistance to hormone therapy

→ New England Journal of Medicine

Everolimus combined with the aromatase inhibitor exemestane extended progression-free survival in postmenopausal women with advanced hormone-receptor-positive breast cancer, the BOLERO-2 study has found. The international phase III study, first published online to coincide with presentation at the 2011 San Antonio Breast Cancer Symposium, showed that combination treatment more than doubled progression-free survival compared to exemestane alone.

Resistance to endocrine therapy in breast cancer has been associated with activation of the mammalian target of rapamycin (mTOR) intracellular signalling pathway. Everolimus, an immunosuppressant agent used to prevent organ transplant rejection, is known to inhibit the mTOR protein. In preclinical studies, everolimus in combination with aromatase inhibitors resulted in both the synergistic inhibition of proliferation and the induction of apoptosis.

In the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study, José Baselga, from Massachusetts General Hospital Cancer Center, Boston, and international colleagues, randomly assigned 724 women with hormone-receptor-positive advanced breast cancer to receive either the combination of everolimus and exemestane (n=485; combination-therapy group) or exemestane and placebo (n=239; exemestane only group). The patients, who were recruited from 189 centres in 24 countries, had experienced either recurrence or disease

progression while receiving previous therapy with a nonsteroidal aromatase inhibitor (anastrozole or letrozole) in the adjuvant setting or to treat advanced disease.

At interim analysis the median progression-free survival was 6.9 months in the combination therapy group versus 2.8 months in the exemestane-alone group (HR 0.43, 95%CI 0.35–0.54; $P<0.001$). According to central assessment, the median progression-free survival was 10.6 months in the combination therapy group versus 4.1 months in the exemestane-alone group (HR 0.36, 95%CI 0.27–0.47; $P<0.001$).

Serious adverse events were reported by 23% of patients in the combination therapy group versus 11% in the exemestane-alone group. Stomatitis was the most common grade 3 or 4 adverse event, occurring in 8% of patients in the combination group versus 1% in the exemestane-alone group. This was followed by anaemia (6% vs >1%), dyspnoea (4% vs 1%) and hyperglycaemia (4% vs >1%).

The positive results in the study, write the authors, are consistent with the outcomes of two earlier studies of everolimus and anti-oestrogen therapy in hormone-receptor-positive breast cancer patients. In one study, neoadjuvant everolimus combined with letrozole improved the clinical response rate and decreased tumour cell proliferation in patients with newly diagnosed breast cancer; while in a second study the combination of everolimus and tamoxifen increased progression-free survival in women with oestrogen-positive advanced breast cancer previously treated with an aromatase inhibitor.

"Taken together, these studies suggest that everolimus adds to the anticancer activity of antiestrogen therapy in a variety of clinical settings and with different classes of endocrine agents," write the authors.

But benefits should be weighed against the side-effects observed with everolimus, they add. "The potential of everolimus to benefit patient survival is not yet known," they caution.

■ J Baselga, M Campone, M Piccart et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *NEJM* 9 February 2012, 366:520–529

Adjuvant chemotherapy adds no benefit over chemoradiation alone in nasopharyngeal cancer

➜ Lancet Oncology

Adding adjuvant cisplatin and fluorouracil chemotherapy to concurrent chemoradiotherapy in patients with nasopharyngeal carcinoma confers no survival benefit, reports a Chinese study.

In recent years, seven randomised phase III studies comparing chemoradiation with radiotherapy alone have confirmed the value of chemotherapy on survival for advanced nasopharyngeal carcinoma. However, with three of these trials adding concurrent chemotherapy to radiotherapy only and four using the regimen of concurrent chemoradiotherapy plus adjuvant chemotherapy, investigators have been "unclear" as to whether adjuvant chemotherapy might deliver additional survival benefits over concurrent chemoradiotherapy.

In the current study, Jun Ma and colleagues, from Sun Yat-Sen University Cancer Centre, Guangzhou, China, set out to investigate whether addition of adjuvant chemotherapy to concurrent chemoradiotherapy delivered further benefits. Between June 2006 and March 2010, 508 patients with non-metastatic stage III or IV nasopharyngeal carcinoma were randomised to receive concurrent chemoradiotherapy plus adjuvant chemotherapy (n=251) or concurrent chemoradiotherapy alone (n=257).

Patients in both groups received 40 mg/m² cisplatin weekly for up to seven weeks, given concurrently with radiotherapy at 2.0–2.27 Gy per fraction, with five daily fractions per week for six to seven weeks. In addition, the chemotherapy adjuvant group received 80 mg/m² adjuvant cisplatin and 800 mg/m² per day fluorouracil for 120 h every four weeks for three cycles. The study was conducted in seven institutions in China.

At a median follow-up of 37.8 months, the estimated two-year failure-free survival was 86% in the chemoradiotherapy plus adjuvant chemotherapy group, versus 84% in the chemoradiotherapy only group (P=0.13). Adverse events were similar in both groups, with the most common being stomatitis, which occurred in 31% of patients receiving chemoradiotherapy plus adjuvant treatment and 32% receiving chemoradiotherapy alone.

"In our trial, adjuvant cisplatin and fluorouracil chemotherapy did not improve outcome, with no significant effect on the risk of treatment failure, or estimated 2 year failure-free survival, overall survival, distant failure-free survival, or locoregional failure-free survival," write the authors.

One possibility, they add, is that adjuvant cisplatin and fluorouracil does not represent an effective combination for eradication of micrometastases in nasopharyngeal carcinoma. "New combinations of more tolerable drugs that might improve efficacy of chemotherapy as an adjunct in advanced nasopharyngeal chemotherapy should be investigated," they write.

In an accompanying commentary, Joseph Wee, from Duke-NUS Graduate Medical School, Singapore, writes that two recent reports suggest that chemoradiation with first-generation drugs appears to work only in patients with earlier stage disease with lower distant tumour burden.

This raises the question, he adds, of whether the addition of a third or fourth agent might make a difference to outcomes. "This strategy is being investigated by several groups in the phase 3 setting, and are being done in the neoadjuvant setting to overcome the poor compliance if chemotherapy is given after radiotherapy," he writes.

■ L Chen, C Hu, X Zhong et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol* February 2012, 13:163–171

■ J Wee. Nasopharyngeal cancer: a promising future. *ibid*, pp 116–117

Prostate cancer units: it's about options and quality

Peter McIntyre

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Men diagnosed with prostate cancer have a wealth of options on how to proceed, but they can pay a high price if the quality of treatment is substandard. Could delivering all prostate care through specialist multiprofessional units be the answer to safeguarding both standards and choice?

The most common cancer in men has seen a rapid increase in cases and treatments over the past two decades. About 382,000 men in Europe are diagnosed with prostate cancer each year, and there are 89,000 deaths. However, there has been a lack of clarity over the best way to match the right treatment to the right patient.

There are at least three treatments, each about as good as the other in skilled hands: surgery (radical prostatectomy), radiotherapy and brachytherapy, in some cases combined with hormonal therapy. After a rapid increase in the number of surgical cases in the 1990s and early years of this century there has been a pull back from aggressive treatment in early or indolent cancers.

The after-effects of treatment, particularly impotence or incontinence, scare a lot of men and there is increasing recognition that quality of life is of great concern, alongside a desire to be rid of the cancer.

Patients who are newly diagnosed with prostate cancer have choices to

make. Do they opt for immediate treatment or for active surveillance? If they opt for treatment, which is best for them?

There is a third choice, of which patients may not be sufficiently aware, and that concerns the kind of centre where their treatment and care will take place.

It is widely accepted that cancer is best treated in a multidisciplinary setting by specialists with expertise in the particular disease, backed by a multiprofessional team. While this is becoming the norm for breast cancer, it is not widely practised for prostate cancer.

Last year the *European Journal of Cancer* published a discussion paper from the European School of Oncology (ESO) promoting specialist prostate cancer units and setting out proposals for what that might mean in terms of professional staff and experience (see box, p 62). The paper was reminiscent of proposals for breast cancer specialist centres published in the 1990s as part of a European movement to improve treatment and prevent overtreatment. It meant in effect that unless a surgeon or radiotherapist was going to specialise in this disease, they had no business dabbling in it.

The same thing may happen, eventually, for prostate cancer, but the movement is slow to gather momentum. The Deutsche Krebsgesellschaft (German Cancer Society) has taken the lead by setting up a network of certified prostate cancer units. The UK National Institute for Health and Clinical Excellence (NICE) has set minimum standards, under which, for example, specialist urology teams should undertake a minimum of 50 radical operations per year.

Speaking the same language

Riccardo Valdagni is director of the Prostate Cancer Programme at the Istituto Nazionale Tumori, in Milan, coordinator of ESO's Prostate Cancer Programme and lead author of the ESO paper. He says that moving to a multidisciplinary approach is a challenge. "Urologists, radiation oncologists and medical oncologists have different approaches to the disease and speak different languages. The most ambitious – though necessary – step when the Prostate Cancer Programme was established was to share evidence-based as well as institution-adapted guidelines for the diagnosis, therapy, observation, and follow-up of prostate cancer patients.

"The general worldwide approach is that the patient has a biopsy, he receives a prostate cancer diagnosis from the urologist, and then the urologist generally makes the first proposal of therapy. We prefer to have a urologist, radiation oncologist and psychologist (with a medical oncologist on demand) meet with the patient, discuss the therapeutic and observational options, and offer support for decision making. International guidelines all over the world say we have three equally effective therapies, so we cannot decide, as doctors, which is the best."

Patients are then encouraged to choose the treatment, weighting their values and priorities, says Valdagni. Is erectile dysfunction a major issue for them? What about urinary incontinence? "One patient may say, 'yes, very important'. Another may say, 'I don't mind about side-effects, I want the cancer out of my body as soon as possible.'"

In Valdagni's centre, few patients ask the clinician what he would do in their shoes. He thinks this is because they have enough time and information to make a decision, with psychological support if necessary.

"In general, the problem of saying 'Hey doctor, what would you do?' is related to the psychological effect of being diagnosed with cancer. Patients may prefer at first to have someone take the decision for them. Offering exhaustive information on all his options and supporting him psychologically, we try to help the patient find his way. The patient, instead of being an object of physician care, can become the subject of his care, deciding what is best for his quality of life."

At the Milan Prostate Cancer Programme, most patients with small or clinically indolent disease choose active surveillance. Of those who drop out from active surveillance and have treatment, about 45% choose surgery, 50% radiotherapy and 5% brachytherapy.

The pattern in monospecialist centres is quite different, and it seems that unless they work together, specialists, perhaps unconsciously, influence patients in favour of their speciality. One paper suggests that, if the patient sees only a urologist, 70–80% opt for surgery. If they also see a radiation oncologist, 70% choose radiation.

Louis Denis speaks as a founding member of the European prostate cancer patient group Europa Uomo, which advocates for patient-centred care where quality of life is as important as survival. He is also the director of the Antwerp Oncology Centre, and says that, while multidisciplinary care is widely accepted in theory and is a legal requirement in Belgium, it is not widely implemented. "We still face the dilemma between the traditional freedom of treatment choice for the individual specialist and

"We have three equally effective therapies, so we cannot decide, as doctors, which is best"

Making the choice

"IT WAS A PERSONAL DECISION TO DEFEND MY QUALITY OF LIFE"

Enrico Rambaldi is Professor of Philosophy at the University of Milan, an expert in bioethics and editor of the *Italian Journal of History of Philosophy*.

He found that his skills and training had not prepared him for making a decision about his prostate cancer.

He was diagnosed in 2008, at the age of 72. He not only had prostate cancer but also an associated sepsis that nearly killed him. "For some days I was between death and life," he says.

When he recovered he visited some of the best specialists in Milan to ask their advice. "I was just going from one to another asking what they suggested. The choice which was offered to me was between a surgical operation and radiotherapy.

"My reaction was not very good. I was worried about the dangers in relation to sexual activity and incontinence. I was really very, very unhappy.

"I was changing my mind from one day to another day. One day I'd say, 'I have to have radiotherapy,' talking with my wife. Then I decided to go for surgical intervention. I fixed the date for my operation and every two or three days I changed my mind.

"As a philosopher I don't know anything about my body. I am dependent on external information."

In the end Rambaldi opted for active surveillance.

"I decided to start the active surveillance after several talks with Valdagni. I thought that it would be unwise to put the quality of my life in danger. It really was a personal decision to defend my quality of life. I didn't want to get into problems with incontinence or no sexual activity because I was afraid. I feel well supported from the psychological point of view.

"It was a very good decision. I don't even take any medication. I go for a PSA check every three or four months, a consultation twice a year and one biopsy in the four years."

Rambaldi says that the quality of his life has actually improved since he was diagnosed. "I appreciate more than before the pace of time. I am more careful not to waste my time and to produce as much as I can in my philosophy."

the better outcomes of cancer treatment by multidisciplinary management.

"There is known overtreatment for patients with prostate cancer for a number of reasons. Among these we should recognise lack of correct evaluation of the patient's health status, ignorance of the clinical course of low-risk, low-volume prostate cancer and the availability of advanced technology that cannot rest idle. The slogan of Europa Uomo remains: 'First the Patient, then his Cancer'."

UNDERSTANDING THE OPTIONS

Lawrence Drudge-Coates, clinical nurse specialist in urological oncology at King's College Hospital, in London, agrees. His is a specialist unit in all but name, with 260 new prostate cancer patients a year. As one of two key workers for patients, he runs his own clinics and encourages patients to take their time in making an informed decision.

"One of the key roles that the clinical nurse specialist plays is to take patients through the pros and cons in more detail in laymen's terms. I explain what we have found from the biopsies and scans and whether it is an aggressive tumour. I go through the treatment options, but not in too much detail. If a patient is being given a diagnosis, their ability to take in information is very greatly reduced. You give a bit of information and supplement it with good literature, and I give the patient my contact details as key worker, and the opportunity to discuss issues further.

"Offering exhaustive information on all his options, we try to help the patient find his way"

Feeling cleansed by surgery – at a world class centre

For Daniel Sencier, who was diagnosed with prostate cancer in the UK at the age of 58, choosing surgery felt like cleansing himself of the cancer.

After some bad experiences with lost notes and other problems at his local hospital in Cumbria, he opted to travel to a specialist urology centre at Addenbrooke's in Cambridge, where he had a robot-assisted laparoscopic prostatectomy in November 2010.

"I imagined having radiation and my prostate being fried inside of me and ending up as this ball of dead junk you would be carrying around inside you for the rest of your life. You could never be sure. Surgery seemed very clinical to me. It meant somebody looking at something, seeing that it was bad, cutting it out and throwing it in the bin. So that when I had surgery my prostate was in Addenbrooke's and I was back in Penrith, a long way removed from it."

In a blog, Sencier described the contrast between his local hospital and a specialist centre. "At [my local hospital] they are all lovely well-meaning people and they all want to do the best by you with every bone in their bodies. They are just drowning and don't have the quality people or the facilities to cope. My Urology Nurse, Jill at [the district hospital], is not just the Urology Nurse. She is a secretary, counsellor, cleaner, tea maker and multi tasked nurse. I saw about 12 different people at Addenbrookes who all did just a small part of Jill's job, but did it to perfection, because they simply had the time to."

Speaking to *Cancer World*, Sencier said, "At hospitals like Addenbrooke's, where they have the robotic surgery machine, the surgeons have all been out in America for training. All the support staff go there and they have a mentor who comes over from the States and works with the teams until they have done about 50 operations. There is a huge programme going on. While in a hospital like [the district hospital] where the guy does maybe 20 operations a year, he does his best with the knowledge he has got. It is a lonely place for him I guess.

"It is not just the removal of the cancer that makes the difference at the specialist hospitals, it is the continence and the erectile dysfunction. You are more or less guaranteed if you go to Addenbrooke's that you are not going to be incontinent for more than a few weeks afterwards, but I hear terrible stories in the chat rooms of guys who are still incontinent several years afterwards."

"Not all cancers have to be treated and I think this is still quite an alien concept for most patients. If active surveillance is an option I would explain why. It may be a cancer that is not particularly aggressive. In many cases we advise them to have further biopsies. There is a contract between myself and the patient."

Drudge-Coates takes time to talk about the major possible effects of treatment – erectile dysfunction and incontinence. "You have to be very upfront and state that these are key issues in relation to surgery and radiotherapy. I don't call them a side-effect because it belittles them. However, many patients already have erectile dysfunction prior to treatment because of prostate cancer or other medical issues, which we always assess prior to treatment.

"You can treat erectile dysfunction, and what we do here is actually begin patients on PDE5 inhibitors such as Viagra after the urethral catheter has been removed following surgery. There is evidence to suggest that the earlier you introduce treatment, the more effective it is likely to be."

The specialist nurse advises patients that incontinence should gradually improve over time if they undergo a course of pelvic floor exercises. "A small number of patients are never going to be completely continent, related to a number of issues, including the complexity of the surgery."

Drudge-Coates advises patients to be upfront in questioning surgeons about

"Not all cancers have to be treated and I think this is still quite an alien concept for most patients"

incidence rates for incontinence and erectile dysfunction. "I openly tell patients these are things you have got to be aware of because these are life-changing events. In the UK we are seeing patients cherry-picking where they go for surgery based on the experience of the surgeon and based on the outcome, which makes perfect sense.

"I think this will evolve as cancer centres publish their results. In my experience patients are asking surgeons more direct questions about complication rates and incontinence. 'How good are you as a surgeon?' 'How many of these procedures have you done?'"

Just as urologists and radiotherapy oncologists have to specialise in prostate cancer, so too do nurses. Drudge-Coates is on the board of the European Association of Urology Nurses, which is in the process of defining the core competencies of the specialist nurse and their training needs.

What outcomes should a centre achieve?

The ESO discussion paper published online in December 2010 did not attempt to specify what outcomes specialist prostate cancer centres should achieve, and may be criticised for advocating something without clear evidence of improved outcomes.

However, Valdagni is confident that the evidence will come. "We know that caseload is strongly related to the quality of radical prostatectomy and we also know that caseload in radiation therapy is related to less use of secondary treatment. That means that if the centre has a high caseload and works with a lot of prostate cancer patients, radiation will be better and results will be better and secondary treatment for failure will be less."

A network of certified units across Europe

The ESO discussion paper, 'The requirements of a specialist Prostate Cancer Unit',[1] argues that prostate cancer units are the most suitable structures for organising specialist multidisciplinary care for patients at all stages of the disease, and that the multidisciplinary approach offers patients the best chance of receiving high-quality medical procedures administered by a team of specialists, which is able to tailor treatment and observational strategies to their needs, and ensure access to specialist counselling, supportive care and rehabilitation. The paper proposes general recommendations and mandatory requirements for prostate cancer units, with a view to laying the basis for a network of certified units across Europe.

- Prostate Cancer Units are best established in large or medium sized hospitals covering populations of at least 300,000 people and seeing more than 100 newly diagnosed cases of prostate cancer each year, and within a multiprofessional team, where supportive care as well as clinical excellence can develop.
- Units must have written protocols for diagnosis and the management record and on diagnosis pathology, treatment clinical outcomes and follow-up, including side-effects and complications. The data must be available for audit.
- Uro-pathologists specialising in prostate disease should see at least 150 sets of prostate biopsies a year and spend 50% of their time working in this field. Each centre should have two or more urologists trained in prostate cancer, each carrying out at least 25 radical prostatectomies a year and spending 30% of their time on prostate disease. Radiation oncologists should treat at least 25 prostate cancer patients a year or 15 prostate cancer brachytherapy procedures. Similar levels of caseload and time are set for medical oncologists.
- In addition a centre should have one or more nurse specialists in prostate care, as well as specialist radiologists, medical physicists, radiation therapy technicians, physiotherapists with special training, palliative care specialists, and professionals who can offer psychological support and counselling about changes in sexual function.
- Members of the Prostate Cancer Unit core team must attend weekly multidisciplinary meetings where 90% of cases would be discussed for audit and for external verification.
- The patients' right to information and self-determination should be respected and men offered clear and easy-to-understand written and oral information. Patient advocates should be part of the network and every patient should be provided with a copy of his treatment and follow-up plan.
- Services may need to be reconfigured to staff specialist units. However, the paper says that such changes can provide financial savings and avoid multiple consultations.

The paper concludes that European countries "should consider the certification of Prostate Cancer Units as a necessary way forward to ensure that men with prostate cancer receive optimal treatment and care."

1. R Valdagni et al. (2011) The requirements of a specialist Prostate Cancer Unit: a discussion paper from the European School of Oncology. *Eur J Cancer* 47:1–7

"We are seeing patients cherry-picking where they go for surgery based on the experience of the surgeon"