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Michael Baumann

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Hope or hype?

Kathy Redmond ■ EDITOR

Decades of experience have taught us to guard against the temptation to trumpet early impressive results as breakthroughs. Yet some of the comments over the promising results from trials testing Herceptin (trastuzumab) in early-stage breast cancer raise questions about how well that lesson has been learnt.

In a glowing NEJM editorial, Gabriel Hortobagyi, a breast cancer specialist at the MD Anderson Cancer Center in Texas, described the results as "revolutionary", "simply stunning" and "maybe even a cure". Jo Anne Zujewski, director of breast cancer research at the US NCI, said the findings support her belief that breast cancer has become curable in increasing numbers of women.

Predictably, these statements fuelled demand for early access to Herceptin from patients concerned that they would die without this drug and, not surprisingly, sections of the popular press gave over their front pages to champion their cause. Such was the pressure in the UK that the government instructed local health authorities that they should not restrict use of the drug in patients with early breast cancer on the grounds of cost, even though the drug was not licensed for use in this setting, and indeed the manufacturers had yet to submit an application to EMEA.

This decision may return to haunt the UK government when equally compelling and emotional situations arise, as they inevitably will.

In a tough editorial, the *Lancet's* editor, Richard Horton, voiced strong criticism of decisions in the UK and other countries to bypass official approval procedures. He pointed out that available evidence on the drug's safety and efficacy in the adjuvant setting is insufficient to make reliable judgements, particularly since interim results are prone to showing large treatment effects that may not stand the test of time.

Some US-based breast cancer advocacy organisations agree with this assessment and have chastised cancer experts for using the word "cure", because such premature confidence may fuel unrealistic expectations.

We cannot overlook the situation facing either the women newly diagnosed with HER2+ breast cancer right now who are desperate to optimise their chances of survival, or the doctors who must tell their patients that only those who can afford to pay will get the drug. But should we accept that complex decisions on access to cancer therapies are made in haste, in reaction to sensationalist media campaigns?

Faced with the challenge of spiralling healthcare spending there is a need for balanced debate to tease out when, if ever, it is acceptable for a cancer drug to be paid out of the public purse prior to the drug's approval for a specific indication.

Michael Baumann: the dynamo of Dresden

Marc Beishon

Michael Baumann went into radiation oncology because it has all the biological interest of medical oncology with added technical excitement. He claims the new targeted therapies will only come into their own when combined with radiotherapy, and last year he cofounded OncoRay, a state-of-the-art research facility, to help find out how this can best be done.

Last October, dignitaries flocked to Dresden to witness the reconsecration of the Frauenkirche, the great church reduced to rubble in World War Two, and rebuilt remarkably quickly after the reunification of East and West Germany. Meanwhile, another project was taking shape that is far from a reconstruction of the past – a new medical school at the city's University of Technology, the youngest and possibly the most progressive school in the country.

After reunification, federal funds poured into the old East Germany for many such projects – and attracted professionals such as radiation oncologist Michael Baumann, who in 1995 seized the opportunity to help carve out a new interdisciplinary cancer centre at the Carl Gustav Carus medical faculty and university hospital. Fast-forward 10 years, and he's now a director of the centre, professor of radiation oncology and has recently taken on the presidency of ESTRO, the European Society for Therapeutic Radiology and Oncology.

Both Baumann and the work he's set up in Dresden – including for example a new research facility called OncoRay – are becoming important markers in the European cancer community, and especially in radiation oncology – a specialty that despite its long history of effectiveness has suffered from lack of recognition and investment. While Baumann hammers home time and again the absolute imperative for all specialties to work far more closely together, there's no doubt that he's a champion of the radiation oncologists' cause through long-standing involvement in ESTRO's education and training committee, and a forensic knowledge of the key role of radiotherapy in cutting-edge cancer research.

"I believe radiotherapy is the optimal environment to bring in new molecular targeted substances, which are far from being curative themselves," he says. "We can prove that radiotherapy is extremely effective in eliminating cancer cells. If we fail, a recurrence could be down to just a few surviving cells – that's all. The combination of a weak biological agent and a

TOBIAS KOCH

At the opening of the OncoRay Centre, Dresden, June 2005. Baumann is a founding father of this state-of-the-art radiation research facility, which does pioneering work on molecular and biological imaging and targeting

"Radiotherapy is the best setting to bring in targeted drugs, which are far from curative themselves"

"You have the same biological principles relevant to medical oncology, but also all the technical issues"

very strong local modality in radiotherapy is very promising."

Radiotherapy, he adds, is also the most cost effective of all treatments, borne out for example in a recent ESTRO study called QUARTS (Quantification of Radiation Therapy Infrastructure and Staffing needs – see also *Cancer World* 9, October 2005). "That should convince anyone to invest – but they're not doing it," says Baumann, who points to a wide diversity in radiotherapy provision and practice across Europe.

The cost of the machinery, competing demands on health service budgets, and the trend to make short-term purchasing decisions are clear factors that contribute to this 'blind spot' about radiotherapy, comments Baumann. But it also suffers from a poor image among the public and politicians – especially in countries such as Germany, where there is a strong anti-nuclear power lobby that muddies the waters when it comes to discriminating between 'good' and 'bad' radiation.

All this can also feed back into the education system and deter young doctors and other scientists from pursuing a career in radiation oncology and related topics such as radiobiology and radiation physics. In Baumann's case, as in many others who get turned on to a particular specialty, it was by chance that he found himself inspired by a good teacher of radiobiology at an early stage at medical school in Hamburg.

"I wanted to do medicine because it combines biology and social science, and it has a strong component of interaction with people – although I could also have been an historian, and I'm still very interested in history." At medical school, Baumann opted early on to combine science and research in his training and to become a 'doctor' (in Germany, those who train only as physicians are plain 'mister').

"What really stimulated me about radiobiology was not the radiation protection side but its application to cancer research. At Hamburg, the radiation biology lab was already working on tumour models directly related to cancer – whole tumours, not single cells – and bringing these complex tumour models into a clinical setting. They were doing fractionated radiotherapy [breaking up the total dose into many shorter sessions], for example, and it was very easy to explain to students why it had a direct impact on clinical practice." The scene was also set for work on perfusion, hypoxia and imaging, although molecular targeting was not yet on the table.

Apart from the facts about radiotherapy – that for example 50% of patients cured of cancer have a radiotherapy component (a figure that is rising) – Baumann found it more diverse than medical oncology as a specialism. "You have the same biological principles relevant to medical oncology, but also all the technical issues such as imaging, and the possibility of not only administering drugs intravenously and over different times, but also to shape your agent by local or spatial means. It's a fascinating way of treating cancer – you have to know as much about your patients as a medical oncologist, but those extra technological aspects are turning out to have a real resonance today."

In Germany, as in several other countries, radiation oncologists also administer chemotherapy in conjunction with radiotherapy, but the term 'clinical oncologist' is not used – which does add to the problem of knowing who does what around Europe, comments Baumann.

As a specialty, radiation oncology is not very visible in many medical schools, he feels. "It's not taught at some schools – students may just be shown a linac [linear accelerator], which is hardly very interesting." Needless to say, at Dresden there's an interdisciplinary oncology course in the medical school that lasts eight weeks.

Baumann's interest in research at Hamburg saw him leave for a two-year laboratory spell at Harvard Medical School almost immediately after graduating and before he started work as a radiation oncology resident at the Hamburg-Eppendorf University Hospital. It's a path well trodden by many high flyers featured in *Cancer World* – as Baumann reiterates, it's very hard to build even a small research interest while working long hours in the clinic if you don't have the grounding in setting up lab projects, writing papers and obtaining grants.

It's also a great opportunity to make career-long contacts – it's no surprise that Baumann cites as his key mentors not only his Hamburg thesis supervisors but also radiation oncology luminary Herman Suit, who is now officially retired from Harvard and Massachusetts General but who continues to impress with a 'can do' attitude and ability to get projects moving.

Commenting on the strengths of the US, he notes that some European centres are actually ahead of America in the use of certain clinical techniques, such as Heidelberg with ion therapy. Regarding possible controversies in the use of radiotherapy, for example the different application in rectal cancer in various countries, he considers that historical treatment regimens and strengths are often key factors. Germany, for example, has a track record in highly skilled head and neck surgery, which means less radiotherapy is used for these tumours than in the US and elsewhere.

In many cases, he adds, there just aren't enough data to make hard and fast judgements on the increasingly complicated treatment options, and he points to the increasing availability of European cancer statistics as a good first step in highlighting the wide variations in outcomes among countries, which will hopefully fuel more large-scale trials.

JÖRG GLÄSCHER / LAIF

What Baumann is certain about is the need for all specialties to have the best grounding and up-to-date knowledge in their fields. This became apparent in his specialty during his residency at the University Hospital in Hamburg, in the early 1990s, when a serious problem came to light regarding late damage to a large number of patients who had received radiotherapy at that hospital during the 1980s. Baumann says the problems, which mainly affected patients treated for prostate and rectal cancer, were largely the result of a lack of clinical radiobiology understanding, and the whole episode had a profound effect on him.

"It brought home to me that radiation oncology is a very specialised field and you need a very sound education to be a good clinician,

Some European centres are actually ahead of the US in the use of certain clinical techniques

JÖRG GLÄSCHER / LAIF

particularly if you are applying new treatments. I also learnt that to make changes in clinical practice you must do them in formal study settings, and most importantly you need good follow-up of patients who are treated with anything other than completely standard therapy."

As Baumann adds, late damage is unique to radiotherapy – or at least we don't know yet of very-long-term effects of chemotherapy. Since the Hamburg incident, all radiation oncology treatment has to be followed up in Germany – possibly the only country with such a requirement, he reckons.

Meanwhile he completed his residency at Hamburg while also running an experimental radiotherapy lab, where among the hot topics was modified fractionation, later to appear in clinical practice. It was there that he laid the groundwork for his present clinical specialties: treatment of head and neck, lung and sarcoma. Then – it being usual to move on in German career progression – Baumann chose to move to Dresden, although the problems at Hamburg gave added impetus.

"I did have several options, including moving abroad. But it was clear there was going to be a boost to science and medicine in the old East Germany and there were plans to really put Dresden on the map with support for academic research." Dresden is also a nice city, he adds, and his wife Bettina, a nuclear medicine specialist, had already moved there in advance.

It's certainly the case that Dresden's medical faculty has picked up a reputation for being rather less stuffy than the more traditional institutions in Germany, with younger senior staff (Baumann arrived aged just 33), and a progressive attitude. "Dresden's medical faculty has been ranked as the most dynamic in Germany," he says (and the medical faculty's dean has been quoted as saying, "Our main principle is to make unconventional things happen.").

There are two paths that the medical school is pioneering in general. One is a change to problem-based learning for students, an approach developed in partnership with Harvard Medical School. The idea is to give students far more work to do on their own initiative rather than passively attending lots of traditional lectures. As Baumann explains, they are set problems such as 'theoretical' patients presenting with certain symptoms, and have to spend time researching and discussing the implications in small tutor groups.

"Now I don't have enough lecture slots to teach a systematic approach to radiotherapy – I can only give a couple of examples. At first we were worried that students would be less good at their exams – which are common to all German students – but they have been much better than average."

The upshot is that students are more tuned in to both clinical bedside issues and research. Indeed, Baumann says that, increasingly, real patient data will be introduced to a model that is actually more radical at present than Harvard's. "But you still need some systematic lectures,

"Dresden's medical faculty has been ranked as the most dynamic in Germany"

"It should be a European right to talk to both a urology surgeon and a radiation oncologist"

and we'll be putting more in as the curriculum develops," he adds. Academic staff are also trained in the new approach – "It's not usual for us to receive teacher training," he says.

The other trend is to fast track the right students into research, especially clinical research, and to help young doctors avoid the conflict between training and research that is as acute in Germany as in other countries, according to Baumann. The idea is to give doctors the kind of break that he enjoyed at Harvard – time out in the lab at an early stage, either at Dresden or abroad, and either for long spells or for, say, one week in every four.

There is also a strong emphasis on building up opportunities for translational research through close-knit interdisciplinary working, which Baumann says is critical to the success of the clinical side of the cancer centre.

For Baumann's work, early success in bringing in grants for experimental radiotherapy and radiation biology have led, 10 years later, to Dresden being one of the world leaders in preclinical testing of new radiotherapy approaches. "That's true for normal tissue research, run by a colleague, and tumour research, run by my group," he says. The approaches include modified fractionation, identifying mechanisms of resistance to radiotherapy, testing molecular targeted substances in combination with radiotherapy, and developing imaging modalities. "Hopefully in a couple of years we'll be able to stratify patients for particular treatments," he says.

One of the recent highlights for Baumann has been the establishment last year of the OncoRay centre – a snappy title that helped raise the visibility of its work from the start, he feels (its full title translates as Centre for Innovation Competence for Radiation Research in Oncology). This is one of six such federally funded science centres. It has several research programmes in train on the core topics of molecular and biological imaging and targeting, with state-of-the-art equipment in place, enabling the combined use of CT and PET (positron emission tomography), and four-dimensional techniques – moving radiotherapy through space and time. OncoRay is seeded with funding of some 12 million euros for five years, after which its results may enable it to become self-funding.

Baumann adds that other oncology research specialities are also strong in Dresden – he mentions a medical oncology colleague who has recently obtained a grant for stem cell work in conjunction with a branch of the Max Planck Institute in the city.

Much has gone according to plan in Baumann's research aims. The hard work to gain visibility in the early years has definitely paid off with large-scale funding today. However, there was one huge setback – a flood in 2002, when the river Elbe burst its banks and the basement labs in the hospital grounds were inundated. "It took about a year to set it up again," he says. "There was a lot of sympathy from funding agencies – but that only goes so far."

Baumann is also very happy with the way the cancer centre and clinical work has developed. He's currently director of the university cancer centre, a position that rotates among the oncology specialties so that no one feels their department is less valuable. A system of interdisciplinary tumour boards is in place, meeting at least three times a week to plan treatment. "Our feeling is that we should provide a service before treatment and even before diagnostic procedures – we have joint guidelines on how to proceed, so it doesn't matter who sees a patient first."

Such multidisciplinary working has, however, come fairly late to Germany, he adds, but all academic centres are going in this direction in

JÖRG GLÄSCHER / LAIF

the country. However, the psychological barriers and competition between specialties are tough to break down. As he says, a prostate cancer patient should have equal access to both a urology surgeon and a radiation oncologist to make a decision about a choice of effective treatments. "It should be a European right to talk to both – but it's not European fact. Competition is only good if you talk about it and put forward the arguments. Quality for a department is often defined by quantity – say the number of surgical procedures performed – and that's not always medically driven."

A big obstacle is also the resources needed to run a multidisciplinary centre "We don't get any extra funds at Dresden to provide the service – it needs time and personnel – but our patient surveys show how popular it is. Budget-holders must provide money for such services."

As he says, there is only one chance to get things right in curative settings, and so many things that can go wrong, including on the palliative side. He adds that, with studies showing that current best practice would lead to an overall survival gain of at least 10% even in developed countries, he is keen to take the messages to the wider platforms of ESTRO and FECS (Federation of European Cancer Societies).

As president of ESTRO, there are pressing investment and image concerns about radiotherapy to address. The recent enlargement of the European Union, in particular, has exposed a wide variability in radiotherapy provision – not surprising, when you consider the costs of linacs, radiation protection buildings and imaging facilities, and competing demands for other machinery such as MRI scanners. "Most healthcare budgets are too short term – a linac needs to be costed over 10 years or so," says Baumann.

The lobby for radiotherapy is much weaker than the drugs lobby, he adds, and equipment makers have relatively little clout compared with their pharma counterparts. Outdated equipment is a real problem, given the advances in imaging, planning software and dosimetry kit.

Personnel is another issue – apart from a shortage of radiation oncologists in some countries, Baumann points out that radiotherapy is always inter-disciplinary in itself, "We can't afford the shortage in radiation physicists either." He warns too of a trend towards having too many small centres – which is the case in Germany. One linac and a very low number of radiation oncologists simply can't provide good specialist care for curative treatment, he says.

But he picks out the image and importance

A big obstacle is also the resources needed to run a multidisciplinary centre

of radiotherapy as probably the key issue, and says there is a lot of excitement when he discusses in lectures the very promising pathways for combined radio- and molecular-targeted chemotherapy.

His priorities for his two-year ESTRO presidency are to expand the society to properly cover all European countries, and to build up the education and training work further (ESTRO has made good progress in establishing Europe-wide training records to aid professional mobility, for example).

He sees no contradiction between promoting radiation oncology as a strong specialty and improved interdisciplinary organ-based subspecialisation envisaged by FECS. If anything, discipline-based specialism will only increase as branches of oncology become more complex, and there's no way that ESTRO is going to stop arguing the case for, say, more linacs per head of population. What's needed at a higher level, he feels, are clear aims before any discussion of structure takes place, given the premise that there can only be a set of strong specialties in oncology.

"The question of whether we need a federation or a single society is not too interesting for me – we should first define aims, which I feel should include providing a good lobbying instrument for patients, good conferences and fostering oncology research at all levels." The aims he has in mind are really a scaling-up of the kind of inclusive, interdisciplinary cancer centre work he's involved in at Dresden. Good PR and 'branding', and concerted efforts to make the general population more aware of treatment alternatives, should also be cultivated at European level, he says.

That said, "I feel though that a federation could work well, and we should look at why FECS doesn't appear at the moment to be the unambiguous voice of oncology."

To some extent the debate will be shaped by both medical and technological progress, and radiation oncologists have no shortage of exciting tools either in action now or on the horizon. All important, as Baumann restates, is molecular targeting, either protecting normal tissues or for sensitisation of tumours, by integrating radiotherapy with molecular targets. Biological imaging using PET and MRI "will offer a host of information on how tumours are reacting" and is clearly a major step up from conventional anatomical imaging.

IMRT (intensity modulated radiation therapy) is also now in play, while more equipment such as proton and ion machines might be worthwhile, although some commentators are sceptical about possible gains. "The investment is huge – but that can't be an argument not to do it. For specialised indications – such as for children – reducing the volume of irradiated tissues say at the base of the skull is clearly advantageous."

Baumann doesn't have 100 million euros for an ion machine in the OncoRay unit at present, but few would bet against the Dresden team's ability to come up with the grants. In any case, he's keeping an eye on other possible routes, such as laser technology, which is developing apace (and for which the last Nobel prize in physics was awarded).

At home, Baumann likes to get away from work – classical music including opera is among his interests, as are reading history, biographies and mystery novels. He has no plans to move from Dresden but doesn't rule anything out.

At work, he says his team works on close personal terms – but he considers himself to be a demanding boss. "I see nothing wrong with that. If you don't move you are dead." The whole set up brings to mind the name, if not the current performance, of another feature of the city – its football team, Dynamo Dresden.

"Discipline-based specialism will only increase as branches of oncology become more complex"

Lost in translation

Anna Wagstaff

Cancer drugs often deliver less than they promise. The BDA believes the problem may lie not in the drugs themselves, but in the way they are targeted, tested and used. It organises regular get-togethers where the main players can share information and discuss strategies for the future.

With all the amazing imaging technologies now available, we should be able to design drugs to intervene with surgical precision in patient populations identified by predictive biomarkers. So why is it that most of the targeted drugs that have made it to the market have been less than spectacular successes?

Is it that cancer cells are too devious – they will always be one step ahead, finding little known back ways or creating new ones when their main pathways are blocked? Or is it simply that drug developers are having trouble getting their science right?

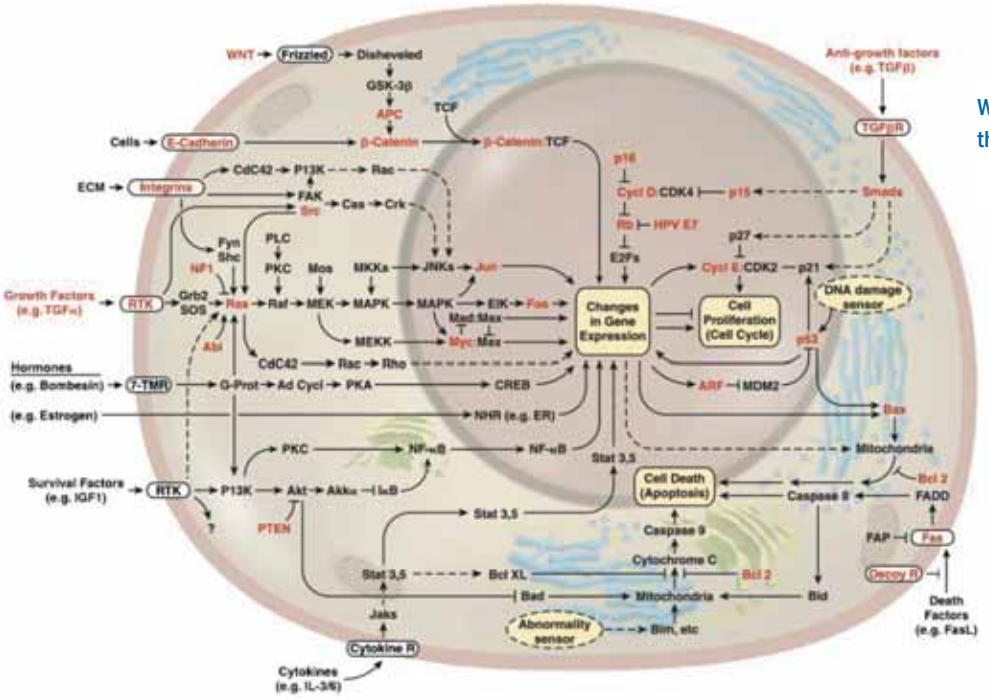
Heinz Zwierzina, chairman of the Biotherapy Development Association (BDA), is convinced it is the latter. He cofounded the Association in 2002 in order to promote the effective development of the new generation of cancer biotherapies. Zwierzina believes effective new therapies are being discarded at an early stage of development because of failings in the translational research and trial protocols. By the same token, he argues that many drugs that have made it to the market could be used to far greater effect if further work were done to establish the most effective dose and schedules, and to define the most responsive patient group and the most appropriate treatment setting.

One answer lies in bringing together drug developers, clinical research organisations and companies involved in diagnostics with regulators, translational and clinical researchers, and patient organisations, to try to develop a common approach to getting effective drugs to market. To that end, the BDA organises select conferences every 18 months, where representatives from all these areas meet in a secluded atmosphere, mull over the implications of recent developments and talk about lessons for the future.

Uncharted territory

The second such conference took place in Innsbruck at the beginning of October, under the title "Harmonisation of next-generation oncology drug development".

The need for harmonisation has come about because new imaging techniques have effectively torn up the traditional drug development rule book. Not only is this uncharted territory, there is not even agreement on how to conduct the exploration. Which of the burgeoning alternative tests and technologies are most appropriate for measuring what? Which biomarkers have a real clinical relevance and what do they tell us?



We are only just beginning to map the complexity of cell signalling pathways

Source:
Reprinted from D Hanahan and R Weinberg. The Hallmarks of Cancer. *Cell* 100:57–70. © 2000, with permission from Elsevier

Not only is this uncharted territory, there is not even agreement on how to conduct the exploration

Which protocols are most appropriate for drawing out the information we need to use a drug to maximum effect? These conferences aim to establish and expand common ground. And some common ground there certainly is.

For instance, it is commonly accepted that targeted drugs are generally very much less harmful than cytotoxics, which means less need for phase I trials – many trials are now collapsing the phase I into a single phase I/II.

Phase II trials, however, are now seen as absolutely essential. No longer are they just pilot studies to see whether it is worth investing in a phase III. They should be exploratory trials using translational research to try to establish proof of the principle of the mechanism of the drug in humans, to identify the characteristics that predict which patients will respond best, and to establish the most effective dose and schedule. Well that's the theory anyway.

Nick Botwood from AstraZeneca talked about the lessons they had learned from the development of Iressa (gefitinib) – a drug for non-small-cell lung cancer (NSCLC) that AstraZeneca withdrew from review by the European Medicines Agency (EMEA) very early in 2005 because some impressive evidence of tumour regression in early clinical trials did not translate into a statistically significant increase in survival compared to placebo in the overall population.

Iressa had been designed to work in patients with NSCLC exhibiting EGFR over-expression identified using an immuno-histochemistry test.

However, it has since transpired that there are at least four communicating receptors, some more important than others, and 14 possible mutations have been identified, each associated with different levels of response. It now turns out that Iressa actually works best in patients exhibiting an amplified EGFR which does not show up using immuno-histochemistry, but is detectable by the FISH (fluorescence in situ hybridisation) test. However, in the meantime, Roche got approval for a rival drug, Tarceva (erlotinib), whose phase III

IMPACT OF VEGFR-2 INHIBITORS ON OTHER TYROSINE KINASES

Compound	Phase	VEGFR-1	VEGFR-3	C-Kit	PDGFRB	c-Raf	b-Raf	Src	Flt-3	FGFR-1	EGFR
Vatalanib	III	2	18	13.5	13.5	-	-	-	-	-	-
Sorafenib	III	-	0.1	0.53	0.3	0.07	0.24	-	0.64	6.4	-
Sunitinib	III	≤ 1	≤ 1	≤ 1	≤ 1	-	-	-	≤ 1	90	10,000
AZD-6474	III	40	-	-	27.5	-	-	-	-	90	12.5
CP-547632	II	-	-	-	79	-	-	-	-	0.8	545
CEP-7055	I	0.8	1	-	-	-	-	-	0.3	27	-
Axitinib	I	1.4	-	0.5	≤ 1	-	-	-	-	12.8	-
GW-786034	I	5	1	-	-	-	-	150	-	-	590
Chir 258	I	1	1	0.15	2	-	-	508	0.008	1	169

Courtesy of Renzo Canetta, Bristol-Myers Squibb

The compounds in the left column are all designed to block VEGFR-2. The data show how selective each compound is for a range of other tyrosine kinases compared to its intended target (fold-selectivity vs VEGFR-2)

survival benefit was significant at p=0.001.

Bob Milsted, AstraZeneca's global head of regulatory affairs for oncology, accepts that there is a problem getting the science right, but he stresses that people must have realistic expectations about what can be achieved within a given time period. He argues that it will always be the case that when a new drug is ready for the market, researchers will only just have begun to understand how it works, and he points out that methotrexate, which is targeted at a specific enzyme, has been on the market for a good 40 years and there are still no validated biomarkers to indicate which patients respond best to it. What many people don't realise about targeted drugs, he says, is that you need a drug capable of hitting a given target before you can start to look at what the effects of hitting that target might be.

"When a new drug appears on the scene it is two things. One is a drug in development. The second is a pharmacological tool. It is not until I have the drug that I can shut down that signalling pathway and see what happens and start to explore the science. That is when I can start to tease out whether the pathway is driving the malignant phenotype in all patients, or only in some of them, and if it is only some, can I recognise them?"

Rachel Humphrey from Bristol-Myers Squibb, cast doubt on whether it would ever be possible to identify precise mechanisms, or indeed to establish whether a given drug is actually hitting its target rather than something else. Tyrosine kinases, for instance, are all so similar in structure, she said, that it is very likely that whichever pathway you aim at, you will end up blocking other pathways as well, and there is no way of knowing which is the pathway of greatest significance. The best chance of progress, she suggested, now lies in using combinations of inhibitors aimed at multiple targets.

Missing the target

What does this mean for our dream of the perfectly targeted anti-cancer drug? Jan Liliemark from the Swedish Medical Products Agency found Humphrey's message realistic but depressing. "For a drug that hits 20 different kinases or pathways, there is no point in investigating precisely how it works. There is no reason to believe that we can tell for each patient what this drug is actually doing or not doing." But his colleague Bertil Jonsson emphasised that this does not mean we give up trying to understand. "I believe it is our duty to try to understand what is happening. Of course we will always make mistakes, but a purely empirical approach cannot be the way forward."

Industry representatives, however, seem fairly relaxed in the face of this dawning recognition that we may never know the precise mechanism of drugs. A senior executive from Merck (KGaA) voiced strong optimism about the potential of intelligent combinations of targeted drugs. Merck, he said, is already working with other pharmaceutical companies to test the effectiveness of approved drugs used in combination. One example is a trial of Erbitux (cetuximab) used in combination with Iressa.

Issues of commercial confidentiality, competition and legal liability, once seen as serious obstacles to cooperation, are being circumvented by using non-commercial third parties – in this case it is José Baselga's team

You need a drug capable of hitting a given target before you can look at the effects of hitting it

in Barcelona that is doing the work. Interestingly, Merck is also looking at combinations in which either one or both of the drugs are still in phase I or II (within their own development pipeline). One example is an angiogenesis inhibitor still in development, which had shown unimpressive clinical response in phase II. "We asked the German Cancer Centre in Heidelberg to do some clinical models combining this drug with Erbitux, and they were extremely excited about the synergistic effects," he said.

The new approach to drug development has had a profound effect on the approval process. As targeted drugs tend to be far less harmful than traditional cytotoxics, there is pressure on the regulators to speed up their decision making.

Raj Puri from the US regulatory body the Food and Drug Administration (FDA) talked about new guidelines issued in April 2005, designed to make it easier for drug developers to obtain important pharmacokinetic information at a much earlier stage of development. Using the new 'exploratory IND [investigational new drug] studies', US investigators can now combine preclinical data with 'first-in-human data' (phase 0) to help them select the most promising drugs before moving into phase I/II trials.

"Rather than doing a full phase I trial, they are directed towards pharmacokinetics and pharmacodynamics as a way of getting into clinical trial. They can gain insight, for instance, on how to dose, based on preclinical data. This option was not open to them before," said Puri.

Questions were also raised about whether regulators are right to withhold approval of a drug that carries low risk and had been shown to be of value to some patients, even when the benefit failed to reach statistical significance at phase III. Milsted said that the phase I/II evidence of a response to Iressa in some patients was so dramatic that when he received the CT scans he asked whether there was any doubt about the original diagnosis, because "the tumour looked more like a lymphoma than NSCLC." He believes this should have been enough to tip the balance in favour of approval, despite the phase III survival figures falling just short of significance.

Conditional approval?

A number of delegates pointed out that the FDA had in the past granted approval on the basis of phase II results alone, under their 'accelerated approval' procedure, and asked why the same could not be done in Europe.

Jonsson from the Swedish Medical Products Agency replied that Europe is generally more cautious in its approach to novel medicines than the US, and he defended EMEA's approach, arguing that the FDA is itself uneasy about the way accelerated approval has worked in practice.

EFFICACY PROFILES IN RENAL CELL CARCINOMA: ANTIBODIES (Abs) vs TYROSINE KINASE INHIBITORS (TKIs) vs COMBINATION

Agent or Combination	Known Targets Inhibited	Observed Objective Response Rate (Phase II)	Observed Rate of "Clinical Benefit" (CR+PR+SD) (Phase II)
Bevacizumab (Abs)	VEGF	10%	-
Gefitinib (TKI)	EGFR	0%	38%
Sorafenib (TKI)	Raf, VEGF, PDGF, Flt-3,	14%	(Ph III: PFS doubled) 89%
Sunitinib (TKI)	VEGFR, PDGF, Flt-3, c-KIT, FGF	40%	68%
Axitinib (TKI)	VEGFR, PDGF	40%	86%
Bevacizumab plus Erlotinib (combo)	VEGF plus EGFR	21%	86%

CR, complete response; PR, partial response; SD stable disease. Courtesy of Rachel Humphrey, Bristol-Myers Squibb

Intelligent combinations of monoclonal antibodies and tyrosine kinase inhibitors may be the way forward

This secluded spot in the Austrian Tyrol provides the perfect setting for informal discussions between industry, academics and the regulators

The procedure was introduced to give patients with serious or life-threatening diseases quicker access to drugs that appear to offer a meaningful improvement over anything already available. The applicant has to demonstrate that their drug has an effect on a surrogate endpoint that is 'reasonably likely to predict clinical benefit', and approval is granted only on condition that further studies are done to verify that the predictions of clinical benefit are borne out by the evidence. However, the FDA have found poor compliance with the conditions, because once the drug is on the market, it is not in the interests of the company to devote its resources to further research – particularly if that research indicates the drug is not as effective as predicted, or is effective only in a very limited group of patients. Though the FDA has the right to take the drug off the market if that research is not done, or indeed if the drug turns out to be less effective than predicted, this has proved hard to do in practice.

Jonsson said that while he recognised that the biggest hurdle for effective drug development is identifying good predictor markers, if the regulators allow too many drugs through without insisting that the company first identify how their drug can be used to best effect, the market could fill up with very expensive drugs that have only marginal clinical benefit in an unselected patient population, and there is a danger that faith in the whole system will collapse. He said that EMEA would soon have similar powers to the FDA to grant conditional approval, and that there needs to be a lot of discussion about how these powers should be used.

Some voices argued that it may be only after the drug has been widely

New FDA guidelines aim to make it easier to obtain vital pharmacokinetic information much earlier

"I don't understand why they don't use tissue samples more to come a bit closer to the real cancer"

used for a number of years that it becomes possible to define which patients respond the best. They made the point that, had Iressa failed to get approval in the US and Japan as happened in Europe, then the information we now have about the particular mutation that predicts a strong response would quite possibly never have come to light.

One delegate came up with a novel suggestion for giving trials teams access to previously untreated patients on the scale needed for more detailed phase II analysis. As a molecular response is often apparent within days, they argued, it should be possible to administer the drug in the neoadjuvant setting to newly diagnosed patients during the normal waiting period between diagnosis and surgery.

Another suggested that if response could be detected so quickly, even if companies had failed to identify which patients would be most likely to respond, every patient could be given the chance to try all possible drugs at least for a week or so, without too great a burden on health budgets.

Commenting later on the whole discussion, Milsted said, "The idea that we can solve all the problems in a few years is unrealistic. But some academics and regulators don't understand that. They say 'You must have developed a biomarker that will tell me who will benefit from this drug.' And you have to say, 'I'm sorry but the science is not available for us to do that. We can only start to do that now because we have treated 3000 patients and we have some data.' "

Jonsson, however, clearly believes companies could do more in phase II to analyse how their drugs perform in real tumour tissue, and said he had taken the opportunity provided by the conference to have an informal discussion with delegates from one of the companies about the use of breast tumour samples.

"I don't understand why the company doesn't use them more to come a bit closer to the real cancer," he said. "You can only treat a patient with one compound, not ten. In a laboratory, however, you can treat the cells with ten compounds and look for markers and look for activity.

"Perhaps from these in-vitro experiments you can find the phenotype that makes it more likely that you have activity."

The problem, he said, lies not so much in the logistics of setting up good-quality tissue banks, but getting access to that tissue – not just for academics but for the industry as well.

Approving combinations

But it is when we start looking at the approval process of combination therapies that things get really complex. Would two drugs approved for use separately need to go through a separate approval process to be used in combination? Yes they would, said the regulators, because we need to know both the combined benefits and the combined side-effects.

What about combining experimental drugs? Would each drug have to be approved for use separately before approval could be sought for the combination? If so, what if one or both the drugs proved too toxic when used alone, but were far less toxic in combination?

Hmm… said the Swedish regulators. We'd have to see the data. If there are clear benefits for patients, we should be able to find ways to resolve the regulatory issues. However, no drugs developer has yet been brave enough to come forward with a test case, so we can't say….

So what about Merck? Would they be up for trying a test case? "I am encouraged at least by the Swedish authorities," said a Merck executive. "I think with these authorities we can talk, and as they mentioned, go for scientific advice. You would not go all the way through phase III trials, and then go and ask them to approve. You would do it stepwise. Initially share the concept. Then ask specific questions, where you get scientific advice. Then come back when you have data. And then discuss the phase III design. It needs a dialogue always."

That dialogue, and step-by-step approach, is exactly what the BDA conferences hope to achieve in terms of developing an agreed overall approach to effective drug development. When it meets again in March 2007, lessons from the first trials of combinations of exploratory drugs, and an assessment of the use of EMEA's conditional approval instrument will be two topics that are likely to find a place on the agenda.

What's coming up in colorectal cancer?

Mary Rice

A panel of experts is predicting that colorectal cancer patients will soon feel the benefits of the sort of individualised therapies that are beginning to be used in breast cancer. More effort is needed to promote a multidisciplinary approach, improve staging and raise awareness of the benefits of screening.

Some catching up to do compared with some other cancers, but otherwise treatment for colorectal cancer is making good progress. This was the overall view of the experts gathered in Barcelona for the first Colorectal Cancer Observatory, organised by the European School of Oncology. Clinicians and patient representatives from Europe and the US were asked to predict how they saw treatment, diagnosis, screening and patient advocacy evolving over the coming 12 months, so that all participants could see their work in the context of a wider arena.

The single most important thing that could happen to improve colorectal cancer treatment, said Observatory chair Mario Dicato, of the Centre Hospitalier de Luxembourg, would be improving our ability to predict risk of progression. "Because we are not as advanced in this field as they are in breast cancer, for example," he said, "it is certain that a number of patients are still under- or over-treated. We are still unable to delineate clearly between sub-groups at different risk. We do not have predictive markers for the use of Avastin [bevacizumab] in the same way breast cancer patients have for Herceptin [trastuzumab], and this is bad both for patients and for healthcare systems, which have to foot the bills for treatment that we know is sometimes unnecessary. The current problem is knowing for whom it is unnecessary."

Europe-wide guidelines for colorectal cancer were called for by Cornelis van de Velde, of the Leiden University Medical Centre in the Netherlands. Some countries have no guidelines at all, he said. For a start, multidisciplinary treatment planning should be made mandatory for everyone. Staging is also a big problem.

OBSERVATORY PANEL

- **Mario Dicato** (chair), medical oncologist, Luxembourg
- **Lynn Faulds Wood** (co-chair), patient advocate, UK
- **Philippe Rougier**, medical oncologist, France
- **Hans-Joachim Schmoll**, medical oncologist, Germany
- **Margaret Tempero**, medical oncologist, US
- **Cornelis van de Velde**, surgeon, the Netherlands
- **Chris Verslype**, medical oncologist, Belgium

FELIX BURDA FOUNDATION 2005

"My Ferrari has to be checked out regularly. Me too!". Michael Schumacher does his bit to promote screening in this campaign run by the Felix Burda Foundation in Germany, but much more needs to be done to raise awareness about Europe's second biggest cancer killer

Accurate staging is vital, he stressed, both pre-operatively, by radiology, and post-operatively by the pathologist. "At the moment it is imprecise. Patients are still mis-staged, particularly in stages 2 and 3, and this hampers the chances of targeting and optimising treatment," he said, adding that pre-operative MRI, essential for staging, is obligatory in some countries, while in other countries it is simply not an option.

But despite having some catching up to do, things are moving at a great rate, he said. "In 1988 there was an editorial in JAMA which looked at whether chemotherapy had a role in colorectal cancer. This was followed by a study that showed that it had survival benefits in patients with lymph node metastases. This seems extraordinary now, but in fact it was only following in the same pattern as breast cancer, and we can expect to see the same kind of progress both in diagnosis, treatment, and survival benefits."

Laparoscopic surgery will become an integral part of colorectal cancer surgery, he predicted. "Currently some people get it and some don't – and this is true even within countries, for example in the UK. The pioneers who thought it would enhance survival have found that this is not the case, but with careful technique the results can be equal to open surgery, at less burden to the patient. It takes more operating time, but is easier to recover from, and the quality of life benefits to the patient are considerable."

Providing better information to patients so that they can be properly involved in the decision-making process could also bring benefits all round, he said. "For example, people are very much opposed to the idea of having a stoma. But to avoid this we have to do highly technically demanding operations, which can sometimes make the patient incontinent. We need to get better at explaining to patients exactly what is involved when there is a choice of procedures, so that they can fully understand and pick the one that is better for them. A stoma can avoid many problems, but because this is not always properly explained, patients sometimes choose an alternative that has a far more deleterious effect on their quality of life."

Margaret Tempero, from the Department of Medicine, University of California at San Francisco, USA, also emphasised the importance of markers for improving decisions on whether or not to treat. She predicted

METASTATIC CRC

In metastatic CRC in the coming year Schmoll predicts:

1. In chemotherapy backbones

- 5FU/oxaliplatin will continue to be an ideal backbone for chemo/targeted combinations
- CapOx and XELOX (oxaliplatin/capecitabine combinations in different schedules) will be used more frequently due to promising data, in particular on safety
- XELIRI (irenotecan + capecitabine) will disappear
- Data on the relative benefits of CapOx vs FU/oxaliplatin will be available in June

2. In targeted therapies

- Bevacizumab will be used more in combination with FOLFOX (oxaliplatin+5FU+leucovorin) and possibly also with CapOx in the 1st- and 2nd-line setting
- Cetuximab will be shown to have strong efficacy when used in combination with chemotherapy in 1st-line treatment, but it will remain unclear whether it is equally effective as FOLFOX/bevacizumab
- Small molecule vascular endothelial growth factor [VEGF] tyrosine kinase inhibitors will not yet be on the market

ADJUVANT THERAPY

In adjuvant therapy in the coming year Schmoll predicts:

- The use of oxaliplatin-based combinations will strongly increase following supportive data from the NSABP C07 study and 4-year MOSAIC update
- Safety data support the use of XELOX, but this combination will not be used in an adjuvant setting at least until 2007, when we will have early data on its efficacy
- For patients who are not candidates for oxaliplatin, FOLFIRI will still be an option (better than 5FU alone)
- Oxaliplatin remains favourable with any 5FU backbone

that research into the management of colorectal cancer will undergo a dramatic shift as genomic predictors of outcome emerge from the analysis of candidate biomarkers in banked tissue. "This will prompt prospective trials to validate the biomarkers as diagnostic indicators to treat or not to treat. A second wave of research on biomarkers predicting sensitivity or resistance will lead to tailored treatment selection," she said.

Lynn Faulds Wood, representing the European Cancer Patient Coalition, and a former colorectal cancer patient herself, set out the wish list for patients over the next year. Public health campaigns must be a priority, she said: it is the second biggest cancer killer across Europe, yet there is very low awareness of the disease and its symptoms. It would help if agreement could be reached on a single name for the disease, which, she pointed out, is "confusingly known around Europe as colorectal, colon, and bowel cancer".

Widespread implementation of screening programmes would be the best way to save many thousands of lives over the next few years, she said, while better access to various forms of treatment would bring improvements for patients. Some patients have to wait months for radiotherapy. Access to life-prolonging and potentially life-saving drugs is too slow, with official approval taking many months longer in Europe than in the US. And better access to carefully targeted therapies is needed.

Hope was held out on that last sentiment by Hans-Joachim Schmoll, of the Martin Luther University, Halle, Germany. He believes that in the next 12 months combinations of chemo-therapy and targeted agents will increase long-term survival rates in metastatic colorectal cancer. New drugs based on oxaliplatin will play an increasing role in adjuvant therapy.

Such expert predictions are useful both in keeping people informed and in giving them a better understanding of what their colleagues in different disciplines are doing, concluded Dicato. "I believe that by helping us understand what is likely to evolve in the next few years, we can benefit not just ourselves, but also patients and healthcare systems. In particular, the promise held out by micro-arrays and targeted treatment in colorectal cancer is something that should be better known by a wider public."

"In the next 12 months combinations of chemo and targeted agents will increase long-term survival"

Gynaecological oncology: Hungary has a word for it

➜ Peter McIntyre

Péter Bösze, professor, gynaecologist, geneticist, chemotherapist, radiotherapist and teacher, helped found the Budapest school of radical surgery. Today he is still encouraging young gynae-oncologists to think radically and practise holistically – and he is helping ensure that they can do both in their own mother tongue.

Péter Bösze pioneered the development of gynaecological oncology in Hungary and in Europe, and is a leading figure in a movement for radical surgery that today sees young surgeons from around the world seeking training opportunities in his home country.

He is polymath: a surgeon who is also a geneticist, chemotherapist and a board-certified specialist in radiotherapy. He believes that the gynae-oncologist has a holistic role in the medical care of women, and should practise with a broad range of skills and tools. He is excited about the prospects of a prophylactic vaccine for cervical cancer and looks forward to better drugs to treat ovarian cancers. Yet he upholds, above all, the role of surgery in cervical, endometrial and ovarian cancers as being the most likely to prevent relapse and the least likely to cause complications. He also believes that gynae-oncologists are the natural people to specialise in breast cancer surgery, and has won the right for this in Hungary. He believes that there is almost nothing a skilled surgeon cannot accomplish, so long as he or she is properly trained, keeps up to date with the latest research and sees enough patients to be a genuine specialist in their field.

Still a full-time practising consultant at St Stephen's Hospital in Budapest, he devotes time to publishing, writing and teaching at Semmelweis University, instilling in young men and (increasingly) women the training, skills and confidence to take surgery forward and bring the results of basic research into daily practice. He is also leading a movement to adapt Hungarian medical language so that everything that needs to be known and understood about cell mutation, genetics, surgery and cancer can be said in his native tongue.

If Bösze has a determination that gynaecological oncologists will not be compartmentalised, he probably owes some of his self-confidence to the pernicious regime that tried to prevent him from following his chosen career.

Bösze qualified from Semmelweis Medical University in Budapest in 1963, seven years after the Hungarian uprising was put down by the Soviet army. "I was against the system, as far

as it was possible," he says. With no family members in the Communist Party, he was denied a job in Budapest and the right to become an obstetrician and gynaecologist.

Instead, he was sent to the town hospital of Karcag, 150 km east of Budapest, and told to train as a general practitioner (GP). This turned out to be a brilliant mistake on behalf of the authorities, as the head of obstetrics and gynaecology at Karcag was desperate for help and Bösze was thrown in at the deep end.

The basics

"It was a world with no modern technology, nothing. Sometimes there was no light, and we used a candle," Bösze recalls. "The obs and gynae operating theatre was 500 metres away, and sometimes there was no ambulance to take a patient. If there was an emergency Caesarean section, I just put my hands in iodine and did the operation in the delivery room with the nurse. The boy who was the porter was also the anaesthetist. He was excellent with ether and chloroform; there were no accidents and everyone survived.

"Sometimes it happened that there was no blood for transfusions. We took out the blood from the abdominal cavity and filtered it and screened it and gave it back to the patient. This was 40 years ago, my first experience of autotransfusion.

"I was on duty 28 days a month for six years. I was enthusiastic. I was allowed to do everything. It is no way for a medical doctor to be trained, but there was no alternative. It was a kind of auto-training. I have to tell you that I loved it. I really loved it."

Once a fortnight he was allowed to attend the medical school at Debrecen University and he found time to publish 16 papers from Karcag. In 1970, the Director of the Medical

I was allowed to do everything. It is no way for a doctor to be trained, but there was no alternative

Postgraduate University in Budapest invited Bösze to join the staff. There he received a thorough academic training in obstetrics and gynaecology, and was put in charge of the cytogenetics laboratory, where he worked on structural chromosomal abnormalities, pursuing an interest in infertility and gonadal dysgenesis.

The awards began to flow, and in 1974 he spent a year in Edinburgh doing genetic research. On his return to Hungary, Bösze achieved certification in human genetics, and later in radiotherapy, and he completed his PhD in primary ovarian failure.

The more he practised, the more he felt that gynaecological cancer demanded its own sub-specialty. "I wanted to devote all my time to gynaecology and genetics regarding malignancies and tumours. Obstetrics and gynaecology training was far from enough to treat cancer patients, and there was a desperate need for adequate surgery."

In 1988, he was appointed to head the gynae-oncology department at the National Institute of Oncology in Budapest, directed by Sándor Eckhardt, later to become President of the International Union Against Cancer (UICC). Bösze introduced radical surgery. His team was the first in Hungary to carry out a pelvic exenteration, to remove the uterus, vagina, ovaries, and lymph nodes, lower colon, rectum, and bladder, and to create stomata for faeces and urine.

At international meetings, Bösze made a practice of visiting one of his hosts in their operating theatre and learning every technique that could push back the boundaries. In six years as head of gynaecological oncology at the Institute, he not only expanded the role of surgery, but oversaw 1,000 chemotherapy treatments a year and a similar number of brachytherapy (intracavity radiotherapy) episodes.

When Eckhardt was injured in an accident and stood down as Director of the Institute, Bösze did not see eye to eye with his successor and left. He eventually joined a strong gynaecological oncology team (many of whom he had helped to train) at St Stephen's Hospital, as a consultant. "We have trainees from all over the world, and I am really proud of our surgery. I am not head of this department and it is my colleagues who do the major work, but I am proud that I started it."

Radical surgery

Here, the Budapest school of radical surgery flourished, for example, extending radical hysterectomy to remove not only the womb, parametrium and lymph nodes, but also scattered lymph nodes beyond the internal iliac veins and

The more he practised, the more he felt that gynaecological cancer needed its own sub-specialty

He believes genetics will show surgery to be the best stand-alone treatment for a range of cancers

arteries that had been considered unreachable, in effect clearing the pelvic side wall.

Bösze says, "With this technique, we totally changed our five-year survival rate for cervical cancer in stage 2B. Our five-year survival is over 80%, while using combination therapies it is perhaps not more than 60%. We very rarely use combination therapy in operable cervical cancer. We consider that lymph node dissection is a therapeutic curative approach."

The department also invented radical abdominal trachelectomy (ART) to remove the cervix, parametrium and lymph nodes, but preserve the fundus of the uterus so that a woman can still carry a child. László Ungár, head of the St Stephen's team, recently went to the US to carry out this operation there.

Bösze believes that genetic advances will show surgery to be the best stand-alone treatment for a range of cancers. "I would say that 70% or 80% or higher percentage of early cases of gynaecological cancers are treated with surgery with or without adjuvant therapy. If you perform radical hysterectomy in early-stage cervical cancer (stage 1B1), you find secondary metastatic nodes in no more than 20% of the cases. But how can you separate which are the 20% and which are the 80%? Genetic research will find out who requires radical treatment and who requires a simple hysterectomy or amputation of the cervix. In my view, this is the challenge of our time; to individualise treatment and management."

Specialist surgery can also reduce the need for radiotherapy. Some endometrial cancers can be cured by a simple surgery, hysterectomy and bilateral salpingo-oophorectomy (removal of the uterus, ovaries and fallopian tubes). However, some patients have a higher risk of lymph node metastases, and Bösze estimates that 50%–60% also require adequate lymph node dissection. General gynaecologists rarely offer this extra step, which means that patients receive unnecessary post-operative radiotherapy.

"The question is whether the risk and the complications of lymph node dissection can be compared to the risk of adjuvant radiation therapy. I am certainly in favour of lymph node dissection. Removing the lymph nodes from the pelvis is very rarely associated with any kind of complications in skilled hands, and certainly does not have the long-term complications associated with radiation therapy. Radiation therapy is not a harmless procedure, and it invariably damages normal tissue."

Problems associated with radiotherapy are sometimes downplayed, because radiation-induced fistulae and bowel damage rarely occur within five years of treatment, which is the time used as the standard measure of effectiveness. However, Bösze says that some patients die from radiation complications 15 or 20 years later.

Pre-operative radiotherapy is also being dramatically reduced. "There was a tradition for pre-operative intracavitary radiation therapy in endometrial or cervical cancer. Now we have cut this tradition, and established guidelines where surgery alone is enough, and sparing radiation therapy."

Bösze believes that gynae-oncologists must keep themselves up to date with chemotherapy and radiotherapy. "You have to know, in detail, when chemotherapy should be given, how should it be given, and what are the principles of why it works.

"The same is true for radiation therapy. If you don't have any idea of the place for radiation therapy or chemotherapy, when there is a meeting of the board, and the radiation therapist says 'yes we should do radiation therapy,' that is a one-person decision, not a team decision. Even in highly qualified centres, patients may get radiation therapy because radiation therapy wants patients."

"Genetic research will find out who requires radical treatment and who requires minor surgery"

Traditional tools

As well as keeping up to date with new sciences, Bösze is a great advocate of some traditional tools of his trade, especially the colposcope. He does not understand why western European countries rely on smear testing alone for screening, sending only women with abnormal smears for colposcopy, with all the attendant anxiety during the waiting period. In Hungary and eastern Europe, colposcopy is a routine part of gynaecological examination.

"I use the colposcope all the time. It has a lot of advantages. It makes me sure that nothing is wrong on the cervix or the vulva or the vagina. When you examine the vagina with a speculum and explore the cervix with a colposcope as part of the gynaecological examination, the cervix is in front of you and you look and can see if it is normal or not. It is an absolutely harmless procedure.

"If the transformation zone (where precancerous epithelial changes take place) is fully visible, you can be 100% sure that nothing is wrong, that there is no cancer. In 99% of cases I can tell the patient right now that there is nothing wrong or that there is some suspicion and we have to await the result of the cytology."

Bösze is on the board of the International Federation of Cervical Pathology and Colposcopy (IFCPC), which is seeking to balance out the benefits of cytology and colposcopy. Cytology is associated with a high false-negative rate, missing 10%–15% of abnormal cervical intra-epithelial neoplasia, while perhaps half of the suspicious findings identified by colposcopy turn out to be benign.

Ovarian cancer, known as the silent killer because of lack of symptoms in its early stages, gives least grounds for optimism. Research into CA-125 screening (a blood test) and transvaginal ultrasound is discouraging. The US-based Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial reported in the *American Journal of Obstetrics and Gynecology* in November 2005 that, of 570 women who had surgery following screening, 541 did not have cancer.

Bösze says, "This is a nasty cancer and, unfortunately, the vast majority are found in an advanced stage. It is important to treat these patients in centres that can remove all the tumours from the abdominal cavity and retroperitoneum, taking out and sectioning abdominal organs. Once the tumour is out of the ovary, the only chance is to remove all visible tumours."

About 5%–10% of ovarian cancers occur in women with BRCA 1 or 2 mutation – the same genetic susceptibility that gives a higher risk for breast cancer. Women who carry this gene mutation can have their ovaries removed. Younger women can go on the pill until they are ready to conceive, and have their ovaries removed after they complete their families.

Bösze is one of the founders of the Hungarian Cancer Genetic Service, which he now heads. He believes that the common genetic link strengthens the case for gynae-oncologists treating breast cancer. The Hungarian Colleges for Surgery and for Oncology have accepted this, and gynaecological oncologists at St Stephen's operate on more than 200 women with breast cancer each year.

This fits Bösze's belief that gynaecological oncologists should be holistic and multi-skilled. "I started the practice that the gynae-oncologist should treat breast cancer. Breast cancer surgery is simple compared with radical hysterectomy or exenteration. The gynaecologist deals with all kinds of benign diseases of the breast, and a gynae-oncological examination cannot be made without palpating the breast. The important thing is you should be trained well enough and see enough patients. Patients should be treated in centres, but whether they are called breast

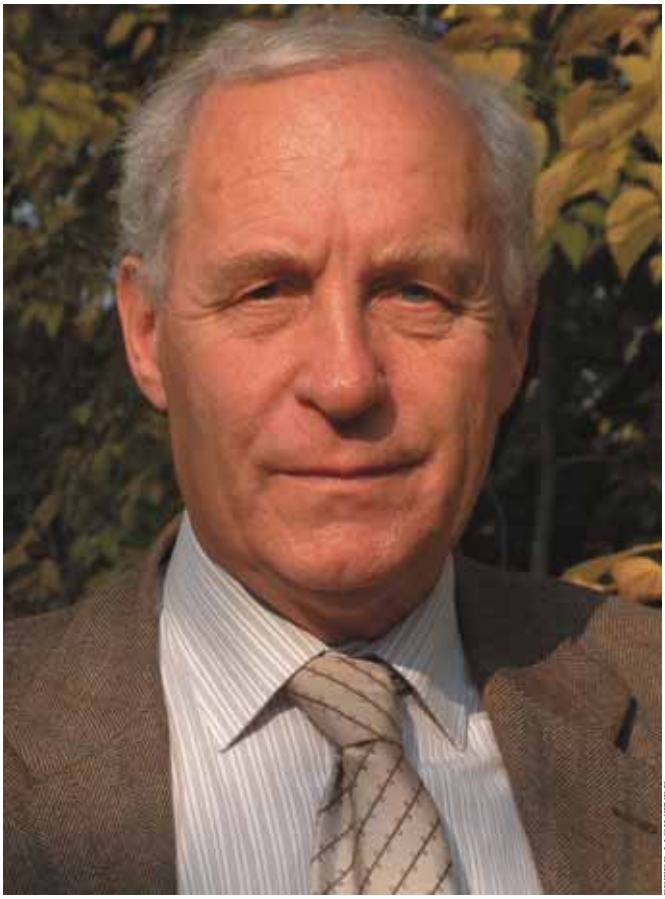
cancer centres or gynae-oncology centres does not matter."

Recognition

Bösze fought to win wider recognition for gynaecological oncologists during his presidency of the European Society of Gynaecological Oncology (ESGO), from 1997 to 1999. He approached the European Board and College of Obstetrics and Gynaecology (EBCOG) which, "after many debates", accepted that gynaecological oncology should be a sub-specialty – the first time that the European Union of Medical Specialists (UEMS) recognised a sub-specialty. EBCOG and ESGO also developed training guidelines for gynae-oncologists. He also affiliated ESGO as an associate member of the Federation of European Cancer Societies (FECS). He describes these two steps as "breakthroughs" that allowed the Society to become the voice of gynaecological oncology in Europe.

Bösze is the founding president of the Hungarian Society of Gynaecological Oncologists and editor of its journal, the *Hungarian Journal of Gynaecological Oncology*. Publishing takes an increasing share of his attention. He is joint editor in chief (with Antonio Annis) of the *European Journal of Gynaecological Oncology*, and Eastern European editor of the *European Journal of Obstetrics and Gynaecology and Reproductive Biology*.

In 1999, he founded the European Academy of Gynaecological Cancer (EAGC) to support learning. The Academy now publishes the CME *Journal of Gynaecological Oncology,* which he also started, in collaboration with the European School of Oncology. Bösze explains, "Practising clinicians very much like review articles that give an insight into a topic, but review articles usually have a page limit. My idea was to establish a journal with chapters, each devoted to a particular topic, as a kind of in-depth symposium from basic principles to latest results."



PETER MCINTYRE

The journal, now in its tenth year, goes out to gynae-oncologists all over the world three times a year, with contributions from specialists in many countries. In his career, Bösze has attended more than 200 congresses as speaker or chairman, and many academic gynaecological-oncologists became his friend. He laughs, "When I send an e-mail saying, 'please write an article for me,' they don't say no!"

An EAGC *Course Book on Colposcopy*, edited by Bösze with David Luesley from Birmingham, UK, was published in 2004 with

He believes the common genetic link strengthens the case for gynae-oncologists treating breast cancer

an impressive list of 35 international contributors. *What gynaecologic oncologists should know about chemotherapy*, edited with Maurie Markman of the MD Anderson Cancer Center, Houston, was published in December 2005, and a third title will follow, on cancer and genetics.

Bösze recently founded the journal *Hungarian Medical Language (Magyar orvosi nyelv)*, to ensure that whatever happens in genetics, oncology or gynaecology, Hungarians have a word for it. Otherwise, he believes that doctors will lose touch with patients.

"The molecular biology of medicine is a revolutionary one with new terms every day, all in English. Doctors in Latin America, France, Italy, Hungary and everywhere realised that we were talking to each other in English. Our duty is to explain to a woman what we think about her disease and what management is available, so we can make this decision together. You have to explain this to her in her own language. But many terms have not got a Hungarian translation. This journal keeps the Hungarian medical language up to date and preserves the structure of the sentences.

"Medicine is science, art and language, and language partly determines your way of thinking. If you cannot use proper words, it is not only a problem for patients, you mislead your colleagues and cannot give instructions to nurses. Your national language is the key to your personal and national identity.

"This has nothing to do with chauvinism. Europe is a colourful continent because of different nations, languages and cultures with 1,000 years or more of history. I am not against speaking English – we should have a common language to understand each other. But an English-speaking Europe would be a terrible copy of the continent on the other side of the ocean."

This 21st century concern about the downside of globalisation reflects the tradition of the Hungarian Academy of Science, from where Bösze received his doctorate in 1992. The Academy – originally the Hungarian Learned Society – was founded in 1825 for 'the study and propagation of the sciences in Hungarian'. Much of its early work was spent defining technical terms for the new sciences of the 19th century. Hungarian writer and poet János Arany described its activities as "bee-like busy collection of dialectal words and technical terms … in short, aspirations to improve and expand the Hungarian language, to propagate science in Hungarian."

Just as 19th century Academy members wanted to keep up with the latest learning and at the same time to assert a national identity, so today in the 21st century Péter Bösze is leading his colleagues to do the same.

Hungarian language must keep abreast of science, or doctors will lose touch with their patients

Can science win back public trust?

Venice Charter starts the dialogue

➜ Anna Wagstaff

Confidence in science is becoming dangerously eroded in the face of a rise in religious fundamentalism and a general scepticism that scientific advances will be used for the good of humanity as a whole. Will a global alliance for science win back some respect?

IT must have been a long time since the magnificent Doge's Palace in Venice hosted such a bold piece of diplomacy. Victor Chernomyrdin, plenipotentiary minister in Russia's government, was at the top table with Kathleen Kennedy Townsend, niece of the assassinated US President John F Kennedy, by his side.

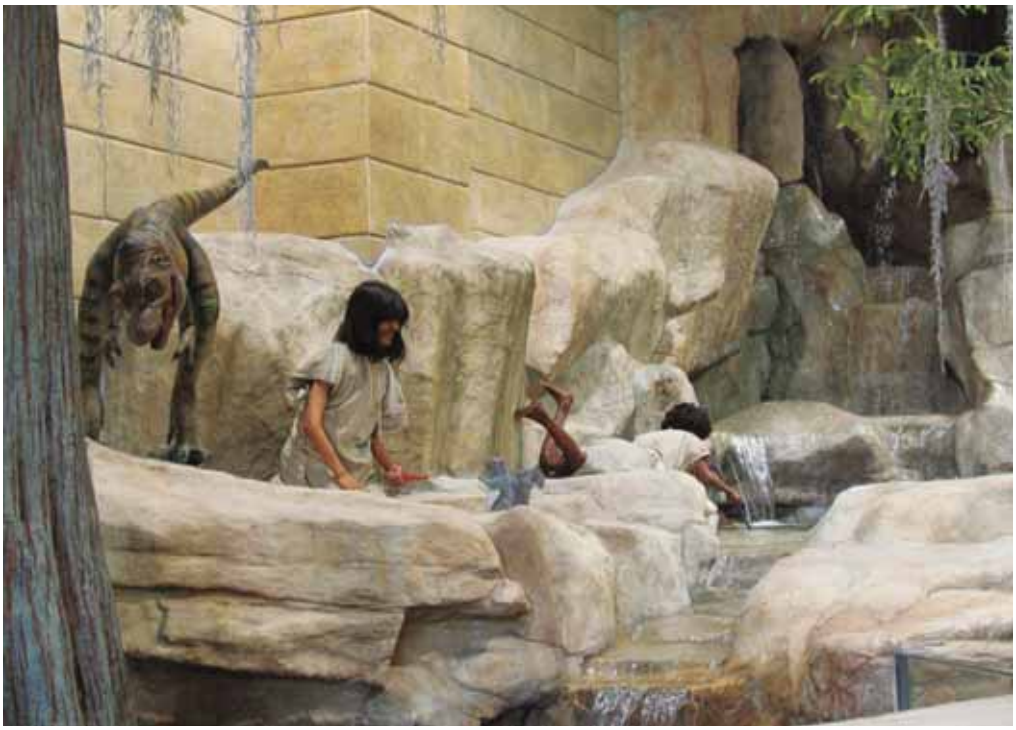
Despite appearances, this was not a summit looking to reconcile differences between political powers. This was the grand opening of the First World Conference on the Future of Science, organised by the Umberto Veronesi Foundation. Among those present were government ministers, a representative of the Vatican and other religious authorities, and the director of the United Nations Educational, Scientific and Cultural Organization (UNESCO) regional bureau for science.

The differences this conference sought to reconcile concerned a breach between science and society that seems to be widening in communities across the globe. The alliance it hoped to forge was a global alliance for science, "involving scientists, philosophers, theologians, politicians, industrialists, jurists, and all interested parties."

There was even a declaration – the Venice Charter – which affirms the importance of science as a force for progress and human well-being. It talks of the need for scientific progress to be fully and openly debated by society, particularly the areas of genetics, astrophysics and information technology – and it commits the signatories to promoting and participating in such dialogue.

Given the grandeur of the setting and the stature of the top table, one might have expected a document resonating with the sort of vision Kennedy Townsend's uncle used to rally the people behind the US space exploration programme. Yet, the Venice Charter is essentially a cautious document, reflecting not so much a lack of ambition, as a recognition that attitudes towards science have changed, leaving it feeling beleaguered and misunderstood.

Kennedy Townsend talked about how the US, the super-power that landed the first man on the moon and has led scientific and technological innovation for half a century, seems to be turning its back on science. Almost two-thirds of US Americans now say they are open to the teachings of 'intelligent design' – a bible-based explanation of the origin of life, touched up with a quasi-scientific veneer. One third would like to see 'intelligent design' replace evolutionary theory in the school curriculum.



MUSEUM OF CREATION

Science rejected. The Cincinnati Museum of Creation presents as historical fact this tableau of children playing alongside dinosaurs

Decisions over issues such as stem cell research or the withdrawal of life support where brain death has occurred are turned into emotive articles of faith by the Christian fundamentalists who make up President Bush's electoral base, making rational debate very difficult.

A parallel rise in religious fundamentalism in the Islamic world, where the arts and sciences were for centuries nurtured with pride, is exerting an increasing influence over cultural and social life. Interestingly, however, Darius Atighetchi, professor of Islamic Bioethics at the Second University of Naples, indicated that gene therapy, in-vitro fertilisation, cloning and stem cell research – issues that have become flashpoints in the US and in strongly Catholic countries – have posed less of a problem in Islamic countries. When the UN General Assembly adopted a declaration virtually prohibiting all forms of human cloning, most Islamic countries abstained.

Religious fundamentalism is by no means the only problem. Science is also suffering from increasing constraints on the freedom of information on the grounds of national security, where the concept of 'dual use' can cover a wide area of scientific research. In China, which is investing heavily in biotechnology and other sciences, and where religion has little influence, progress is held back by constraints on movement and freedom of information. In Europe, academic clinical research is hampered by unnecessarily bureaucratic regulations designed with pharmaceutical companies in mind.

The threats

The conference looked at the way governments increasingly see science as simply a part of their economic development policy. Funding for basic science, where researchers have freedom to follow their own leads, is being squeezed in favour of project-based funding concentrated on potential economic growth areas.

The free exchange of ideas is being threatened as universities are encouraged to patent their research findings to earn extra revenue – a practice that started in the US and is now spreading to Europe. Increasingly intense competition for funding between academic institutions deters an open and collaborative approach. A policy of cutting back on tenured positions means that by the time science graduates can settle down to work on a permanent contract they are often past their most productive age. Having constantly to compete for jobs and funding means they become slave to their impact factor, and the need to publish may bias their choice of research.

Drug development, once seen as

The super-power that landed the first man on the moon seems to be turning its back on science

part of a state's social responsibility, is now left almost entirely to the private sector. With huge sums of private investment riding on what academic researchers and journals publish about these drugs and what clinicians prescribe, public trust in the integrity of the system has been undermined. As a result, there are plenty of people who suspect that bird flu is a scare inspired by the pharmaceutical industry. The widespread distrust of genetically modified crops is another example.

Genetic scientists talked of their astonishment at the public rejection of what they see as a technological advance with the potential to address the food needs of the world's poorest populations. This was a public argument between industrial scientists and the western environmental lobby – and the public sided with the environmentalists against the weight of scientific opinion.

Attempts by the US government to give credibility to scientific theories that dispute the overwhelming evidence of global warming were also mentioned as helping to discredit science in the eyes of the public as an objective method of investigation.

The image of science as a means to resolve the major problems afflicting mankind is also undermined by the allocation of resources. Vast sums of money are ploughed into finding ways to keep the world's wealthy populations healthier, looking younger and living longer, and into technologies of war. Meanwhile, the world's poorest die from preventable malnutrition, malaria, and lack of clean drinking water and sanitation, and future generations are threatened by lack of attention to issues of sustainability.

But this remarkable gathering in Venice, which included philosophers, theologians, jurists, economists and politicians in addition to scientists versed in genetics, bio-informatics, neurology, climate change, bio-agriculture and energy, had not been convened just to bewail the low position of science. It aimed to examine ways to restore public belief and confidence in science, the scientific community and scientific methodology.

The debates

The first session, including theologians of several religions and a chemistry professor, looked at whether it is possible to bridge the gap between religion and science, or at least find a common language to discuss issues of life, death and humanity. No conclusions were reached, and evidence for any intellectual basis for common ground was hard to detect. Perhaps the most pertinent contribution came from Kennedy Townsend, who has to build bridges as a politician. She emphasised that people are more open to rational argument in an atmosphere of tolerance and mutual respect. "The important thing is not to fan flames of fear," she said. "Scientists should say nice things about God."

There was, however, a recognition that advances in neuroscience and genetics present an unsettling challenge not just to the religious concept of the soul, but also to the deeper sense of individual identity. Much of the world has had trouble enough coming to terms with the concept of evolution – that mankind is separated from the animal kingdom chiefly by its level of intellectual development. Now we are asked to accept that who we are, how we perceive and understand things and what actions we take are all determined by our genetic make up and neurophysiology. And to cap it all, with advances in cloning, even our genetic make up can be reproduced.

Daniel Dennett, Director of the Center for Cognitive Studies at Tufts University, Massachusetts, and Philip Pettit, Professor of Politics and Human Values at Princeton University, New Jersey, presented fascinating accounts of what science has uncovered about the relation between a person acting and that person willing that act, and offered a comforting philosophical treatise about what all this means for the whole concept of free will.

In a nutshell, our brains give the order to act split seconds before we are aware of willing the action. However, our own neurophysiological make up is constantly evolving as we interact with our surroundings, so we are not stuck with some predetermined and unchanging hardwiring; we develop in a unique way. So long as we can accept that our millions of neurons are what we are, and don't insist on having some intermediary 'I' giving the orders, then the perception that our actions are our own is still philosophically viable, and human dignity can remain intact. "We are not in the loop – we are the loop." Or in

ENLSC

Crossing boundaries. Judges at the ENLSC seminar donned lab coats and picked up their pipettes to get a feel for the realities of scientific investigation

the language of attempted bridge building, "Yes we have a soul, but it is made of trillions of tiny robots."

The threat posed by scientific progress, however, goes beyond problems of philosophy and self-identity. Advances in genetics hold the key to tackling many of the diseases and hereditary conditions that have defeated traditional medicine, but they also threaten to open the way to new forms of discrimination and social exclusion.

Women with a family history of BRCA-related breast cancer, for instance, could jeopardise their chances of qualifying for a mortgage or insurance if they follow medical advice to be tested for the BRCA mutation. Some countries have now introduced legislation to prohibit companies from requesting information on any genetic test results when they ask potential clients to divulge their medical history.

But the implications of a known genetic predisposition go beyond the interests of one individual. In a recent case in Iceland, a court upheld a mother's request that the hereditary cause of her partner's death should not be given on his death certificate because the information could jeopardise their daughter's interests.

This is a foretaste of what is to come. Research into the genetic risk for alcohol and drug addiction or mental health problems is opening up the potential for discrimination against entire gene pools. The new knowledge is also open to selective interpretation and misuse by people pursuing racist or sectarian agendas.

Advances in neurology are also fraught with ethical dilemmas. The development of drugs to combat, for instance, memory loss in the elderly, opens question about whether healthy people who can afford to buy the drugs privately should be allowed to use them, for instance, to boost their exam performance.

Amedeo Santosuosso is based at the Department of Law at Pavia University and is a founding member of the European Network for Life Sciences, Health and the Courts (ENLSC, www.unipv.it/enlsc/). He told the conference how, in recent decades, lawyers all over the world have had to find ways of responding to these new scientific developments. Western law, he said, has traditionally taken as its starting point the concept of the 'private sphere' and 'the social sphere' developed by John Stewart Mill back in the mid-nineteenth century. As advances in genetics have blurred that distinction, jurists have had to think on their feet and search around for other reference points.

Unlike scientists, said Santosuosso, jurists tend to work within their own legal systems – and also in their mother tongue. He told of what a revelation it had been when the ENLSC called an international meeting in Pavia to see how other countries were dealing with these issues. Fifteen nationalities were represented, and it soon became

ANDREA CHIOZZOTTO

ANDREA CHIOZZOTTO

An Alliance for Science. ***Left to right:*** **Giuliano Amato, veteran Italian/European political campaigner; Federico Mayor, chair of the European Research Council Expert Group, Janez Potočnik, EC Commissioner for Science and Research and,** ***far right*****, Conference President Umberto Veronesi**

apparent, he said, that all of them had been taking the same basic approach, using universal reference points that transcend national boundaries, such as self-determination and liberty.

"As we started to discuss cases within the Network for the first time, we realised that in practice we were drawing up a sort of 'universal charter of rights'," said Santosuosso. "And we thought: 'Who are we to do this?' But there is no other process."

The remedies

What the jurists were doing goes to the heart of what this conference was all about. On the one hand, professionals were engaging in a welcome debate, grappling with the implications of scientific advances for society and its laws. On the other hand, they also recognised that such debate has to take place in a far wider forum.

Exactly how this will happen was the subject of the final session, which concluded that scientists have a responsibility to engage with the public. "You have to get actively involved," said Kennedy Townsend, "Learn to be articulate, explain what you are doing and don't talk in code."

This session was chaired by Giuliano Amato, a veteran political campaigner who at various times has served as Italy's prime minister and chancellor, and vice-president of the EU Convention in Europe. In the months leading up to the conference, Amato had been a leading voice, together with Umberto Veronesi, calling for a 'yes' vote in the Italian referendum on stem cell research, which was lost because of a high level of abstentions. He believes that the results of the referendum might have been different "if scientists and philosophers and so on spoke directly to the people, instead of leaving it to the politicians, who had only learnt about the subject a short while before."

He urged scientists to trust the public judgement. "People can learn to evaluate the significance of research without understanding all the details." But they have to be given the opportunity. "Scientists should speak more with the public."

He joined many other speakers in the session in calling for science to be taught better, and for more and better coverage in the media. But he also stressed that supporters of science must use the institutions of participatory democracy – polls, referenda, consensus conferences, and citizens' juries – to argue their case.

Veronesi, the renowned Italian oncologist and prime mover behind the Venice Charter, was delighted by the response to the Venice Conference, but says it is only the beginning of a global project. "The problems and dilemmas of unrelenting technological progress are not being adequately discussed in society as a whole. Hopefully, through setting up an alliance, we can move in a direction to change this. We are now planning to promote the Charter worldwide, as we did last November with the presentation to the New York Academy of Science. Next step will be the presentation to the European Commission."

The rocky road to unity

Anna Wagstaff

As FECS prepares to welcome organ-based societies through the front door, the medical oncologists threaten to leave by the back.

Following a year of intense internal debate about the future of the Federation of European Cancer Societies (FECS), a FECS council meeting held at the beginning of November at the Paris ECCO conference decided FECS would open its doors to organ-based societies. It described the decision as part of its "One Voice, Once Vision" approach, which seeks to provide a strong and united voice for oncology in Europe, that is as representative as possible of all parts of the oncology community.

According to this decision, organ-based societies that are already affiliated to FECS can join as full members. This would include the mastologists' society (EUSOMA) and the gynaecological and neurological oncologists' societies (ESGO and EANO). The declared intention, however, is to go well beyond the ranks of existing affiliates to find ways to bring in important groups like the urologists, coloproctologists, pneumologists and gastroenterologists, which have traditionally had little to do with either FECS or ECCO (the FECS congress), despite the fact that many – often the majority – of their members treat cancer patients.

Much of the talk during the preceding year had focused on the possibility of dissolving the societies in the Federation and moving towards a single membership-based European cancer society, but the council meeting in Paris decided that such a move would be premature.

Speaking shortly after the FECS council meeting, John Smyth, incoming president of FECS, said, "It was incredibly frenetic at the Paris conference, there was a huge amount of debate and discussion, but I was very pleased with the outcome of the FECS council meeting, which was based on listening to all the discussions. There is a greater need for coordinating things than ever before. What we are going to explore is how to open the Federation to other societies, particularly what are now referred to as the organ-based societies, because a lot of meetings and, more importantly, clinical practice, are very much specialised around different types of cancer – breast cancer, colorectal and neural and so on."

Initial responses from some of the organ-based societies have been warm. Ignace Vergote, outgoing president of the European Society of Gynaecological Oncology (ESGO) – a FECS affiliate since 2000 – said, "We have been trying to get this decision for five or six years. It will make a big difference. We will be more involved in all the important things that FECS is doing. Not only the congress [ECCO], where we will have a greater influence, but also in the political work, where it is important to act with the other societies."

All aboard

Not all organ-based specialists have their own oncological societies,

Not all organ-based specialists have their own oncological societies

however, and the question of how best to draw in these practitioners is one of the issues a newly established FECS 'strategic committee' was assigned to look at. Urologists, for example, play the central role in treating the majority of prostate, bladder and testicular cancer patients in Europe, but only a tiny proportion of them specialise exclusively in oncology.

Hein Van Poppel, Chairman of the Department of Urology at the University Hospital Gasthuisberg, Katholieke Universiteit Leuven, Belgium, says, "Most urologists do some oncology – many do tumours of the bladder and kidney, and they all do prostate cancer, but for most of them oncology is not their only activity". Van Poppel himself treats only cancer patients, but he says there are probably no more than ten other people like him in the whole of Belgium.

This situation is reflected in the way urologists are organised. Though there is a body named the European Society of Oncological Urology (ESOU), this is not an independent membership-based organisation like the gynaecologists' ESGO, but one of 13 sections of the European Association of Urology (EAU). Van Poppel says that the EAU is keen to look at how it may be able to cooperate with FECS, and is likely to recommend some form of liaison or coordination via the ESOU board.

Vergote and Van Poppel are themselves convinced of the importance of getting all cancer practitioners more involved in multidisciplinary forums as a way of raising standards throughout Europe. However, they caution that there is much work to be done. As the trend towards organ-specialisation has spread, many strong national and European societies have been built, each with its own congress and hierarchy of 'must-attend' meetings.

"I only go to ECCO for one or two invited talks," says Vergote, "because the ESGO meeting is three weeks before, and this is more specific – five days only on gynaecological cancers, where we have not only gynaecologists but also medical oncologists, radiation oncologists, and translational researchers who are interested in gynaecological cancers."

"It is not the congress where I submit my research," says Van Poppel. "I submit it at the EAU or the AUA [American Urological Association], and we are not absolutely sure that FECS is going to change its attitude, because it is always radiation oncologists and medical oncologists going to that type of meeting, and surgeons are not involved. So how is FECS going to be successful in organising an attendance from oncologic urologists – that is the question."

That said, both of them acknowledge that attempts to attract more organ-based specialists by including hot organ-specific topics and speakers on the ECCO agenda are beginning to pay off. "Urologists are more and more involved, and the urology sessions are now better attended," says Van Poppel.

The fact that, as a full member, ESGO will now have a strong say over 'its part' of the ECCO agenda, will also make a difference says Vergote. And as for the timing of conferences, and content overlap, that can always be sorted out. "I think the goal of ECCO should be that it becomes as important as ASCO, but for Europe," he said.

One step forward, one step back

Allowing organ-based societies to affiliate to FECS would enable the Federation to bring a whole new layer of cancer practitioners under its umbrella. However, the decision infuriated the medical oncologists' society, ESMO – a founding member of FECS – which says it feels deeply threatened.

In the closing days of 2005, ESMO announced it was pulling out of FECS activities and would focus instead on expanding its own organisation "into a multidisciplinary member-based society" with its own annual congress starting in 2008. One reason for the decision was undoubtedly frustration over FECS' decision not to turn the Federation into a single membership-based society, which ESMO has long advocated as vital for raising the profile of oncology in Europe. But ESMO President Håkan Mellstedt also cites FECS' decision to allow in organ-based societies as an important factor behind his society's decision to disengage.

In many European countries, medical oncologists are still fighting to be recognised as a specialist

discipline, alongside surgical oncologists and radiation oncologists. ESMO argues that organ-based specialists, whose primary training is usually in surgery, should not be handling drug treatments, and that allowing organ-based societies to affiliate to FECS undermines the medical oncologists' quest for recognition.

Mellstedt said "It is still a problem that medical oncology is not recognised in many countries in Europe, and we have to protect that discipline for the best interests of the patients of the future. With the present decision [by FECS], ESMO would have disappeared or would have been greatly reduced to a very small society. Our judgement is that it is better for us to step out of the Federation, because we have to survive in a milieu where we can defend ourselves."

At the heart of the matter is a genuine difference of approach to patient treatment. The organ specialists feel they are the ones with the expertise. "We do the diagnosis, the staging, the treatment, we use hormonal treatment, and we use bisphosphonates, angiogenesis inhibitors and endothelin receptor blockers, just like medical oncologists do," says Van Poppel, adding that while most medical oncologists treat many malignant diseases, urological oncologists treat only urological malignancies, "It would be good to also have medical oncologists who specialise exclusively in urological tumours."

Mellstedt counters, however, that "You don't treat the cancer, you treat the patient. You need supportive care, you may need palliative care, and I doubt that all these organ specialists have that spectrum of knowledge." He also points out that medical treatment of cancer patients is becoming increasingly complex, with new chemotherapy and targeted agents, new diagnostic procedures, and tailored therapies. "All this has to be included in the treatment of cancer patients, and for that you need basic training both in internal medicine and medical oncology."

A BUMPY RIDE

There are areas of common ground between medical oncologists and organ specialists, for those who wish to find them. Mellstedt accepts that many smaller hospitals won't be able to support their own medical oncology department, but says there should be specialist medical oncologists within every department of internal medicine.

He says that ESMO is very keen to collaborate directly with organ-based societies, but not within the Federation. He even says he is open to the principle of organ-specialist oncology bodies like ESGO affiliating to FECS, but draws the line at organ-based societies that include non-oncologists.

Van Poppel, for his part, agrees that medical oncologists should be involved in the multidisciplinary planning of each patient's treatment, but argues that where the treatment is not toxic and is easily available, it can be delivered either by the urologist or by the medical oncologist.

All the players in this unrolling saga know full well the price to be paid in terms of the clout and standing of oncology in Europe if they cannot come together in a united front.

The question remains, however, what shape that unity will take. Judging by recent events, there is still some way to go before a solution is reached that everyone can live with, and we may be in for a bumpy ride.

FECS

The Federation of Cancer Societies is a multidisciplinary umbrella group for Europe's main oncology societies

It has six full members:

- European Association for Cancer Research (EACR)
- European Oncology Nursing Society (EONS)
- European Society for Medical Oncology (ESMO)
- European Society of Surgical Oncology (ESSO)
- European Society for Therapeutic Radiology and Oncology (ESTRO)
- International Society of Paediatric Oncology, European Branch (SIOP Europe)

It has eight affiliated members

- European Association for Neuro-Oncology (EANO)
- European Group for Blood and Marrow Transplantation (EBMT)
- European Organisation for Research and Treatment of Cancer (EORTC)
- European Society of Gynaecological Oncology (ESGO)
- European Society of Oncology Pharmacy (ESOP)
- European Society of Mastology (EUSOMA)
- Flims Alumni Club (FAC)
- Organisation of European Cancer Institutes (OECI)

At its council meeting in November, FECS agreed to invite its organ-based affiliates EANO, ESGO and EUSOMA to join as full members. It also decided to explore how to open the Federation to non-affiliated organ-based societies

Coming out for breast cancer country by country

Walks to raise awareness of breast cancer are established traditions in many countries. But in many more, breast cancer remains hidden from public and political agendas. Avon's Walk Around the World helped connect everyone fighting to raise the profile of breast cancer across the globe.

Throughout October tens of thousands of men and women from more than 30 countries across the world took to the streets as part of the Avon Walk Around the World for Breast Cancer. Many of the walks were linked by a Global Connection Ribbon that was passed on from a survivor in one country to the next in a chain of solidarity. The event, also supported by Novartis, was organised to mark the 50th anniversary of the Avon Foundation, set up to support initiatives to improve the lives of women, with a particular focus on breast cancer.

The Avon Foundation prides itself on taking an intelligent, needs-based approach to supporting the fight against breast cancer. It focuses on promoting medical research,

CHINA

GERMANY TO BULGARIA

MEXICO

FRANCE


HUNGARY

Walk Around the World for Breast Cancer events took place in more than 30 countries. In Europe, this included Bulgaria, Czech Republic, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain, Turkey, Ukraine and the UK

CANADA

awareness, and access to care, screening and high-quality diagnostics, and on supporting community-based groups that can reach the most poorly served populations.

Though the Avon Foundation is based in the US, Avon philanthropy is active worldwide. In Europe, it supports organisations like Mamazone in Germany and Amazons in Poland – two very effective advocacy groups, both heavily geared towards helping patients get the information they need. The Foundation is also funding fellowships for breast cancer doctors from eastern Europe to study in the US.

Walk Around the World for Breast Cancer provided an opportunity to show solidarity between breast cancer survivors in different parts of the world fighting for greater awareness of breast cancer under very different conditions – from the US, where women put breast cancer on the political map decades ago, to countries in central/eastern and southern Europe, China and East Asia, in many of which breast cancer remains a taboo.

Wang Boaling is a 58-year-old breast cancer survivor from Beijing, who joined the Chinese leg of Walk Around the World, up the Great Wall. She welcomed the chance to speak out about breast cancer. "If women paid more attention to their health it would be easier to find the cancer and treat it. Here in China breast cancer is still something you do not talk about easily. After my operation, I reflected a lot on what I could do. I wanted to show the world that cancer did not stop me and show other women that it should not stop them either. It was very impressive to stand on such a powerful


POLAND


RUSSIAN SURVIVORS

symbolic monument as the Great Wall and look out and see the hundreds of women with their families and friends who were also climbing the Wall for the same reason."

Reluctance to speak about breast cancer is also hampering progress in dealing with the disease in much of Europe. Patient organisations in Romania talk of difficulties in securing local authority grants, because of the assumption that people with cancer are going to die and there is nothing anyone can do about it. The Avon walk – the first ever in Bucharest – therefore offered a welcome opportunity to raise the profile of breast cancer. "The whole initiative, from the press conference to the walk and after-walk festivities was a success," said Judy Zerwitz, a 65-year-old breast cancer survivor representing the US, who had flown over to join the Romanian walk. "About 500 lively and energetic people turned up to show their support for breast cancer. There was music and people were having fun; it was all out in the open – both literally and figuratively speaking."

Avon has organised walks to raise breast cancer awareness in a number of countries for many years. Last October's Walk Around the World for Breast Cancer provided the impetus to organise walks for the first time in places that do not have this tradition, and the Global Connection Ribbon focused on the importance of solidarity between advocacy groups in different countries. This is important because levels of cancer awareness differ substantially across Europe, and it is only when cancer becomes a significant public issue that politicians and decision makers start to do something about it.

I wanted to show the world that cancer did not stop me and it should not stop other women either


UK TO IRELAND


USA - SAN FRANCISCO


ARGENTINA


PORTUGAL


ROMANIA TO GERMANY

Radiofrequency ablation in hepatocellular carcinoma

Nahum Goldberg*

A new study supports the use of image-guided radiofrequency ablation as a first-line treatment for well-selected cirrhotic patients with early-stage hepatocellular carcinoma.

Over the past decade, there has been increased interest in image-guided radiofrequency ablation (RFA) of focal tumours using needle-like applicators, because of the minimal morbidity and mortality compared with conventional surgical resection [1]. Clinical interest has focused upon treating hepatocellular carcinoma (HCC), because most patients have underlying liver disease and/or coagulopathies, which substantially increase surgical morbidity, and most patients develop additional foci of disease [1–4].

The use of heat energy in the form of localised radiofrequency to coagulate and ablate tumour has begun replacing prior methods, such as ethanol injection. This is because of the reduced number of treatments required and at least equivalent efficacy of RFA compared with ethanol injection [2,3]. Although there are many optimistic preliminary reports with short-term follow-up, RFA has nevertheless been criticised by some as 'untested', owing to a paucity of long-term results, particularly the absence of five-year survival data [1–3].

Lencioni et al. provide an initial report of promising longer follow-up data, as they demonstrate five-year survival similar to surgical series for similarly stratified patients (see opposite).

The authors performed a prospective, intention-to-treat clinical trial in patients with hepatic cirrhosis (Child-Turcotte-Pugh class A or B) and early-stage HCC in whom percutaneous image-guided RFA was the only first-line anticancer treatment.

In total, 206 nonsurgical patients with either a single HCC ≤5 cm in diameter or up to three HCCs ≤3 cm each were enrolled. RFA was performed in 187 patients (91%).

Safety of the procedure was demonstrated, as there were no periprocedural deaths and only 2% had major complications. Overall survival was 97% at one year, 67% at three years, and 41% at five years, by intention-to-treat analysis, with a 48% five-year survival rate for those undergoing RFA. Median survival was 57 months.

Overall, the one-year, three-year, and five-year recurrence rates were 14%, 49%, and 81% respectively for the emergence of new tumours, highlighting the noncurative nature of local resection, and 4%, 10%, and 10% for local tumour progression, confirming that RFA in skilled hands can be effective at eradicating focal, but not distant, disease. The authors further confirmed prior interventional oncology literature, noting that Child-Turcotte-Pugh class and tumour multiplicity were additional predictors of survival.

These results suggest there is probably enough evidence to justify using image-guided RFA as a first-line treatment for cirrhotic patients with early-stage HCC with limited, well-defined tumour burden. Indeed, this is the practice at our institution, where RFA is also used as an adjunct to liver transplantation.

Nevertheless, the need for further studies, including larger and longer series and ideally a randomised direct comparison between surgery and image-guided ablation (RFA and other), must be

Cancer World has reached agreement with the Nature Publishing Group for the reprinting of articles from the Practice Points section of *Nature Clinical Practice Oncology*. This and the following article first appeared in the September and July 2005 issues respectively

The study

R. Lencioni et al. (2005) **Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation.** *Radiology* 234:961–967

Background. Patients with cirrhosis are at high risk of developing hepatocellular carcinoma (HCC). Radiofrequency ablation (RFA) is a promising treatment for early-stage HCC, but there are few data on its long-term efficacy.

Objective. To assess long-term survival rates in patients with early-stage HCC and underlying cirrhosis treated with percutaneous image-guided RFA as a first-line therapy.

Design & intervention. This prospective, single-arm trial recruited consecutive patients with Child-Turcotte-Pugh class A or B cirrhosis and early-stage HCC between June 1996 and January 2003. Patients who were suitable for liver transplantation or tumour resection were excluded. Percutaneous sonography-guided RFA was performed using a 460 kHz generator of 50 W, 150 W or 200 W. Target intratumoural temperatures were 95ºC for the 50 W generator, and 105ºC for the 150 W and 200 W generators. Needle tracks were ablated after all procedures. Patients with CT evidence of incomplete tumour ablation 1 month after treatment received a further dose. Patients who failed to improve after two sessions or who developed metastases were offered segmental transcatheter arterial chemoembolisation. Patients were followed up and tumour recurrence was monitored by 3-monthly ultrasonography and 6-monthly spiral CT, for a mean follow-up period of 24 months (range 3–78 months).

Outcome measures. The primary outcome measure was overall survival.

Results. Of 206 patients (69% male; mean age 67 years) who entered the study, 187 (91%) underwent RFA. Of the patients given RFA (70% male; mean age 67 years), 61 were treated using a 50 W generator and 126 were treated using a 150 W or a 200 W generator. After one or two sessions of RFA, complete tumour regression was observed in 169 of 187 patients (90%) and 222 of 240 tumours (92%) at 1 month. Respective survival rates in the intention-to-treat population and in the RFA-treated patients were 97% and 97% at 1 year, 67% and 71% at 3 years and 41% and 48% at 5 years, respectively. Survival did not differ significantly between the two groups (P=0.5094). Among patients treated with RFA, survival was significantly greater in those with Child-Turcotte-Pugh class A cirrhosis than in those with Child-Turcotte-Pugh class B cirrhosis (P=0.0006), and in those with one tumour compared with those with several tumours (P=0.0133). Local tumour progression occurred in 4% of RFA-treated tumours at 1 year, 10% at 3 years and 10% at 5 years; metastasis was seen in 14%, 49% and 81%, respectively. Serious adverse events (including one case of tumour dissemination via the needle track) occurred in three patients, and minor complications were reported in nine patients.

Conclusion. First-line anticancer treatment with percutaneous image-guided RFA is effective in patients with cirrhosis and early-stage HCC for whom surgical resection is not indicated.

Acknowledgement. This synopsis was written by Jean-Francois Geschwind, associate professor and director of vascular and interventional radiology, Johns Hopkins Hospital, Baltimore, MD, USA.

acknowledged, because the study was of short follow-up duration, with a mean of two years, with wide variation.

Furthermore, the best way to perform tumour ablation in terms of technique, device selection, and potential combination with other therapies, such as chemoembolisation and adjuvant treatments to improve local and distant disease control, requires further study. Each of these variables can potentially influence the study outcome.

Better definition of indications and treatment guidelines is also needed, with caution being urged against overoptimistically translating these promising data for the treatment of more advanced HCC (i.e. larger tumours) or other types of tumour (e.g. intrahepatic colorectal metastases), which are more difficult to treat with ablative techniques [1,4].

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

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Competing interests: Dr Goldberg receives sponsored research support and is on the advisory board of Valleylab, USA, a manufacturer of radiofrequency ablation devices. He also receives research support from the NCI

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Relapsed Hodgkin's lymphoma: new twist to the standard regimen

Fredrick Hagemeister*

Results of a multicentre study show that a sequential high-dose chemotherapy variant of the standard treatment is safe and effective in relapsed Hodgkin's patients.

High-dose chemotherapy followed by autologous stem-cell transplantation (ASCT) has been the standard care for patients with relapsed Hodgkin's lymphoma for many years, achieving better results than MINI-BEAM (low-dose carmustine, etoposide, cytarabine, and melphalan) and DEXA-BEAM (dexamethasone, carmustine, etoposide, cytarabine and melphalan) in randomised studies. However, many questions remain regarding the conduct of such a programme for relapsed and refractory disease, including the best selection of patients, optimal choice and sequencing of drugs prior to high-dose treatment, and value of allogeneic stem-cell sources.

In a large multicentre study by the German Hodgkin Lymphoma Study Group, reported by Josting et al. (see opposite), patients with primary refractory and relapsed Hodgkin's lymphoma received two cycles of DHAP (dexamethasone, high-dose cytarabine and cisplatin), and responders underwent sequential high-dose chemotherapy followed by standard and high-dose BEAM chemotherapy (carmustine, etoposide, cytarabine and melphalan) and ASCT.

Most patients were in first relapse following primary therapy, and all patients were considered in the final analysis. Overall results of this trial were good: at 30 months, freedom from second treatment failure (FF2F) and overall survival rates were 59% and 78%, respectively. Results for FF2F were strongly affected by stage at relapse, type of remission at entry into study, and sensitivity to DHAP.

For overall survival, response to DHAP, type of remission, and presence of anaemia were strong determinants of outcome. The investigators have planned a large multicentre randomised study in which all patients with relapsed Hodgkin's lymphoma will receive two cycles of DHAP followed by either BEAM and ASCT or sequential high-dose therapy and BEAM with ASCT for patients with a complete response or partial response after DHAP.

The Goldie–Coleman hypothesis, according to which non-cross-resistant drugs should be used at lower doses in combination for initial treatment of chemo-sensitive lymphomas, has been challenged by this study. The results lend support, instead, to the Norton–Simon hypothesis, which suggests that maximum doses of sequential agents should be delivered to overcome potential resistance in patients with relapsed disease.

In general, investigators have used two methods to select patients with Hodgkin's lymphoma for ASCT. In one method, patients are induced into remission and then undergo pheresis with a regimen different from that used for induction; in the other, the same regimen is used for induction and pheresis [1,2]. Josting et al. used the former model, but with a twist: patients undergo the same type of sequential high-dose therapy for cytoreduction as employed by Gianni et al. in relapsed aggressive lymphomas and Hodgkin's lymphoma [3,4], with the added benefit of improving the quality of stem-cell products obtained.

In those reports, results were very favourable, although critics could not conclude that there was any benefit of such an approach in these single-armed trials. Nonetheless, Josting et al. have confirmed the feasibility of such a programme in a multicentre study, and have reported results in ways that strengthen support for this approach. Others have also demonstrated that this approach is feasible in therapy of follicular lymphomas and relapsed Hodgkin's lymphoma, in

The study

A. Josting et al. (2005) **Cologne high-dose sequential chemotherapy in relapsed and refractory Hodgkin lymphoma: results of a large multicenter study of the German Hodgkin Lymphoma Study Group**. *Ann Oncol* 16: 116–123

Background. The current treatment of choice for patients with relapsed or refractory Hodgkin's lymphoma is high-dose chemotherapy followed by autologous stem-cell transplantation (ASCT). In line with the Norton–Simon hypothesis, sequential high-dose chemotherapy (HDSCT) – where non-cross-resistant agents are administered at brief intervals – is suggested by the authors of this study as an alternative to conventional high-dose chemotherapy in these poor-risk patients.

Objectives. To determine whether a dose-intensified and time-intensified HDSCT regimen improves outcome in patients with relapsed or refractory Hodgkin's lymphoma.

Design. This phase II study enrolled patients aged between 18 and 65 years (median age 34) with biopsy-confirmed, relapsed or progressive Hodgkin's lymphoma from 34 treatment centres in Germany. Among other criteria, eligible patients had an Eastern Cooperative Oncology Group performance status of ≤2, were free of infection and negative for HIV. All patients had undergone first-line polychemotherapy with one of a number of standard regimens, such as COPP/ABVD (cyclophosphamide, vincristine, procarbazine and prednisone, alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone).

Intervention. Upon relapse or progression, all patients underwent initial cytoreduction with two cycles of DHAP (dexamethasone, high-dose cytarabine and cisplatin), 14 days apart, accompanied by ondansetron on the first and second day of each cycle to minimise nausea and vomiting. Granulocyte-colony-stimulating factor was also administered to aid haematologic recovery. Patients who showed a partial response (PR) or complete response (CR) then received an HDSCT regimen comprising 4000 mg/m^2 cyclophosphamide – after which peripheral-blood stem cells were harvested by pheresis – followed by high-dose methotrexate (8000 mg/m^2), vincristine (1.4 mg/m^2), high-dose etoposide and myeloablative treatment with BEAM (carmustine, etoposide, cytarabine and melphalan). Patients then underwent ASCT. Follow-up assessments took place 100 days after ASCT, every 3 months for the first year, then every 6 months. This was reduced to once a year after 5 years.

Outcome measures. The primary endpoints were freedom from second failure (FF2F) and overall survival. Toxicity of DHAP and HDSCT were also assessed.

Results. Of the 102 patients enrolled in the study, 88% showed some degree of response (PR 67%, CR 21%) after two cycles of DHAP, and went on to receive HDSCT. After a median follow-up time of 30 months (range 3–61 months) the overall response rate was 80% (PR 8%, CR 72%), including patients who had failed after DHAP. The FF2F and overall survival for all patients were 59% and 78%, respectively. Disease progression accounted for 23 deaths (22%), and two patients (2%) died from septic shock during neutropaenia. Significant prognostic factors for FF2F were relapse status (P=0.0051), stage at relapse (P=0.0358) and chemosensitivity after DHAP (P<0.0001). Duration of first remission (P=0.0017) and anaemia at relapse (P=0.019) were significant for overall survival.

Conclusion. Salvage therapy with DHAP, followed by the prescribed HDSCT regimen, is safe and effective in patients with relapsed and refractory Hodgkin's lymphoma.

Acknowledgement. This synopsis was written by Alexandra King, *Nature Clinical Practice*.

single-armed multicentre studies [5,6]. A randomised study will be necessary to demonstrate that the FF2F achieved by Josting et al. using this approach is better than results achieved with standard methods.

Finally, questions remain over whether one could improve on these results, not only for patients with favourable relapse but also for those with unfavourable disease. Are regimens employing etoposide, gemcitabine, or other drugs better than DHAP at inducing remission? Are allogeneic stem cells useful? Will antibodies play a role in treatment? Investigators may have to utilise more novel approaches to significantly improve results for patients with recurrent Hodgkin's lymphoma.

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

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NEWSROUND

Selected press reports compiled by the ESO Cancer Media Centre

Chromosome alterations in neuroblastomas may help predict survival

➔ New England Journal of Medicine

New tumour biomarkers may help to identify outcomes for patients with neuroblastoma, a form of childhood cancer, according to a study published in the *New England Journal of Medicine*. Neuroblastoma is one of the most common cancers found in babies or young children, with two-thirds of cases diagnosed in children younger than five years of age.

The disease originates in the adrenal medulla or other sites where sympathetic nervous system tissue is present. There are different types of neuroblastoma tumours. Some are highly aggressive and require assertive treatment, others will remain slow-growing and can spontaneously regress.

Treatment for neuroblastoma varies greatly, depending on the stage of the disease and its ferocity. It is important that doctors can identify the strain of neuroblastoma so that patients can be given the appropriate treatment.

Scientists in the latest published study examined over 900 different samples of neuroblastoma, and looked at the abnormalities of chromosomes 1p and 11q. The results suggested that abnormalities in patients with the disease are associated with worse outcomes. Three-year event-free and overall survival rates were worse for those with the chromosome abnormalities. In the future, scientists will be able to screen tumours for the presence of abnormalities, to determine the appropriate form of treatment for the cancer patient. In some cases more aggressive chemotherapy and immediate bone marrow transplant may be appropriate to improve chances of survival.

■ Chromosome 1p and 11q deletions and outcome in neuroblastoma. EF Attiyeh, WB London, YP Mossé, et al. *NEJM* 24 November 2005, 353:2243-2253

Diabetics have a higher risk of colorectal cancer

➔ Journal of the National Cancer Institute

Diabetes is associated with an increased risk of colorectal cancer according to a meta-analysis published in the *Journal of the National Cancer Institute*. Previous studies have been inconclusive about the link between the two conditions.

Colorectal cancer is the most common form of cancer in the European Union, but it is one of the most curable cancers if caught early enough. Diabetes currently affects 5% of the world's population and occurs when the body cannot break down sugar in the normal way. Obesity is a risk factor for both conditions and may provide evidence for the link.

Scientists examined 15 published studies including just over 2.5 million participants. The meta-analysis found that people with diabetes were at a higher risk of colorectal cancer than those without diabetes. Previous studies have indicated that men with diabetes may be more at risk; however, the study proved that the link between colorectal cancer and diabetes did not differ significantly by sex or by cancer sub-site.

The study also revealed that people with diabetes are more likely to die from colorectal cancer. Scientists are unsure what causes the relationship between diabetes and the increased risk of colorectal cancer. It seems that the high sugar levels found in diabetics may hold the key; or alternatively hormonal changes associated with diabetes could promote tumour risk. Further research is needed to fully understand the link.

■ Diabetes mellitus and risk of colorectal cancer: a meta-analysis. SC Larsson, N Orsini, A Wolk. *JNCI* 16 November 2005, 97:1679-1687

Chemotherapy improves survival for patients with endometrial cancer

➔ Journal of Clinical Oncology

A new study published in the *Journal of Clinical Oncology* has found that chemotherapy improved survival for patients with advanced endometrial cancer when compared to radiation therapy.

Women who take tamoxifen for breast cancer are at increased risk of endometrial cancer, as are women taking oestrogen (without progesterone) as a type of birth control or to treat menopausal symptoms.

The US study compared the two types of treatments currently given to endometrial

cancer patients – irradiation of the abdomen versus chemotherapy with doxorubicin-cisplatin. Nearly 400 women (average age 63) with advanced endometrial cancer (stage 3 or 4) took part in the study. Approximately half of the study population was given radiation and the other half chemotherapy. The patients were then monitored and followed up for a number of years.

The study found that, at five years, after adjusting the results to take into account the different stages of the disease, 50% of the patients receiving chemotherapy were predicted to be alive and disease free compared to just 38% of patients receiving radiation therapy. Moreover, 55% of women treated with chemotherapy were predicted to be alive compared to 42% of patients treated with radiation therapy.

The results clearly showed that chemotherapy with doxorubicin-cisplatin significantly improved progression-free and overall survival compared with radiation therapy. However, scientists did find that there was greater acute toxicity seen with chemotherapy, and further advances are needed in reducing the levels of toxicity.

■ Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: A Gynecologic Oncology Group Study. ME Randall, VL Filiaci, H Muss, et al. *JCO*, published online 5 December 2005, doi: 10.1200/JCO.2004.00.7617

Fentanyl patch is a safe and effective alternative to oral opioids for children

➔ Cancer

A new study has found that using a transdermal patch to deliver the opioid fentanyl is an effective way to control pain in children. Results from an international study published in *Cancer* indicate that the fentanyl patch is safe for children aged 2–16 years.

Opioids, such as morphine, have been shown to clearly reduce pain and improve quality of life in adults. However, little is known about the safety and efficacy of this class of analgesics in children. Until recently, children were thought to feel pain to a lesser degree and have a higher risk of addiction than adults. Newer information indicates that children experience severe pain and have the same addiction risk as adults.

They are also at greater risk for psychological disturbances that have an immediate and long-term developmental impact. However, children often have difficulty taking opioids; they may not like swallowing pills and get distressed at injections.

Julia Finkel, of the Children's National Medical Center in Washington DC, and international colleagues, examined 173 children from between the ages of 2 and 16 years, many of whom were cancer patients and had a history of chronic severe pain and previous oral opioid use.

They were given the fentanyl patch that equalled the amount of oral analgesics they had received, and were followed for 15 days. The researchers found that subjective pain and quality of life improved significantly. By day 16, the average daily pain intensity score had decreased. Many patients elected to continue in the study for three months. After one month, quality of life scores improved. At the end of three months, average play performance scores also showed significant improvement.

There were no more adverse experiences than reported in adults, and no adverse experiences specific for the paediatric population. The authors conclude: "Results from global measurements of pain treatment, safety and quality of life indicate that transdermal fentanyl is an acceptable alternative to oral opioid therapy in children."

■ Transdermal fentanyl in the management of children with chronic severe pain: results from an international study. JC Finkel, A Finley, C Greco, et al. *Cancer*, published online 14 November 2005, doi: 10.1002/cncr.21497

Discovery of molecular signature will help treat patients with brain cancer

➔ New England Journal of Medicine

Researchers at the University of California at Los Angeles Jonsson Cancer Centre have identified key characteristics in certain fatal brain tumours that make those tumours more likely to respond to a specific class of drugs than tumours where the specific molecular signature is absent.

The discovery of this molecular signature (the expression of a mutant protein and a tumour suppressor protein called PTEN) will allow researchers to identify patients who are likely to respond to the drug treatment, before they embark on therapies that might not work.

According to Paul Mischel, an associate professor of pathology and laboratory medicine and a Jonsson Cancer Center researcher, the discovery of this treatment could change the way doctors treat glioblastoma, which is the most common type of malignant brain tumour and one of the most lethal forms of cancer. "In a biologically aggressive disease like glioblastoma, it's vital to be able to stratify patients up front so we can treat them with drugs that they are more likely to respond to...this will help prevent patients from having needless therapies that are toxic and not beneficial. With the short survival times associated with glioblastoma, this is critical."

Quality of life is an important factor, as patient survival is on average less than one year. Although treatment may prolong life, most malignant brain tumours are not curable, making the search for better treatments even more urgent. Epidermal growth factor receptor (EGFR) is commonly over-produced in glioblastoma, making it the focus for therapies.

Mischel and his team studied a group

of 26 glioblastoma patients who either responded very well or very poorly to EGFR-blocking drugs, and developed a way to test their brain tumours for the presence of both mutant and PTEN proteins. Mischel's team found that patients with both genetic variations were 51 times more likely to respond to EGFR blockers. They also lived five times longer after having the therapy than those without the variation, surviving for 253 days instead of 50.

Mischel and his team also took 33 tissue samples from brain cancer patients treated at another facility. They were able to replicate their results, confirming that those with both genetic variations were more likely to respond to EGFR blocking drugs. The study shows that glioblastoma patients can respond to targeted agents, and suggests that patients likely to benefit from treatment can be identified by molecular testing.

The study also raised the possibility that patients whose tumours lacked the genetic variations in the molecular signature could possibly be treated with drugs to make them more sensitive to EGFR blockers. "Many cancers have a similar combination of a mutant cancer-causing protein and either the expression or loss of the PTEN protein…The interactions of the two may be important in determining response to targeted agents."

About 10%–20% of patients have the combination of the mutant and PTEN proteins.

Mischel and his team are also working to uncover the molecular signatures in the tumours of non-responders, so they can determine which therapies might be most effective for those patients.

"Glioblastoma is still a difficult disease, but the idea that it may be possible to induce long-term disease suppression gives reason for hope."

■ Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. IK Mellinghoff et al. *NEJM* 10 November 2005, 353:2012–2024

Survival rates for colon cancer patients improve

➜ JAMA

More patients with stage 3 colon cancer are receiving chemotherapy after surgery, improving their five-year survival rates, according to a study in the December 7 issue of JAMA.

However, women, black patients and the elderly, are less likely to receive adjuvant treatment.

The National Institutes of Health Consensus Conference recommended in 1990 that adjuvant chemotherapy (5-fluorouracil-based regimen) should be given to all patients with stage 3 colon cancer. Researchers looked at information from almost 86,000 patients entered into the National Cancer Data Base between 1990 and 2002 to see whether the Conferences' recommendations had been followed.

The researchers found an increase in the use of adjuvant chemotherapy for all patients with stage 3 colon cancers, from 39% of patients in 1990 to 64% in 2002. Between 1991 and 1997, the five-year survival rate almost doubled in patients who had adjuvant chemotherapy compared to those who had surgery alone.

The study also revealed that the use of adjuvant chemotherapy was lower in female and elderly patients. Significantly, 3% fewer women than men received adjuvant chemotherapy after surgery, even though the treatment is equally beneficial in both.

Elderly patients were also given adjuvant chemotherapy less frequently, despite the fact that they benefit as much as young patients.

■ Adjuvant chemotherapy for stage III colon cancer. Implications of race/ethnicity, age and differentiation. JM Jessup, A Stewart, FL Greene, et al. *JAMA* 7 December 2005, 294:2703-2711

Breast cancer treatment may be affected by altered gene

➜ Journal of Clinical Oncology

A new study has found that Tamoxifen may be less effective in treating women with breast cancer if they have a relatively common genetic variation, according to research published in the *Journal of Clinical Oncology*.

Tamoxifen usually reduces the risk of breast cancer recurrence by almost 50% in women with oestrogen-receptor positive breast cancer. However, this study indicates that women whose CYP2D6 gene is altered have a higher risk of relapse when treated with tamoxifen for five years compared to women who do not have the altered gene.

The genetic alteration, which occurs in about one in ten women, affects the level of CYP2D6, a liver enzyme that is involved in metabolising the drug. Researchers found that normally the enzyme CYP2D6 converts tamoxifen to a metabolite called endoxifen – an anti-oestrogen that is nearly one hundred times stronger than tamoxifen itself. However in women with the altered gene, the process does not work as well, and the tamoxifen may be less effective at preventing relapse.

The study looked at 223 tumour and tissue samples from tamoxifen-treated women who took part in the American Phase III North Central Cancer Treatment Group adjuvant breast cancer trial.

The results showed that women with the altered gene tend to have a higher risk of disease relapse and a lower incidence of hot flashes.

A larger study is needed in order to corroborate the findings.

■ Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. MP Goetz et al. *JCO* 20 December 2005, 23:9312-9318

Two sides to every study

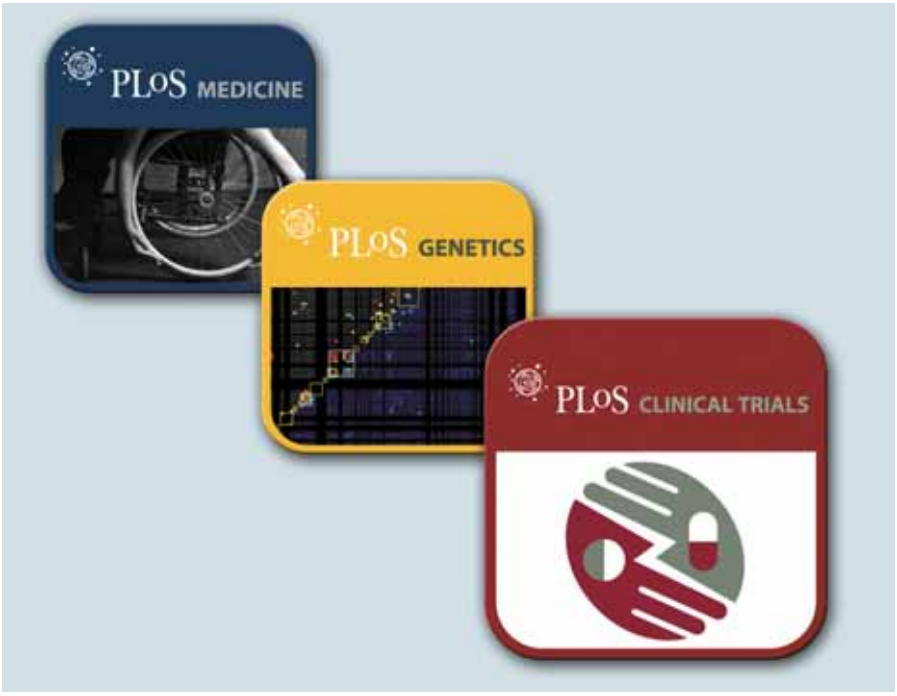
Margaret McCartney*

If research is worth funding at all, isn't it worth paying a little extra to make the results – positive or negative – available as freely and speedily as possible?

We hear an awful lot about some research findings. But what about the research we never find out about at all? Put it another way. You may spend several years slaving over high-quality, relevant research, but fame is never guaranteed. Your study may have been beautiful, statisticians may swoon over your elegant way with chi-squares, but if your results were indeterminate, or you didn't get to disprove your null hypothesis, you can probably kiss goodbye to a call from the Today radio news programme. For we know from detailed investigation that "publication bias" shapes what the world hears about most often. Basically, the most widely read journals, those that make most media impact, carry positive findings more often than negative ones. In other words, if your trial shows that a drug is effective, you will have a better chance of publishing it in a well-known journal than if your trial has shown that the drug made little or no difference. In these circumstances, the chances are that only a small or obscure journal will publish it – if it is published at all. No Today programme, no headlines; back, my dear, to the lab. This is important because we need 'negative' studies. In fact, we should treasure them just as much as 'positive' ones. If negative studies are ignored and not published, we end up with a skew of results sitting – artificially – in a treatment's favour. We end up with a treatment or drug thought to be better – or less harmful – than it actually is. Yet it is understood that about 50% of clinical trials never reach publication. Unless we can be certain that we are in possession of all the research relating to a drug or treatment, we cannot be confident in our assessment of it.

We can hardly blame the media for over-hyping medical stories when medical presses are guilty of much the same thing. Most medical journals are a business – the more popular UK journals cost between £20 and £360 (30–530 euros) for an individual subscription. Institutions are charged a great deal more again, and certain journals can cost thousands of pounds a year. The big journal names need to remain in the public eye and need to effectively 'sell stories' in order to remain medical must-reads. This has to be part of the reason why negative studies tend not to get the attention of the wider media. Then there is the issue of reprints. Small and slender extracts of favourable research from journals are handed out in quantity to doctors at conferences or by pharma reps as a PR exercise. Richard Smith, ex-editor of the *British Medical Journal*, this year wrote in *Medicine*, the online Public Library of Science (Plos) journal, that: "Publishers know that pharmaceutical companies will often purchase thousands of dollars' worth of reprints, and the profit margin on reprints is likely to be 70 per cent. Editors, too, know that publishing such studies is highly profitable and editors are increasingly responsible for the budgets of their journals and for producing a profit for the owners. An editor may thus face a frighteningly stark conflict of interest: publish a trial that will bring $100,000 of profit, or meet the end-of-year budget by firing an editor."

If negative studies are not published, the results become artificially skewed in a treatment's favour



PLOS

Some of the titles published by the Public Library of Science (Plos). Many funding bodies, including the powerful Wellcome Trust in the UK, support Plos and factor the cost of open-access publication into their research grants

A GOOD ALTERNATIVE

Is there another way? Yes, and the mess that is medical research might actually be beginning to get cleaned up. The non-profit organisation Plos, which mainly publishes online, recently launched another journal, entitled *Plos Clinical Trials*. Already, there are several Plos titles – *Genetics* and *Pathogens* as well as *Medicine* – which have attracted a great deal of attention because of the stark difference between the way they accept and publish research compared with most other medical publications.

Firstly, the authors or researchers pay in the region of $2,000–$2,500 (1,700–2,150 euros) to have their publications printed in Plos journals. But this is no vanity publishing. While this fee is waived for researchers unable to afford it, it is logical that, in the main, the cost of publication is simply part of the overall costing for a piece of research. If the research was important enough to do in the first place, it is surely just as important to make the results as freely and rapidly available as possible – no matter what they are.

I have started to put references to research or papers I mention on the *Financial Times* website but, if you click to the links on ft.com, you will find that in many cases only the abstract, or summary, of the research is available free. To gain access to the full body of research on most journals, you have to pay. By contrast, Plos aims to make all its published research – peer-reviewed just like any other journal – available online for no charge. As far as publication goes, it is a model of excellence. There can be no logic in the current situation, whereby you could decide to participate as a patient in a clinical trial, even over several years, spending time and effort in undertaking follow-up tests, only to find that not only must you pay to access the results but also that neither the scientific nor the medical communities at large have immediate access to the results. The scientific advances the trial promised, and which you thought you were aiding, instead end up trickling down to the medical community over months and years.

Some publishers may feel threatened by open-access publishing, but organisations including the Wellcome Trust have made their support clear. It has said it will include the cost of open-access publication in research funding. The open-access model results in a bigger, faster impact for research – better for patients, better for funders – whether the results make headline news or not.

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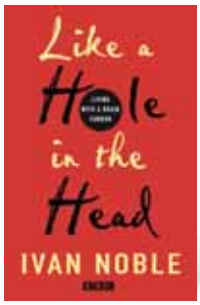
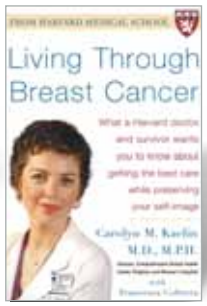
First published in the *Financial Times*, November 12/13 2005.

"Publishers know that pharma companies will often purchase thousands of dollars' worth of reprints"

The drowned and the saved





➜ Raphaël Brenner

In recounting their personal stories, cancer patients are not only sharing their experiences and feelings – they are providing practical support to others and are gradually influencing the way cancer is perceived and treated.

IN August 2002 Ivan Noble's life was turned upside down. While working as a science journalist for BBC News online in London, 35-year-old Noble was diagnosed with a malignant brain tumour. The "strong urge to fight back" against the powerlessness of his condition inspired Noble to chronicle his struggle against the disease in a diary, which he courageously decided to share with readers of BBC news. Noble's blog (short for weblog), in which he combined his knowledge as a science journalist with his personal story, became an instant hit and triggered thousands of e-mails from readers. It has now been published as a book together with a selection of the e-mails he received.

Noble's narrative is a straightforward chronicle of how a rational, atheistic journalist courageously fought cancer, while continuing to work and pursue family life with his baby daughter, and of how he finally succumbed. "Dealing with cancer became my job," writes Noble. The journalist in him did not prevent Noble from expressing his pain – as he swayed between hope and despair, remission and relapse, life and death. One cannot but feel sympathy when reading about the clumsy manner in which he was told of his illness. "A few more encouraging words would have made that first week so much less painful," writes Noble as he recalls how his oncologist announced the bad news. He suggests that oncologists spend more time with patients, explaining to them what is actually taking place in terms of the illness and what may happen next, and he wishes they would have the courage to look patients in the eye, rather than looking at their own feet. He reminds us that "it is easy for doctors to lose sight of what it is like to be a patient."

Like a Hole in the Head
Ivan Noble
Hodder & Stoughton, 176 pp, £6.99

Cancer du sein. L'annonce, le traitement, la rémission
Stéphanie Honoré
Seuil, 224 pp, euro 19.00

Living through Breast Cancer. What a Harvard Doctor and Survivor wants you to Know about getting the Best Care while Preserving your Self-image
Carolyn M. Kaelin with Francesca Coltrera
McGraw-Hill, 384 pp, $22.95

Beyond Slash, Burn, and Poison. Transforming Breast Cancer Stories into Action
Marcy Jane Knopf-Newman
Rutgers University Press, 224 pp, £14.95

As is evident from the e-mails received by Noble, cancer patients found his diary inspiring and supportive. Noble's blog hit a chord. It expressed the unvoiced feelings of the silent mass of cancer patients and exposed their need to share their experiences, talk freely and be comforted by others.

All profits from *Like a Hole in the Head* go to Médecins Sans Frontières.

Stéphanie Honoré and Carolyn M Kaelin, both mothers of two children, were 32 and 42 respectively when they were diagnosed with breast cancer. They survived and their books belong to the testimonial-cum-guide genre that offers practical tips and advice to women diagnosed with cancer.

Honoré wrote her book in order to enable women to understand and

express their feelings as cancer victims, as well as to familiarise them with the coded jargon of the medical profession. In concise, easy-to-read chapters, she explains the different stages of treatment and provides a wealth of explanations and useful advice on all aspects of the disease, from how to announce the bad news to one's family and talk about death with one's children, to the intricacies of breast cancer imaging and modern forms of treatment, including psychological therapies and alternative medicine.

What makes her book noteworthy is its personal touch: Honoré brings an inner dimension to whatever she discusses, whether it is man/woman's survival instinct, the brutalism of hospitals, the negative way in which the medical establishment deals with cancer patients or reconstructive surgery. At the end of each chapter, we are given boxes called 'antidotes' with advice on how to survive in the hostile environment of hospitals. "Oncologists use many protocols and guidelines," she writes, "it is now time for patients to write guidelines for use by doctors."

Like Honoré, Kaelin – one of America's top female breast health specialists – aims to demythologise breast cancer by explaining every step of the disease in plain English. As director of the Comprehensive Breast Center at Brigham and Women's Hospital, Boston, Massachusetts, and surgical oncologist with the Dana Farber Cancer Institute, also in Boston, Kaelin is superlatively qualified to provide a scientific guide for women undergoing breast cancer treatment.

Her book, replete with illustrations, offers more in-depth information on breast cancer, particularly on the side-effects of chemotherapy, sexuality, surgery, reconstructive surgery and the need to obtain a second opinion. She also covers sensitive issues relating to women's body image, which are rarely discussed, such as breast forms, ways of dealing with loss of hair, eyebrows, pubic hair and teeth, skin care, exercise and nutrition. On the negative side, she levels no criticism whatsoever at her own profession, and could have dealt more thoroughly with the needs of survivors following completion of treatment – an element also lacking in Honoré.

Certain topics will interest only US readers, nonetheless this highly comprehensive book makes an important contribution to breast cancer literature.

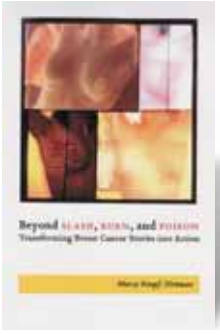
The daughter of a breast cancer victim and a professor of English, Marcy Jane Knopf-Newman has produced an excellent book (much better written than the above two) on the history of breast cancer, in which she reveals "the deep impact that narratives can have on a person's experience and, in turn the significant effect literature can have on political and public culture."

Knopf-Newman argues that the way breast cancer is perceived and treated, at least in the US, has been shaped by the narratives and public disclosures of a few key people such as biologist Rachel Carson's book *Silent Spring*, and her testimony at a Senate hearing in the 1960s on the influence of the environment on cancer. At around the same time, surgeon George Crile published a book challenging the widespread use of Halsted's radical mastectomy.

In 1974 Betty Ford became one of the first major figures to publicly disclose that she suffered from breast cancer. She was followed by activist Rose Kushner, whose watershed book "led to new relationships and better communication between doctors and patients." Kushner's book helped empower women to make their own decisions about their bodies, and request the specialists and forms of surgery they desired. In her congressional testimony, Kushner also noted the economic incentives that discouraged surgeons from offering women alternative choices to the Halsted mastectomy.

Finally, in the '80s and '90s, poet activist Andre Lorde wrote a book which questioned the dominant medical practices in breast cancer treatment, galvanised women to take a more active role in their healthcare and helped widen the range of choices available to women – particularly black, lesbian and disadvantaged women. Lorde's influence is clearly felt in *Dr. Susan Love's Breast Book*, the number one bestseller on breast cancer in the US.

Although Knopf-Newman's book is written from a US perspective, it has much that is relevant to European patients. In Europe too, breast cancer patients have had to fight not only their illness but also the medical establishment. To what extent patient narratives will influence public policy and medical practice remains to be determined, but if the US is anything to go by, patient activism is a force to be reckoned with.



Alif Ba Amrad At-Thadiye
ABC of Breast Diseases: from Prevention to Treatment
Nagi Saghir
Arab Scientific Publishers
232 pp, $10.00

Written by an associate clinical professor of medicine at the American University of Beirut Medical Center, this is the first book of its kind in Arabic. Addressing itself to the lay public, it presents in simple terms the main medical information pertaining to the health and diseases of the breast and provides answers to questions that can cross the minds of women as well as a list of relevant Arab, European and US websites. Saghir's book offers much useful information, support and guidance for women with breast cancer, and discusses the problems resulting from surgery, radiotherapy and chemotherapy. The book also provides instructions for self-examination, with illustrations. Husbands, relatives and friends of cancer patients will also benefit from it. The last chapter deals with breast cancer in men, a subject often ignored and something of a taboo in the Arab world. It is to be hoped that this book will help change the way breast cancer is perceived and dealt with in Arab countries.

Imagerie de la prostate
Edited by François Cornud
Sauramps médical
292 pp, euro 125.00

Cornud's book depicts the prostate pathologies (including normal prostate and benign prostate hypertrophy) as they appear in all the imaging techniques currently available: microscopy, ultrasonography, MR imaging, MR lymphography, lymphoscintigraphy, PET-CT, spectroscopic imaging, etc. It also discusses the indications of these techniques for each stage of a malignant evolution (for diagnostics and therapeutics), and analyses the role of imaging in radiotherapy of localised prostate cancers. The book is lavishly illustrated in four-colour printing, and each indication is accompanied by a list of the most recent references. For French-speaking (radio) oncologists, this is the ultimate reference book on medical imaging of prostate cancer.

Onkologie
Unkonventionelle und supportive Therapiestrategien
Edited by Clemens Unger
and Joachim Weis
Wissenschaftliche Verlagsgesellschaft,
196 pp, euro 24.00

Psychotherapie bei somatischen Erkrankungen
Krankheitsmodelle und Therapiepraxis – störungsspezifisch und schulenübergreifend
Edited by Hermann Faller
Thieme, 240 pp, euro 39.95

The popularity of complementary and alternative medicine (CAM) in the western world continues to grow, especially among cancer patients. In Europe, 30% of patients on average use at least one type of CAM, while in Germany and Switzerland the figure is over 50%. Despite the fact that most physicians do not approve of CAM as a whole, the practice has become a reality. Hence the pragmatism of Unger and Weis – both professors of oncology in Freiburg, Germany – and their goal to acquaint physicians and other professionals involved with cancer with the fundamental principles of non-conventional therapies.
Such knowledge, it is hoped, will help to ensure professional control over non-conventional methods, protect patients from charlatan practitioners and prevent detrimental interactions of plants with chemotherapy or radiotherapy.
The book is thoroughly comprehensive: the authors analyse the most popular CAM methods, explaining their indications, pharmacology and side-effects, and discuss the available

scientific data, with a wealth of references. The first part of the book deals with the various therapies – sport and physical activity, diets (fruits and vegetables), psycho-oncology, and anti-tumour immune response (IL-2, TNF-α, etc.), while the second part is devoted to non-conventional drugs. Mistletoe (widely used in Germany), anti-oxidants, melatonin, enzymes, thymic hormones, Boswellic acids (against brain tumours) and aloe vera are some of the main remedies reviewed in the book. The authors note that these products cannot be recommended according to the rules of evidence-based medicine, and they call for more prospective studies, but they also note that they are not harmful and can often improve a patient's quality of life.

German-speaking readers interested in psycho-oncology will find a good overview of this discipline in the textbook edited by Hermann Faller. According to Faller, psychological therapy is highly effective for cancer patients, as it strengthens their ability to cope with the illness, gives them hope, and facilitates communication with their oncologist. Although cancer causes great psychological stress and suffering in patients and their families (including depression, anxiety and somatoform symptoms), psychological therapies regrettably remain underused.

Textbook of Neuro-oncology
Edited by Mitchel S. Berger
and Michael D. Prados
Elsevier Saunders, 876 pp, £134.00

Principles of Neuro-oncology
Edited by David Schiff
and Brian Patrick O'Neill
McGraw-Hill, 768 pp, £95.00

Minimally invasive Neurosurgery
Edited by Marc R. Proctor
and Peter M. Black
Humana Press, 448 pp, £103.00

Despite the impressive advances in molecular biology and brain imaging, these methods are "still short of achieving major improvements in patient care and survival", acknowledges Nicholas Vick in *Principles of Neuro-oncology*. This is why brain tumours remain "the most dreadful form of cancer". The two textbooks by Berger/Prados and Schiff/O'Neill provide an encompassing study of neuro-oncology, catering to all those who wish to understand more about brain tumours, from neuro-radiologists to students. They successfully decipher the complex issues behind brain tumourigenesis and enhance the reader's intellectual curiosity.

Both books cover first the scientific underpinnings and principles of diagnosis and treatment, before addressing specific tumours. However, Berger/Prados is more beautifully produced, in four-colour printing, and benefits from a clearer layout and a richer iconography than Schiff/O'Neill. The content is also richer, containing a more detailed discussion of rare diseases such as glioblastoma multiforme and Lhermitte-Duclos, and is presented in a more coherent manner. This is especially true of the section devoted to paediatric neuro-oncology.

For their part, Schiff/O'Neill provide useful summaries at the beginning of the chapters and include an interesting chapter on the neurological complications of radiotherapy and chemotherapy. Both books deal at length with cerebral metastases, a subject under-represented in other textbooks even though metastases are the most common form of brain tumour in adults.

The advances in imaging of the central nervous system (CT, MRI) have been crucial to the development of minimally invasive neurosurgery (MIS), which means surgery through small openings or surgery that is minimally disruptive to the patient. In part I of *Minimally Invasive Neurosurgery*, clinical neurosurgery and neuroradiology experts review cutting-edge techniques and technologies. They offer a comprehensive survey of neurosurgical endoscopic equipment, one of the mainstays of MIS, as well as of gene-based and viral-based therapies. Part II is devoted to the application of MIS in the different fields of neurosurgery, including brain tumours. This is a fast-moving field. Where image-guided neurosurgery dominated the advances of the last decade, laser hypothermia and focused ultrasound may radically change our ability to treat specific tumours in the future. A highly recommended book for clinical neuroscientists interested in MIS.