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Education & knowledge through people & facts

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Laura van 't Veer

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Getting serious about e-qual @ccess

Kathy Redmond ■ EDITOR

More and more cancer patients are using the Internet to find out about their disease and treatment, to seek support from online patient communities and to communicate with their professional carers and loved ones. However, not everyone is benefiting from this digital revolution.

A recent Eurostat survey on the 25 Member States has shown a significant divide between the 'haves' and the 'have-nots'. Young people are much more likely to use the Internet than people over 55. Those of us who don't have a job, live in a rural area and have no child in the household are less likely to use the Internet. Big differences were also reported between countries: while Internet use is common in Scandinavia, Germany, the Netherlands and the UK, it is used far less in many of the new Member States. In the EU candidate countries, Internet use is very low. Inadequate telecommunication infrastructures, limited computer skills, economic factors and language all play a role in sustaining this digital divide.

In 2004 the European Commission adopted an action plan on how information and communication technologies can be used to deliver better quality health care to European citizens. The "e-Health action plan" covers everything from electronic prescriptions and computerised health records to using new systems and services that cut down waiting times and reduce errors.

As part of this plan the Commission is developing an EU health portal that will provide a single point of access to public health and health-related information produced by the EU and its agencies. It was scheduled to be launched in 2005, but the site has not yet gone live. A nod to those of us not yet online was made in a commitment to 'monitor actions taken by Member States to make health information as accessible as possible'.

The importance of extending Internet access was recognised in March by the UN General Assembly, when it endorsed the 'Tunis commitment', adopted by the World Summit on the Information Society at the end of last year (www.itu.int/wsis).

Hopefully, this commitment, to which the world's governments have now signed up, will stimulate European governments to step up efforts at European, national and local levels, to enable all European patients, particularly those living in countries with limited resources, to benefit from the digital revolution.

All correspondence should be sent to the Editor at editor@esoncology.org

Laura van 't Veer: the person behind personalised treatments

Marc Beishon

Our new-found ability to profile the gene expression of a tumour is transforming the way we characterise cancers and decide on treatment. Laura van 't Veer was there from the start, and she's now splitting her time between the academic and biotech sector, driving the translation of the new technique into diagnostic tools not just for research but for everyday clinical use.

When Laura van 't Veer was asked to apply for a job in the pathology department at the Netherlands Cancer Institute (NKI) in Amsterdam back in 1993, research colleagues warned her off, saying that diagnostics was rather a boring area to work in. What they did not appreciate – unlike the more far-sighted institute management – was that the post involved setting up a brand new subdivision in the NKI's hospital, namely molecular pathology, which is now among the hottest areas of cancer research, with excellent prospects for a wave of new diagnostic – and prognostic – tools that should hit clinics worldwide in the next few years.

Van 't Veer's own work as head of molecular pathology at the NKI has led to the rapid development of a microarray gene expression profiling technique for breast cancer that has propelled her onto the world cancer stage. She is now also chief operating officer of Agendia, a biotech company jointly set up by the NKI and venture capital funds, which has been the first firm to launch a commercial implementation of the technique, called MammaPrint. Since she and colleagues authored a letter to *Nature* in 2002, explaining how the gene expression profile could largely eliminate unnecessary and possibly harmful treatment for women at low risk of disease spread, she's barely stood still as commercial interests have weighed in with offers – and the 'competition' with critiques of the results.

"When people realised that it could change their way of clinical practice they tried to find holes in it – some got very worried and overreacted," says van 't Veer. "That is fine for me – it means we are on to something very promising as they wouldn't pay so much attention to it otherwise." In fact, she adds, there could be as many as 200 papers already published that use her group's data – "And we've always been honest and fully described the possible pitfalls."

In any case, she points out, reproducing results with independent cohorts was always going to take time, and indeed more papers that build on the findings are due out this year. Further, the microarray technique is a

ELIGIO PAONI / CONTRASTO

"When people realised that it could change their way of clinical practice they tried to find holes in it"

highly complex amalgam of technology, bioinformatics, biostatistics and oncology – at present it simply is not feasible for any laboratory to achieve reproducible results using home-grown equipment. "That is why Agendia was set up – to create a 'black box' system that can be widely used for breast and other cancers," says van 't Veer.

"My driving force for bringing it forward is that it is really of benefit to implement this type of diagnostic – it will give a better insight into the disease someone has, and insight into best therapy – so it's important that everyone starts using it. But sometimes I feel I'm pushing too hard."

Although her eye is now firmly on this clinical setting, van 't Veer's background is in basic research, and it was the scope of the job offer at the NKI that has been a key enabler. "I was the first molecular biologist to be appointed to work in both the hospital and the research part of the NKI," she says. "Few people have appointments in both." The dual role has been especially beneficial as not only has she been able to proceed with both diagnostic and research-based molecular pathology, but she also moved quickly to

The gene pool. On holiday with her family in Schiermonnikoog, an island off the north coast of the Netherlands

establish a family cancer clinic to help and gather data on those with hereditary disease.

So there could hardly be a better place to work for someone whose primary interest at school was biology – and in particular DNA and genes. At high school in the 1970s, her biology teacher was a ready source of such information, and when van 't Veer went to university to study biology she thought at first that embryology would be her speciality, until by chance she met the wife of a colleague who worked at the NKI, who asked if she would like to do a placement there.

This proved to be a fruitful route during her undergraduate and masters years, as she first carried out work on DNA repair and then worked with Roeland Nusse (now at Stanford) on a human homologue of a mouse gene – "This went very quickly – in a couple of weeks I had identified the gene, which was really spectacular." She ended up working for a year with Nusse and majoring in molecular oncology, and was present at the founding stages of the science. "When I cloned this human homologue involved in mouse breast cancer, I also started to see whether we could find alterations in genes in human tumours, which was quite new then. I can remember reading Robert Weinberg's paper on the activated *Ras* oncogene in a human bladder cancer cell line, which was really very new. It's amazing progress that in 20 years I've moved from working in laboratory research on human oncogenes, as we called them then, to working with patients."

Van 't Veer moved on to take a PhD at the University of Leiden, completing an education that took some 13 years, which she followed up with two years in Boston.

Although recognising that it is not necessary to go to the US to gain post-doc research experience, van 't Veer reckons that it is just as important to experience a change in cultural attitudes to research and life in general that America can bring to young scientists and practitioners. "I enjoyed it greatly and of course there are just so many people in Boston working in molecular and cell biology and oncology research that there is critical mass that just speeds things up."

She was fortunate to join a group of five young principal investigators at a new cancer

centre at Harvard Medical School, including René Bernards, a Dutch countryman who is now a close colleague at the NKI and Agendia, and Stephen Friend, who went on to co-found Rosetta Inpharmatics (now part of Merck and co. Inc), set up in 1996 to develop the microarray gene expression technology that van 't Veer was later to use in her own work.

"This group generated a lot of excitement – they'd all come from big labs and were working on experimental cancer biology, and I did the most basic research I've done, on cell cycle control. But in Friend's group they found germline mutations in the *P53* gene that could help explain part of Li-Fraumeni syndrome [a rare autosomal dominant syndrome in which patients are predisposed to cancer]. The result was that several of us who returned to Europe and elsewhere from this group started family cancer clinics in the hospitals where we ended up working – because for the first time we could see that genes could explain hereditary cancer syndromes." So focused was this group, she adds, that their computer database was dubbed the 'candidate gene approach', thanks to the work on *P53*.

René Bernards was then appointed a professor at the NKI, and asked van 't Veer to join him as a fellow in the department of molecular carcinogenesis. 'The post-doc time is when you have the most freedom but you have to decide at some point what you want to do," she says. "I was very lucky – I didn't have to return home and worry about writing proposals and applying for grants, which is a struggle for many when they look for work."

Then a year later, the then NKI director, Piet Borst, led a brainstorm on where advances would be, and came up with the new molecular pathology post to further interest in translational research. "As I'd worked on gene characteristics of human tumours in my PhD, it was of interest to me, and as a new job, it would be up to me to create the work programme. And as it also involved research I thought I'd be an idiot not to take it." Despite the rather negative image of diagnostics, she first had to beat off 50 other applicants for the post.

She started with just two technicians, working alongside 'conventional' pathologists, and began to develop relationships with surgeons, medical oncologists and radiotherapists. "I gave presentations and we started to understand each other's language," she says. "I explained what a mutated BRCA 1 gene could mean to cancer risk to our head of surgery – afterwards he told me I was the first person he dared to ask what point mutations are – there was no one else so close he could directly ask."

She did a similar knowledge exchange with Emiel Rutgers, head of the breast clinic (and a current close colleague in the microarray research) – the NKI is a first-line centre for breast treatment. "I discovered what adjuvant treatment was, and found that many women were asking them for advice. But they didn't deal with the genetic side – it was not yet part of their clinical practice. In any case, 12 years ago it was only haemato-pathologists treating leukaemia and lymphoma who used the chromosomal break points as molecular diagnostics."

Van 't Veer established a family cancer clinic to provide advice and support on hereditary disease, and notes that now everyone treating cancer patients needs to know about genes in daily practice. She's stayed mainly with breast cancer for her work, thanks to the NKI's specialism and because so many things happen first with this disease. Another branch of her work is molecular epidemiology – a current large study, for example, is on gene–environment interactions in hereditary breast cancer.

After five years, van 't Veer split her team into diagnostic and research groups, and worked

"In 20 years I've moved from working on human oncogenes, as we called them, to working with patients"

"Reducing unnecessary treatment was one of two main discussion points we came up with"

to gain ISO quality certification for DNA diagnostic work. "While it's not obligatory we felt that in doing genetic tests for heredity cancers major decisions were going to be made on a single result, so we made sure it was quality controlled." On the research side, she focused on single-gene, single effects – until the NKI, like many other institutes, decided to start work with microarrays in the late 1990s. "We had to decide whether to wait until it was developed and buy something, or start our own microarray facility and build up experience, and we chose the latter. I became involved together with other pathologists because we had tumour series that would be very interesting to study using microarrays. But it was a big hurdle in the first years to produce microarrays to high standards. There can be a lot of variation in hybridisation between one array and another."

There are several types of microarrays and applications apart from cancer (for a good primer on the subject, see www.ncbi.nlm.nih.gov/about/primer/microarrays.html). However, the gene expression segment has become one of the biggest application areas, and already represents a market approaching a billion dollars. Van 't Veer and colleagues – including Marc van de Vijver, co-author on many papers – realised that one of the main planks in making progress is the production of reliable microarrays, where the private sector had a role, and it was Bernards who used his contacts with Rosetta Inpharmatics to start a collaboration that led to the breast cancer gene expression profile.

"Rosetta had the microarrays and analysis expertise, but we came up with the clinical question and the patient information," explains van 't Veer. The NKI is one of the few centres with a large bank of frozen breast cancer tissue, thanks to a far-sighted pathologist who started a standardised biobank back in 1983, and the particular microarrays used by the NKI are able to profile gene expression in frozen tissue. As breast cancer patients have long been followed up at the institute, clinical outcomes were also known.

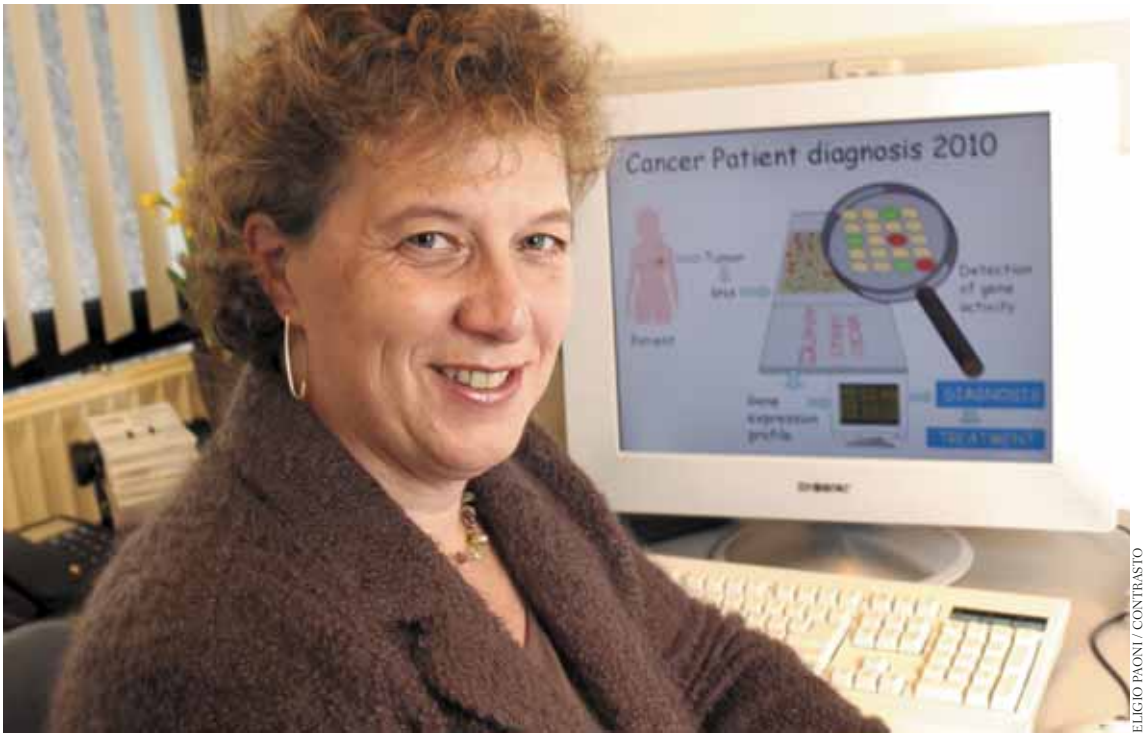
Van 't Veer found herself in the centre of a multidisciplinary team that took the initial question – predicting the risk of metastatic disease – and after much mathematical analysis and discussion emerged with a translation into the clinical setting – reducing unnecessary treatment of women at low risk using a 70-gene 'signature'. It has involved working with physicists at Rosetta on the bioinformatics methodology, checking and refining the data analysis with a biostatistician at the NKI, and talking with many research colleagues, and has been a hugely enjoyable experience for van 't Veer.*

"Reducing unnecessary treatment was one of two main discussion points we came up with – the other was that the profile actually shows you very early on in the development of a tumour that the programme for metastatic risk is laid down, or hard-wired." In a news item van 't Veer co-authored for *Nature* in 2003, she references a paper published in the *Lancet* in 1889 that hypothesised this hard-wiring – a startling connection with medical history.

"The impact of both findings has surprised me, as has the ongoing work on the integration of all the specialities. I never expected this small group to go so far and that everyone would know the paper in *Nature* and I would have people coming up to me in meetings saying, 'Ah now we can see you for real.'"

Van 't Veer has presented the gene profiling story many times now, and continues to do so – "It's because people thought microarray technol-

*For more on gene expression profiling and breast cancer, see *Nature* 415:530-536 and *Journal of Clinical Oncology* 23:1631-1635



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ogy would bring advances never seen before and it shows that all the billions of dollars invested in universities and institutes can make fast progress."

The NKI, she says, soon realised it could not attract funding to take the 70-gene test (MammaPrint) and other research to market, and decided to set up a spin-off company, namely Agendia, with van 't Veer and Bernards as two of the directors. The company has grown rapidly and now numbers over 30 employees (and much credit must go to a commercial director poached from British biotech giant, Amersham). The major investors are Europe-based, while some funding arrives via the European Union Framework programme. Although a bit hesitant at taking the plunge into commercial life, van 't Veer feels that such start-ups are critical for rapid realisation of the results of translational research, commenting that larger companies are not as fleet of foot when it comes to innovation. "This type of academic spin-off is common in the US but not so much in Europe," she notes.

Further, she says that having been at the centre of the profiling research, she felt a responsibility to continue to play a key role, not least to drive the quality and robustness of the use of microarrays and DNA diagnostics, and to benefit NKI by collaborating in trials. There has, however, been a steep learning curve in dealing with the venture capital community and also with regulatory processes, while there have been quite a few criticisms levelled at the work. She and colleagues have had to fend off accusations of conflict of interest between the NKI and Agendia, for example.

The NKI soon realised it could not attract funding to take the 70-gene test and other research to market

Private profile. Van 't Veer with Agendia co-directors Bernhard Sixt (left), and René Bernards

"But as we look at more complicated diagnostics and targeted therapies, such as the EGF receptor drugs, it's hard to do the development quickly," she says. "Small companies have a role to play in being close to academic centres and moving things out into the commercial setting."

Agendia now buys in custom microarrays from Agilent (to which Rosetta had sold its technology) and is both a fully commercial supplier of MammaPrint and other products, and a clinical trials collaborator with the NKI and other research organisations. Trials involving the 70-gene signature include a 500-patient cohort started in 2004 in the Netherlands, where the test result is given in addition to other information on risk of recurrence. "What we are evaluating here is what patients and doctors do with the information," says van 't Veer. Another trial is the major European Union-sponsored MINDACT (Microarray for Node Negative Disease may Avoid Chemotherapy) prospective project, run by the EORTC (European Organisation for Research and Treatment of Cancer) and TRANSBIG, the translational research network of the Breast International Group (see also *Cancer World* 7).

Other critics have felt that gene expression signatures such as the Amsterdam one are being rushed out too quickly, are over-optimistic, and do not pass methodological 'litmus tests'. One recent paper asks, for example, whether a doctor would be "prepared to withhold adjuvant chemotherapy in a young patient with a node-negative, HER2-positive breast cancer and a good-prognosis signature". Van 't Veer and colleagues, such as Martine Piccart, founder of TRANSBIG, report that independent validation of the Amsterdam signature is more than good enough to proceed with prospective clinical trials, while recognising that refinements and new signatures are bound to arrive sooner rather than later.

Van 't Veer adds that a group in Rotterdam has come up with near identical results using a different microarray platform, and that different mathematical techniques used have all been found to point at the same tumour subgroups, i.e. low- and high-risk groups. "As we have more tumours analysed we will be able to have more subgroups. I do realise the 70-gene signature can be improved – but to do that we need to do trials such as MINDACT."

Outside of trials, van 't Veer says that "technically the profile can be used now in clinical practice – with Agendia we have shown you can carry out robust and reliable testing using microarrays. But it's not that simple. The same person who set up the ISO certified lab at the DNA diagnostics department at NKI has moved to Agendia to set up a similar approved lab – but there are still only a handful of such laboratories in the world that can do microarray work to this standard." That of course is where the 'black box' system comes in. Colorectal cancer will be the next tumour type to benefit from this type of profiling, she says, noting that leukaemia already has a number of tests available, albeit for a much smaller patient population.

The rapid availability of the Agendia test has

"Colorectal cancer will be the next tumour type to benefit from this type of profiling"

taken some by surprise, it seems. While the company has approval to run MammaPrint in Europe, they are waiting to see whether additional approval by the Food and Drug Administration (FDA) will be required before it – and other such tests – can be used in the US. Agendia, which has a US partner (the Molecular Profiling Institute) for MammaPrint, received a letter from the FDA last year expressing concern that the test may require clearance as a diagnostic device. Presenting a united front, van 't Veer and a representative from Agendia's main competitor – US firm Genomic Health, which is actively marketing its Oncotype DX breast cancer test – shared a platform at the recent American Association of Cancer Research conference, and she says that discussions with the FDA are planned.

Some pharmaceutical companies, meanwhile, initially gave the test a lukewarm reception, according to van 't Veer, as the technique could potentially cut the market for their 'blockbuster' drugs. "But they are realising that healthcare systems just cannot pay for expensive treatments such as Herceptin for everyone," she says. "We need to come up with more molecular tests that show who will benefit from these drugs – and the FDA is thinking along these lines for its approval process." Oncologists in private practice, who, in some countries, are paid per course of chemotherapy, will also be affected by new genomic approaches.

Outside of her immediate work, van 't Veer is involved with wider healthcare issues in the Netherlands – she's a member of the advisory committee to the Dutch Cancer Society, for which she's currently writing a paper on biomarkers. She is also a member of the scientific research council of the Dutch Ministry of Health, where she is helping to set the agenda for biotech research over the next 10 years.

As a woman, van 't Veer has been more conscious of her gender during her time in the basic science community, which she says is far more male dominated than clinical research. But as a role model, she reckons that some women are put off by the sheer amount of work she does. Recognition outside of oncology came last year, in Oprah Winfrey's magazine, of all places, which included her and Martine Piccart in a feature on 'the five biggest health breakthroughs by women scientists'.

Beyond her personal achievement, this level of public interest says a lot about how the status of molecular pathology has grown since van 't Veer decided to go for that job at the NKI. Once very much a poor relation among oncology disciplines, it is now leading the way into the new era of personalised therapies. And with a Europe-wide shortage of molecular pathologists, and pathologists in general, it is surely a tempting career option for any young oncologist with the determination to navigate themselves into a specialty that is too young, as yet, to have established pathways.

Van 't Veer reckons she's a fairly forceful character, but not aggressively so, and the realities of running a commercial enterprise have certainly been an eye opener. A good clue, though, to her drive for success lies in one of her main hobbies – she's been a competitive rower since her teenage years. Another big interest is contemporary classical music.

Presently, the working arrangement she has with the NKI is to do four days a week for the institute and just one at Agendia. A decision point is bound to come soon as to whether she will do more on the commercial side – she won't be drawn though, "I like doing both." But with Agendia put forward by the EU as one of the most successful biotech firms involved in the Sixth Framework programme – and her desire to see the gene signature tests widely used – in practice, that nominal 'one day' is no doubt already a lot more time in her overall working week.

The dream team: when will we make it a reality?

Anna Wagstaff

Multidisciplinary teams provide the best quality cancer care, as specialists come together to discuss diagnoses and plan treatments. They raise standards, improve patient experiences and save lives. Sadly, most of Europe's cancer patients never have the chance to feel their benefits.

For the 2.9 million people in Europe who will be diagnosed with cancer during the coming year, evidence-based guidelines will recommend a treatment programme that is likely to involve complex combinations of surgery, radiotherapy, systemic therapies and supportive care.

Getting that treatment programme right for each individual patient, with their own specific diagnosis and their own co-morbidities, needs and preferences, is beyond the powers of any individual practitioner. It needs a multidisciplinary approach to care, in which a team composed of all relevant medical and allied health disciplines work with one another and with the patient to diagnose, treat and manage the cancer.

But while the principle of multidisciplinary treatment is widely accepted, the vast majority of these 2.9 million patients will never have their cases considered by a group of experts in a multidisciplinary meeting. Many treatments will be suboptimal, patients will feel poorly supported and lives will be lost.

Traditionally, most cancers were primarily the domain of the surgeon. Though radiotherapy has been used to treat cancers for more than 110 years, and medical oncology has been used for the best part of the last century, these treatments were seen as alternatives or even as rivals.

It was in the early 1970s that the value of adjuvant chemotherapy in breast cancer became established. Gianni Bonadonna in Italy and Bernie Fisher in the US recall battles to convince the medical establishment (for which read "surgeons") of the value of routine chemotherapy following surgery for breast cancer. They got their evidence through a meta-analysis of many trials, conducted by the Oxford Early Breast Cancer Collaborative Group, which marked the beginning of large-scale international cooperation on analysing clinical trials. This opened the way to the use of combinations of treatments in routine primary management and to generalise the multidisciplinary approach to other cancers, making possible many of the improvements over the last decades.

Breast cancer still leads the way, with a huge number of options combining surgical techniques with chemotherapy, hormone therapy and radiotherapy administered in various sequences. However, other cancers are rapidly catching up. So whether the cancer is in the lung or the liver, whether it is a glioma or a myosarcoma, the evidence shows – and the

guidelines stipulate – that the patient does best with careful selection of surgical, radiotherapy and systemic treatments.

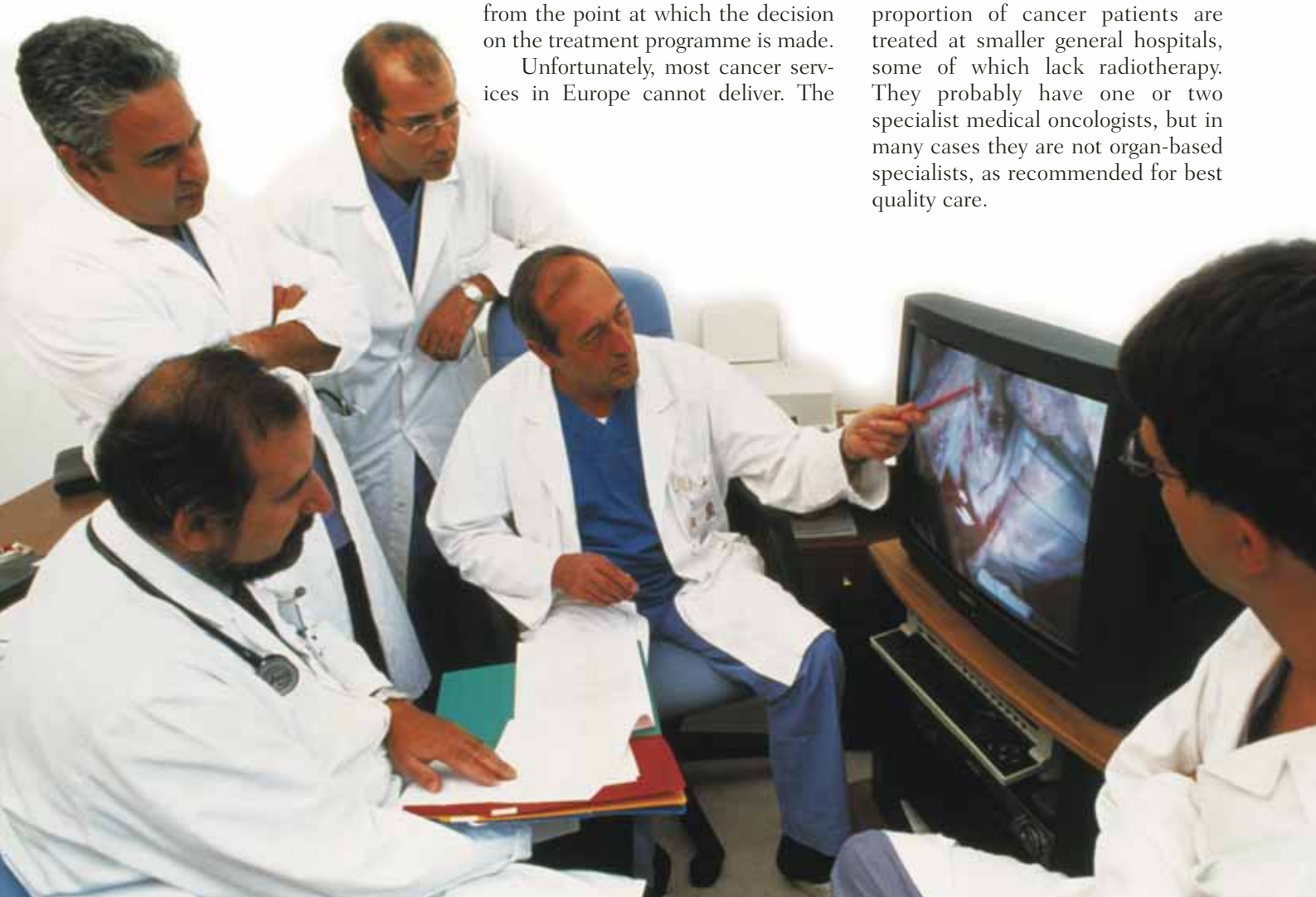
Recent decades have also brought a cultural change towards a far more patient-centred approach to medicine in general, and cancer treatment in particular. More attention now tends to be paid to aspects of treatment such as control of pain, fatigue, nausea and other symptoms, and support in coping with the stress of a life-threatening disease, or in coming to terms with the potential loss of fertility or living with a stoma. Greater care tends to be taken to help the patient play a role in decisions to do with their treatment, which entails taking the time and effort to provide them with understandable information, and to listen to them.

Branches of medicine dealing with these aspects of care, including psycho-oncology, and palliative care, have been steadily growing in most of Europe over past decades, and in some countries specialist cancer nurses have taken on an increasing role in areas such as symptom management and the provision of information. But there remains a major problem in integrating these aspects into the routine care of patients; many patients who could benefit are not being referred to the specialists who could help them. The multidisciplinary approach overcomes this problem by involving all specialists with a role to play in the patient's care from the point at which the decision on the treatment programme is made.

Unfortunately, most cancer services in Europe cannot deliver. The centres of excellence, prestigious cancer institutes, major university hospitals that offer high-quality multidisciplinary care, are exceptions. The majority of Europe's patients are diagnosed and treated by specialists who have little training or practice in a multidisciplinary approach, and who work within structures that discourage or rule out multidisciplinary care.

Patients with breast or ovarian cancers may be treated at gynaecology clinics, where their doctor's primary training is in surgery, and where there are no specialist medical oncologists, radiation facilities or supportive care. In a similar way, many urology clinics routinely treat patients with prostate cancer.

In some countries, a large proportion of cancer patients are treated at smaller general hospitals, some of which lack radiotherapy. They probably have one or two specialist medical oncologists, but in many cases they are not organ-based specialists, as recommended for best quality care.



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Even in large, well-staffed, institutions, patients are shunted from one department to the next, without ever having their cases considered by a gathering of specialist disciplines.

Leading practitioners say that things are moving in the right direction, but that change is slow and largely confined to more prestigious sites. It seems that only the UK and France have strategies in place to ensure that every cancer patient, no matter where treated, has his or her treatment planned and delivered by a multidisciplinary team (MDT). Both countries aim for 100% coverage within a few years.

The dream team

A multidisciplinary approach requires that new cases are discussed at the point of diagnosis, in a setting in which all specialists who have a role to play in diagnosis and care contribute towards a personalised, evidence-based care programme, taking into account the patient's co-morbidities and preferences.

Decisions should be efficiently recorded and communicated, so that professionals understand their roles while the patient understands the plan and is clear about who is responsible for what. Each step should be coordinated and monitored to ensure that information, scans etc. are passed on quickly and efficiently to the right people and that unnecessary delays are avoided.

Straightforward cases may be discussed only briefly. Complex cases may need to be reassessed by the multidisciplinary team to evaluate the patient's response to treatment, and to agree on the next step.

Team members

The precise make-up of a multidisciplinary team varies according to the cancer and the setting. In addition to surgeon, medical oncologist and radiation oncologist, the presence of histopathologist and radiologist is generally seen as essential, because management decisions depend on knowing details of tumour margins or location, or the exact proliferation index.

The inclusion of additional clinical staff may vary, case by case, according to the location of the cancer, or to the culture and tradition of the particular health service. In the UK, clinical nurse specialists are commonly included in multidisciplinary teams, whereas in France this is not the case. Teams treating gastrointestinal cancers may include gastroenterologists and specialist stoma nurses; teams treating breast cancer may involve reconstructive surgeons. Palliative care nurses and psychooncologists may be involved according to patient need.

The extent of specialisation within the team will also vary. Surgeons all over Europe are becoming increasingly specialised to a particular cancer, and often define the subspecialisation of the team. Medical oncologists or radiation oncologists may be involved in a number of multidisciplinary teams dealing with two or more different types of cancers. Specialists who are thin on the ground have to spread themselves across multiple teams.

Patient selection

Methods to select patients for discussion also vary. Bengt Glimelius, a medical and radiation oncologist who works as part of a colorectal cancer team in Uppsala University Hospital, Sweden, says that straightforward cases are simply treated according to protocol, and doctors only put a patient on the list for multidisciplinary discussion if there are additional complications. "You can't discuss every single case; that would be impossible," he says, "unless you are at a teaching hospital, when the 'easier' and more common cases must also be discussed."

Mike Richards, the UK National Cancer Director, responsible for overseeing the national cancer plan, says, "My own preference would be to have every patient at least registered at the meeting. Some can be discussed in under a minute – 'This is a patient with a completely straightforward breast cancer. I've talked to her. She wants breast conserving therapy followed by x or y… Has anybody any concerns?' Everyone can say 'No that's fine' and you move on. But the nurse specialist may say, 'Are you aware that the patient's husband has Alzheimer's disease, and it will be very difficult for her to get to radiotherapy.' That doesn't take very long, but everyone in the team is then aware."

Christine Bara, director of the Department for Innovation and Improving the Quality of Care at the French National Cancer Institute, says that, under the national cancer plan, a similar practice is mandatory within the French system. "All cases are registered. Straightforward cases that require treatment with the standard evidence-based protocol are simply presented very fast. Only those who cannot be treated with a standard protocol are really discussed. A standardised form is completed for each patient, which is held by the cancer network."

Virtual or real?

Variations also exist in the extent to which the team is a physical entity at a single site, or is dispersed across departments in different wings of a

Michael Baumann, radiation oncologist and director of the Dresden Cancer Centre in Germany. The Centre was set up three years ago on the initiative of the surgeons and medical and radiation oncologists at the Dresden University Hospital, and provides an environment where they can work side by side. It has sparked great interest among other university hospitals, many of which have yet to adopt a multidisciplinary approach to treatment. Multidisciplinary working has come late to Germany; even in breast cancer the proportion of patients who have their treatment planned in a multidisciplinary team meeting is probably lower than 20%

hospital or even across two or more institutions. In the latter instance, members travel to meetings or hold videoconferences.

A good example of a single-site team is the cancer centre at the Carl Gustave Carus University Hospital in Dresden, Germany. This centre was set up three years ago on the initiative of the doctors from the hospital's surgical, medical and radiotherapy departments who had worked closely together for many years, but who wanted to establish multidisciplinary outpatient clinics.

Director Michael Baumann says that they felt that this ideal would only flourish in a physical centre. "I am not a big believer in virtual centres. Ours is a real centre. You can go there, there is a door and inside you find medical oncologists, radiation oncologists and surgeons, sitting in neighbouring rooms."

Single-site arrangements also have clear advantages for patients, who have a single point of reference throughout all their stages of treatment. However, such arrangements may not be feasible outside cancer centres, university hospitals or centres of excellence.

It might be undesirable, as well as financially and logistically impossible, to restructure cancer services throughout Europe, so that every patient is treated by a specialist multidisciplinary team located at a single site, rather than at organ-specialist clinics or smaller general hospitals.

Individual practitioners and, by extension, multidisciplinary teams need to treat a minimum number of patients each year to keep their skills up to scratch. This has been shown to be the case for surgeons, not only for difficult procedures such as pancreatic and oesophageal resections, but also for breast, colorectal and other cancers. There is growing evidence that this holds true for other disciplines.

Requiring multidisciplinary teams to operate from a single site while fulfilling minimum volume requirements would result in patients with less common cancers travelling enormous distances for treatment. This may be the best option for certain cancers or types of treatment, but other treatments can be carried out closer to home.

A 'virtual' team may be the best

"Ours is a real centre… there is a door, and inside you find medical and radiation oncologists and surgeons"

Jean-Pierre Gérard, director of the Antoine Lacassagne Cancer Centre in Nice, France. The Centre is one of the 20 cancer centres around which France's cancer services have been organised for decades, and has a long history of multidisciplinary working. Under the French Cancer Plan of 2003, all centres treating cancer, whether public or private, are required to work in a multidisciplinary way, if necessary by cooperating with one another. Around 50% of all French patients are currently treated in a multidisciplinary setting; the aim is to extend this to 95% of patients by the end of 2007

option – particularly if it is supported to overcome obstacles of distance and to function effectively. The alternative is that team members travel to locations closer to the patient. This can work across small distances, with doctors based at one site attending team meetings at another site once a week. However, there is already evidence from many countries that finding time to attend multidisciplinary meetings is putting pressure on hard-pressed team members. Adding in long journeys would exacerbate the situation.

Clearly, there is no single solution or blueprint. In both France and the UK, the emphasis has been on finding flexible, local solutions and allowing the system to evolve.

Bara, of the French National Cancer Institute, says, "These meetings are necessary, but they do take time, and the geographical distribution of doctors can be a problem. What we are trying to do, jointly with the regional agencies and the cancer networks, is to concentrate these meetings in fewer locations in order to guarantee their medical representativity." Providing videoconferencing facilities and effective electronic communications systems is set to play a key role in this.

Jean-Pierre Gérard is director of the Antoine Lacassagne Cancer Centre in Nice, one of 20 cancer centres around which the new regional cancer networks are organised. He says the problem is particularly acute for radiation oncologists as there are no more than 500–600 in France, and their involvement is needed in the discussion of around 80% of cancer patients. "It is a question of time sharing and having videoconferencing, and also increasing the number of these specialists," he says.

Between theory and practice

The logic of using MDTs to plan and deliver multidisciplinary treatment is irrefutable. However, recent studies looking at aspects of how teams function in the UK have revealed striking gaps between theory and practice.

One study (Macaskill et al, *Eur J Cancer*, in press), found that medical oncologists were absent for some of the time in over half of all breast meetings (55.9%). They did not attend at all in 41.2% of cases and attended for only some of the meeting in 14.7% of cases. Clinical oncologists (radiotherapists), by contrast,

More than half of the meetings take place over lunch time… many don't even provide lunch!

Richards identifies good leadership as one of two essential elements for effective team work

were present for the whole meeting in 70% of cases, and surgeons in 98.5% of cases.

One probable reason for this was that only a quarter (28%) of these meetings were held in 'protected time' set aside for the purpose. More than half of the meetings took place over lunch time, with a further quarter (26.5%) scheduled for breakfast time and 6.6% in the evenings.

Lesley Fallowfield, whose psycho-oncology team at Brighton and Sussex Medical School has been researching the functioning of MDTs, points out that many lunch time meetings don't even provide lunch! Breakfast and evening meetings can be particularly difficult for staff with childcare responsibilities. Another problem is that medical and clinical oncologists often have to cover a number of teams, often at different sites.

In the Macaskill study, respondents were asked to choose from a list of suggested improvements to the system. Top of the list (72.8% of respondents) was more time to attend meetings or for them to be held in a protected session.

Similar problems were highlighted in a review of breast cancer services carried out by the Clinical Standards Board in Scotland two years ago. Their report recommended that multidisciplinary meetings should be considered of equal importance to clinics and operating sessions, and should be included in individual job plans.

Finding a suitable venue can also be a problem. Fallowfield recalls one team meeting in a room so small that some members were left standing in doorway straining to hear what was said or see what was shown.

Another team held meetings in a traditional lecture theatre with a top table facing tiered rows of seats. Predictably, she says, seats at the table with microphones were occupied by surgeon, radiologist and pathologist, while registrars and others sat in the first row of seats with breast specialist nursing staff relegated to the back. "Not only were the nurses rarely invited to contribute their opinion about patient care, but even had they wished to, they probably wouldn't have been heard. One recommendation we made was that the nurses should at least have a roving microphone."

The problem of unequal status must be tackled if every specialist discipline is to make its contribution. Fallowfield says, "Most people have been brought up in an educational system that makes it very difficult to get over hierarchical boundaries. Without training, it is very hard for people who have grown up in a world where they make a decision and everybody fits in around that, to operate in a way that will optimally benefit patients and also be helpful to the teams."

A recent study by her psycho-oncology research unit revealed that team members often have a poor awareness of the role their colleagues play in providing information to the patient. All the clinical nurses reported that they regularly discussed physical, functional, social and emotional wellbeing with patients, yet few of their colleagues showed any awareness of this. Some issues were discussed with the patient by several team members, while others – such as clinical trials and family history – were recognised by only a few team members as their responsibility.

Even amongst medical specialists, working as a team and respecting and valuing everyone's contribution can be tricky. Baumann from the Dresden centre says, "One of the things that helps a lot is that the leadership structure is on a rotating system. At the moment I am director as a radiation oncologist, but it will rotate at some time to medical oncology or surgery or any other specialty in the cancer centre. It is not a radiotherapy structure, or a surgeons' structure, but something we carry together."

Mike Richards, the UK National Cancer Director, identifies 'good leadership' as one of two essential elements for effective team work (the other being administrative support). He recommends "an inclusive leader who will facilitate everybody to be part of the team and to make a contribution." He says that the last ten years have been about setting up MDTs, and the next five "should be about making those teams work effectively". Though he admits that much work needs to be done to work out how best to go about this, he mentions a two- to three-day training course that has been run for

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In some European countries, oncology nurse specialists regularly discuss physical, functional, social and emotional wellbeing with patients. A multidisciplinary approach to treatment should ensure that this sort of support is included as an integral part of every patient's care plan

colorectal teams as an interesting example.

The course aimed to raise the technical skills of teams around the technique of meso-rectal excision, but Richards says it has proved to have a very helpful spin-off in bringing teams together. It offered teams the opportunity to exchange ideas about how they worked, which is something they would never usually do.

"I went to one of the courses, and talked to the team. The surgeon said, 'Now I really know how to do the procedure properly. I thought I did before I went.' The radiologist said, 'Now I understand why they want the MRI scan done in a particular way.' The pathologist said, 'Now I understand why they want me to report the circumferential margins in a particular way.' The nurse specialist said, 'Now I understand how to explain this operation to a patient.' And they all said, 'It has been valuable time working together and we feel we all know each other better and we will work together better.' We are beginning to get feedback that teams are doing things differently, so we are seeing an evolution.

"We never said people had to go on the CRC programme, but word of mouth has been very effective. Once you get the first ten teams saying, 'That was very helpful,' then others say, 'Actually we want to do the same.' We reckon that within the next few months almost all of the 186 CRC teams in England will have been on that course."

Richards believes this example could be followed for other cancers. "I'm sufficiently impressed that I would like to encourage it for other disease areas."

Oiling the machine

Another crucial area showing serious gaps between theory and practice has to do with the quality and completeness of information, and procedures for recording decisions and ensuring they are implemented.

A review of decisions taken by an upper gastrointestinal multidisciplinary team published earlier this year (*Ann Oncol* 17:457–460) found that in just over 15% of the cases, decisions were not implemented. The most common reason was that information on the patient's co-morbidity had not been available or had been given insufficient consideration during the meeting. The report recommended that methods be standardised to ensure the inclusion of co-morbidity data in MDT meetings.

The other main reason for decisions not being implemented was patient preference. This raises complex issues. Is it feasible to find out about patient preferences before a multidisciplinary team meeting con-

The problem of unequal status must be tackled if every specialist discipline is to make its contribution

Extra resources for administrative staff will be key to encouraging a multidisciplinary approach

siders the options? The report gave an open verdict, saying simply that the matter warrants further research.

Fallowfield identifies a problem in ensuring that every member of the team is aware of decisions, and that patients receive a consistent message. During an MDT training session, a rectal cancer patient listened with dismay as a nurse explained colostomies – what they look like, how the patient should care for them. The patient had been told that there was no need for a colostomy, because the MDT decided that sphincter-saving surgery would be safe, but the nurse had not been present at that meeting.

MDTs must be well enough resourced to ensure that every meeting has access to a full set of information (patient files, scans and other diagnostic results), that every team member knows which patients are due to be discussed and where and when meetings are held, and that decisions are recorded and communicated effectively.

Getting the administrative side right was the second element identified by Richards as vital for teams to work effectively. His view is endorsed by others in different countries and different settings. Asked what single measure would most improve the effectiveness of MDTs, Bengt Glimelius, clinical oncologist in the colorectal team at Uppsala, Sweden, says, "To have more time and not to have to do all those extra administrative tasks that fall on you. We need more admin support."

In Dresden, Baumann believes that funding for infrastructure was essential in making multidisciplinary care a reality. Without it, he says that management of patients would have continued to be driven by separate departments. His hospital struggled to find funds from existing departmental budgets. Baumann argues that allocating extra resources for the essential administrative staff is the single most useful thing authorities can do to encourage hospitals to move towards multidisciplinary care.

In France, the state allocates funding to all hospitals, clinics and cancer centres where cancer patients are treated, whether they are in the public or private sector. Funding is specifically for the establishment of cancer coordinating committees – 'the 3 Cs' – whose role is to support the delivery of care through specialist multidisciplinary teams, which is being made mandatory under the French national cancer plan.

Cancer coordinating committees are responsible not only for organising multidisciplinary meetings, recording decisions, and computerising patient information, but also for auditing their effectiveness through systematic reporting of a range of activity and quality indicators, including patient outcomes.

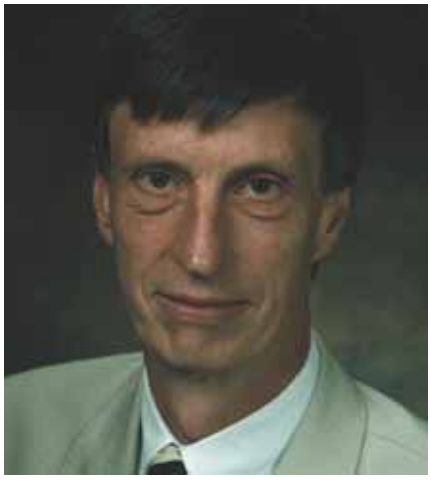
In the UK, cancer services were already being provided within a single infrastructure – the National Health Service. The cancer plan required that infrastructure to be reorganised.

Richards says that the nature of administrative support for MDTs is decided at local level. "Some hospitals advertise for a separate post, while others may allocate the task of servicing MDTs to one of the nursing staff. Depending on the size of the team and the throughput of patients, you might be able to have a coordinator who covers more than one MDT. Alternatively, the person who coordinates team meetings might also navigate or track patients through the system, knowing where the patients are and what is going on, and making sure the CT scan comes back and is acted on, and the next appointment is made and so on."

Many teams function well, but Fallowfield has come across teams with no additional support that are struggling. The Macaskill study into breast teams found that almost 6% of MTD decisions were not recorded in patient notes or on a special form. The study says that this raises questions about whether the decision is truly available for patients and staff members who were not at the meeting. "It also raises the question of the relevance of the decisions made at the MDM where they are not recorded."

No turning back

While some studies have revealed improvements from multidisciplinary working – including better diagnostic practice, closer compliance with guidelines, a more consistent provision of psychosocial support, a stronger input from nurses, and improved care co-ordination – it places heavy pressure on team members' time and as yet



Bengt Glimelius, medical and radiation oncologist in the colorectal cancer team at Uppsala University Hospital in Sweden. Glimelius has conducted patient consultations jointly with the colorectal surgeon for the past 25 years. More recently a radiologist and often a pathologist have also been present. Though a large proportion of breast cancer patients are now treated in a multidisciplinary setting in Sweden, the figure for colorectal cancers is closer to 40%, while for prostate, lung or gastric cancers, it is more like 10-20%. Multidisciplinary teams are likely to be included in new quality indicators currently being drawn up for Sweden's hospitals

there is little robust evidence to show that it improves clinical outcomes. However, ask any of the practitioners in the UK or France who have been obliged to start working in this way and, despite grumblings and misgivings, the principle is no longer in question and there is no mood to return to old ways.

"I say at virtually every talk I give, that I believe the most important step we have taken in the last 10 years is to move to MDT working, and I never get anyone saying – Mike you are wrong about that," says Richards. "I can assure you they can be vocal about things that they don't like. For a lot of people, it is a source of job satisfaction because you get a lot of peer support from your group and you know you are doing the best you can for the patient."

In France, moves to extend MDTs to cover all cancer patients started three years ago, and already they are reporting around 50% coverage, with the aim of reaching 100% by the end of 2007. Given the diverse nature of the institutions that have to work together – not least the mix of private and public – some level of friction was to be expected. However, Bara of the National Cancer Institute says the principle is now completely accepted, and emphasises the role of the regional networks in this success. "Everybody is saying the same thing. 'Multidisciplinary meetings are necessary and have a huge educational value.' Any resistance now only comes from isolated persons. Doctors working in cancer today say they can no longer imagine working without recourse to multidisciplinarity."

Patients also appear to be giving the system the thumbs up. The Dresden Cancer Centre conducts systematic audits of patients, and Baumann says the feedback has been very positive. "They understand that we need specialists. We don't want generalists who think they can do everything. And they understand that for this reason they have to move to different places – to go for surgery to a surgeon and for radiotherapy to the RT department. But they like to have this cancer centre as a joint structure that they can always go back to – they know their whole treatment is steered by this structure."

Surveys conducted in the UK in 2000 and 2004 show patient satisfaction increasing by 4 to 16 percentage points on issues ranging from, "Given written information at diagnosis" (from 45% to 61%), to communication "Given completely understandable explanations about side-effects" (from 63% to 76%), symptom control "Felt everything had been done to relieve pain" (from 81% to 85%) and general issues "Always treated with respect and dignity" (from 79% to 87%). Richards believes that the MDT approach is responsible for a large part of this improvement.

Multidisciplinary meetings also raise the overall quality of cancer services, not just in individual cases. In effect they offer continual peer review, making it easier to detect and correct practitioners who consistently stray from best evidence-based

practice. They provide a superb setting for specialists to learn more about the contribution of other disciplines in the care of their patients, and for younger practitioners to learn from more experienced hands.

Glimelius says, "It takes time to have 10 or 20 people sitting there. You listen to ten cases, and are involved directly in maybe only two. But listening to the others, and understanding why a decision was made in one direction or other, helps your future patients. I'm not sure how a health economics study could put a value on that."

Jean-Pierre Gérard does venture to put a figure on the impact on patient outcome. "It is usually said that if the best treatment was applied to all patients, we would improve the cure rate by between 5% and 10%. In France we have 150,000 deaths from cancer every year, which would be reduced by up to 15,000 if everybody got the best treatment. I think half of this will be gained by MDTs."

This, he says, will mainly come about through raising standards in smaller establishments – public and private – closer to the standards found in academic institutes.

The carrot or the stick?

Sadly, the consensus on the principle of MDTs among those who already work in this way will not benefit most of the 2.9 million Europeans who will be diagnosed with cancer in the coming year. They need the principle to be put into practice in every location.

Richards says that he does not believe it would be possible to extend MDTs to all treatment centres in the UK without some form of national cancer plan. Bara agrees. The French cancer plan has driven change, provided the policies and the finance to implement them and supported pilot schemes to get them right. "That's how it has been possible to move so quickly, and I think that in 2007, MDTs will be one of the measures [of the national cancer plan] we will achieve successfully."

But what works in one country may not in another. A working group in Australia has offered a useful contribution to this debate. Rather than map out any particular organisational solution, they have drawn up a set of "Principles of multidisciplinary care," (see Zorbas et al, *Med J Aust* 179:528–531), which "aim to accommodate a variety of delivery models and to enable clinicians to apply them according to the geographical, social and cultural context in which they work." The principles emphasise the importance of the team approach, good communication, access to the full range of therapies, maintaining standards of care, and involving the patient in decision-making.

Australia is a country of vast distances, where the closest specialist radiation oncology services for breast cancer patients living in the city of Darwin, for instance, are located 3,000 kilometres away, in Adelaide. If Australia can map out how to organise a national network of specialist MDTs, surely there is little excuse for failure in any European country.

That is not to say that this is an easy process. Former central and eastern European health systems may have unified structures in common with the UK National Health Service, but many have an acute shortage of pathologists, medical oncologists or radiation oncologists, constraining moves towards MDT working.

Other European countries have no such single unified healthcare provider. The French national cancer plan is interesting because it encompasses public and private provision within a single network. The MDTs at the Antoine Lacassagne Centre are open to private clinics within the onc-Azur regional cancer network, says Gérard, and some private doctors do attend. Conversely, in Cannes, public hospitals work with private radiotherapy clinics, because they have no facilities of their own.

But while this public–private mix is typical of many European health systems, not all of them have France's tradition of a strong central state. In Germany, responsibility for health is devolved to a regional level and doctors retain a high level of autonomy over how they organise their work. Baumann believes they need the carrot rather than the stick. He accepts that Germany has been slow to take on board MDTs, and that even among university hospitals, many are still not working in the new way. But he says there is a great interest in what they have done in Dresden, and the most helpful thing would be for resources to be allocated to support the change.

There is a need to inject a sense of urgency among those who can influence Europe's cancer services

MEP Karin Jöns is a breast cancer survivor and the German representative for the European Breast Cancer Coalition advocacy group, Europa Donna. She says the German healthcare system is very fragmented and there are few levers for effecting change, no matter how strong the evidence base. Health policy is organised in a federal way and is in the hands of the 16 regional governments (Länder), but it is the doctors, together with the health insurances (there are no fewer than 55 of them), who hold the real power.

She believes that, for Germany and other public healthcare systems, the way forward lies in a system of reliable accreditation and re-accreditation for specialist units that offer diagnosis and treatment that comply with specified quality criteria. Patients would then be able to make an informed choice about where to go for the best quality treatment, and hospitals and clinics would have an incentive to raise their quality of care.

This approach has been pioneered by the European Society of Mastology (EUSOMA), which wants to see all Europe's breast cancer patients treated by multidisciplinary teams of breast specialists within accredited breast units fulfilling strict criteria on staffing of the medical team, treatment procedures and minimum case loads.

Jöns played a key role in getting many of these criteria – particularly the multidisciplinary approach – adopted by the European Parliament as part of the European Breast Cancer Resolution in 2003. Since then, she has been campaigning to get the recommendations implemented throughout Europe, focusing particularly on her own country, but she is not satisfied with the pace of change.

Though the German Cancer Society accredits breast units, it has adopted quality criteria that are far less stringent than both the EUSOMA and the EU guidelines. Jöns says that hospitals are pooling patient numbers to show they treat a minimum of 150 new cases a year, even though they are not working together as an integrated breast unit. Many so-called breast units, she says, have no in-house pathologists, and have to get the pathology done at another hospital, and are therefore unable to control the quality. Most don't have breast nurses – or even know what a breast nurse should be. And while the EU guidelines call for multidisciplinary team discussions pre- and post-treatment in 100% of cases, certification is being handed out in Germany to hospitals that can show 20% of patient cases are considered at some point by an MDT, so long as the hospitals give assurances they are moving towards 40%.

Jöns believes this provides window dressing without a commitment to real change. "Most hospitals want to get certified as a breast unit so that they get a better image. But often they do not work in a serious multidisciplinary way. Some doctors still believe they know everything and can do as they please without reference to any guidelines. They say 'We've always done it in this way, and in our country everything is OK.'"

That everything is far from OK is evidenced by a report into breast cancer operations compiled by the Bundesgeschäftsstelle Qualitätssicherung. It found that in 622 of a sample of 691 hospitals, surgical 'security' margins were smaller than evidence-based guidelines. Jöns believes that this is largely a diagnostic failure. "In 50% of cases of breast cancer they only realise during surgery that it is cancer. If they had done it in a multidisciplinary way and had known the diagnosis in advance, then the surgery would have been done in the right way. Unfortunately this is not the only problem with breast surgery."

Such monitoring can play an important role in combating complacency and convincing the medical establishment of the need for change. The Swedish government is also developing quality indicators which county councils will be obliged to monitor. Glimelius expects MDTs to feature. "It won't be a law, but there will be the chance to check whether or not it has happened."

Current and future cancer patients across Europe hope that a combination of national cancer plans and accreditation backed by EU guidelines and recommendations will deliver top-quality multidisciplinary care. But how long will it take?

Jöns points out the EU adopted guidelines on breast cancer screening 15 years ago, but this service will not be available throughout Germany until the end of 2007. Women in many other EU countries will have to wait even longer.

There is a need to inject a sense of urgency among those who have an influence over the shape Europe's cancer services – the sense of urgency that convinced Jacques Chirac and Tony Blair to put some political clout behind their countries' respective cancer plans.

Currently 1.7 million European citizens die from cancer each year. If Gérard at the Antoine Lacassagne Cancer Centre is right in estimating that MDT working could increase the cure rate by 2.5%–5%, that alone could save as many as 85,000 lives a year. As Gérard himself put it, "Not bad eh?"

PHARE: shining a light for academic research in Europe

Anna Wagstaff

Clinical research activity may be plummeting in the rest of Europe, but in France they're determined to substantially increase the numbers of hospitals and patients involved in clinical trials – starting with a strategic trial on Herceptin.

Reaping the rewards of the new era of molecular biology is proving harder than many had anticipated. Just as the trickle of so-called targeted drugs is turning into a steady flow, each one more expensive than the last, bureaucratic restrictions on clinical trials compounded by a lack of public funding for research are closing down opportunities to discover how to use these new drugs to greatest effect.

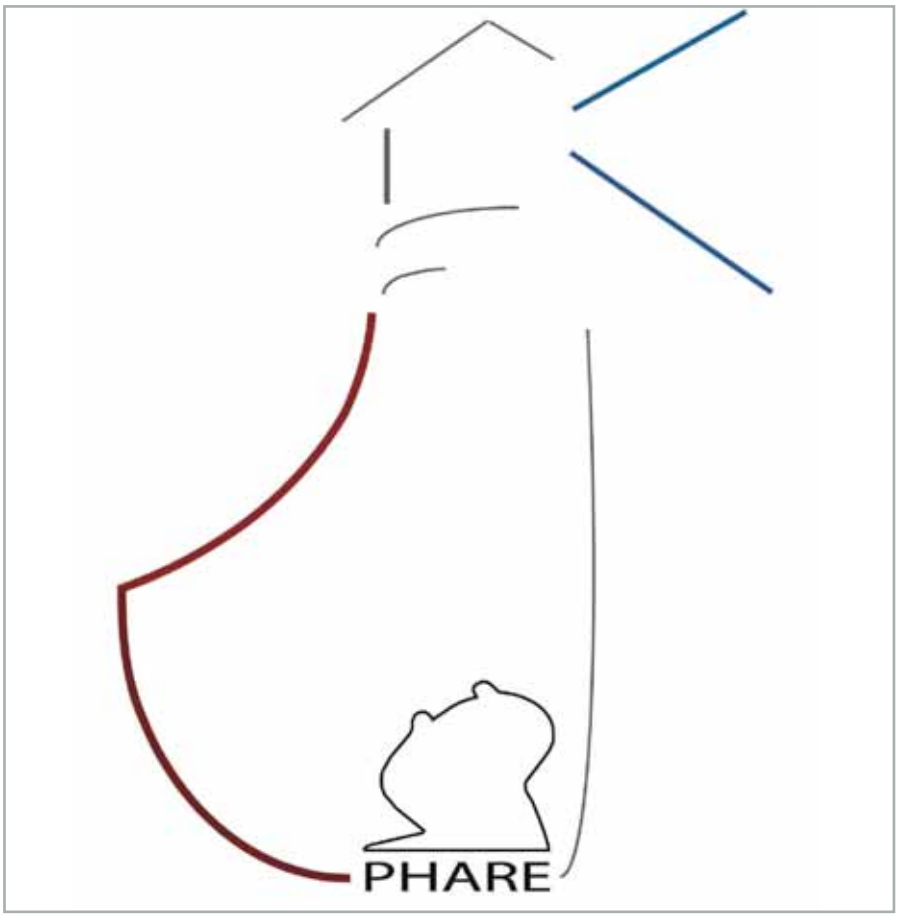
Not in France, however. Here the newly established National Institute for Cancer, INCa, is set to launch its first ever clinical trial. It will seek to clarify the optimal duration of adjuvant Herceptin (trastuzumab) treatment. And in admirable contrast to the clinical trials directive, it is specifically designed to encourage as many French cancer treatment centres as possible to join in. Now, trial coordinator Xavier Pivot, from the Besançon University Hospital, is inviting European researchers to join the project by setting up similar trials in their own countries.

The PHARE trial – Protocol of Herceptin Adjuvant with Reduced Exposure – is based on the French Temporary Treatment Protocol for Herceptin (www.enqueteinca.fr/medias/pttdefeng2710.pdf), which was drawn up under the auspices of INCa to enable eligible patients to receive adjuvant Herceptin pending approval by the European Medicines Agency (EMEA). It is a non-inferiority trial, with the main objective of establishing whether treatment for 6 months gives results that are no worse than treatment for 12 months. There are two secondary objectives, says Pivot. One is to compare Herceptin given sequentially to chemotherapy (as in the HERA trial, *New Engl J Med* 353:1659–1672), with Herceptin given concomitantly with a taxane-based chemotherapy (as in the BCIRG trial, www.bcirg.org). The second is to see whether the optimal duration of treatment varies according to whether the tumour is oestrogen-receptor positive or negative (ER+ or ER-).

Non-inferiority trials require a large number of patients and events in order to give statistically significant results, and PHARE is looking to recruit 7000 patients over the next two years. Given that only 1%–2% of French cancer patients are currently enrolled in clinical trials, this is a very ambitious target. But for the oncologists at INCa, this is the whole point. Much though they would like to know the answer to the PHARE questions, they are equally interested in simply extending the number of centres involved in clinical trials – any clinical trials – because they believe, on the basis of strong evidence, that centres involved in trials provide better quality treatment.

One of the targets INCa has set itself is to raise the proportion of patients in clinical trials to 10%. In order to help smaller hospitals and even private practices to participate in these trials, it has put together a team of 'flying data managers' who can be dispatched to give support as and when necessary. In addition to undertaking its own trials, like PHARE, INCa will also give support to trials organised by other bodies – whether they be French or international organisations such as the European Organisation for Research and Treatment of Cancer (EORTC) or the Breast International Group. Twenty-eight clinical studies groups have now been set up under the auspices of INCa – for lung, breast, colorectal, radiation therapy, etc – each with 10–12 experts who will select the trials INCa will support and propose new trials where they are needed.

The key to making this work is to keep things simple. The PHARE trial



was designed with an 'ultra-simple' protocol, which requires the same amount of work as normal treatment. It uses an 'ultra-simple' Case Report Form, and an 'ultra-simple' randomisation. All the documents will be downloadable from INCa's website. Sources within INCa stress that it is still possible to achieve this degree of simplicity at the level of the treating physician, even under the terms of the European clinical trials directive. This is because the additional bureaucracy and expense involved in complying with the directive fall directly on INCa, as the sponsor, and INCa has the resources, staff and experience to cope.

Keeping things simple doesn't just help when it comes to widening the group of French treatment centres involved in clinical trials. It also makes it easy for research groups in other countries to run similar trials with a view to conducting meta-analyses that could further clarify the best way to use adjuvant Herceptin. Pivot is very keen to see this happen, because he believes the results of the PHARE trial will simply open the way to further questions that need answering: "My belief is that we have a subset of patients who require maybe 6 months, probably a subset who require less and probably a subset who require more."

Working out which patients do best with which protocols will be a complex business, and the more groups who join the search, the better. "It is a French project, but my belief is that this project should not remain a purely French one, it should take on a European dimension, and other countries can participate in such a study or undertake similar studies, because it is a very simple one.

"If we have 5000 patients enrolled in France and 4000 in UK and 5000 in Germany and 4000 in Italy, we can be absolutely sure of the results. And in terms of subset analysis, if we want to identify a difference between the concomitant versus sequential administration or between ER- and ER+ tumours, we will probably need this type of meta-analysis, so a European dimension to such an approach would be very effective."

Whether or not research groups in other countries choose to take up this invitation, there is no doubt that finding how to use cancer drugs more effectively will be key to ensuring that Europe's patients can benefit from the very expensive new drugs that are coming on the market. And as Pivot points out, pharmaceutical companies are hardly going to volunteer to do studies like PHARE that may result in halving the period for which their drug is used.

"There is an urgent need," he says, "for more strategic, academic trials like PHARE", and he hopes that similar trials will soon be up and running for other targeted drugs, such as Avastin (bevacizumab).

France does not have an outstanding track-record on leading clinical trials, and those in Europe who have been plugging away at this for decades may be forgiven the odd wry comment about the fervour of the converted. That said, amidst the despondency created by the European directive and often chaotic way decisions are made over new drugs – who gets them and how they are used – the new "can do" approach of French oncologists in INCa will surely be welcomed as a ray of hope on the European scene.

If the cardiologists can do it, so can we

Elizabeth DeVita-Raeburn

Michael Sporn believes the best bet for controlling cancer is to pick up the warning signs and nip it in the bud. A pot of gold awaits any drugs company that can come up with a Lipitor for cancer, says Sporn, and easy-to-use biomarkers would already be on the market had one-tenth of the research dollars poured into chemotherapy been invested in proteomics.

From his fifth floor office at Dartmouth Medical School, in the bucolic town of Hanover, New Hampshire, Michael Sporn, the man who coined the term "chemoprevention," is still waging his own version of the war on cancer. That it is one largely devoid of research dollars and ignored by pharmaceutical companies has left him frustrated, but undaunted. There is no greater motivation for him to keep at it than the fact that many of his good friends and colleagues have already died from carcinoma and, he says, "hundreds of thousands more like them are slipping through the back door every day."

The answer, he believes, is not to be found in diet and lifestyle changes, the subjects that often come to mind when the word 'prevention' arises, and which are largely the focus of the US National Cancer Institute's prevention programme. "We're not going to fix this dietarily," says Sporn. "Living well and eating well isn't going to make cancer go away. Vitamin C has been a failure. Vitamin D hasn't been much better, and low-fat diet hasn't worked either." Sporn's ideas, in fact, are less about preventing the disease than identifying people at the early stages of malignant cell differentiation and nipping that process in the bud with drugs. "This is a nasty disease that involves genetic dysfunction, and we need some real medicine to deal with it," he says.

His model is based on what cardiologists have done to reduce mortality from heart disease: identify people when they're first showing signs of trouble – high blood pressure or cholesterol – and medicate them before they're too sick to save. His favourite graphic shows two simultaneous curves – one downward slope, indicating decreased mortality from heart disease over the years, superimposed upon a flat line reflecting the static mortality from cancer. "Lipitor is a classic chemopreventive agent," says Sporn. "Pfizer may not want to call it that, but that's what it is."

Granted, cancer is more complex than heart disease. Chemoprevention studies are prohibitively long and expensive; pharmaceutical companies are averse to the risk of treating so-called 'healthy' patients with any medication that might cause lawsuit-worthy side-effects; and, perhaps most challenging, there are as yet no easy

biomarkers for cancer. "You put someone on 20 mgs of Lipitor, measure their cholesterol that day and then again in three months, and you can tell them their cholesterol and blood pressure are down," says Sporn. Not so with cancer.

Not, says Sporn, because it's impossible, but because little effort has been made. "For all the molecular biology that has been done on cancer, there hasn't been much of a crash on biomarkers," he says. "The bottom line is that the dollars are simply not there, even though chemoprevention would be more cost-effective. Meanwhile, we still have three hundred thousand useful lives being snuffed out every year. And you can only trot out Lance Armstrong so much. Sometimes," he admits, "my frustration over the lack of progress wakes me up at night."

Serendipity

Sporn's path to becoming an advocate for cancer chemoprevention was serendipitous. Born in 1933, he spent his childhood "smack in the middle" of New York City, which he didn't much enjoy. "I didn't like the general pushiness of it," says Sporn, who lived all over the city, and worked as a delivery boy for a florist in his free time. College was Harvard University, where pushiness took the form of grade competition. He didn't like that either. It wasn't until the summer of his second year in college that he started to get a sense of what he *did* like. "I went to Cornell and took a summer school class in comparative anatomy with an anatomist named Perry Gilbert," he says. "It was a formative experience."

Gilbert, famous for his expertise in shark

"Living well and eating well isn't going to make cancer go away"

"We were just a couple of bright kids with a dream of doing research"

anatomy, had a reputation as a mentor to students. He kept a card on each one he taught over the course of his career, complete with their picture, exam scores and personal details. This was a different world to Sporn. "When I was at Harvard, there was never any meaningful personal interaction between professors and students," he says. Gilbert, on the other hand, loved to be with his students, and was known to roll up his sleeves and help them with dissections. "He even took the class on a picnic," says Sporn. The experience gave Sporn a life-long taste for congenial and idealistic research environments that would guide every step of his career.

Because of his experience with Gilbert, he turned down Harvard Medical School, opting, instead, for the University of Rochester, the first medical school to be founded after the Flexner Report of 1910, which changed American medicine by creating a higher standard for modern medical education and effectively closed two-thirds of the US medical schools. Rochester was exactly what Sporn wanted. "It was a very strong, very holistic, integrated place," says Sporn. "And a very nurturing one." Research was encouraged, but never allowed to become separate from reality – the basic science part of the school was separated from the hospital only by a set of double doors. Students and teachers, basic scientists and clinicians, shared a cafeteria.

Nor was the school simply about producing doctors every four years. "Somewhere along the line, various faculty members would tell you to take a year out and do research," says Sporn. When his turn came, he took 15 months out to study with the British psychiatrist and theoretician Ross Ashby, one of the founding fathers of cybernetics. "He was totally uninterested in anything by way of the laboratory, but he let me do whatever I wanted," says Sporn. "So I was exposed to a really world class theoretician and at the same time I was allowed to sow my wild oats in the lab. I was learning how to work in a laboratory and given total freedom to explore things."

He returned to Rochester "totally bitten by this way of life." He finished his last two years of medical school, at which point two "absolutely wonderful" faculty members, John Romano and George Engel, both professors of psychiatry and long-time collaborators themselves, helped him and a friend of his get a $50,000 grant from the National Institutes of Health (NIH) to set up their own lab and do basic research. He still can't believe his luck. "We had no preliminary data, no nothing. We were just a couple of bright kids with a dream of doing research." Together, he and his partner did some of the first papers on amino acid metabolism in the brain, showed that the brain can make its own urea, and did one of the first studies on the biochemical basis of memory.

When the money ran out, Romano and Engel helped Sporn and his lab partner get jobs as research associates at what was then the biggest research Mecca in the US – the NIH.

In the US in the early '60s, if you wanted a research career, NIH was where you wanted to be. The public, and the government, placed an enormous trust in the power of science, and the money flowed freely. "The sky was the limit," says Sporn, still marveling over it after all these years. "Jim Shannon, the director, would go down to Congress and ask for money for something, and they'd say, 'You're not asking for *enough* money, doctor, you need *more*.' There was no political interference, either. We might as well have been living in a magical land of Oz, divorced from the world of politics." Like Rochester, the labs and the wards of the NIH were separated only by a hallway, reinforcing the ideal of lab-to-bedside medicine, and the scientists were all part of one big community. "No one even knew what institute anyone else was in."

From 1960 to 1964, Sporn worked on the

nucleic acids of brain cells at the Neurology Institute. Though he had once imagined a career as a general practitioner, those four years changed that for good. "If I had any thoughts of going back into clinical medicine, they were gone," he says. When his four years were up, he decided he wanted to stay. The problem, by then, was that Vietnam had changed everything. Even young doctors who hadn't envisioned research careers were competing for spots at the NIH because it was part of the Public Health Service, and working there meant you didn't have to go to war.

The challenge of cancer

To make matters worse, there was a hiring freeze on. Sporn went to every institute director at the NIH in search of an opening, with no luck. "A freeze was a freeze," says Sporn. Then, one night, at a poker game, one of his co-workers overheard something about a new carcinogenesis programme the National Cancer Institute (NCI) had managed to set up on a contract basis. And they *were* hiring. He'd never given any serious thought to doing cancer research before. But he jumped at the opportunity, not only because he needed the job, but because he'd started to feel an urge to do something more clinically applicable. "I knew there was a big challenge in cancer," he says.

He knew because his wife, Kitte, a paediatric nurse at the NIH, took care of many cancer patients. Nightly, she regaled him with stories of children dying of leukaemia, before the era of platelets and supportive therapy, and patients struggling to overcome "kamikaze" maxillofacial procedures and hemi-pelvectomies. "Kitte took care of one patient without a face," he says. One Sunday morning, he'd met one of her patients, a young, pale, girl named Debbie, who, he knew, would inevitably die. "She was like a poster child for everything the NIH was trying to do," he says.

This was 1964, two years after Rachel

Carson, a former marine biologist with the US Fish and Wildlife Service, set off a public firestorm with *Silent Spring*, a book that argued that the pesticide DDT was killing fish and wildlife, and raised speculation that chemicals in the environment might have a negative effect on the human population, as well. The NCI was as interested as anyone in sorting out the connection between chemicals and cancer. As for Sporn, it was no big leap, he says, to go from studying the nucleic acids of brain cells to studying the nucleic acids of rat cells that had been exposed to common carcinogens like Azo dyes, such as butter yellow, or the chemical aflatoxin which is the product of a mold that often grows on spoiled grain, and acetyl amino fluorine (AAF).

"The popular hypothesis back then was that chemical carcinogens caused cancer by binding

"The public, and the government, placed an enormous trust in science, and the money flowed freely"

He can't see the difference between someone with high blood pressure and someone with severe dysplasia

to key protein targets," he says. "We did some of the first studies that showed that chemical carcinogens would bind to DNA and cause dysfunction." They also showed that the non-carcinogenic analogues of those chemicals *didn't* bind to DNA. "The greater the carcinogenicity of a substance, the higher the level of DNA binding," says Sporn.

Six years passed, and as intellectually exciting as the research was, it still didn't feel terribly helpful to the patients Kitte was caring for. "I started thinking, where is this going," he says, "what does it mean?" Then Umberto Saffiotti, an Italian pathologist, became director of the NCI carcinogenesis programme. Saffiotti had a research interest in vitamin A. He'd done hamster studies that showed that vitamin A could suppress carcinogenesis. He asked Sporn to look into vitamin A and lung cancer. Sporn knew little about either, but he started reading up, and discovered that vitamin A acts more like a hormone than a vitamin. "It controls the differentiation of almost all the epithelial tissues in the body," he says. He was also stunned by another, earlier, discovery: the histology of tissues in rats with vitamin A deficiency resembled the histology of early carcinogenesis in humans.

"It got me really excited," says Sporn. If one could control or reverse early abnormal differentiation, vitamin A could be a true preventive tool at a very early stage. But there were two major problems: First, high doses of vitamin A caused toxicity. And second, natural forms of vitamin A didn't necessarily reach target tissues, such as the lungs, where one wanted to prevent cancer. "I got the idea to make synthetic analogues of vitamin A, for which we coined the new term, 'retinoids'," says Sporn. He set up a collaboration, first with Hoffmann-LaRoche and then with Johnson and Johnson, and also set up a new programme for chemists throughout the country to make new retinoids. "In those days, there were no patents at the NIH and no MTAs [material transfer agreements, which allow one party to perform research using the materials of another party]." They tested several hundred vitamin A analogues on well over twenty thousand hamster tracheas. It quickly became clear, he says, that a number of the analogues could reverse the abnormal differentiation.

Early results

By 1976, they had their first animal data. "We could take lesions in hamster tracheas that resembled those of heavy smokers and reverse them," he says. Further work showed similar success in animal models with cancer of the bladder, oesophagus, colon and breast. "We would screen an agent first in an organ culture system, and if it looked really promising, then we'd do the preliminary animal experiment, and then we'd do full-blown carcinogenesis studies," he says. Some of the agents they worked with, including one retinoid for clinical prevention of breast cancer that was tested in Italy, got very good results. And some have even gone on to be widely used – but almost always in the context of treatment, never in chemoprevention.

"Drug companies are not very interested in this," says Sporn. "They're terrified of liability suits." It's an issue that frustrates him, he says, because, rationally speaking, he doesn't see the difference between someone with high cholesterol, or blood pressure, and someone with severe dysplasia (abnormal epithelial cells), seen on biopsy or in cytology smears. The latter group, he says, are no healthier than the former. But the concern is that the risk of dosing this seemingly healthy group with chemopreventive drugs might outweigh the benefit. Sporn doesn't think that's the case, and cites the outstanding success of tamoxifen and raloxifene in preventing breast cancer as examples. "Those

"We're not ready to put chemopreventive agents in the cornflakes yet"

drugs are old, we can do much better than that now," he says, but acknowledges that more work needs to be done to prove it and to develop even safer agents. "We're not ready to put chemopreventive agents in the cornflakes yet."

In 1995, Sporn decided to leave the NIH for Dartmouth, returning to a part of the country he and his wife love. "I have roots that go way back to this part of the world," he says. He spent five summers away at camp there, a respite from the New York City he was never comfortable in. He and his wife spent their honeymoon at nearby Mount Washington, and they used to take ski trips here with his two boys, Tom and Paul, when they were kids. In 1975, he and Kitte bought an old farmhouse out in the countryside, with an eye toward moving there some day.

But another reason for the move was also to get back to chemoprevention work, which he'd drifted from a bit in his last ten years at NIH, and do something "totally off the wall." And by that he means studying triterpenoids, a family of mildly anticarcinogenic and anti-inflammatory chemicals that occur in a wide variety of plants, including rosemary. Upon getting interested in them, Sporn promptly did exactly what he did with vitamin A – he asked a bunch of chemists to make him as many analogues as they could come up with. Although this time, he didn't have to ask drug companies and chemists across the country – he just had to go across the street to Dartmouth's chemistry department, where he asked Gordon Gribble, a professor of chemistry, and Tadashi Honda, an associate professor, to come up with over 300 derivatives. "They're all home brewed," he says.

One of the most exciting things to come out

"I believe that essentially all the common forms of epithelial cancer are preventable"

of the research thus far, he says, is the revelation that triterpenoids have multiple functions. They're markedly anti-inflammatory, anti-proliferative, can induce apoptosis, and are cytoprotective. "We think they'll be useful for both chemoprevention and chemotherapy," says Sporn. In fact, the US Food and Drug Administration (FDA) has approved two of them for phase I trials in leukaemia and end-stage solid tumours, studies which are due to start soon at MD Anderson, Dana Farber and possibly the NIH. "Nothing ever goes into prevention first," he sighs.

An act of faith

He does think the field will gravitate to his point of view, eventually. Not that chemoprevention will replace the other treatment modalities, but rather be the first step in approaching someone at risk. "It's something of an act of faith, but I believe that essentially all the common forms of epithelial cancer are preventable, if we can get at the solutions in the early states of abnormal differentiation and prevent progression," he says. There are problems that need to be solved first, of course.

Drug companies need to shed their fear of liability, and see that cancer chemoprevention drugs can be just as profitable for them as drugs like Lipitor, he says. To assuage them about liability issues, Sporn envisions an insurance pool which could protect both corporations and individual physicians against specific liability, and which could be funded by a tiny surtax on preventive drugs.

Easy-to-use biomarkers, obtained from nothing more complicated than a blood sample, are needed to make chemoprevention studies more economically feasible. And the FDA needs to be persuaded to let drug companies use them. "If a tenth of the budget that has been put into chemotherapy had been put into development of proteomics I think we would have a blood test," he says.

On the day that we last spoke, Sporn was, as he said himself, in a very optimistic mood. He and his colleagues at Dartmouth had figured out a way to detect tiny amounts of tumour in an anaesthetised mouse lying spread-eagled in an NMR (nuclear magnetic resonance) machine. "We have this huge amount of technology we've developed to do all these studies, but I don't think they've ever been applied to prevention before," he says. "We detected a tumour less than a millimeter across."

When he's not doing research, he spends time doing what the teachers he once revered did for him – leaving his office door open so that he's always available to his students, and working one-on-one with them when they need him. He's hopeful that his students, in the not-so-distant future, will finish the job he's started.

"There are a huge number of drugs we can make as preventive agents and we have to find a way between support from the government, the private sector, big Pharma and the oncology community to see that they get developed for chemoprevention," he says.

"If it's going to happen, it needs to be a co-operative effort."

"Drug companies need to see that chemoprevention drugs can be just as profitable as drugs like Lipitor"

Chernobyl 20 years on

The cancer incidence graphs are still rising

➜ Peter McIntyre

Estimates of the death toll from the nuclear reactor disaster at Chernobyl vary widely depending on who you listen to. But with leukaemia rates still rising, and a recent marked increase in solid tumours among the 600,000 workers who were sent in to clean up the mess, the real question is whether the worst may be yet to come.

On 25 April 1986, the crew of number 4 reactor at the Chernobyl nuclear power plant in Northern Ukraine began tests for a routine shut-down. The power plants were of poor design and procedures had become sloppy. As the reactor began to close down, the flow of coolant water diminished and power output rose instead of falling.

At this point, a design fault led to a dramatic power surge that ruptured the fuel elements. Shortly after 1.30 am on 26 April an explosion blew the covering plate and roof off the reactor, releasing fission products into the atmosphere. A second explosion threw out fragments of burning fuel and graphite, and as air rushed in, the graphite moderator burst into flames.

The graphite burned for nine days, releasing about 12x1018 Bq of radioactivity into the atmosphere, made up of xenon gas, iodine, caesium and other radioactive material. Most of the material was deposited close by as dust and debris, while lighter material was carried by the wind over Ukraine, Belarus and Russia. Enough material was carried further afield to cause major concerns in Scandinavia, Europe and the rest of the world.

In the first few hours, firefighters and other emergency teams struggled to get fires under control and to start to make the nuclear reactor 'safe'. About 1,000 people, including on-site staff, were irradiated with up to 20,000 millisieverts (mSv) on the first day. Of these 1000, 58 were to die from the effects of acute radiation syndrome.

On the day of the accident the winds were from the south, blowing the fallout towards Belarus only a dozen kilometres away. Later the wind veered, blowing the fallout towards West Ukraine. Finally, it came from the north, blowing southwards towards Kiev.

At first, the public was told little about the accident, as secrecy took precedence over public safety. In nearby Prypiat, on the day of the explosion, a teacher took her children onto the bridge to watch the fire. On April 27, 49,360 people were evacuated from Prypiat, with no official announcement. Two days later, weddings were still being held in Chernobyl, and people were celebrating amidst the nuclear fallout.

Communist Party leaders went ahead with the May Day celebrations in Kiev and other cities, despite the radiation cloud covering the area. An international cycle race also went ahead as planned. It wasn't until May 2 and 3, a week after the accident, that 45,000 people were evacuated from a 30-kilometre radius of the power plant. A further 116,000 people were later relocated.

KOSTIN IGOR / CORBIS SYGMA

Where are they now? After the explosion, staff continued to be bussed into work to monitor and maintain the three remaining undamaged reactors. Their flimsy caps and face-masks show how little appreciation there was of the risks of working in such a heavily contaminated environment

While many clean-up workers believed radiation was harmless, there was something akin to panic in Kiev

Between 1989 and 2001, life expectancy for men in Ukraine fell from 66 to 63 years

After two weeks of panic and spontaneous evacuation, on May 6 Anatoly Romanenko, Minister of Health, finally went on state TV. His advice was that people should close their windows and wash their hands and feet.

Over the next period, 600,000 people from Russia, Belarus and Ukraine were involved as "liquidators" or "clean-up workers", carrying out emergency work and cleaning up contamination. In all about 250,000 people were evacuated from affected areas in Ukraine, Belarus and Russia, and resettled elsewhere. Only a few thousand of these have ever returned.

In those early weeks, while many of the clean-up workers believed that radiation was harmless, there was something akin to panic 100 kilometres away, in Kiev.

Volodymyr Yavorivsky, a Kiev deputy in the USSR Supreme Soviet and a critic of the regime, later told the *Wall Street Journal* how people packed their children into trains, buses and planes. "My seven-year-old daughter went to stay with friends in the Carpathian Mountains, but eventually I learned that it was precisely there that a plume of dangerous radioactive fallout had fallen. Meanwhile the elite had their children evacuated to safe zones on the first day of the accident."

Today, 20 years later, there are still two truths about Chernobyl. The conservative line is that the explosion was directly responsible for 58 deaths and about 4,000 cases of thyroid cancer in children (attributing only nine child deaths from thyroid cancer to radiation). The UN Atomic Energy Agency predicts that there will eventually be 4,000 deaths as a result of Chernobyl. A report in September 2005, *Chernobyl: The True Scale of the Accident*, endorsed by UN AEA, the World Health Organization and the UN Development Programme, said that "no evidence or likelihood of decreased fertility among the affected population has been found, nor has there been any evidence of increases in congenital malformations that can be attributed to radiation exposure."

The other truth suggests a worldwide cover-up of catastrophic consequences. In the run-up to the 20th anniversary this year, the European Greens launched *The Other Report on Chernobyl*, claiming that fallout contaminated 40% of Europe's surface area, and predicting 30,000–60,000 excess cancer deaths. The British *Guardian* newspaper even carried a report claiming that 500,000 people have already died because of the accident, although this figure is widely disputed.

The lack of agreement on data relating to the number of deaths or cancers caused by Chernobyl is in part because all figures are seen as having a political angle. But there are also genuine difficulties in understanding and interpreting the data.

In 1986, soon after the disaster, the Research Centre for Radiation Medicine was established to address an anticipated increase in cancer cases and to treat acute radiation syndrome and other diseases. Today it is housed in a ten-storey building in a Kiev suburb, treating 400 adults and 134 children who are considered 'victims of Chernobyl'.

The centre has collaborated with the US National Cancer Institute and with researchers from France, Germany, Italy and Japan to try to predict how many people will develop cancer because of the Chernobyl explosion.

Anaytoly Prysyazhnyuk, head of the cancer epidemiology laboratory at the centre, took charge of data collection soon after the accident, visiting contaminated areas – including his parental home at Narodychi – and making studies of what he found.

Prysyazhnyuk has worked on a range of studies with a Russian team and a French team from the International Agency for Research on Cancer in Lyon.

His best estimate is that there has been an increase of more than 8,000 cancer cases in the affected areas of Russia, Belarus and Ukraine. However, he says that there was already evidence of a rising trend in cancers before Chernobyl, and when this is taken into account the real number of 'excess cancers' is about 5,400 from 1986 to 2004.

In the year following the accident there were repeated reports from districts around Chernobyl of large increases in cancer. He says that, when he investigated, he found many were due to the improvements in registration.

PETER MCINTYRE

A potential timebomb. Dimitry Bazyka, from the Research Centre for Radiation Medicine in Kiev, says the biggest rise in solid tumours caused by the Chernobyl explosion is still to come

The most alarming statistic is the falling life expectancy in Ukraine. Between 1989 and 2001, life expectancy for men in Ukraine fell from 66 to 63 years and for women from 75 to 73.8 years. In 2001 the European figures for life expectancy were 75.2 years for men and 81.4 years for women.

The economic situation, a rise in poverty, and an increase in drinking have all been implicated in shortening life spans. However, the Chernobyl accident, the massive dislocation of populations, anxiety about future health prospects and the increase in cancers are all factors.

Dimitry Bazyka, an immunologist and deputy director of the Research Centre for Radiation Medicine in Kiev, has lived with the after-effects of Chernobyl personally and professionally. His father, Anatoli Bazyka, had been a doctor working in an area of the Soviet Union where nuclear testing was carried out, but in 1986 had just retired. On the day of the accident he was visiting land he had bought for his retirement home close to the Chernobyl power station. He received a significant dose of radiation, and three months later he was diagnosed with liver cancer, which rapidly killed him.

Bazyka says his father was an example of the way that radiation promotes existing cancers. "We cannot say that his cancer started on 26 April, when three months later it was manifested clinically. It started several years before. But after the second irradiation it started to move very quickly. So this is what we mean by 'promoting' cancer."

Later come the cancers induced by radiation: leukaemia, thyroid cancer, lung, urinary, renal, colon and breast cancers. The question is: How many, and how much later?

Using protocols established at the International Commission on Radiation Protection, the first predictions in 1986 were of 50,000 deaths worldwide from all causes.

Since 1996, there has been a joint study between Ukraine, Belarus and Russia with France and Germany, of cancers, child mortality and other diseases in the most affected areas. A report on data for eight years is due this year.

Leukaemia is recognised as a marker for radiation-induced cancers, since it is induced many years earlier than solid tumours. The three countries have completed a separate study of leukaemia cases in clean-up workers, working with the US National Cancer Institute. The figures are not due to be released until later this year, but are expected to show a significant increase, with leukaemias in this group running at more than twice the rate expected in a similar-sized population.

Sergeiy Klymenko, a researcher at the Institute of Clinical Radiology in Kiev, says that these cases are very

PETER MCINTYRE

Vicious circle. Sergeiy Klymenko, from the Institute of Clinical Radiology in Kiev, says foreign tissue banks won't help them find bone marrow donors because they have too little experience handling the cells. "But if you cannot get access to donors you cannot gain experience"

hard to treat. "We can see that Chernobyl leukaemias are worse than spontaneous leukaemias. The Chernobyl cases have a lot of negative prognostic markers, and we can see in the clinic that they behave worse. The complete remission rate is lower and the survival is shorter."

So not only are clean-up workers more likely to develop leukaemia, they are much more likely to die. The overall survival of those with acute myeloid leukaemia is about half of other AML patients.

The Kiev team is keen to treat these patients with allogenic bone marrow transplantation. This is not yet a core programme in the Ukraine, partly because of expense and partly because of lack of matching donors. A blood and bone marrow donor registry run by the former Soviet Union was closed down a few years after the Soviet Union broke up. Klymenko says: "We cannot apply to world tissue banks for donors. There is a vicious circle. In order to apply for foreign donors we have to demonstrate we have enough experience to use these cells, but if you cannot gain access to donors you cannot gain enough experience."

Compared with the pattern of cancers in Japan after nuclear bombs were dropped on Hiroshima and Nagasaki, Ukraine is seeing cancers later, and it is seeing a steadily rising graph, rather than peaks as exhibited in Japan.

Bazyka says that the graph of leukaemias is still rising, which has worrying implications for solid tumour cancers. "We can predict that the increase in cancer numbers will be later than in Japan. Not 10 to 20 years but maybe 20 to 50 years later."

They are now beginning to see a rise in lung and colon cancers among clean-up workers and also breast cancer. "We have a cohort of 6,000 females who were clean-up workers and the numbers are higher in this cohort than in Ukraine in general. Thirty years ago the rates of breast cancer were quite low in this country, lower than in European countries, but now there is a dramatic increase."

Many nuclear industry professionals seriously underestimate risk, says Bazyka. He recalls a visit to Slavutich (built to replace the neighbouring town of Prypiat), where one nuclear worker who had been exposed to radiation told him he was sure that there were no harmful effects. "Five minutes later he told me about a doctor who had saved his life by finding he had renal cancer and carrying out surgery. He insisted it was not connected to radiation."

The term "Chernobyl victims" is widely used in Ukraine. A sense of fatalism is the flip side of the poor understanding of risk by many of the clean-up workers, and it is compounding the threat to their lives. Despite the neglect suffered by Ukraine's public healthcare system as the country decides which direction to move in, many of these cancers can be treated effectively provided they are picked up early, as the data from Ukraine's revamped and highly effective cancer registry can demonstrate. "Our big problem is that people don't know about survival," says Liudmila Goulak, head of the cancer registry. "People are afraid of cancer. Some people avoid treatment and prepare for death. Our data show that a lot is being done for people with cancer and a lot of people are being cured."

Putting cancer on the global agenda

➜ Páraic Réamonn*

The International Union Against Cancer has launched a childhood cancer campaign to show that better awareness, early detection and appropriate treatment can make a difference in the developing world.

Cancer is largely a disease of affluent and aging industrialised populations, and fighting cancer is well beyond the means of any developing country. These two dangerous misconceptions between them share a large part of the blame for the absence of cancer from health policies for the emerging world over recent decades. More than half of all new cases of cancer occur in the developing world. Many of them could be treated successfully if caught early enough. Many more could be prevented.

Six years ago, the World Summit Against Cancer in the New Millennium called for "an invincible alliance between researchers, healthcare professionals, patients, government, industry and media to fight cancer and its greatest allies which are fear, ignorance and complacency," and urged that, each year, 4 February be observed as World Cancer Day.

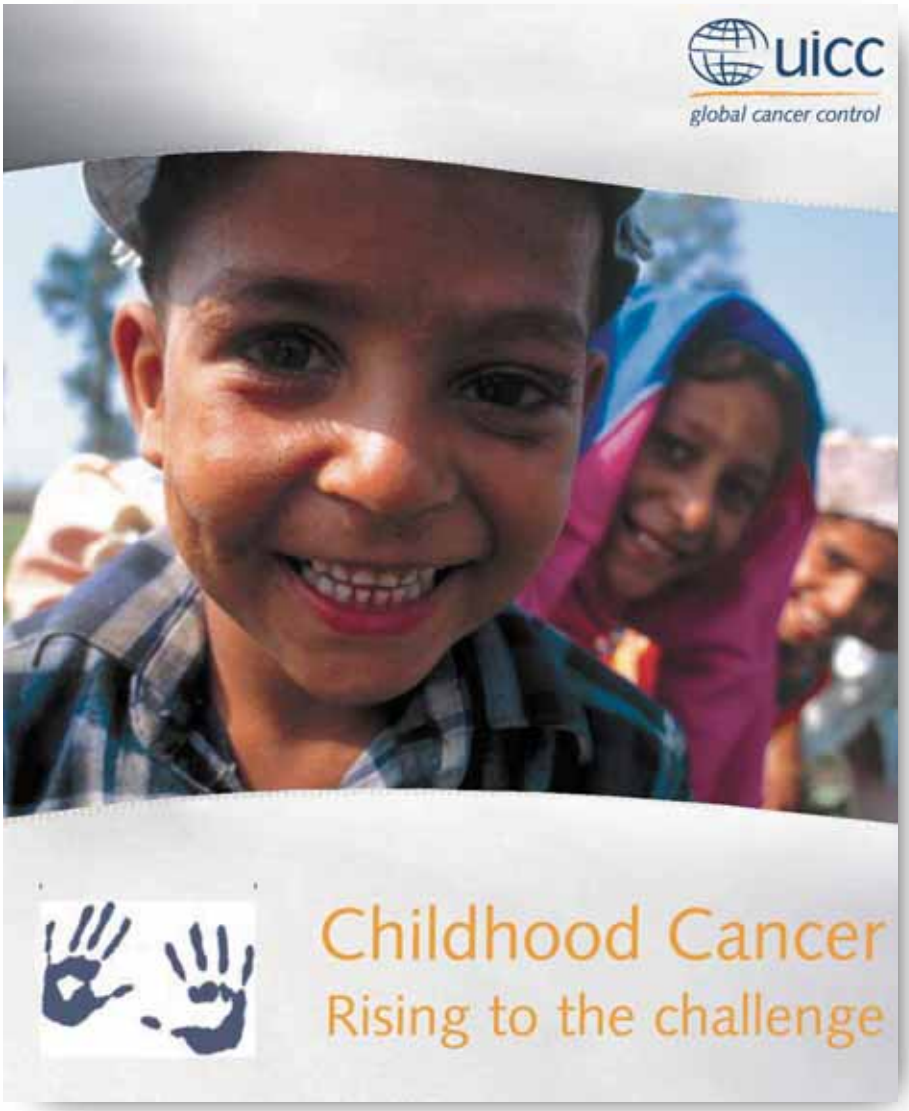
The appearance of the first ever resolution on cancer prevention and control on the agenda of the World Health Assembly last year is an encouraging sign that things are moving in the right direction. But it takes more than a resolution to change the reality on the ground. This is why, three years ago, the International Union Against Cancer (UICC) committed itself to promoting World Cancer Day as part of a global campaign "to raise awareness of the cancer burden and to promote cancer control and patient needs in all countries throughout the world", and last year it launched its own World Cancer Campaign – starting with the 'My Child Matters' initiative on childhood cancers.

Starting with the children

Last November, the My Child Matters initiative awarded grants to 14 childhood cancer projects in 10 resource-constrained countries – Bangladesh, Egypt, Honduras, Morocco, the Philippines, Senegal, Tanzania, Ukraine, Venezuela and Vietnam. The projects were financed by sanofi-aventis, with top-up funding from the US National Cancer Institute making it possible to fund 14 projects instead of the 10 originally proposed.

Why the focus on children? "Childhood cancer is a small fraction of the global cancer burden, yet for children with cancer and their families it can be deeply distressing," explains Isabel Mortara, UICC's executive director. "This is especially so in poorer countries, where childhood cancer is often detected too late to be treated effectively and appropriate treatment is often not available or affordable."

*Páraic Réamonn is UICC's information and resources coordinator



UICC

In such countries, she notes, three out of every five children with cancer will die. But given the minimal conditions for early detection and correct treatment, many of these children could be saved.

Here, relatively little money can make a big difference. "We start with the children," says Franco Cavalli, who chairs the My Child Matters committee and will take over as UICC's president at the World Cancer Congress in Washington DC this July, "because by demonstrating that we can cure children, we show that we can do something against cancer."

Advocating

In Calgary this March, Stéphane Lambiel of Switzerland held on to the world figure-skating title he won in Moscow last year. In between the two championships, he agreed to serve as an ambassador in UICC's childhood cancer campaign. "Cancer is a terrible thing at any age, but especially among the very young," Lambiel says. "My heart goes out to those children in many countries – the little princes and princesses of our world – who get cancer but don't get the early diagnosis and prompt and effective treatment they need to save their lives."

Another advocate for children with cancer is Barbara Bush, the former United States First Lady, who lost her daughter Robin to leukaemia. Also supporting the My Child Matters initiative are two European football legends – England's Gary Lineker and Germany's Franz Beckenbauer. Lineker's oldest son is a childhood leukaemia survivor. "My family and I are proud to support a campaign that aims to raise awareness of childhood cancer," he says. "We believe that children with cancer should never stop having hope and dreaming of their future life."

Educating

As part of the My Child Matters initiative, UICC recently published a special report, *Childhood Cancer: Rising to the Challenge*. With two chapters by the International Agency for Research on Cancer, a third chapter by the International Psycho-Oncology Society, and an introduction by Tim Eden, the president of the International Society of Paediatric Oncology (SIOP), it gives a glimpse of the "invincible alliance" called for six years ago.

A second report, making a comprehensive analysis of the chain of care in paediatric oncology in the 10 countries initially selected in the initiative, with proposals to improve the allocation of resources, will be published later.

The My Child Matters initiative will last for at least three years, with

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Claudia Sánchez Machuca from the Dr Luis Razetti Oncological Institute in Caracas, Venezuela, and Mhamed Harif of the Moroccan Society of Haematology and Paediatric Oncology, speaking at the launch of 'My Child Matters' in Paris last February. They represented two of the 14 institutions who received grants from the campaign

"By demonstrating that we can cure children, we show that we can do something against cancer"

projects in five more countries selected for funding this year.

UICC hopes that over the years, the projects supported will do more than show what can be done – they will serve as a wake-up call for politicians and decision-makers for whom cancer is often still not a priority.

UICC's campaign comes at an opportune moment. For years, developing countries have regarded cancer and other chronic diseases as a priority – for richer nations. Not any longer.

Following the resolution at the World Health Assembly last May, the World Health Organization published a landmark report entitled *Preventing Chronic Diseases: a Vital Investment*.

In this report, WHO proposes a new global goal: to reduce the projected trend of chronic disease death rates by 2% each year until 2015. If achieved, this would avert over 8 million deaths due to cancer in the next decade.

Richard Horton, the editor of the *Lancet*, introducing an influential series of *Lancet* articles on what he calls the "neglected epidemic" of chronic disease, says, "While the political fashions have embraced some diseases – HIV/AIDS, malaria, and tuberculosis, in particular – many other common conditions remain marginal to the mainstream of global action on health. Chronic diseases are among those neglected conditions."

It seems that fashions are changing. With World Cancer Day and its World Cancer Campaign, UICC is determined to see that they do.

Founded in 1933, UICC (www.uicc.org) is the only international non-governmental organisation that is dedicated exclusively to the global control of cancer. For further information, contact info@uicc.org

When should radiotherapy for low-grade glioma be given: straight after surgery or at progression?

Samuel T Chao and John H Suh*

Upfront radiation improves progression-free survival and should be offered as an option to patients presenting with low-grade gliomas.

The European Organisation for Research and Treatment of Cancer (EORTC) study 22845 (see opposite) is an important trial in a series of dose–response studies for low-grade gliomas. Previous Radiation Therapy Oncology Group (RTOG) and EORTC studies failed to show an improvement in local control or survival with high doses of radiation.[1,2] The current study addressed a very important, but unanswered question: can radiation be delayed for low-grade gliomas?

While the study showed no improvement in overall survival, the five-year progression-free survival in the upfront radiation arm was 55%, compared with 35% in the control arm (log-rank $P<0.0001$). As speculated by the authors, the lack of an overall survival benefit could be due to the effectiveness of salvage radiation. The acute toxicity of the radiation was modest, with only six patients having treatment interruptions. Radiation did not cause malignant transformation of low-grade gliomas in this study, and other studies that used careful neuropsychological assessments failed to show cognitive deficits from radiation.[3,4] The argument that radiation might cause malignant transformation of low-grade gliomas or neurotoxicity is not sufficiently compelling to omit upfront therapy in low-grade gliomas.

Since no difference in survival was noted in this study, an important question to address is quality of life. Unfortunately, since this component of the study was optional and few participated, this issue could not be addressed. Progression of disease can lead to worsening neurological impairment. As demonstrated in this study, seizures were better controlled in the upfront radiation arm. Some patients might worry about the lack of active treatment and higher rate of progression without upfront treatment. A key question that needs to be answered is what impact delaying radiation therapy has on quality of life.

Are there subsets of patients in whom upfront radiation might not provide any advantage? Based on the data from the RTOG 9110 trial, patients who are younger than 40 years old, have tumours less than 5 cm, and have a gross total resection, have a better overall survival.[2] To test the hypothesis that radiation can be delayed in these patients, the phase II arm of RTOG 9802 observed patients who were younger than 40 years old and underwent gross total resections. RTOG 9802 also assessed the role of adjuvant PCV (procarbazine, lomustine and vincristine) chemotherapy in a phase III setting for older patients and those with less than a gross total resection. RTOG 9802 has completed enrolment and we await the results. Given the efficacy of temozolomide (an oral agent that alkylates DNA at the O6 and N7 positions of guanine) in brain tumours, particularly glioblastoma multiforme,[5] RTOG 0424 is assessing the role of concurrent and

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adjuvant temozolomide with radiation for high-risk, low-grade gliomas.

Another question to be answered is whether upfront chemotherapy can replace radiation as the initial therapy for low-grade gliomas. The EORTC is conducting a study comparing temozolomide alone to radiation alone. In addition to studying progression-free survival, quality of life will be assessed.

The EORTC 22845 study addressed a key question and showed a benefit for upfront radiation. Yet, there are many questions to be answered regarding the optimal treatment of low-grade gliomas, many of which will be addressed by the above-mentioned studies. Further understanding of the biology of low-grade gliomas and identification of molecular markers is needed to develop individualised treatment strategies.

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

Synopsis

MJ van den Bent, D Afra, O de Witte, et al (2005) **Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial.** *Lancet 366:985–990*

Background. There are no evidence-based guidelines to direct the treatment of patients with low-grade glioma, and it remains unclear whether early treatment has an impact on outcome.

Objective. To compare the long-term efficacy of early, postoperative radiotherapy for low-grade glioma with that of delayed treatment, including radiotherapy, when tumour progression occurs.

Design and intervention. Patients aged 16–65 years were included if they had supratentorial and histologically proven low-grade astrocytoma, or low-grade oligoastrocytoma or oligodendroglioma, WHO performance status* of 0–2 or Karnofsky performance status** (KPS) ≥60, and no other systemic diseases or malignancies. Participants were randomised to receive early radiotherapy (within 8 weeks of resective surgery), or treatment, including radiotherapy, when tumour progression occurred (control). Clinical and CT examination were carried out at baseline, every 4 months for 2 years, and then every year until tumour recurrence. The total radiotherapy dose was 54 Gy (in 5 fractions of 1.8 Gy/week for 6 weeks). Data were analysed by intention to treat. Event-free rates were assessed using Kaplan-Meier analysis, a conditional probability strategy used for estimation of survival in clinical trials with censored observations. The two study groups were compared using the log-rank test.

Outcome measures. The primary outcomes were the durations of progression-free survival and overall survival times, both calculated from the date of randomisation to the date of progression.

Results. Among the 311 patients randomised, after a median of 7.8 years of follow-up, tumour progression had occurred in 217 patients (70%), and 156 patients (50%) had died. Known causes of death were progressive brain tumour (n = 142, 91%) and unrelated causes (n = 12, 8%). Low-grade gliomas were identified pathologically in 186/253 patients (74%), and anaplastic tumours (including astrocytomas, oligoastrocytomas and oligodendrogliomas) were found in 48/253 patients (19%). The median overall survival was 7.4 years (95% CI 6.1–8.9 years) in the control group and 7.2 years (95% CI 6.4–8.6 years) in the treatment group (hazard ratio 0.97, 95% CI 0.71–1.34), with no significant difference between groups (log-rank P = 0.873). Median progression-free survival was 3.4 years (95% CI 2.9–4.4 years) among control patients, and 5.3 years (95% CI 4.6–6.3 years) in the early radiotherapy group (hazard ratio 0.59, 95% CI 0.45–0.77), with significantly longer progression-free survival in those receiving early radiotherapy (log-rank P <0.0001). After progression, survival times were 3.4 years in the control group and 1.0 year in the radiotherapy group (overall log-rank P<0.0001). Seizure control was similar in the two groups at baseline, but 1 year after surgery the number of progression-free patients with seizures was 26/102 (25%) in the radiotherapy group, and 29/71 (41%) in the control group (P = 0.0329). Radiotherapy was interrupted owing to acute reactions in six patients; other toxic effects were moderate, including skin reactions, otitis and mild headache.

Conclusions. Compared with treatment at the time of tumour progression, immediate postoperative radiotherapy lengthens progression-free survival by 2 years, but overall survival is unchanged.

Acknowledgement: The synopsis was written by Emma Campbell, Locum Editor, *Nature Clinical Practice*

** A scale designed by the World Health Organization and used by doctors to describe the physical health of patients, ranging from 0 (most active) to 4 (least active)*

*** A 0% (dead) to 100% (fully active) scoring system to assess the well being of cancer patients and their ability to perform ordinary tasks*

Is intraoperative lymphatic mapping and sentinel node biopsy effective and safe in early-stage melanoma?

Marco Gipponi*

Lymphatic mapping and sentinel lymph node biopsy is a safe, accurate, and low-morbidity method for the pathologic staging of the regional nodal basin in primary cutaneous melanoma.

The tumour status of regional lymph nodes is the single most important prognostic factor in patients with cutaneous melanoma.[1] In the early 1990s, complete lymph node dissection (CLND) of the regional basin was the only method available to identify regional nodal metastasis, but this approach had two important drawbacks. First, almost 80% of patients undergoing CLND had no lymph node metastasis, so they would have gained no benefit in terms of staging or survival, but were at increased risk for acute and chronic morbidity as a result of the procedure. Second, the pathologic staging of all regional lymph nodes underestimates the true frequency of nodal metastasis by as much as 14% compared with the focused analysis of one or a few sentinel lymph nodes (SLNs).[2,3] Hence, lymphatic mapping/SLN biopsy (LM/SLNB) has been proposed as a minimally invasive surgical procedure for staging of the regional nodal basin that detects occult metastasis to allow an early therapeutic CLND to be performed.

The results of the international Multicenter Selective Lymphadenectomy Trial MSLT-1 (see opposite) clearly define the feasibility, accuracy and morbidity rate of LM/SLNB within a randomised clinical trial. The overall rate of SLN identification was 95.3%, with the highest rate in the inguinal basin (99.3%), followed by the axillary (96.6%) and the cervical (84.5%) area. The poor rate of SLN identification in the cervical area might be related to the complex lymphatic drainage in the head and neck region. The accuracy of identification was estimated by assessing the incidence of same-basin recurrence in patients who had tumour-negative SLNs. Overall, 59/944 patients (6.3%) with tumour-negative SLNs developed regional nodal metastases, although 11 of these 59 patients had recurrence in a basin that was not sampled. Fifty-two of the 944 patients (5.5%) had local or in-transit recurrence, and in 8 patients this occurred before nodal recurrence, which could have been the source of metastasis to the previously dissected lymph basin ('biological failure'). Notably, the dissected-basin recurrence rate was 10.3% for the first 25 cases of the trial, but this rate decreased to 5.2% after 25 cases, suggesting an increase in the surgeon's proficiency with the procedure following the 'learning phase'. As the MSLT-1 was designed with a mandatory 30-case 'learning phase', and each surgeon had documented at least 15 consecutive cases, surgeons who treat only a few melanoma patients each year do not seem to have the experience required for a high degree of mapping accuracy. LM/SLNB did not influence the incidence of morbidity at the primary site, and only minimally increased regional and systemic complications, whereas complications in the dissected basin were significantly more frequent when LM/SLNB was immediately followed by CLND

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(incidence of complications 10% and 37.2%, respectively; $P<0.0001$).

Certainly, the final results of the survival analysis of the MSLT-1 are awaited with great interest, although preliminary data seem to indicate a survival benefit in the subset of patients with lymph node metastases.[4] The randomisation of a large number of patients has assured an even distribution of prognostic factors between the study arms and, in the observation arm, there were similar incidence rates for tumour-positive SLNs and clinical nodal recurrence. The latter finding suggests that LM/SLNB can provide early identification of patients with occult nodal metastases who would develop clinically appreciable nodal metastases and would be less curable at that far advanced stage of disease.

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

Synopsis

DL Morton, AJ Cochran, JF Thompson, et al. (2005) **Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial.** *Ann Surg* 242:302–311

Background. Studies in breast cancer, melanoma, colon cancer, lung cancer and almost all solid malignancies that spread to lymph nodes have confirmed that metastatic cells move in an orderly manner from the primary site through the lymphatic system to one or two regional sentinel nodes. Lymphatic mapping and sentinel lymph node biopsy (LM/SLNB) is used to identify occult nodal metastases and thus stage the regional nodal basin to target the subset of patients who would benefit from complete lymph node dissection (CLND). LM/SLNB has become an important and well established technique for the staging of melanoma.

Objective. To assess the accuracy and clinical efficacy of LM/SLNB for staging of the regional nodal basin, and to establish its effect on the incidence of morbidity in patients with early-stage melanoma.

Design and intervention. In the international phase III Multicenter Selective Lymphadenectomy Trial (MSLT-1), patients aged 18–75 years with primary cutaneous melanoma (Breslow's thickness* ≥ 1 mm with Clark level** ≥ III, or any Breslow's thickness with Clark level of IV or V) were accrued over 11 years. Sites of melanoma were the trunk, head and neck, extremities, sole of the foot, palm of the hand or a subungual site. In a 'learning phase' of 30 consecutive cases, each of 18 centres in the USA, Europe and Australia were required to demonstrate a sentinel lymph node (SLN) identification rate that was 85% accurate. Patients were randomly assigned to wide excision (WE) plus observation with complete lymphadenectomy if nodal metastases subsequently became clinically evident, or WE plus LM/SLNB with immediate CLND for any sentinel node metastases.

Outcome measures. The accuracy of LM/SLNB and the incidence of early morbidity were assessed.

Results. After a median follow-up of 54 months (range 3 months–10 years), 1,973 patients were eligible for analysis, 800 of whom received WE plus observation and 1,173 of whom received WE plus LM/SLNB. The rate of identification of SLN using LM/SLNB was 95.3% overall, and such rates were higher in the inguinal and axillary regions than in the cervical region (99.3% and 96.6% vs 84.5%). Among the 944 patients with tumour-negative SLNs, regional nodal recurrence occurred in 59 patients (6.3%), and 11 of these patients had recurrence in a basin that had not been sampled. Fifty-two patients had local or in-transit recurrence, which developed in eight patients before nodal recurrence. In 10 centres, which had accrued a total of 918 patients in the study, the dissected-basin recurrence rate was 10.3% for the first 25 cases and 5.2% after 25 further cases. No operative mortalities were reported, surgical complications associated with WE were low, and LM/SLNB did not affect the incidence of surgical morbidity at the primary site. Addition of the CLND procedure in patients undergoing LM/SLNB increased the rate of complications in the dissected basin from 10.1% to 37.2% ($P<0.0001$).

Conclusions. LM/SLNB can accurately identify occult nodal metastases with an associated low morbidity rate; these subclinical lymph node metastases are likely to develop to more advanced, palpable nodal disease if left untreated.

Acknowledgement: The synopsis was written by Petra Roberts, Associate Editor, *Nature Clinical Practice*

** Depth of melanoma penetration, measured from the outermost to innermost extent of the tumour; used to estimate survival after tumour excision*

*** Method for measuring the depth of skin penetration of a melanoma according to the anatomic layer (epidermis, dermis, or subcutis) of deepest tumour penetration*

NEWSROUND

Selected press reports compiled by the ESO Cancer Media Centre

Combination therapy improves AIDS-related lymphoma outcome

→ Cancer

Survival rates in HIV patients suffering from aggressive malignant non-Hodgkin's lymphoma improved when treated with a combination of HIV therapy and chemotherapy, according to a new study published in the journal *Cancer*.

The benefits of combining the two therapy treatments were most obvious in HIV patients who did not have severely damaged immune functions. These patients survived just as long as the lymphoma patients who didn't have HIV.

Lymphomas are cancers of the immune system's white blood cells, and are treated with chemotherapy. People with HIV are at an increased risk of developing aggressive, fast-growing lymphomas known as 'AIDS-related lymphomas' (ARL) – these generally have a worse outcome than non-HIV-related lymphomas.

'Highly active antiretroviral therapy' (HAART) has revolutionised the care of HIV-positive men and women by improving their survival and delaying the onset of AIDS and AIDS-related cancers – including lymphomas. Scientists looked at combining HAART with the chemotherapy regimen CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone). Rudolf Weiss, of the Specialist Practice for Haematology, Oncology and Infectious Diseases in Bremen, Germany, who led the study, treated 72 HIV patients who had ARL. He divided them into high-risk and standard-risk groups and treated both groups with combined chemotherapy and HAART adapted to the risk level. The study found that the combined therapy improved survival rates for patients with ARL and a standard level of risk to rates comparable to lymphoma patients who didn't have HIV and were treated with CHOP, and superior to previously published rates achieved by CHOP alone.

For standard-risk ARL patients, 79% achieved complete remission. By the end of the study, with 47 months' follow-up, more than 50% of patients had survived. Only 40% reported moderate drug toxicity. For high-risk ARL patients, only 29% achieved complete remission and median survival was only 7.2 months; 69% reported moderate toxicity.

The authors concluded that "The present study showed that our risk-adapted strategy for concomitant administration of HAART with CHOP is effective and safe."

■ Acquired immunodeficiency syndrome-related lymphoma: simultaneous treatment with combined cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and highly active antiretroviral therapy is safe and improves survival. Results of the German Multicenter Trial. R Weiss, P Mitrou, K Arasteh, et al. *Cancer* 1 April, 106:1560–1568

Thalidomide should be added to treatment for multiple myeloma

→ The Lancet

Adding thalidomide to the standard combination of drugs used to treat multiple myeloma in elderly patients could improve event-free survival, according to a randomised trial reported recently in *The Lancet*.

Multiple myeloma accounts for about 1% of all cancers diagnosed in Europe. Its incidence increases with age, and more than 80% of cases are diagnosed in people over 60 years old. Since 1960 oral melphalan and prednisone (MP) have been regarded as the standard of care in elderly multiple myeloma patients.

Thalidomide has shown some promise in previous clinical trials when combined with chemotherapy agents. The drug was originally developed to prevent morning sickness in pregnant women; tragically it caused birth defects in the unborn foetus. Researchers discovered that thalidomide interfered with the growth of blood vessels in foetal limbs and reasoned that thalidomide might also interfere with the growth of blood vessels in tumours.

In a trial involving 255 patients, Antonio Palumbo (University of Torino, Italy) and colleagues found that those treated with melphalan, prednisone, and thalidomide had higher response rates and longer event-free survival than those who were treated with MP alone. This benefit, however, must be balanced against increased rates of thrombosis, neurological toxic effects and infection, warn the authors.

Palumbo concludes, "After 50 years of unsuccessful attempts to find new and more effective treatment approaches suitable for most patients with myeloma, our results lend support to the use of thalidomide in the initial treatment of elderly patients with multiple myeloma."

In an accompanying comment, Shaji Kumar (Mayo Clinic, Rochester, USA) states that these results, combined with the preliminary results of a study in France, are enough to change clinical practice. He calls this an 'historic moment in myeloma therapy'.

■ Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma. A Palumbo, S Bringhen, T Caravita, et al. *The Lancet* 11 March, 367:825–831; Progress in the treatment of multiple myeloma. S Kumar, ibid, pp791–792

Patient treatment decisions may be influenced by media coverage

➜ JNCI

A study reported in the *Journal of the National Cancer Institute* has shown that the oral presentation of data from a single study at a national cancer conference changed patient treatment, even before the study's publication or approval by the US Food and Drug Administration (FDA).

The authors found that use of taxanes increased after the May 1998 annual meeting of the American Society of Clinical Oncology (ASCO). At the conference preliminary data were presented suggesting that the use of taxanes as adjuvant therapy could improve survival in women with lymph-node-positive breast cancer. The research was covered by key media, including the *New York Times, Wall Street Journal,* and *U.S. News and World Report.*

Researchers from the University of Texas MD Anderson Cancer Center set out to investigate the impact of the ASCO taxane presentation. One of the taxanes they looked at was the drug paclitaxel. This did not receive FDA approval for adjuvant breast cancer until October 1999, and the final study report was not published until 2003.

The researchers studied chemotherapy use in 3,341 women older than age 65, identified in the Surveillance, Epidemiology, and End Results Medicare database, who were diagnosed with stage 1–3 breast cancer between 1994 and 1999 and received adjuvant chemotherapy within 1 year of diagnosis.

The percentage of women receiving adjuvant chemotherapy who received taxanes such as paclitaxel remained at around 10% from 1994 to early 1998, and after early 1998 the rate of increase over time increased more than seven fold.

Rates of taxane use increased primarily in women with node-positive breast cancer in early 1998, and it also increased in women with node-negative breast cancer by the end of 1999, even though such women were not included in the taxane study.

The authors suggest that the increased use resulted from publicity at ASCO and consequent media coverage.

They caution that medical decisions based on premature data from a meeting presentation may pose a risk for patients who could be exposed to drugs that may have toxic effects before the drug's benefits have been definitively established.

The authors write, "Although in many ways this example represents a best-case scenario, in which the meeting report of a multicenter randomised trial turns out to have stimulated the adoption of a treatment that has eventually become part of evidence-based practice, it also illustrates the enormous power of highly publicised meeting presentations.

"Investigators should be aware of the potential impact of their presentations and exercise appropriate caution and judgement in their interpretation of research findings."

■ Impact of a scientific presentation on community treatment patterns for primary breast cancer. SH Giordano, Z Duan, Y-F Kuo, et al. *Journal of the National Cancer Institute* 15 March, 98:382–388

Treatment duration may be critical for best results in pre-leukaemia disease

➜ Cancer

According to a new study, longer courses of a mild form of chemotherapy may help patients with a pre-malignant form of leukaemia called myelodysplastic syndrome (MDS). Patients with MDS have been shown to benefit from a new DNA hypo-methylating agent: decitabine. Researchers, led by Michael Lubbert of the University of Freiburg Medical Centre, Germany, assessed the efficacy of retreating on relapse high-risk MDS patients who had already received initial treatment with the drug. Patients had a median of three further courses of decitabine, and 45% of patients responded, but had a poorer response than was shown after the first treatment. As a result of the study, researchers believe that longer initial treatments of decitabine may be more beneficial to patient outcome.

Ten out of 22 patients responded to decitabine when given an average of three courses of the drug. Three patients achieved a partial or complete response in red cells, white cells and platelets. The other seven patients experienced at least a 50% drop in blood transfusion requirements and higher cell counts in one or two of the blood cell lines. All patients had an average survival of 28 months. Patients who were retreated with decitabine had a median survival of 13 months after their relapse.

The authors conclude, "Results of the present analysis point to the importance of extending therapy with low-dose decitabine beyond the point of first response, and strongly support institution of a maintenance treatment."

■ Superiority of prolonged low-dose azanucleoside administration? Results of 5-Aza-2'-deoxycytidine retreatment in high-risk myelodysplasia patients. B Ruter, P Wijermans, M Lubbert, et al. *Cancer* doi: 10.1002/cncr, published online 13 March

Action is needed to safeguard cancer research in Europe

➜ British Medical Journal

Research looking at clinical trials has found a dramatic drop in the number of new trials undertaken since the EU clinical trials directive came into force in 2004. The clinical trials directive was intended to protect patients and improve research standards. But many investigators warned at the time that the labour-intensive, bureaucratic, and expensive endeavour of running a clinical trial would become worse under the new rules.

In particular, grant-funded academic researchers, who performed most cancer trials, raised concerns that their resources might not suffice to meet the requirements of the new directive.

An analysis of research undertaken since the directive was implemented suggests that many of those fears have been realised. For example, the number of new trials fell from 19 in 2004 to 7 in 2005 (a 63% decrease), and a third fewer patients were enrolled.

Simultaneously, trial costs increased by 85% and insurance costs from 70 mn to 140 mn euros. Trial initiation took about five months longer than in 2004, while paperwork and documentation increased.

Instead of benefiting patients, the analysis suggests that the directive has hindered their access to new treatments.

"Our own experiences are in accordance with these findings," say the authors Akseli Hemminki and Pirkko-Liisa Kellokumpu-Lehtinen, from Helsinki University Central Hospital and Tampere University Hospital, in Finland. The number of approved applications for both academic and company-sponsored cancer trials in Helsinki steadily decreased, from 120 in 2002 to 70 in 2005 (42% decrease), but the workload of the ethics committee increased.

These numbers seem to confirm the initial worries about the future of investigator-initiated clinical cancer research, conclude the authors, adding that new directives on clinical research are in preparation, and physicians, patients, universities, and politicians need to take action to ensure that academic research can continue in Europe.

■ Harmful impact of EU clinical trials directive. A Hemminki and P-L Kellokumpu-Lehtinen. *British Medical Journal* 4 March, 332:501–502

Advocates, clinicians and researchers call for action on breast cancer

➜ EBCC – Nice

Organisers of the European Breast Cancer Conference (EBCC) – Europa Donna (the European Breast Cancer Coalition), the European Organisation for Research and Treatment of Cancer (EORTC) and the European Society of Mastology (EUSOMA) – have issued a manifesto in order to highlight what needs to be done to support breast cancer research and improve patient outcomes. The Nice Manifesto highlights seven areas for action:

1. *Improve the number and quality of European screening programmes.* Population-based screening programmes carried out in accordance with EU guidelines for quality assurance in mammography screening help to detect early breast cancer and save lives. Increasing the number of screening programmes free at the point of access and improving their quality would save the lives of many European women. Women should be encouraged to participate in screening programmes.

2. *Support breast cancer research.* Independent academic research is under threat due to insufficient funding in many European countries. It is a driving force in improving our knowledge of cancer and developing tailored, potentially cost-saving therapies. Studies which answer important clinical questions and which have the potential to increase our knowledge of the biological and genetic basis of the disease should be given priority.

3. *Rethink the breast cancer staging system.* Researchers and clinicians should be creative in designing new quality-assured diagnostic and staging systems which improve prediction of outcome. The genetic make-up of the tumour, for instance, should be defined in greater detail to identify the natural history of the disease in each individual patient, and the likelihood of response to standard therapies and molecular targeted treatments.

4. *Define metastatic breast cancer guidelines.* Most women still die from metastatic breast cancer. The general criteria on how to manage metastatic breast cancer need to be defined. Specific guidelines can help the patient and the clinician make the right choice.

5. *Increase the number of breast care nurses.* In most European countries today there are no breast care nurses. Breast care nurses can improve the treatment and management of breast cancer for patients. Greater involvement will improve patient care and quality of life.

6. *Expand the Breast Unit accreditation process.* Breast units should be accredited to ensure that they meet guideline requirements for standardisation of best care. Accreditation guidelines for carrying this out should be developed not only by professionals, but also by patient advocacy groups. Women should have equity of access and the choice to select appropriate facilities for diagnosis and treatment and be sure they are getting gold standard care.

7. *Give recognition to the essential role played by charities in independent breast cancer research.*
Encourage those charities to realise the potential benefits of their effort for all European patients and to expand their work even further.

Cooperation on medicines regulation intensified

➜ European Medicines Agency

The European Commission, the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) have agreed to increase the degree to which they cooperate on different aspects of drug regulation. Under the EU–FDA confidentiality agreement, the two agencies are providing parallel scientific advice in order to facilitate the development of safe and effective medicines, as well as sharing information about pharmacovigilance so as to enhance patient safety. The agencies have agreed to intensify transatlantic cooperation in the area of medicinal products, with particular focus on vaccines (including preparedness for an influenza pandemic), medicines for children, medicines for rare diseases ('orphans'), oncology and pharmacogenomics.

HPV virus may cause skin cancer

➜ JNCI

A study published in the *Journal of the National Cancer Institute* has found that the human papilloma virus (HPV) may cause a common form of skin cancer known as squamous cell carcinoma (SCC).

HPVs are a group of more than 70 different types of virus. They are given numbers to distinguish them. Strains of the HPV virus have been associated with other epithelial cancers such as cervical cancer (particularly numbers 16, 18, 30 and 33) and oesophagus cancers. HPV types 5 and 8 have been detected in skin tumours and previous studies have suggested they may play a role in the development of these cancers. Several vaccines are in development to help prevent infection from the two most prevalent cancer-causing types of the human papilloma virus, HPV 16 and 18, which together are responsible for over 70% of cervical cancers.

Margaret Karagas, of Dartmouth Medical School, and colleagues searched for antibodies to 16 different HPV types in plasma samples from 252 patients with squamous cell carcinoma, 525 patients with basal cell carcinomas (BCC), and 461 control subjects.

The authors detected genus beta type HPV antibodies in patients diagnosed with SCC more frequently than in control subjects, particularly HPV 5. No difference was found in the presence of HPV antibodies in patients with BCC compared to control subjects.

The authors write, "Although sun exposure and sun sensitivity are the major risk factors for [skin] cancers, our data support a role of HPV, particularly beta HPVs, in the development of SCC."

It may be possible in the future to produce a vaccination that can help prevent some cases of squamous cell carcinoma.

■ Human papillomavirus infection and incidence of squamous cell and basal cell carcinomas of the skin. MR Karagas, HH Nelson, P Sehr, et al. *Journal of the National Cancer Institute* 15 March, 98:389–395

EMEA reveals names of scientific advisors

➜ European Medicines Agency

EMEA has published a new section on its website that provides an overview of the CHMP (Committee for Human Medicinal Products) working parties, scientific advisory groups and other groups. Scientific advisory groups provide advice in connection with the evaluation of specific types of medicinal products or treatments. They consist of European experts selected according to the particular expertise required, on the basis of nominations from the CHMP or EMEA.

The current members of the scientific advisory group for oncology are: Jonas Bergh, Lothar Bergmann, Steen Hansen, Michel Marty (Chair), José Maria Moraleda, Jan Schellens, John Smyth, Patrick Therasse and Allan van Oosterom (Vice Chair).

Breast cancer risk and HRT

➜ EBCC–Nice

Recent research from the 'million women study', presented at the European Breast Cancer Conference in Nice, found that taking hormone replacement therapy (HRT) increased the risk of some types of breast cancer, but not others. The research found that women who took HRT had an increased risk of developing lobular cancer (affecting the cells in the ducts of the milk-producing glands) and tubular cancer. There was not such an increased risk of developing ductal breast cancer, the most common type of breast cancer that affects the cells lining the milk duct. There was no increase in the risk of medullary breast cancer, a kind of cancer that is common in women with a genetic predisposition to breast cancer.

The study demonstrated that women who had taken combined HRT (oestrogen and progesterone) had an even greater risk of developing lobular and tubular breast cancer than women on oestrogen-only HRT. The researchers also discovered similar findings for women with breast cancer in situ – when the cancer has not spread to the surrounding tissues in the breast or other parts of the body. Women who took HRT had a significantly greater risk of developing lobular cancer in situ than ductal carcinoma in situ.

Gillian Reeves, who presented the findings, comments, "One possible explanation for the findings is that certain types of breast cancer are more likely than others to be hormone receptive. Further research into this topic could greatly help our understanding of the biological mechanisms underlying the development of breast cancer."

Breast tissue changes may cause pregnancy-associated breast cancer

➜ Nature Reviews Cancer

A study by scientists from The University of Colorado Cancer Center has found that pregnancy-associated breast cancer may be linked to changes in the breast, when the mammary gland regresses to its pre-pregnancy state.

Breast cancer associated with pregnancy has a poor prognosis, including an increased risk of metastases. Researchers found that late diagnosis and increased hormone production during pregnancy may not be sufficient to account for increased mortality. There is overwhelming evidence to suggest that pregnancy has a preventative effect on breast cancer. However, some studies indicate that pregnancy may cause a period of tumour promotion before it produces its protective effect. The short duration of increase in breast cancer following pregnancy was found to peak 6 years after pregnancy and to carry on approximately 10 years following childbirth. Breast cancer diagnosis during this period is referred to as pregnancy-associated breast cancer.

After pregnancy and lactation, the mammary gland that produces the milk regresses to its pre-pregnancy state by a tissue remodelling process. The Colorado researchers found that this remodelling, which is associated with pro-inflammatory and wound-healing mechanisms, may help tumour cells spread.

In healthy women, after pregnancy the mammary gland reverts to its pre-pregnancy state and pro-inflammatory pathways are activated, but the balance of pro- to anti-inflammatory signals leans towards preventing inflammation. The authors suggest that, in women with hidden breast tumours, this may aggravate the tumour-promoting micro-environment, by tipping the balance towards overt inflammation. Women with hidden disease after pregnancy might be at an increased risk of tumour cell dissemination. Pepper Schedin, author of the paper, states that, "Effective breast cancer screening in recently pregnant women is warranted immediately."

■ Pregnancy-associated breast cancer and metastasis. P Schedin. *Nature Reviews Cancer* 6:281–291

Teenagers more likely to survive cancer in countries with public health systems

➜ Teenage and Young Adult Cancer Medicine Conference

Countries that have national health services easily accessible to people of all ages are likely to have better survival rates for their teenagers and young adults (TYAs) with cancer than are countries where individuals have to pay for their own medical insurance.

This is the suggestion that arises from new research presented at the 4th International Conference on Teenage and Young Adult Cancer Medicine, in which the health care systems of the United States of America and Australia were compared.

Archie Bleyer, medical advisor at the Cancer Treatment Center, St Charles Medical Center, Bend, Oregon, told the conference that Australia's system of health insurance for all, regardless of age, meant that TYAs were more likely to survive cancer in Australia than they were in the USA.

"Our previous research has shown that the survival of older teenagers and young adults with cancer in the United States has lagged behind progress in younger and older patients. We found that diagnosis was delayed in TYAs who either lacked health insurance or had inadequate insurance, and therefore this lack of progress might be due to the USA health care system, and less expected in countries with national health insurance.

"During the past year we compared survival of TYAs in the USA with those in Australia, a country similar in many demographics to the USA, but with health insurance provided to all citizens regardless of age.

"From 1982 to 1998, the rate of improvement in the 5-year survival from invasive cancer in Australia exceeded that which occurred in the USA, such that by the late 1990s, TYAs in Australia had an overall 5-year cancer survival that was higher than in the USA. The deficit begins at 16 and ends at 55, the same years that national health insurance is not available in the USA. It ranges from 5% for 18 to 25 year-olds to 12% for those aged 30 to 35. This difference suggests that the health care system in Australia, with universal health insurance, was able to provide better cancer care to its TYAs.

"The advantage for Australian TYAs was not apparent in their children or older adults with cancer. This suggests that the need for private health insurance in the USA is responsible for the worse survival of TYAs, in that children and older adults in the USA are more adequately insured than TYAs."

Global pharmaceutical market grew 7% in 2005

➜ IMS Health

New data released by *IMS Health* show that in 2005 global pharmaceutical sales grew 7% to $602 billion. North America accounted for 47% of global sales, while only 30% of sales were in Europe, probably reflecting the strict cost-containment measures adopted by European governments.

There was an 18.6% increase in sales of anti-cancer drugs (cytostatics), with global sales of $28.5 billion. For the first time cancer drug sales overtook anti-ulcerants, and now cancer drugs rank as the second biggest sellers after cholesterol-lowering agents.

In 2005, more than 2,300 products were in clinical development, up 31% percent over the past three years. Ninety-six oncology products are now in Phase III clinical trials or pre-approval stage.

Nurses show the way

➜ Raphaël Brenner

Palliative nursing care is playing an increasingly vital role in providing hope, comfort and solace to seriously sick patients. Much can be learnt from the integrative, humane approach shown in this book.

Nurses were the first to respond to the challenge of palliative care – a discipline born at the end of the '60s at the initiative of the late Dame Cicely Saunders* (a British nurse, social worker and physician). Saunders always saw nurses as the lynch pin for palliative care, writing, in the foreword to the 1st edition of this book (2001), that they "remain the core of the personal and professional drive to enable people to find relief, support and meaning at the end of their lives."

With 67 chapters, organised in 10 parts, the new edition is intended to be a comprehensive resource for nurses in the emerging field of palliative care. "The approach has been to incorporate the principles of palliative care nursing throughout the course of a chronic, progressive, incurable disease rather than only at the end of life," writes Nessa Coyle.

Part I provides a general introduction to palliative nursing care, with an extensive, excellent chapter on communication – this being the cornerstone of end-of-life care.

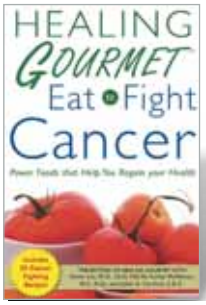
Part II covers the critical area of symptom assessment and management, without omitting subjects such as fatigue, sexuality and complementary/alternative therapies. Part III addresses psychosocial support and Part IV spiritual support, which includes a chapter on "meaning in illness". Further sections cover special patient populations (the poor, homeless, etc.), end-of-life care in various areas (home care, palliative chemotherapy and clinical trials in advanced cancer), paediatric palliative care, which includes a chapter on end-of-life decision-making in paediatric oncology, special issues for nurses working in end-of-life care (ethics, research) and innovative community projects.

Textbook of Palliative Nursing
2nd edition
Edited by Betty R Ferrell and Nessa Coyle
Oxford University Press,
1268 pp, £60 (hardback)

Beyond this, the book has several unique features. The content of each chapter is illustrated at the top by a quote from a patient or family member and case examples are used to anchor the theoretical and practical content in real-life situations. One finds, for example, a narrative on dying based on a spouse's perspective. The book also goes beyond the biological model of cancer to illustrate that cancer is an illness with panoramic social and psychological ramifications rather than just an organ-based disease. "You have to treat a person like a whole person, not like a textbook," says the daughter of a patient, and indeed palliative care nursing reflects a holistic philosophy where the patient and family comprise the unit of care.

I do not remember being moved by a textbook before, but I found this beautiful book moving, because of its humanity, its sensitivity towards the other, and its empathy with the loneliness of human beings when confronted with serious illness. The book has the courage to deal with the complexities of life and to look at the sick as unique individuals. This is a model of what a medical book should be: science-based but always in touch with the men and women we call patients. Physicians should definitely take a leaf out of this exemplary book.

* *Cicely Saunders: Selected Writings 1958-2004* has just been published by OUP



Healing Gourmet, Eat to Fight Cancer
Edited by the editors of Healing Gourmet with Simin Liu, Kathy McManus and John A Carlino
McGraw-Hill, 304 pp, £9.99

Can eating grilled fruit kebabs or triple crucifer soup really help us to fight cancer? The authors of this book say 'yes', and in their book they explain the cancer–diet connection, advise on how to select the right fats and carbohydrates to stave off cancer, and list the foods, herbs and spices which they consider to be healthy nutrients. The book also describes numerous cancer-preventing meals and mouthwatering recipes that are supposed to help fight cancer as well as offset the side-effects of treatment. A wealth of scientific references are included in every chapter to support the main thesis, and the studies selected, naturally, tend to prove the preventive influence of diet on cancer. But just as with the connection between stress and cancer, actual proof is contradictory. The public, however, is very eager for answers, even if the answers are not definitive. Preventing and fighting cancer through sound nutritional principles is therefore a popular notion, even if not always sustained by evidence-based medicine. The fibre hypothesis, which claims that high-fibre foods help prevent cancer, has enormous appeal, even though a study by the US National Cancer Institute found no effect of fibre on colon polyps. The very recent publication of the results of the Women's Health Initiative Dietary Modification Prevention Study – the largest randomised controlled clinical trial ever carried out on diet and breast cancer – did show that a reduction in dietary fats and an increased intake of fruits, grains and vegetables has a small impact on invasive breast cancer in some women after an average of eight years. But according to the authors of the study, "the health implications of a low-fat dietary pattern may take years to be fully realized." Many other studies will be needed in order to obtain clearer proof of the complex link between cancer and diet. Until then, most would agree that the dietary recommendations put forward in this book are not harmful and may help protect against heart disease, even if they have no significant effect on cancer.

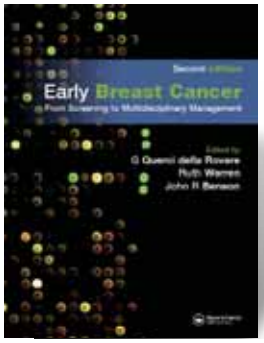
Comment une cellule devient-elle cancéreuse?
Moshe Yaniv and Nicolas Martin
Le Bord de l'eau (coll. K)
72 pp, euro 10

The text of this book is based on a lecture given by Moshe Yaniv, head of the Department of Genetic Expression and Diseases at the Pasteur Institute in Paris, and provides an excellent explanation for patients of how a cell becomes cancerous. The authors display a vigorous prose style and a gift for clear explanation. They include a wealth of explanatory notes, inserted in the text itself, to clarify technical terms. Thus, without betraying the complexity of a multi-stage process about which much remains unknown, they offer a scholarly and balanced review of the advances made in carcinogenesis. These advances are already pointing the way to new methods of treatment.

Lymphome
Neue Erkentnisse und Therapiestrategien
Edited by Wolfgang Hiddeman, Martin Dreyling and Harald Stein
Thieme, 240 pp, euro 79.95

This fully illustrated book, with contributions by 21 authors, offers a comprehensive review of all lymphoproliferative malignancies (Hodgkin's disease, large B-cell lymphoma, mantle cell lymphoma, gastric lymphoma, etc.). Lymphomas have increased in incidence faster than any other haematological malignant disease in the last decades. Concomitantly, significant advances have been achieved in this field: for

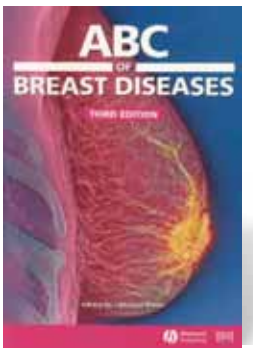
the first time, we now have an internationally recognised classification of lymphoma subtypes and, in therapeutics, the use of monoclonal antibodies and intensive sequential chemotherapy followed by stem cell transplantation is already well established. This useful book very clearly delineates the main points general practitioners and specialists need to know in order to keep abreast of new developments in the classification, diagnosis and treatment of lymphomas.



Early Breast Cancer: from Screening to Multidisciplinary Management
2nd edition
Edited by Guidubaldo Querci della Rovere, Ruth Warren and John R Benson
Taylor & Francis
504 pp, £140.00, (hardback)

ABC of Breast Diseases
3rd edition
Edited by J Michael Dixon
Blackwell Publishing/BMJ Books
120 pp, £24.95

Despite the modest decrease in mortality rates over the last 20 years, the incidence of breast cancer continues to rise in Western societies. Even with the impact of the molecular biology approach to cancer, which will soon be felt in diagnostics, prognostics and tailored therapies, recent evidence shows that breast cancer is an exceedingly complex, enigmatic phenomenon that cannot be viewed as a single disease. In light of the increase in early diagnoses, *Early Breast Cancer* is a welcome book. It provides a clear account of the subject and imparts to established practitioners, trainees in breast cancer and other healthcare professionals a solid understanding, from epidemiology, genetics and screening, to pathology, diagnosis, treatment and prevention. The book sheds light on the innumerable problems of early breast cancer, without eschewing controversial areas. The issue of genetic testing is particularly well discussed, providing useful references, and there is an extensive section on screening, with an interesting chapter on the biological basis for screening, and an extensive section on breast imaging.



Therapeutic aspects are grouped together in a section titled 'Multidisciplinary management of BC'. The Anglo-Italian authors stress that breast cancer must be treated by specialised breast teams but, alas, except for a few lines on the psychological effects of screening and on the need to give support when breaking bad news, they almost completely ignore the human and psychological side of breast cancer. This omission is all the more worrying given the wealth of technical detail and information provided on subjects such as advanced breast biopsy instrumentation or informed consent in the management and research of breast cancer. What about the women themselves, who are forced to undertake a life-changing journey as a result of being diagnosed with breast cancer?

The distress and anxiety provoked by such a diagnosis, as well as other psychosocial issues, are not forgotten in Dixon's book. As the title suggests, this is a book that targets a wide readership, catering to general practitioners, nurses, trainee oncologists and medical students alike. Its all-British line-up of authors deserve praise for succeeding in writing an up-to-date, concise, clear, superbly illustrated (pictures, tables and diagrams), evidence-based work that covers all the various aspects of breast cancer (including breast reconstruction, male breast cancer etc.), as well as benign breast conditions.

They are also to be commended for their balanced, nuanced account of breast cancer. They describe what "we think we know and understand" as well as the challenges, uncertainties and unknowns of breast diseases. The book provides a thorough overview of adjuvant therapy (including the new aromatase inhibitor trials) and metastatic breast cancer, as well as excellent chapters on the systemic treatment of primary operable breast cancer (with reference to ongoing trials) and on clinical trials on the management of early breast cancer. Highly recommended for all non-specialists interested in this topic.