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Clifton Leaf

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SPECIAL REPORT ON ESO'S 25TH ANNIVERSARY MEDIA FORUM

Clifton Leaf:

asking the difficult questions

Marc Beishon

Clifton Leaf sparked a lively public debate with a hard-hitting cover story for *Fortune* magazine, which asserted that America's 'war on cancer' is being lost. He calls on the cancer research community to show stronger leadership, increased cooperation, better focus and, above all, greater honesty about its successes and its shortcomings.

Few people outside the US will have heard of journalist Clifton Leaf and his crusade to challenge the cancer establishment on its lack of progress since president Richard Nixon launched America's 'war on cancer' in 1971. Those who have seen his lengthy cover story in *Fortune* magazine in 2004 – in which he takes a first shot at exposing what he sees as a dysfunctional, indeed 'broken', cancer research system – may have dismissed it as a local dispute between a business writer and the mandarins in charge of American research budgets. That would be to miss some of the toughest questions yet asked of the cancer community, which have ramifications worldwide not only for basic science researchers, but also for clinicians, advocates, regulators and politicians.

After looking at the raw data – the 'balance sheet' of the American cancer world – as only a financial writer could, Leaf's initial rosy view of the 'bang per buck' the country was getting from its investment turned to outrage when he discovered the true story that mortality statistics were telling.

"I found there were two stories being told," he says. "One was the patients' story – often heroic and very moving, told through advocacy organisations that were clamouring for more money to step up efforts to fight cancer. The other story came from the scientific echelons of cancer – that they had discovered the holy grail with targeted therapies and the genetic underpinnings of the disease. That's all I heard – and not that we were making little significant progress and were actually losing the war."

Leaf initially unpicked some of the issues he believes are undermining the research effort. He looked at why those wonder drugs widely hyped then – Avastin, Erbitux, Herceptin and even Glivec – were not going to make much of a dent in the mortality rates, and working back, how the research community is set up to tackle relatively small parts of the biology of cancer, expending most of its effort to catalogue ever smaller components of individual signalling pathways while paying little heed to the dynamic interplay between them. He found an emphasis on developing drugs that may hold up tumour progression but do not actually address metastasis, and asked why much more effort is not being placed on carcinogenesis, screening and prevention.

In doing so, he scratched the surface of the structures and vested interests that he sees as obscuring

LUIGI INNAMORATI

"People run miles and miles for cancer, but we have not harnessed this human power into political will"

the big picture, including the way research grants are awarded in the US, the methodology and regulations associated with clinical trials, and the ownership of intellectual property. In true investigative style, Leaf has since 'followed the money' to find out why these and other 'establishment' issues have led to what he sees as such poor outcomes.

The phrase he uses to summarise the situation – "All the incentives are misaligned with the goals" – sounds like business speak, but as he explains, the ultimate goal is defeating cancer – and it just will not happen as long as researchers are being directed down the wrong tracks.

Among the top concerns are intellectual property (IP) and the infrastructure in which researchers currently work. "We have let IP rules run amok and allowed ownership of even gene data, which has prevented much basic and clinical research from being done. And we have pushed drug costs up to astronomical levels – there is no reason why they should be so much more expensive than in the past, save for the IP rules. We are granting patents to universities for the knowledge gained from taxpayer-funded work. And they turn around and sell this knowledge exclusively to developers who, by virtue of their monopolies, rack up the prices."

Leaf extends his point to information sharing across the board, noting an often glacial speed for new drugs and techniques to become widely used, and a cultural resistance in any case to new ideas among the medical community. In the US, he is struck by the lack of a national biospecimen network. "We have a plethora of freezers with millions of specimens but no way of knowing what's inside of them."

There is a project looking at such a national tumour network, led by the National Cancer Institute, but as Leaf adds: "It's not getting the money or push it needs. We don't really have centralised leadership in the US – the NCI has historically been more like a cash machine, doling out money to the comprehensive cancer centres and research institutions, and the cooperative groups that control the clinical trials apparatus – this is where the real power lies. They are the plutocrats and are resistant to anything that will take away their power.

"It has shocked me that we don't have the political will to force change in this culture. For all the people running miles and miles to raise money for cancer, we have not yet harnessed this human power into political will, and I find that amazing."

Leaf's critique so far has focused mainly on America, but of course nearly all involved with cancer abroad look to the US. No other country has as many top clinical and research centres, and if the NCI is coming in for some criticism, Europe has not even the germ of a cross-border institution that could be its rival, and European efforts are seen as even more fragmented. As Leaf adds, since 2004 he has travelled extensively both home and abroad, and it is clear that not only must the US reform its cancer infrastructure, it must also tackle its traditional insularity and collaborate much more widely internationally.

In short, Leaf is asking people in what he calls the 'cancer culture' to become much more honest about these shortcomings, from the true mortality statistics to the systemic dysfunctions. Indeed, if he has one watch word for the future it is 'honesty' – in the same way that the movers and shakers on Wall Street, the City of London and the other financial centres have had to confront deep flaws in public reporting and decision making – and are still having to do so – cancer will also need root and branch reform in reporting progress and investing wisely.

In researching the cancer culture, Leaf has made some extraordinary connections with people in the community, including the heads of the major cancer centres such as MD Anderson and Dana-Farber, directors of advocacy organisations such as Susan G Komen for the Cure, where he is now on the board, and most appositely, from his investigative standpoint, the visionary – even maverick – researchers and clinicians who he feels have shaped most progress in the cancer battle.

Critical press. These articles cover many of the issues that Leaf believes are obstacles to progress: fragmentation and poor leadership in the cancer research community, the privatisation of knowledge generated in public institutions and an excessively risk-averse attitude towards potentially life-saving drugs

The momentum of all this analysis and advocacy has now totally changed Leaf's professional life. Last year he left *Fortune* to carry on his advocacy work full time, and to complete a book (with publisher Alfred A. Knopf), which the magazine had kindly given him a year's start to write. The book will be his major contribution to date on where we are in the cancer war, and he promises it will be no sterile rehash of the many political and structural issues he's uncovered so far, but rather a much more lively – and optimistic – story based on his many conversations with those he sees as contributing most.

Leaf is himself a cancer survivor, which outwardly has played little part in his arrival in the cancer world. He was diagnosed with Hodgkin's disease as a teenager in the 1970s and was cured thanks to a 'brutal' experimental protocol involving MOPP, the first combination of chemotherapy drugs to treat the condition successfully. Treated at the NCI by among others Bruce Chabner – now at Harvard and one of Leaf's insightful sources on the American research enterprise – he was subjected to a ping-pong regime of chemotherapy, alternating with radiotherapy, which caused much sickness but effected a cure, at the expense of his thyroid gland, removed after accidental irradiation.

"Undoubtedly, much progress has been made across many fronts, from nausea control to vastly improved cancer care, not least for children, to societal acceptance of the disease," says Leaf. "When I was treated it was after the Three Mile Island nuclear power plant accident – some of my schoolfriends were uneasy about coming near me."

But his own experience, and subsequent revisiting of how cancer has been tackled since then, does reveal a striking difference. "We were more willing to build up experimental knowledge quickly and inch forward – in the early history of childhood leukaemia there were rapid-fire protocols and little to get in the way such as review boards and other regulatory hurdles, and political turf battles between the cooperative groups that run clinical trials. It was more seat-of-the-pants experimenting rather than preoccupation with safety, size and statistical significance."

There is a strong element of impatience in Leaf's writing and talks – an urge to cut through what he

"It was more seat-of-the-pants experimenting than preoccupation with safety, size and statistical significance"

"All the talk of increased survival wasn't being reflected in the death certificates"

calls sclerotic and slow processes. This is partly a result of his background in business journalism.

Leaf cut his journalistic teeth on health, fitness and women's magazines, while nurturing dreams of being a novelist, before finding a niche at a personal finance title, *Smart Money*. "That's when I finally thought I'd got a career and was able to write long articles with an element of story telling." A call from *Fortune* came, and he moved in 2000 to become its Wall Street editor, just before the infamous 'dotcom' crash. *Fortune* had long had a reputation for investigative journalism, and Leaf himself wrote a cover story on how corporate thieves were getting away with their crimes. "I wrote about the need to treat white collar criminals with the same severity as any thief."

When he had a chance to meet Dan Vasella, CEO of Glivec developer Novartis, he wasn't very interested at first. "But it developed into an extraordinary conversation about the passions of chief executives and our mutual experiences with people who had died of cancer. I ended up writing very favourably about him and his book – *Magic Cancer Bullet*. I thought, here was an amazing targeted medicine that could stop cancer in its tracks."

That prompted a further article on the evolution of cancer treatment. "I began by looking at what you might call the 'financial statements' of our anti-cancer campaign. One thing we financial journalists are trained to do is to look at the numbers." He soon found official indicators on mortality, incidence, survival, and what was being spent each year on treatment. "The cancer establishment was saying great progress was being made, and yet, here were the data: all the trendlines had been heading the wrong way for decades." That's when alarm bells started to go off for Leaf. "It was the kind of spin I'd heard for years in the corporate world, with chief executives telling you their businesses were in terrific shape just before declaring bankruptcy."

It's worth revisiting the mortality position, as recent US figures continue to make headlines such as 'Cancer on the run', while the country's survival figures are said to be well ahead of most of western Europe. When Leaf first looked at the data he soon found that there had been little progress in reducing the number of life years lost through cancer compared with other conditions such as heart disease, from 1980 to 2002. "All the talk of increased survival wasn't being reflected in the death certificates," he says, and the cost of treatment was "outrageous" in terms of outcomes.

The latest figures put out by the American Cancer Society indicate a 'doubling' of the rate of mortality decline, but Leaf points out that such declines as have taken place are largely down to just one tumour – colorectal cancer, particularly among men. While some other cancers such as lung have gone down, again among men, others have gone up. "But this murkiness allows the American cancer leadership to boast about declining deaths in a number of specific cancers while ignoring the rest. Of course, the reductions in colorectal and lung cancers are mostly attributable to screening and lower smoking rates – not to the billions of dollars we've spent on cancer science and drug development."

Breast cancer – where much effort has gone on targeted therapies – shows very little decline in mortality, adds Leaf. About 40,000 women have been dying each year in the US since 1987.

Leaf has focused on drugs a good deal, led by both the cancer community's emphasis on the promised land of targeted therapies and his observation of the lack of progress in treating advanced disease.

"The vast majority of research grants and drugs are not aimed at combating what actually kills people"

An oft-mentioned point he makes is that the vast majority of research grants and drugs are simply not aimed at combating what actually kills people.

"I went to see Harold Varmus – he's head of Memorial Sloan-Kettering and was previously director of the NCI, and of course is a Nobel Laureate for his work on oncogenes. His line is that it is a miracle we have come so far and that the problems would go away with the targeted paradigm, as demonstrated by Glivec, and by having several therapies working in concert for more complex cancers. I'm not one to call a Nobel Laureate naïve but, given what is known about the diversity and evolution of tumour cell populations, genomic instability, drug resistance and so on, I feel these phenomenally expensive drugs are missing the mark."

After a nerve-wracking plenary talk at the American Association of Cancer Research annual meeting – in front of several thousand people – Leaf started to receive calls from researchers such as Judah Folkman, the 'founder' of angiogenesis, and met other scientists working on the edges of cancer science. "Angiogenesis is a critical idea – that tumour cells send out signals to recruit blood vessels – but postdocs were told to stay out of Folkman's lab by those who said that he was 'crazy'. The same was true of Mina Bissell and her work on the micro-environment surrounding breast cancer, and Howard Temin, who challenged the molecular biologists' dogma with reverse transcription, turning RNA back to DNA, which has become crucial for understanding the genetic basis of cancer."

He has forged a particularly close association with Michael Sporn, at Dartmouth Medical School, an expert in chemoprevention (indeed he is said to have coined the term). It is from Sporn and others in his camp that Leaf has formed his views about the need to intervene much earlier in the cancer process, and they have shed light on where research priorities are going astray, especially the emphasis on trying to tackle genetically unstable, advanced tumours.

Working back, Leaf has now looked at the way researchers are channelled into the cancer orthodoxy through the many hoops needed to get grants, which he says in the US seem almost designed to iron out innovation. And academic knowledge that is generated is hamstrung by a culture that is slow to share on national and international stages, and which ties findings and tools up with complex contracts and licensing agreements before they can be exchanged among centres. As he wrote in a subsequent *Fortune* article, "Imagine a carpenter having to pay Black & Decker a percentage of every kitchen he builds." A vivid cancer example he cites is the race to find the BRCA1 and BRCA2 genes implicated in breast cancer where, despite a collaborative effort, a patent for testing now resides with one company founded by the 'winner' – though the company was denied a similar patent in Europe.

"People are starting to realise that the IP issue is paralysing academic exchange – we need a universal agreement for knowledge transfer, not each institution having its own." Publishing is another bugbear – Leaf reckons that a huge amount of information from diverse sources such as symposia is not finding its way into the public domain, let alone into a common database, and he is a firm advocate of open source journals. "One reason many old medicines are only now coming to the clinic for the first time is a failure of our information systems," he says.

That feeds into another theme he's majored on – a view that we are being far too cautious in drug testing, erring on the side of safety at all costs. Rather than

Still friends. Leaf in the bosom of the cancer establishment, at a dinner sponsored by the Friends of Cancer Research, where he was presented with a Leadership Award. Left to right: Ellen Sigal (FOCR co-chair), Lester Crawford (then acting Commissioner of the FDA), Anna Barker (NCI deputy director), Leaf, Marlene Malek (FOCR co-chair), Andrew von Eschenbach, (then director of the NCI, now commissioner of the FDA), Janet Woodcock (deputy commissioner of the FDA)

"Imagine a carpenter having to pay Black & Decker a percentage of every kitchen he builds"

"Leaf is not surprisingly a great fan of advocacy groups and is now an active member in the movement"

At home. With wife Alicia Slimmer and daughter Sofia

balancing risks by including the risk of doing nothing, experiences with now-withdrawn drugs such as Vioxx have led to even more caution, he contends, and the protracted processes in the current clinical trials structure are exacerbating delays. Leaf places the blame on regulators (in particular the US Federal Drug Administration) and the pharmaceutical companies, which have essentially created a privatised clinical trials system, where the commercial sponsors call the shots in pushing for positive results above other findings.

"We have been promised early sight of the results, good and bad, on an easily accessible website, which would help identify more quickly what drugs are working and what the toxicities are," he says. This is not yet a reality. "The other problem we have is testing drugs in combination. We know the answer is likely to lie in chemotherapeutic cocktails. But the regulations – and the unwillingness of companies to add to their financial risk – make it all but impossible to explore the possible synergies of drug combinations until each agent has been approved. Trouble is, once a new drug is approved for sale, there's often little incentive for the maker to explore novel combinations." The result, he says, is years and years of unnecessary delay.

As for the most effective agents of change, Leaf is not surprisingly a great fan of advocacy organisations, and is now an active member in the movement through his board position at Susan G Komen, although he is keen not to single it out (it is though probably one of the world's biggest, having raised over $1 billion, mostly for breast cancer). He points out that the charities have addressed successfully many grassroots issues such as the quality of mammography, and are now extending their reach to the key infrastructure problems, such as the 'tissue issue' (the lack of a biospecimen network), channelling research funds in the right direction, tackling health inequalities, and in Susan G Komen's case, running international programmes in areas such as the Middle East.

He speaks highly of Kathy Giusti – founder of the Multiple Myeloma Research Foundation – as a role model for knowing how to bring disparate groups together and in rejecting proposals that do not meet a tough research agenda. Mike Milken – the junk bond trader who went to jail – has done much more useful work founding the Prostate Cancer Foundation, which Leaf says has similarly brought this disease into greater focus. He knows most of the top advocates and high-profile survivors, such as Lance Armstrong (of whom he is an enormous fan), from a cancer tour where he has met more than 2,000 players, and he has been honoured with a string of awards.

He has even given a talk at the NCI's 'Grand Rounds' event, calling for a Google-like search engine for biomedical research data, and presented at the President's Cancer Panel, on research barriers. And despite being a staunch capitalist in most respects he sees healthcare as fundamentally different, and reckons a Democrat as the next US President will pave the way for much needed reforms such as better insurance coverage, and hopefully changes in cancer research. "The American Cancer Society has moved all its marketing budget to push for universal health-

care in the US – it's one of the most exciting things I've seen it do," he notes.

What is striking about Leaf is that he has engaged the great and the good in cancer without alienating them. As he points out, nearly all have one or more big issues that concern them: "These usually emerge after 40 minutes or so in an interview and they often disagree with others." Perhaps the best indicator of Leaf's impact comes from John Mendelsohn, president of MD Anderson, who not only wanted to meet Leaf after his *Fortune* article, but wrote an extensive reply, describing what he had got right and wrong.

On the credit side, Mendelsohn agrees with Leaf's key points about the funding favouring smaller research projects, the slow speed of clinical trials and the role of intellectual property. "There is no question that IP gets in the way." But he points out that running research centres is very costly. It was also right to challenge the use of animal models, a lack of translational research, and progress in biomarkers and early detection, but there is significant work in these areas. On the minus side, he considered the effort in understanding the molecular basis of cancer and carrying out basic science to be crucial; that treating chronic disease and not effecting a cure is important (and also done with conditions such as heart disease); and that generally it is unfair to compare the cancer effort with putting a man on the moon.

The advocacy organisations have taken Leaf to heart and agree with most of his views. Nancy Brinker, founder of Susan G Komen, says above all he has given them professional access to the media and a powerful voice, "taking no prisoners" and fostering provocative thinking, "even if some of his ideas are not practical". Virgil Simons, head of The Prostate Net, says he has 'mainstreamed' the issue of healthcare costs, and tried to break down the elitism in the research community and the derivative nature of much research that is funded.

Leaf lives in Brooklyn, New York, with his wife Alicia, who is a filmmaker, and young daughter Sofia. Travel has become the family hobby – and he says he'd like to live for a spell in Europe, which could make Eurocrats in healthcare a bit nervous.

Journalists hate being the centre of a story – Leaf was reluctant to say anything about his own cancer when writing the first *Fortune* article. Now that he has become well known in the US as an advocate he is surely more comfortable having left the cosy fold of the magazine to be an independent operator, wearing several 'hats'. Despite his criticisms of the establishment, Leaf says he is an optimist by nature, and is sure that much of what's broken will be fixed, and there will be a move towards earlier intervention. But he certainly does not believe there will be the kind of breakthroughs by 2015 that luminaries were still predicting in response to his article. There is also a view among some in the upper echelons that the *Fortune* article is now history, despite being written only in 2004. But Leaf maintains there has been little substantial change and he is not letting up.

"My strength, if I have one, is in knowing how little I do know about the science and being willing to ask dumb questions," he says. "I'm not afraid to ask people about what progress there has been in the cancer battle – and it is surprising how often the experts have difficulty in explaining where we are." His vision of how science should be done to clarify the position – researchers quickly building on the parcels of knowledge generated by others in an open market – is certainly benefiting from someone who's knocked on more doors, ruffled more feathers and generated more wake-up calls than probably anyone has in such a short time in cancer.

As Frank Torti, director of the comprehensive cancer centre at Wake Forest University, says: "He asks tough questions. He disarms others with his straight talk and clear thinking. Before Cliff, there was no discussion, no energy and no challenge to the status quo."

The views of leading players from cancer research, policy making, regulatory bodies, industry and patient advocacy regarding many of the issues raised by Leaf are presented in Grandround, p 22, which reports on a media event, Time for a Reality Check, organised by the European School of Oncology to promote public debate on how to make faster progress against cancer

"My strength is in knowing how little I do know about the science and being willing to ask dumb questions"

Men's health matters too

Kathy Redmond ■ EDITOR

Europe's women are much more likely to survive a cancer diagnosis than their male counterparts. According to EUROCARE-4, after adjusting for age and case mix, 54.6% of the women diagnosed between 1995 and 1999 survived for at least five years, but only 44.8% of men. The gap is the more worrying because, while differences in survival rates between countries have shown a welcome decrease since EUROCARE-3 (patients diagnosed 1990–1994), the gender gap has remained exactly the same, at 11.4 percentage points.

Perhaps we should not be surprised. The between-country data from EUROCARE-3 was effectively used to pressure governments to take action to improve their performance. The data on the survival gap between men and women, in contrast, barely merited comment. Publication of the EUROCARE-4 results last August offered a second chance to draw attention to this major disparity – but yet again it seems to have passed unnoticed. Why is this? Is there an assumption that nothing can be done? Or is it simply not seen as a priority?

Evidence that might explain the gender survival gap is patchy at best. Differences in tumour biology or host defence mechanisms may work against men; women may be diagnosed earlier or treated better. SEER data from the US show similar five-year survival rates between men and women – 64.6% for men and 65.2% for women – suggesting that biology may not play the major role here. Issues surrounding delays in presentation, however, are attracting increasing interest among the small but growing band of European researchers specialising in men's health. Men are known to be less likely to engage in self-examination, and less able to recognise cancer warning signs. They are also more likely to delay reporting symptoms. Part of this may be social pressures – macho men don't seek help. It could also be that women are simply more used to going to the doctor – for themselves or their children – and are more used to discussing intimate health concerns.

It seems ironic that, while women's health outcomes are so much better than men's, women's health issues receive so much more attention. It is time to change this in cancer, and more coherent policies on tackling cancer in men are required. The UK's Men's Health Forum has taken a lead in flagging up how this might be done (http://tinyurl.com/32eoy9).

Finding better ways to communicate with men could help raise awareness of cancer warning signs. Finding the right settings to offer them advice and health checks could also make a difference. An examination of practices in countries with little or no survival gap between the sexes would help throw light on what works well.

Above all, the European cancer community must state clearly that this gender gap is not acceptable, and action is needed to end it.

No trials about us without us!

Patient advocates demand a seat at the table

➜ Peter McIntyre

Patients are not scientists. But given the chance, they can help clinical researchers design trials that patients want to join and stay with, and that answer questions they care about. They want the culture of the consent form to be replaced by a genuine partnership between researchers and patients.

Researchers design clinical trials to answer scientific questions. But patients who have a life-threatening disease join those trials in the human hope of a cure, better treatment or better quality of life. Patient groups are now asserting their right to be consulted at an early stage so their perspectives can help inform the aims, design, practice and reporting of clinical trials. They also want better access to information about trials that they might want to join.

At ECCO 14 in Barcelona, Lex Eggermont, incoming president of the rebranded European CanCer Organisation (ECCO), spoke out in favour of patient involvement, telling the Patient Forum that patients who are well informed and well prepared will be more likely to want to take part, and can make research more relevant.

However, many cancer researchers continue to treat patients as little more than an input into a scientific exercise.

A PLACE AT THE TABLE

Lia Van Ginneken-Noordman, from the European Myeloma Platform and an advocate for patients with multiple myeloma and Waldenström's macroglobulinaemia in the Netherlands, says, "Patients have a right to be more involved, because it is their disease. Patients should know the aims of the clinical trial, the expected outcome, and for whose benefit the trial is being done. Is it for the benefit of the patient or the researchers or the pharmaceutical company?"

On the other side of the Atlantic, her point is echoed by Norman Scherzer, chief executive of Life Raft, a patient group for people with gastrointestinal stromal tumours (GIST). "Cancer patients enter clinical trials because there are usually no alternatives in terms of effective treatment. The other players in the clinical trial process, although they are looking to be helpful and none means the patients harm, have a different agenda. "The pharmaceutical people want to see if they can bring this drug to market. The focus of the researcher is to conclude the research in a successful way, even if to do so might not be best for certain patients. It is my belief that only a patient group can bring to the table the objectivity needed to put the interests of the patient first.

"The question for those of us representing the patient is, can we even get into the room where decisions are made? The answer is no. Yet it is we and the people we represent who will be subject to whatever risks are involved in this trial."

CAN YOU JOIN A TRIAL?

The first, and possibly biggest, risk is that patients do not find out which trials they might join, and what the benefits might be. Without better information, patients can never be equal partners in research.

The European Cancer Patients Coalition (ECPC), which represents

250 patient organisations across the European Union, has been campaigning since 2003 for better access to information under its slogan, "nothing about us, without us!"

Jan Geissler, vice-president of ECPC, points out that participating in trials can bring significant benefits to patients. For example, phase 1 trials, which are only open to cancer patients who have failed previous therapies, benefit just over 10% of the patients who take part. Phase IV trials, looking at long-term risks and optimisation of effective therapies, make it more likely that resistance to treatment or progression of the disease will be detected earlier.

But, speaking at the ECCO conference in Barcelona, Geissler said that some doctors are ill-informed or unwilling to enrol patients, while a culture of secrecy is enforced by pharma companies. The results of 6 out of 10 clinical trials are never published, while only half report their methodological details adequately. Registration of trials is still poor, especially phase I and II cancer trials, leading to duplication of research and a lack of transparency.

The WHO launched its International Clinical Trials Registry Platform in May 2007, to give clinicians and patients better access to information. This is a search portal – not a separate register – but has the potential to become a 'one-stop shop' for information about trials. However, six months after the launch only four primary registers (plus data from the US-based ClincialTrials.gov) have been included and four more have become collaborating registers, of which only one, Eli Lilly, is a drug company register. The number will increase – another 11 registers are in the process of becoming contributors – but there are still some big gaps.

The European Medicines Agency EMEA has its own database, EudraCT, with more than 13,000 clinical trials recorded by Member States. But it is only accessible by 'competent authorities', not by doctors or the public. Information on paediatric trials will, however, be made

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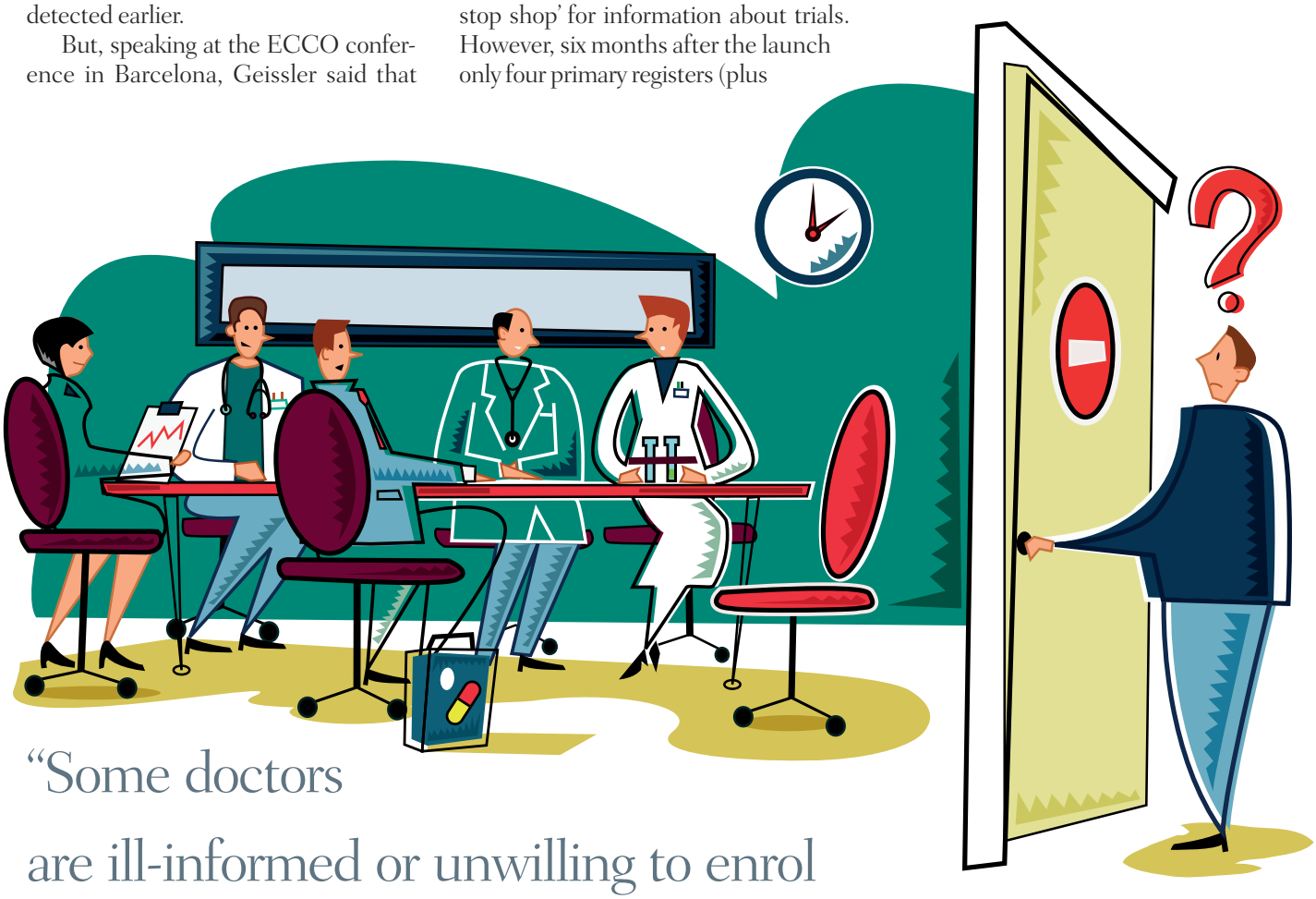

"Some doctors are ill-informed or unwilling to enrol patients and there is a culture of secrecy"

"Patient groups need to adopt a carrot-and-stick approach to enforce change"

generally available under a revised EU regulation on paediatric medicines.
ECPC has been talking to EMEA about greater openness, but recognises that it would require a change in European law to open up EudraCT. However, Geissler sees the exception made for paediatric trials as a positive sign. "This might help to call for greater transparency for adult trials later… little steps will make a large change."

EMEA hosted a meeting with the European Commission in London last October to discuss the operation of the much-criticised Clinical Trials Directive. ECPC used the conference to argue for greater transparency, and for patients to be given a seat on all medical ethics boards.

ECPC is not convinced that patients' rights protection in non-commercial clinical trials or clinical trials sponsored by pharmaceutical companies have improved significantly. "Patient groups were not sufficiently consulted and involved when the Clinical Trials Directive was drawn up and adopted. Even now patients are rarely consulted when new cancer trials are being set up.

"In ECPC's view, participation of patient groups in the design process of clinical trials can improve consent, recruitment and outcome of clinical trials. Involvement of patient groups at the beginning of the trial design would allow patients to contribute their ideas and requirements, and would avoid unnecessary or misleading research work."
Geissler says patient groups need to adopt a carrot-and-stick approach, encouraging patients to join good trials and discouraging participation in those that do not meet the standards. "Patient groups are in the driving seat to enforce change."

Europa Donna, the breast cancer coalition, also believes there is a need for better public information. Executive director Susan Knox says, "Very often a woman hears about a clinical trial when she is being treated and that is already a very traumatic time. To make a decision about a clinical trial without knowing anything about the way that research is conducted is extremely difficult for a patient."

Van Ginneken-Noordman notes that relatively few cancer patients in the Netherlands volunteer for clinical trials because they are not well informed and they can usually obtain the latest therapies from their physicians. However, in eastern Europe joining a clinical trial may be the only way to access the most up-to-date drugs. Clearly, this puts heavy pressure on the patient.

Scherzer warns that it makes informed consent very difficult. "Researchers say we are going to protect the patient by getting them to sign a consent form. Well, the consent form is a sham because this patient is so desperate that they will sign anything including the mortgage to their own home."

Quality of life

Deborah Collyar, president of Patient Advocates in Research (PAIR), has been involved in patient advocacy in the US for 15 years. Ten years ago she chaired an NCI committee whose report led to the creation of the cancer.gov website. However, she does not think that things have changed fast enough in relation to patient involvement in decision making.

"The clinicians and scientists I have worked with through the years are all really dedicated people. At least 99% really want to improve things for their patients. But they are so influenced by the scientific side and their training as medical doctors that often what gets left out is the experiential side of the clinical trial. They want clear scientific objectives. They forget how difficult it may be to participate."

A typical proposal from a researcher might be that each patient gives multiple biopsies during the trial. "We say, 'OK, sanity check!' How difficult is this going to be for someone? Do they really need it or is it just cool science? We explain that eliminating patient barriers may mean better enrolment and adherence to their clinical trials."

Van Ginneken-Noordman agrees that the patient experience is neglected. "The quality of life is very important in cancer treatment and research – the level of illness, tiredness and pain and the level at

"The consent form is a sham because this patient is so desperate that they will sign anything"

"Would you like a 50–50 shot of having a placebo, or a 75–25 chance of getting something?"

which it interferes with daily life. You can go through a very difficult trial with a lot of burden and side-effects and uncertain outcomes. Perhaps it only lengthens your life by one month but makes your life much more miserable. These are issues that patients should decide, not researchers."

In June 2007, the James Lind Alliance and the *Lancet* held a seminar in London to ask how clinical trialists could serve the needs of clinicians and patients more effectively. Hilda Bastien, head of Patient Information and Research at the German Institute for Quality and Efficiency in Healthcare (IQWiG), said patients had a love–hate relationship with research and often felt they were in a maze.

"It is very hard to come up with any direct way to answer the specific questions that people have, like, 'When will I get back to work?' What you have is something that tells you that the average patient feels a 3 on a scale of 5 on something or another. That is quite frustrating."

She says that researchers need better links with patients, clinicians and across disciplines to address relevant questions. "Trialists should each have qualitative researchers they would not dream of taking a step without, and should have relationships with patient advocates and be trying to cooperate with other disciplines."

Patients don't like placebos

One particular issue for people with cancer is the (admittedly small) number of trials that allocate some patients to a placebo.

Collyar recalls that researchers wanted to test a new agent on asymptomatic patients who were at high risk of metastasis. "They were talking about a two-armed study with a placebo and I kept pushing for multiple arms. I told them, 'People gravitate towards hope. Would you like a 50–50 shot of having nothing, or a 25% chance of getting the placebo and a 75% chance of getting something?' It was like light bulbs going on in their heads. They did not understand until then."

The Life Raft group had a dispute with Pfizer Oncology when they were trialling sunitinib (now marketed as Sutent) against a placebo for GIST patients who were showing signs that Glivec (imatinib) was no longer working.

Life Raft argued that the control group should continue to be offered Glivec, since it does not stop working completely. They felt justified when in January 2005, the trial was stopped seven months early, and everyone on a placebo was immediately offered the new drug. In effect, for the duration of the trial, those on the placebo had been at extra risk.

Scherzer said, "If someone proposes a clinical trial where a placebo will be given to a randomised group of people, the burden of proof must be on those who are proposing it that there is no alternative."

Finding out results

Patients not only want to know about trials they might join – they also need to know the results. But trials which show disappointing results are often not reported, while patients in other trials may hear the results first in the media.

Knox from Europa Donna says, "We believe very strongly that all trials should be part of a public registry and that when trial results come out they should be immediately posted for everyone to see. It should be a requirement that all trial results are

A FOOT IN THE DOOR

Patient groups are becoming more assertive about being given a place at the table. The European Myeloma Platform is in discussion with researchers in the European Myeloma Network about being included in their committee. Europa Donna is talking to EUROCAN Plus, the EU-backed initiative to coordinate cancer research in Europe, about a European database accessible to patients, detailing all current and recruiting clinical trials.

The UK Cancer Research Network was set up in the year 2000 and has at least two patient or carer representatives in every group. It has more than tripled the number of patients joining clinical trials. Other UK Networks are now following its lead and the overall UK Clinical Research Network appointed cancer survivor and patient advocate Roger Wilson to be associate director for patient and public involvement.

As Hilda Bastien of the German IQWiG told the James Lind Alliance/*Lancet* meeting: "There are going to be increasing numbers who would like to be in clinical trials, particularly when they have a life-threatening illness. They need to be able to join them and the results need to be fully accessible. It is a joint responsibility between the community and researchers and trialists to improve the image of clinical trials."

"People can be traumatised by hearing results from the media, especially if the results are not good"

reported and available to the public. The participants should find out before it is in the media."

Collyar has been involved in research with medical oncologist Ann Partridge, from the Dana Farber Cancer Institute in Boston, about informing patients of results. In 2004 they published a study suggesting that only 6 out of 10 oncology doctors and nurses routinely gave the results of research to patients, although 8 out of 10 were willing to do so.

Subsequent research on women with breast cancer who had taken part in a trial of Herceptin (trastuzumab), showed that more than a quarter first heard about the results from the media. After learning the results, one-third (mostly those who had received Herceptin) felt less anxious but one-quarter (mostly those who had not) became more anxious. However, only four per cent would not have wanted to know the results.

Collyar says that people can be traumatised by hearing results from the media, especially if the results are not good. "If you look at research about how to treat people better in trials, it is nearly all about how to recruit people. Where are all the trials and studies about how do you break bad news to people in your control group or your intervention group about what has happened?"

Collyar and Partridge are now are co-chairs of a committee in one of the NCI-funded cooperative trial groups which is pushing to ensure that those who take part in research are properly informed about the outcomes.

Positive benefits

There are growing signs that when researchers do involve patients and give them a seat at the table, benefits flow. Europa Donna was involved in helping to plan the TRANSBIG MINDACT trial that focuses on the genetic signature of breast cancer and the risk of recurrence. They were able to influence the provision of patient information, which included a DVD in 13 languages to be used by a doctor or nurse with the patient and then taken home by the patient.

Fatima Cardosa, scientific director of the MINDACT trial, says in the Europa Donna newsletter, "The most difficult part of this trial is explaining it to the patient because it takes time, and time is not something conceded to physicians. When we developed the MINDACT consent forms we involved Europa Donna from the beginning and also we have asked individual patients to read and make sure that the forms were comprehensible."

Life Raft too was able to identify clear benefits for patients and for researchers when they conducted their own quality-of-life survey for patients taking Glivec. There was concern about side-effects, particularly fatigue for people on the drug. Sure enough the survey showed high levels of fatigue. But Scherzer says that they also found something surprising. "We discovered that the side-effects often got better over time, and the more severe the side-effects were, the more dramatically they got better. This discovery was important as it means, for many patients, that if they hold on, rather than abandon the drug, the side-effects get better."

The result of such research has been to build a degree of understanding between the patient group and the drug companies. "Originally the pharmaceutical companies felt very threatened and suspicious, but when we sat down with the companies, Novartis being one of them, they have actually been quite responsive. What they saw was that we were not doing this in a provocative or confrontational way, but were actually adding to the information base."

Deborah Collyar pioneered 'clinical trials and people workshops' between researchers and community groups to improve informed consent. These start by giving people information about clinical trials, but often lead to researchers learning from the public.

"Everybody thinks of informed consent as a way of communicating with the patient, but as you start the dialogue you also begin to identify design flaws or things that could change to make it more amenable to people. When you go into an informed consent discussion, people immediately ask questions about that trial. 'Why was it set up that way? Why not do it this way?' The dialogue can take them in a lot of different directions. If we have patient representatives involved in the development of the trial we will be much more successful because they help to eliminate barriers."

For information on the launch of the World Health Organization Clinical Trial Search Portal see: http://tinyurl.com/2ko7p7. For the current list of participating registers see: http://tinyurl.com/2tbnrp.

See also: A trial of strength: can industry resist the growing demands for greater transparency? *Cancer World* March–April 2006 (issue 11) www.cancerworld.org/magazine

Our responsibility, our choices

ESO invites the media to a reality check on cancer

➜ Anna Wagstaff

The European School of Oncology marked the end of its 25th anniversary year by inviting a top-level line up of experts to debate, in front of the media, how effectively we are tackling cancer and whether a change of direction is needed.

With one in three of us destined to develop cancer and no cure in sight, many doctors and researchers are bemused and frustrated at the apparent public apathy about efforts to control the disease. Perhaps it's not surprising. Cancer is still regarded by the public with a sense of fatalism, and decades of media hype alternating between cancer scares and breakthrough drugs has only obscured the reality that research and better delivery of care is making slow and steady progress – and could make more if it were organised and funded better.

In an effort to promote informed and critical debate about the best way to tackle the rising tide of cancer, the European School of Oncology invited journalists from across Europe to Rome to question leading players drawn from academic research, industry, cancer charities, patient advocacy and regulatory authorities.

The event, held under the title "*Cancer: time for a reality check*" to mark ESO's 25th anniversary, was attended by thirty journalists from newspapers, magazines, TV, radio and new media from 13 European countries, with a further 700 people from across Europe and the US accessing the discussion via a live webcast.

Debates were moderated by four experienced journalists – Jonathon Alter, senior reporter for Newsweek magazine and NBC news in the US, Sarah Boseley, health editor for the UK daily *The Guardian*, Istvan Palugyai, editor of the leading Hungarian daily paper *Népszabadsag* and Paul Benkimoun, health reporter for the French daily *Le Monde*.

Losing the plot?

Cancer researchers have come under fire for focusing on pushing forward the frontiers of basic biology while neglecting innovative ways to tackle cancer – hence the opening session's title, *Quest for a cure: have we lost the plot?* Scott Lippman, professor in medicine and cancer prevention at the MD Anderson Cancer Center, Texas, and Bob Pinedo, director of the Vrije Universiteit medical centre in Amsterdam, looked at the evidence about survival rates over 40 years to draw conclusions about whether we need to refocus research efforts.

Engaging the public. The debate offered valuable background and context to journalists who cover cancer from scientific, health and social standpoints. It was covered in a variety of media, including some of Europe's national press and the *Economist*, which posted a link to the webcast of the debate on its Internet site

Lippman said that the current strategy is now beginning to pay off – understanding the 'sevenless' mutant fruit fly (missing the seventh light receptor normally present in a fruit fly's eye) had contributed directly to knowledge needed to develop targeted medicines. However, the real benefit will only be seen, he stressed, if there is a concerted effort to find out which drugs are effective in which type of patient.

Bob Pinedo: Early detection is the only reasonable and fast solution

Lippman, a lung cancer specialist, highlighted the use of the EGFR inhibitor erlotinib to treat patients with non-small-cell lung cancer. Although the drug offers a median extra survival of only around two months, 10–20% patients respond so dramatically that the treatment could keep them alive for years. Thanks to a huge translational research effort, comparing the tumour gene profiles of good responders with poor responders, we now know that most patients whose tumours shrink dramatically have a specific point mutation.

Scott Lippman: Find the right patients for the right drugs

For this subgroup of patients at least, argues Lippman, targeted therapies have delivered, and we need to give this strategy the best chance to succeed for other patient groups. Lab-based scientists have discovered a host of potentially 'druggable' targets that might be blocked to inhibit the cancer or stimulated to enhance the patient's own resistance. "We must now link the many promising targets/biomarkers to clinical trials designed to identify the right patient for the right drugs. That is personalised medicine. We are getting there."

Pinedo doesn't quibble with the science but worries about the timescale. Even in breast cancer, where the greatest advances have been made in identifying gene signatures, "we have still not seen prognostic selection of patients based on those genes" – let alone selection of personalised treatment. Finding relevant gene signatures is further complicated by the tendency of cancers to mutate, which could mean that the genetic profile of a tumour will change "every six months or even every month".

If we do succeed in matching patients to treatments, said Pinedo, we then have the prospect of turning advanced cancer into a chronic disease, keeping patients alive for longer and longer using combined therapies – an expensive and unsatisfactory solution. For patients with advanced colorectal cancer, for example, "Even excluding palliative treatment like stent, surgical debulking and radioablation of metastases, the cost of treating one patient equals more than 1,000 colonoscopies – this doesn't even include the psychological effects and the social cost."

Pinedo argues that the only "reasonable and fast solution" is to detect the disease early, when it is still curable. He has developed a way of testing stools for aberrant methylation, as an early sign of colorectal cancer. The test picks up 86% of stage I, II and III colorectal cancers, and has a false-positive rate of only 4%. The strategy now is to find a way in which people can use this test in the privacy of their own homes – cheaper and easier than population screening with colonoscopy, and with the potential for a far higher uptake. Pinedo points out that because colorectal cancer is easy to cure when caught early, an effective test would make a huge and immediate impact on what will soon be the major cancer killer in Europe.

Personalised therapies and focusing on early detection are clearly not counterposed – but the question of whether cancer research has the right balance between these approaches was a key theme of the day.

Personalised medicine

Whether the strategy of matching the right patients to the right drugs will be able to deliver on its promises was the subject of another session: *Can tumour gene profiling live up to expectations?* Lex Eggermont, who as former president of the EORTC played a major role in building Europe's capacity to carry out coordinated quality translational research, gave a cautiously optimistic answer: "In time it probably will, because it is solid biologic research."

Gene profiling is a way of capturing the biology of a tumour by analysing the expression of up to 30,000 genes in the tumour tissue. Researchers look for patterns that can help distinguish between different types of cancer, and try to find patterns that predict prognosis or response to various treatments (the key to personalised therapies) by making comparisons between the tissue of patients who survived longer (or responded better), and those who died earlier or failed to respond.

Lex Eggermont: Don't expect too much too soon

Before they can be used for clinical decision making, these 'candidate signatures' have to be validated by testing them in randomised clinical trials

– an operation that requires close cooperation between the labs and companies that do the gene analysis, the clinical team treating the patient, everyone involved in harvesting, transporting and storing the tissue… and the patients, who have to agree to the hassle and discomfort involved in giving biopsy specimens, blood and whatever other samples may be required.

John Ioannidis: We can't afford to underfund this research

Although no gene profile is yet being used to make clinical decisions, Eggermont says that things are already changing. For example, an EORTC trial has validated a gene signature with strong powers to predict which breast cancer patients respond best to taxane- and non-taxane-based chemotherapy. He cautions, however, against expecting too much too soon. Gene profiles change with time and in response to treatments, and it is simply not practical to subject patients to constant biopsies. "You cannot pressure the system," warns Eggermont, "[Gene profiling] will not yield the results everyone expects in three years. Come back in 10 years..."

John Ioannidis, of the University of Ioannina in Greece and Tufts University in Boston, stressed that research into personalised medicine will only deliver if it is done properly – which is often not the case. Looking for gene signatures is a trendy area of research, he said, and with 30,000 genes to choose from, anyone looking for a significant pattern is quite likely to find one. "How do we decide which ones are worth taking to the next step, really trying to make a difference with patients?"

Getting it right will be crucial, he said, as there is a limited amount of good-quality banked tissue with linked clinical histories available for researchers to study. Validating candidate signatures in clinical trials is a major logistical exercise, and patients have the right to expect the samples they donate not to be wasted on research that has little chance of helping future generations.

Ioannidis concludes that this will require more coordination and cooperation, in large and robust clinical trials, and investment in the research infrastructure. He answered the question: "Can we afford to fund such research?" by saying, "If you think that type of research is expensive, then try bad, fragmented uncoordinated research."

The spiralling cost of care

Expense was again a central issue in the session on *Spiralling costs: is rationing expensive cancer drugs the answer?* This offered a rare opportunity for discussion by the main stakeholders, with contributions from the UK's national director of cancer care Mike Richards, AstraZeneca's head of oncology Brent Vose, oncologist and former president of ASCO Larry Norton, pharmacologist and member of the European drug regulatory authority Silvio Garattini and patient advocate Lynn Faulds Wood.

Garattini said the regulatory authorities should insist on better evidence of how a drug works and who benefits before allowing new and expensive therapies onto the market. Most of the cancer drugs approved in the last 10 years, he said, had not been through phase III trials, and had been tested in very late disease, often with no controls or comparator arms. "Let's have better knowledge of the drug at the time of approval."

Silvio Garattini: We know too little about the drugs coming on to the market

From the funder's perspective, Richards argued that it is not possible to continue paying five-figure sums for each course of targeted drugs when only a small minority of patients substantially benefits. "We need new approaches to pricing. We need to look at value-based pricing and risk-sharing opportunities… We need to look at ways, when the industry has done its work, of how to get [the drug] into use in a way that society can bear, and at the same time learn more about them after they've come into use."

Mike Richards: We need to look at value-based pricing and risk-sharing opportunities

Norton, however, warned that rationing expensive drugs risked playing with the lives of patients who could benefit. "It is very hard to look at a patient and say you will only get two weeks so you are not going to get the drug, when that patient may get 20 years." He said that society was reaping the results of having ceded the task of drug development entirely to private industry. "Pharma has a job to do and that is to develop products that sell, so their shareholders can make a profit. As a society we shouldn't fault them for doing what they are supposed to do. The problem is the rest of society is not taking responsibility for curing cancer."

Vose, speaking from the industry, argued strongly against rationing as a solution. "I don't think it's all about pricing. I do think it's about targeting patients who can benefit,

avoiding those who can't, and avoiding those who will get serious side-effects." AstraZeneca, he said, reviews every drug to see if there is a way to select the patients who will benefit, but it is not always easy. "Look at Iressa [gefitinib]. It has been incredibly difficult to find those 10–20% of patients who really get that benefit, and we still don't know. The question is: how long do you want to wait?"

While risk sharing and post-licensing studies could be appropriate, he stressed that each drug is different and the answer lies in working in partnership to find solutions on a case-by-case basis. "I'm concerned that you drive down the road to a single solution that could actually delay the appearance of a drug like Iressa for five years or more while we try to fathom out what this gene profile has to be. That means, with a 10% response rate, you are probably talking about 30,000 patients a year not benefiting in a dramatic way. There has to be a meeting of minds as to how we as a society can take this forward."

Norton: Society is not taking responsibility for curing cancer

While this debate focused almost entirely on the cost of drugs, Richards – echoing the earlier debate on research strategies – argued that there are still big savings to be made by reducing the number of patients who progress to metastatic disease. "We need to invest more in prevention and early diagnosis. In the UK poor survival rates are largely due to later diagnosis. And let's concentrate on surgery. Surgery cures more cancers than any other treatment, and good quality surgery cures more than poor quality. A small investment in training would yield results."

Brent Vose: Each drug is different. We must work in partnership on a case-by-case basis

The point received strong support from Faulds Wood. "We've got the balance wrong. At the moment we're putting all the effort into the drugs, because that's where the money is. But we need to look more to prevention, and we need to look more at screening. Society has to decide at what happens… because in another 16 years all our bud-gets will be bust if we don't sort this."

Lynn Faulds Wood: We should stop focusing exclusively on drugs

Incentives and penalties

Decisions that affect how society organises cancer research receive far less media attention than rationing and reimbursement of expensive drugs. But these decision affect how quickly we make progress against cancer. This was the focus of the session *Are we rewarding mediocrity while penalising real innovation?* Debating this question were: Umberto Veronesi, scientific director of the European Institute of Oncology, Milan and one of the great innovators in breast cancer surgery; Lex Eggermont, former head of EORTC; Dinesh Purundare, GSK's European head of oncology; Harpal Kumar, head of Cancer Research UK and Cliff Leaf, a leading critic of the way cancer research is organised in the US (see also the Cover Story, p 6).

Eggermont talked of the need to foster greater public confidence in science, scientists and doctors. The problem behind the European Clinical Trials Directive, he said, was that it looked at clinical research purely as a potential threat to patients, without any acknowledgement of the huge benefits it is bringing. As a result Europe's clinical research effort has slowed and young researchers feel shackled and demoralised. "We do not mean to reward mediocrity, but we are inhibiting excellence by throwing up all these barriers."

However, Eggermont believes that Europe is also doing many things right. While president of EORTC he helped to organise leading institutions from many countries into a network capable of cooperating on translational research to find new targets and biomarkers and find out what works in which patients. "[This effort] must be multinational and share tissue and information, and have a consortium agreement on how to deal with new inventions. We need to create shared access to these tissues, and to have some of the royalties going back into the system. If you do not create that type of energy behind the system it will fail, and you will have to deal with intellectual property lawyers."

Kumar argued that bodies like Cancer Research UK that are independent of government and shareholders, provide the ideal setting for fostering innovative research. "We can't say what will be important, but we can create environments for creativity and innovation." That includes being able to take risks on innovative ideas with no guarantee of a return. It also means acting in a cooperative manner with the wider cancer research effort. "In CRUK every new tissue collection is required to be made completely available, and we are setting up a portal so we can make clearly identifiable every

tissue everywhere in the country. Every publication has to be put on open access within six months."

Umberto Veronesi is less upbeat about the current thrust of cancer research, arguing that it is focused on areas least likely to generate effective solutions. Western countries, he pointed out, spend 5% of research funding on prevention, 10% on early detection and 85% on treatment, of which 10% goes towards surgery and radiotherapy, and 90% towards medical treatment. "We should reverse this."

Harpal Kumar: The key is to create environments for innovation and creativity

He also spoke up for the primary importance of ideas. Veronesi himself led the early trials into breast conservation, which has saved tens of thousands of women from mastectomy. He also invented and trialled the sentinel node biopsy which allows most breast cancer patients to preserve their axillary lymph node and muscle function. But these trials received minimal funding.

"Everyone agrees on network of core institutions. But trials are becoming larger and longer. Sometimes it takes 5,000 people to discover a 3% difference. This is not innovation. Innovation is totally different. How many people 30–40 years ago believed cancer was a viral disease? Probably only 20 or 30. What is missing are new ideas. We don't have enough new revolutionary ideas."

Lack of innovative ideas is a concern also for Leaf, who argues that the research agenda has been hijacked by an academic system driven by the need to publish in leading scientific and medical journals, to advance careers and to attract grants. Instead of focusing their intelligence and enthusiasm on real innovative approaches to controlling cancer, young researchers are forced to focus research proposals around questions most likely to generate "interesting" results. This explains, says Leaf, why the hundreds of thousands of articles and studies on cancer in past decades have made so little impact, "the age-adjusted death rate from cancer is currently what it was in 1970 and in 1950. ...We have to rethink the mechanisms for rewarding young researchers," he concluded.

Umberto Veronesi: What is missing are revolutionary new ideas

But, as Norton pointed out, most treatment-focused research, in drugs at least, takes place in the private sector where profit, not publication, is the major driver. Here the problem is a competitive environment that is poor at sharing research and tissue, poor at cooperating, and where there are disincentives to narrowing down the patient population that will respond to the drugs.

Purundare from GSK stressed, however, that "the customer is the government" and he called on governments to "send proper signals for rewarding innovative research and development". We need, he added "a shared understanding of what innovation means," for example, how much value is attached to finding ways to deliver drugs orally rather than intravenously.

His point underlined earlier messages about the need for government, industry and the regulators to agree on what constitutes value and how to introduce new drugs in a way that works for industry and society. But it also highlighted the potential for governments to influence the research agenda in both the private and public sector by sending out the correct signals – which is what will have to happen if the research agenda is to shift substantially, for example, in favour of prevention and early detection.

Towards a public debate

In the end, there was no simple take-home message. But then this was never the idea. The 'reality check' was intended to help journalists stimulate public debate about what the priorities for cancer research should be, and how that research should be organised and funded. Comments from the journalists indicated that it went some way towards achieving this. They valued, in particular, the opportunity to hear criticism as well as praise for current research efforts, the diversity of speakers with strong opinions and experience, an opportunity for one-to-one interviews, and the concentrated presentation of so many current debates.

Dinesh Purundare: We need a shared understanding of what innovation means

The speakers also appreciated the chance to engage with the media. "We need more sessions like this where we are all talking together and these kinds of messages, even if there are disagreements, get aired in public," said Norton. "I've made outrageous statements in the US press and they get totally ignored because they are made once only. People have a very short attention span. We have to make this a continuous issue; something that is always discussed."

A webcast of the entire debate can be seen at http://esomediaforum.webcasting.it/

Does a prompt list help patients and caregivers to ask questions about cancer prognosis and care?

Maria Friedrichsen

Results of a randomised controlled trial show that question prompt lists may benefit communication. However, there are still areas to investigate before prompt lists can be described as evidence-based medicine.

Communication in oncology and palliative care (PC) is a complex area to investigate because of its sensitive nature. An ambitious study from Australia (see opposite) provides useful information on how to enhance patient and caregiver participation during consultations with the physician. The results showed that patients and family members who were randomised to the question prompt list (QPL) group asked twice as many questions as controls, without increasing their level of anxiety. These results are also confirmed by other studies. Glynne-Jones et al.[1] found that 65% of patients with cancer thought the prompt sheet was very helpful. Bruera et al.[2] confirmed that patients with breast cancer scored the prompt sheet as very helpful (8.47 of 10). These studies indicate that a prompt list should be used in clinical practice because a majority of patients, family members and physicians find it user-friendly. Patients become more active and may appreciate assistance in formulating questions about sensitive issues such as prognosis. A pivotal question is whether an increased number of questions during a consultation is a sign of quality or merely quantity.

A lot of different factors influence the patient–physician communication process in cancer care, such as patients' status, gender, education, words chosen, emotional state, and communication style and skill.[3,4,5] Most cancer communication studies have focused on an early-stage cancer setting, but it should be recognised that a lot of changes also occur later during a patient's cancer trajectory, even in the palliative phase. In the transition to the late palliative phase, several events can arise, such as bad news about prognosis, the development of infections or new symptoms and the onset of existential and social concerns. Patients' needs may fluctuate as a result of these events. Clayton et al. have focused on patients with advanced cancer who had specific problems but were still well enough to visit their physician. The majority of the patients studied by Clayton et al. had an estimated survival of more than 12 weeks. Is it possible to transfer the prompt list concept to palliative home or hospice care where patients are in the terminal phase of their disease course? If the list is modified and significantly shortened, I believe it would be useful in this context.

There is a complex interplay during palliative care between the patient, family

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caregiver, physician and other individuals and factors. A physician who is not interested in talking about existential matters will probably find the prompt list distressing, as he or she will not, or cannot, answer specific questions. Clayton et al. showed that physician endorsement increased the total number of questions asked by patients. Physicians also claimed that patients might not be prepared to discuss certain topics. The result that 62% of the patients disagreed that the questions in the brochure made them anxious might mean that more than one-third of patients did become anxious. This possibility should be questioned. On the other hand, a prompt list might be a way to legitimise these sensitive questions, help to build relationships and empower both patients and family members. We still do not fully know how patients interpret and recall information, or whether a prompt list will help patients from different cultures.

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Synopsis

Josephine M Clayton, Phyllis N Butow, Martin HN Tattersall et al. (2007) **Randomized controlled trial of a prompt list to help advanced cancer patients and their caregivers to ask questions about prognosis and end-of-life care.** *J Clin Oncol* 25:715–723

Background. Although communication is a critical aspect of medical care at the end of life, formulating questions about prognosis and end-of-life issues is difficult for some patients unless prompting is given.

Objective. To evaluate whether providing a question prompt list (QPL) for patients with advanced cancer and their caregivers improves the usefulness of consultations with a palliative care (PC) physician.

Design and intervention. Fifteen PC physicians at nine specialist services in two Australian states were involved in this randomised controlled trial. Between October 2002 and August 2004 consecutive patients with advanced cancer were identified and asked to participate. Most of the participants were recruited from outpatient PC clinics, and enrollment was generally within three consultations following initial contact with the PC physician. The QPL comprised a 16-page A5 booklet containing 12 questions grouped into nine topics for discussion. Following random assignment to receive either a routine consultation, or the QPL 20–30 minutes before the consultation, discussions with the PC physician took place. The discussions were audiotaped and transcribed, and coded to describe physician endorsement, and questions and concerns raised by the patient or caregiver, as well as other topics of discussion. Patients completed questionnaires before, and at 24 hours and three weeks after the consultation.

Outcome measure. The primary outcome measure was total number of patient questions during the consultation.

Results. There were 174 participants, 92 of whom were randomised to the QPL group. Patients in the QPL group asked 2.3 times more questions than controls (95% CI 1.68–3.18; $P<0.0001$) and raised more issues (expressed either as a direct request for information or a statement inviting a response) than patients in the control group (17.6 vs 12.7 items; ratio 1.39; 95% CI 1.17–1.64; $P=0.0002$). Caregivers in the QPL group asked 2.11 times more questions (95% CI 1.4–3.18; $P=0.0005$) and raised more issues (9.9 vs 6.6; ratio 1.49; 95% CI 1.11–2.00; $P=0.008$) than caregivers in the control group. Mean duration of the consultation was longer in the QPL group than in the control group (37.8 vs 30.5 min; $P=0.002$). In comparison with the control group, both caregivers and patients in the QPL group asked more questions about prognosis. Patients in the QPL group had less unmet need for 8 of 11 individual information items, although this outcome was significant only for "what to expect in the future" ($P=0.04$). There were no overall differences between the groups in anxiety or patient or physician satisfaction following the consultation. The number of questions asked by patients increased with the degree of physician endorsement of the QPL. According to a final questionnaire, 12 of 13 physicians felt the QPL was a useful tool (one physician did not answer those questions).

Conclusion. An abbreviated version of the QPL could be useful for facilitating end-of-life discussions with patients who have advanced cancer, and their caregivers.

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

Does adjuvant radiotherapy increase survival in patients with Merkel cell carcinoma of the skin?

Marc Bischof

The findings of a large retrospective study show that postoperative radiotherapy is associated with a significant improvement in survival, and is indicated in all patients with local or locoregional Merkel cell carcinoma.

The aggressive nature of Merkel cell carcinoma (MCC), combined with high recurrence rates, frequent regional lymph-node metastases and the well-known radiosensitivity of this disease, indicate that a therapeutic regimen combining surgical excision and postoperative radiotherapy should be used to improve local control.

The optimum treatment regimen for MCC remains unclear, however, as the low worldwide incidence of this disease means that only small, retrospective series have been published.

The particular importance of the large series studied by Mojica et al. (see opposite) is that the analysis shows a significant improvement in survival after postoperative radiation therapy. The Surveillance, Epidemiology, and End Results (SEER) programme of the National Cancer Institute, from which data were obtained for this study, did not collect information about local recurrences, so the effect of radiation therapy on this outcome could not be studied. Local recurrence rates have been reported to be as high as 80% after surgical resection alone.[1] The superiority of adjuvant radiotherapy over surgery alone in preventing local recurrences is supported by the findings of various smaller series that each included up to 50 patients.[2] Medina-Franco et al. found a highly significant improvement in local control with adjuvant radiotherapy in a literature review of 1,024 cases.[3] Even the controversial study by Allen et al., who identified no significant improvement of locoregional control after adjuvant radiotherapy, showed nodal recurrence rates of 26% in the group treated with surgery alone, compared with 13% in the group with postoperative radiotherapy. It is possible that significance was not achieved because only a minority of patients (17%) received radiotherapy.[4] It can be supposed, however, that intensified local therapy consisting of surgical resection and postoperative radiotherapy results in better local control, which can be translated into better survival, as shown by Mojica et al.

Mojica et al. discuss the lack of information in the SEER programme

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Synopsis

Pablo Mojica, David Smith and Joshua DI Ellenhorn (2007) **Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin.** *J Clin Oncol 25:1043–1047*

Background. Merkel cell carcinoma (MCC) is a relatively rare, but aggressive, skin cancer, with a high propensity for local recurrence and regional and distant metastases. Most data on MCC are from single-institution retrospective analyses, making it difficult to assess the role of adjuvant radiation therapy in the treatment of this disease. Surgical resection of the primary tumour with extensive margins is the main form of therapy.

Objective. To analyse the role of adjuvant radiotherapy in patients undergoing surgical excision for MCC.

Design and intervention. Data extracted from the Surveillance, Epidemiology, and End Results (SEER) programme of the National Cancer Institute were used to identify patients diagnosed with MCC between 1973 and 2002. Information regarding patient demographics, treatment modalities and tumour characteristics was reviewed. Tumour characteristics documented included site of primary tumour, size at presentation, nodal status of the disease and whether distant metastases were present. Information was available on what surgery was performed at the primary site and lymph nodes, and on the use of adjuvant radiation therapy, but not on the use of chemotherapy or the use of sentinel node biopsy.

Outcome measure. The primary end point of the trial was overall survival.

Results. The SEER registry contained 1,665 cases of MCC over the time period reviewed, with surgery being a component of therapy in 89% of cases (n=1,487). The overall median follow-up was 40 months and the overall median survival was 49 months. Excision or re-excision or minor amputation without lymph-node dissection was performed in 82% of the surgical cohort (n=1,214), and extended surgery with lymph-node dissection or major amputations was performed in 10% of this cohort (n=135). External-beam radiation was the type of radiotherapy most frequently used (98%). Median overall survival was 63 months in patients who received adjuvant radiation therapy and 45 months in patients who did not (P=0.0002). On multivariate analysis, the association of adjuvant radiation therapy with survival was statistically significant (P=0.0122). The use of adjuvant radiation therapy was associated with improved overall median survival across all age groups. When the results were stratified by tumour size, adjuvant radiation therapy was associated with an improved overall median survival in patients with tumours <1 cm in size (from 48 to 93 months; P=0.0447), in patients with tumours 1–2 cm in size (from 52 to 86 months; P=0.0126) and in patients with tumours larger than 2 cm (from 21 to 50 months; P=0.0003).

Conclusion. There was a positive association between adjuvant radiation therapy and overall survival, which remained statistically significant on multivariate analysis.

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

regarding resection status, resection margins and the number of patients with lymph-node dissection. A majority of published series have the same limitations, because of the small numbers of patients and varying treatment paradigms used in different centres and regions and over long study periods. Additionally, because of problems in diagnosis of this rare tumour, patients are often administered adjuvant radiotherapy after excision of the first or second local recurrence.

The implementation of therapy standards for treatment of MCC is of even greater importance now than ever before, because the incidence of this tumour has tripled in the last 20 years. This increase is possibly related to an enhanced awareness of the diagnostic criteria of MCC, including immunohistochemical assessments, which allow a better distinction between MCC and other skin tumours.

Nevertheless, while there is no published evidence from randomised trials to suggest otherwise, postoperative radiotherapy, which is associated with a low risk of complications, is the suggested treatment for MMC. This recommendation is supported by the important findings of Mojica et al.

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Does a prompt list help patients and caregivers to ask questions about cancer prognosis and care?

Maria Friedrichsen

Results of a randomised controlled trial show that question prompt lists may benefit communication. However, there are still areas to investigate before prompt lists can be described as evidence-based medicine.

Communication in oncology and palliative care (PC) is a complex area to investigate because of its sensitive nature. An ambitious study from Australia (see opposite) provides useful information on how to enhance patient and caregiver participation during consultations with the physician. The results showed that patients and family members who were randomised to the question prompt list (QPL) group asked twice as many questions as controls, without increasing their level of anxiety. These results are also confirmed by other studies. Glynne-Jones et al.[1] found that 65% of patients with cancer thought the prompt sheet was very helpful. Bruera et al.[2] confirmed that patients with breast cancer scored the prompt sheet as very helpful (8.47 of 10). These studies indicate that a prompt list should be used in clinical practice because a majority of patients, family members and physicians find it user-friendly. Patients become more active and may appreciate assistance in formulating questions about sensitive issues such as prognosis. A pivotal question is whether an increased number of questions during a consultation is a sign of quality or merely quantity.

A lot of different factors influence the patient–physician communication process in cancer care, such as patients' status, gender, education, words chosen, emotional state, and communication style and skill.[3,4,5] Most cancer communication studies have focused on an early-stage cancer setting, but it should be recognised that a lot of changes also occur later during a patient's cancer trajectory, even in the palliative phase. In the transition to the late palliative phase, several events can arise, such as bad news about prognosis, the development of infections or new symptoms and the onset of existential and social concerns. Patients' needs may fluctuate as a result of these events. Clayton et al. have focused on patients with advanced cancer who had specific problems but were still well enough to visit their physician. The majority of the patients studied by Clayton et al. had an estimated survival of more than 12 weeks. Is it possible to transfer the prompt list concept to palliative home or hospice care where patients are in the terminal phase of their disease course? If the list is modified and significantly shortened, I believe it would be useful in this context.

There is a complex interplay during palliative care between the patient, family

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caregiver, physician and other individuals and factors. A physician who is not interested in talking about existential matters will probably find the prompt list distressing, as he or she will not, or cannot, answer specific questions. Clayton et al. showed that physician endorsement increased the total number of questions asked by patients. Physicians also claimed that patients might not be prepared to discuss certain topics. The result that 62% of the patients disagreed that the questions in the brochure made them anxious might mean that more than one-third of patients did become anxious. This possibility should be questioned. On the other hand, a prompt list might be a way to legitimise these sensitive questions, help to build relationships and empower both patients and family members. We still do not fully know how patients interpret and recall information, or whether a prompt list will help patients from different cultures.

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Synopsis

Josephine M Clayton, Phyllis N Butow, Martin HN Tattersall et al. (2007) **Randomized controlled trial of a prompt list to help advanced cancer patients and their caregivers to ask questions about prognosis and end-of-life care.** *J Clin Oncol* 25:715–723

Background. Although communication is a critical aspect of medical care at the end of life, formulating questions about prognosis and end-of-life issues is difficult for some patients unless prompting is given.

Objective. To evaluate whether providing a question prompt list (QPL) for patients with advanced cancer and their caregivers improves the usefulness of consultations with a palliative care (PC) physician.

Design and intervention. Fifteen PC physicians at nine specialist services in two Australian states were involved in this randomised controlled trial. Between October 2002 and August 2004 consecutive patients with advanced cancer were identified and asked to participate. Most of the participants were recruited from outpatient PC clinics, and enrollment was generally within three consultations following initial contact with the PC physician. The QPL comprised a 16-page A5 booklet containing 12 questions grouped into nine topics for discussion. Following random assignment to receive either a routine consultation, or the QPL 20–30 minutes before the consultation, discussions with the PC physician took place. The discussions were audiotaped and transcribed, and coded to describe physician endorsement, and questions and concerns raised by the patient or caregiver, as well as other topics of discussion. Patients completed questionnaires before, and at 24 hours and three weeks after the consultation.

Outcome measure. The primary outcome measure was total number of patient questions during the consultation.

Results. There were 174 participants, 92 of whom were randomised to the QPL group. Patients in the QPL group asked 2.3 times more questions than controls (95% CI 1.68–3.18; $P<0.0001$) and raised more issues (expressed either as a direct request for information or a statement inviting a response) than patients in the control group (17.6 vs 12.7 items; ratio 1.39; 95% CI 1.17–1.64; $P=0.0002$). Caregivers in the QPL group asked 2.11 times more questions (95% CI 1.4–3.18; $P=0.0005$) and raised more issues (9.9 vs 6.6; ratio 1.49; 95% CI 1.11–2.00; $P=0.008$) than caregivers in the control group. Mean duration of the consultation was longer in the QPL group than in the control group (37.8 vs 30.5 min; $P=0.002$). In comparison with the control group, both caregivers and patients in the QPL group asked more questions about prognosis. Patients in the QPL group had less unmet need for 8 of 11 individual information items, although this outcome was significant only for "what to expect in the future" ($P=0.04$). There were no overall differences between the groups in anxiety or patient or physician satisfaction following the consultation. The number of questions asked by patients increased with the degree of physician endorsement of the QPL. According to a final questionnaire, 12 of 13 physicians felt the QPL was a useful tool (one physician did not answer those questions).

Conclusion. An abbreviated version of the QPL could be useful for facilitating end-of-life discussions with patients who have advanced cancer, and their caregivers.

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

A very useful doctor

Janet Fricker

Ferdy Lejeune went into medicine to be 'useful', and he did well. Thousands of amputations have been avoided thanks to a technique he pioneered. His focus on tumour blood vessels and immunology helped pave the way for some of the most exciting areas of cancer research today. For Lejeune, however, 'useful' is as much a matter of finding out what doesn't work as what does.

Growing up in the Belgian Congo, Ferdinand Lejeune (better known as Ferdy) had an idyllic 'Swallows and Amazons' style childhood, messing about on rivers in boats. The only difference between the Arthur Ransome tale and the exploits of Ferdy and his pals on the Stanley Pool (a lake-like widening at the lower reaches of the Congo River) was that the Belgian boys regularly encountered crocodiles. "While swimming we took it in turns to beat the water with sticks to keep the crocodiles at bay," recalls Lejeune, who on one occasion witnessed a dog being eaten by crocodiles just after he'd left the water. "But even that didn't put us off going in again the next day."

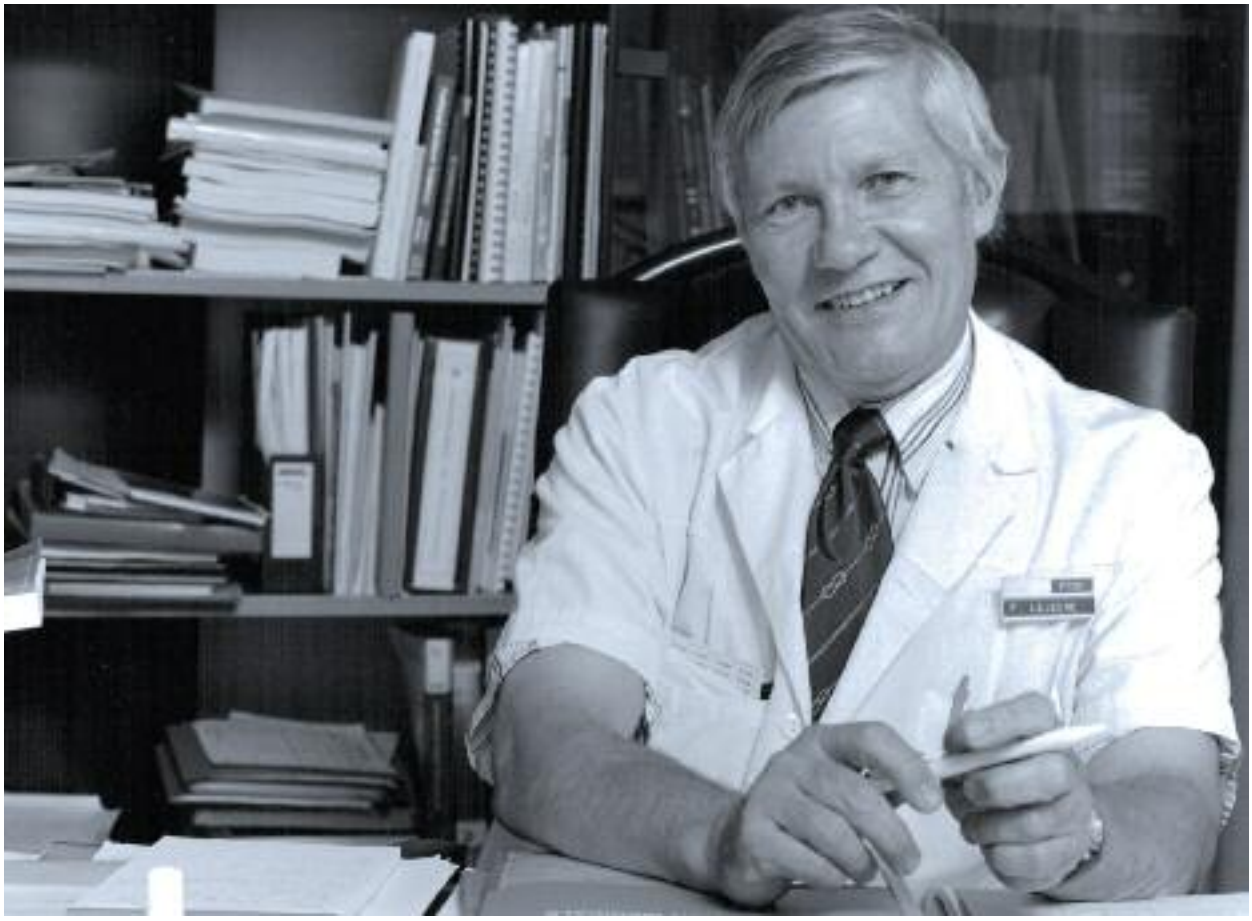
Such *sang-froid* has characterised Lejeune's work as an oncologist and enabled him to take risks, most notably in his pioneering work on use of TNF in isolated limb perfusion. But ironically for someone who has spent a career in melanoma, perhaps the greatest long-term hazard Lejeune encountered as a child was exposure to ultraviolet lamps. "In the Congo, of all places, doctors were worried that UV light was blocked by clouds during the dry season and decided to give us all a course of light treatment. We were herded into big rooms with enormous UV lights and given goggles to protect our eyes."

The Lejeune family settled in the Belgian Congo (now the Democratic Republic of the Congo) in 1946 to escape the deprivation of Belgium after the Second World War. Ferdy's father Ferdinand (who celebrated his 98th birthday last November) had been appointed as an engineer in a cotton textile factory in Leopoldville. The whole experience seemed like a "tropical paradise" to Ferdy, then aged six, and his younger brother and two sisters.

While visiting the factory hospital Lejeune first became interested in medicine. "By becoming a doctor I thought I could make a difference to people's lives. Throughout my life I've wanted to be useful," he says.

In 1957 he enrolled at the Lovanium University, a new Belgian-run college in the Congo staffed entirely by Belgian academics. But the political situation was growing increasingly unstable.

"I remember sitting my pre-clinical exams in the middle of a riot, with shots being fired at the windows," says Lejeune, who despite such distractions still passed with flying colours. In 1960 the Congo gained independence and the Lejeune family relocated to Belgium, with Ferdy switching his medical studies to the Université Libre de Bruxelles. One important legacy from the Congo years was



that it was there Lejeune met his future wife, Claudine Lenain, a biochemistry student. The couple, who married in 1962, recently celebrated their 45th wedding anniversary.

In Belgium Lejeune gained clinical experience at the Jules Bordet Cancer Institute, and felt drawn to oncology. "I appreciated the need for research, because so little was known about cancer. I felt particularly interested in melanoma, since one-third of people getting this cancer are under 40."

In 1970, after training in surgery (where he did breast and melanoma cancer surgery), Lejeune was awarded an International Agency for Research on Cancer (IARC) grant to work at the Chester Beatty Research Institute at the Royal Marsden Hospital in London. At the same time his wife Claudine had been awarded a Royal Society fellowship to research radio-immune assays at the Middlesex Hospital, also in London. Lejeune was trained in electron microscopy by Michael Birbeck (who gave his name to the Birbeck organelles), and used this newly acquired expertise to study melanoma cultures with Peter Alexander and Gordon Hamilton Farley.

Lejeune discovered that there were macrophages within the tumour that were not malignant and were able to eat away at the melanoma cells. The work formed the basis of his PhD thesis (awarded in Belgium in 1976) showing that macrophages are cytotoxic to melanoma.

Magic bullet with a dark side

In 1975 Lloyd Old from the Sloan-Kettering Institute identified 'tumour necrosis factor', or TNF, as the substance secreted by macrophages that attacked tumours. Along with interferon and interleukin, TNF was heralded as one of the most promising 'magic bullets' in molecular biology's assault on cancer, and the race was on to clone the gene. By

By 1988 TNF was being described as a molecule with "too much toxicity and too little efficacy"

1984, the availability of recombinant TNF had paved the way for extensive studies in animals. But to everyone's surprise the studies proved disappointing. TNF had antitumour properties, but it was also a mediator of septic shock and caused hypotension. By 1988 TNF was being described by the *New York Times* as a molecule with a "dark side", with "too much toxicity and too little efficacy".

Back at the Jules Bordet, Lejeune established a thriving melanoma clinic, attracting patients from all over Belgium. The London experience had got him "well and truly hooked on tumour immunology", and he negotiated to spend half his time running a lab exploring the biology of melanoma.

In one of those career-defining, serendipitous moments, Lejeune was offered free access to the disgraced TNF by a drug rep visiting his clinic. "Chance smiles on those with a prepared mind," says Lejeune. "I thought TNF might enhance the melphalan cocktail we were already using in isolated limb perfusion."

Working with Danielle Lienard, Lejeune was performing an innovative procedure known as 'isolated limb perfusion' (ILP) in patients with intransit melanoma metastasis confined to the limb. ILP involved tying off the affected limb from the rest of the body with a surgical tourniquet to minimise the systemic effects of chemotherapy, and subjecting the tissues to high doses of melphalan. Since the treated limb is attached to a heart lung machine, there's no limit to how long it can be exposed to the drug. While elegantly simple in concept, the procedure is technically complex, requiring continuous monitoring of leakage by introducing radio-labelled proteins and probe recording over the heart.

Prior to ILP, intransit melanoma metastasis (a condition occurring in 5%–8% of melanoma patients) was largely treated by palliative amputation. The introduction of ILP with melphalan produced a complete response rate of 50 %.

"We just copied what we were already doing with chemotherapy, and gave ten fold the maximum tolerated dose of TNF. The effects were awesome," recalls Lejeune, who acknowledges that he benefited from the regulations being "extremely relaxed" in Belgium. "We saw something that's very uncommon in oncology – the effects of therapy could be seen in a few hours. The tumours just melted away."

To achieve an even better result, Lejeune devised a combination therapy with TNF, melphalan and gamma interferon. The triple therapy was well tolerated with a complete response rate of around 80%, and an overall objective response greater than 90%. In soft tissue sarcomas that are inextirpable, the technique has resulted in salvage in 80% of cases, a complete response rate of 20% and an objective response rate of 80%. There is, however, no effect on overall survival in either melanoma or sarcoma.

From the outset Lejeune was not without detractors who told him TNF would kill patients. Here he acknowledges the debt he owes Alexander (Lex) Eggermont, now professor of surgical oncology at the University of Rotterdam in the Netherlands, who believed in the data at a time when everyone else put the positive results down to "hyperselection" of patients. "Alexander persuaded his hospital authorities to implement an ILP-TNF programme. Ultimately it was thanks to our synergy that we persuaded Boehringer Ingelheim to invest in the clinical programme, resulting in the development of the appraisal file," says Lejeune.

Today ILP-TNF is widely acknowledged as a

"We gave ten fold the maximum tolerated dose. The effects were awesome"

The TNF trio. Lejeune (left) with Danielle Lienard and Lex Eggermont, Rotterdam 1996

success story for both melanoma and sarcoma, and is available at 40 hospitals in Europe. Triple therapy is recognised as one of the first attempts at combining immunotherapy and chemotherapy.

Later, working with Curzio Ruegg in Lausanne, they demonstrated that the antivascular activity of TNF results from reduced activation of the adhesion receptor integrin alpha(v) beta(3), which decreases endothelial cell adhesion and blood vessel survival. Further elucidating the mechanisms mediating suppression of integrin, he says, could result in more specific and less toxic TNF treatments.

"Ultimately our work on TNF and integrins sensitised the medical world to the importance of blood vessels in cancer treatment and encouraged people designing anti-angiogenic drugs," says Lejeune.

In 1992 Lejeune was appointed professor of oncology and director of the Multidisciplinary Oncology Centre at Lausanne University Hospital. He had a joint appointment with the Ludwig Institute for Cancer Research, where he was recruited as a clinician with experience in basic science to enhance the translational aspects of Jean-Charles Cerottini's melanoma vaccine research programme.

Slow progress

Treatment options for melanoma have advanced little over the course of Lejeune's forty-year career – surgery is limited to early tumours, regional treatment has only a regional effect with little influence on survival, and there is still no standard of care for stage IV disease. Even the much-touted immuno-therapy still hasn't reached the point of showing a clinical effect.

As chairman and secretary of the EORTC Malignant Melanoma Cooperative Group, Lejeune was instrumental in initiating a number of key melanoma trials, but with disappointing results. In two separate phase III EORTC studies, the group, then led by Lex Eggermont and Ulrich Keilholz, showed that combining cisplatinum plus DTIC (dacarbazine) chemotherapy with either interferon alpha and interleukin 2, or with interferon alpha alone, produced no survival benefits in metastatic melanoma. "Such studies are enormously important because, for me, giving false hope is worse than discovering a treatment to be ineffective," he says.

One reason melanoma has proved so challenging, suggests Lejeune, is that melanocytes come from the ectoderm and are endowed from the outset with the capacity to migrate through the body and invade tissue. "We just need to find melanoma's Achilles heel and decipher the molecular mechanisms responsible for melanoma's high metastatic capacity," says Lejeune, who refuses to be disheartened by the current lack of progress.

He is dismissive, however, of the hundreds of 'promising' agents for melanoma that are touted in journals and at meetings, but which then regularly bomb in clinical trials. "Pharma companies just don't appreciate that implanting pea-like tumours under the skin of mice produces tumours with totally different biological properties from a true metastasis. Progress won't be made unless they start to introduce better animal models."

"Our work on TNF sensitised the medical world to the importance of blood vessels in cancer treatment"

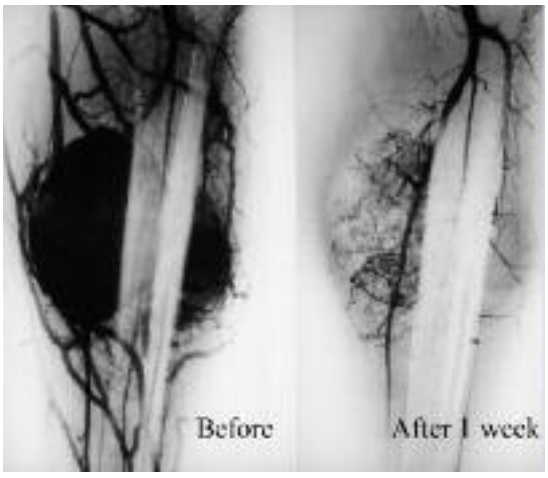
He is dismissive of the hundreds of 'promising' agents for melanoma touted in journals and at meetings

Towards a vaccine

Since joining the Ludwig Institute 15 years ago, Lejeune and his colleagues have been engaged in the quest for the holy grail of melanoma research – an effective vaccine. The team have progressed from injecting tumour cells to utilising the pure peptides found on the surface of tumour cells recognised by lymphocyte receptors. But the whole area has proved unexpectedly complicated. "We've discovered there are several steps in the maturation of lymphocytes, using new tools to gauge whether the resulting lymphocytes are mature enough to kill," says Lejeune.

More recently, they discovered in an *in vivo* model of melanoma that, while CD8 T cells generated in peptide vaccination display robust cytotoxic actions in blood, those extracted directly from tumours are not active. "It appears there's something in the tumour milieu preventing lymphocytes from becoming killers," says Lejeune, who hopes that greater understanding of the mechanism involved will ultimately improve the efficacy of immunotherapy.

The Lausanne team has succeeded in curing mice with a 10^5 melanoma tumour load (100,000 cells, roughly 1/10,000 of 1 cm^3) through vaccination, but found it impossible to cure higher loads.



For the last four years the group has participated in clinical trials, vaccinating patients with metastasis in one lymph node.

But the real future of melanoma vaccination, says Lejeune, may be in protecting individuals deemed to be at high risk of developing the disease.

Lejeune has always been an advocate of melanoma prevention. There are two strategies, he maintains. Persuade people to refrain from sun exposure and make them aware of early warning signs.

"The messages are getting through – the incidence of big melanomas has gone down, and small melanomas up, suggesting earlier diagnosis is occurring. But we're still not identifying medium-sized melanomas quickly enough, and this is serious since any melanoma over 1 mm in thickness can metastasise."

Surprisingly, Lejeune doesn't advocate use of sun screen. In 1999 he took part in a double blind study randomising Swiss and French students to either (sun protection factor) SPF 10 or SPF 30 before they embarked on their holiday. Sun exposure diaries revealed that those allocated the higher factor had 25% longer sun exposure.

The longer exposure, it seems, was subconscious – sun screens delayed sunburn so people felt able to stay out longer. "But burning is a good sign. Burnt cells die, they don't mutate," says Lejeune. "To me the best protection remains wearing a hat and staying in the shade."

Unproven medicines

One negative aspect to practising medicine in Switzerland, he has found, is the tolerance of alternative/complementary medicine. "About 50% of melanoma patients use complementary medicine and I was really shocked when the minister of health decided to allow insurance companies to

Melted away. High-dose TNF has a dramatic impact on leg sarcoma associated vasculature and spares vessels in normal tissues

Student days. Lejeune met his future wife, biochemistry student Claudine Lenain, while studying medicine at a Belgian-run college in the Congo

reimburse alternative medicine without any proof of efficacy," says Lejeune.

His outrage launched his son Stephane on a career debunking complementary medicine. Stephane, who is now married with a daughter, trained first as a sociologist, did his masters in public health and epidemiology and now works for the EORTC. He was instrumental in gaining EORTC funding from the European Commission's 5th Framework to review scientific evidence on complementary medicine and launch a website providing information on the efficacy and safety of alternative medicines used in cancer for the public and health professionals.

Lejeune and his wife also have a daughter, Padmini, whom they adopted in 1978. "Padmini came to us at the age of eight from Madras. She adapted quickly to life in Belgium and spoke fluent French after just three months," remembers Lejeune.

Today Padmini is a dress designer in Belgium and, in addition to looking after two young children, has established her own dress label, making garments with Indian material for Western women.

"It's perfect – Padmini is based in Brussels, but travels regularly to India to source material and keep in touch with her roots."

When Lejeune 'retired' in 2004, his wife and children hoped he'd spend more time with them in Brussels. But today he remains very much at the forefront of melanoma research, and the fact that he no longer has an administration or surgery role gives him the time to think and explore ideas. "I hate games and playing cards and have an obsession with keeping useful," he says.

He still gains enormous pleasure from editing *Melanoma Research*, the translational research journal he launched 17 years ago with Giuseppe Prota and Patrick Riley. Recently, without the pressure to publish, he has found time to write reviews pulling together the latest information on TNF and metastatic melanoma.

A new retirement venture is as a freelance evaluator for a privately owned Swiss research and development company that specialises in partnering opportunities with promising biologics and small-molecule drug candidates.

"In my journal work I've access to developments six months ahead of publication. But here I'm getting fascinating insights into the drugs that'll be around 10 years into the future," says Lejeune.

One hobby he does, however, find time to follow is scouring antique markets for African masks. "I'd completely forgotten about Africa until I came to Lausanne, where something about the reflection of the light from the lake brought it all back and gave me a yen for African culture," says Lejeune, who has accumulated a collection of 30 masks.

"Traditionally the masks are regarded as being inhabited by the spirit of the ancestors, with the concept that everything that happens in life is due to your forebears. I'm very receptive to this message, because as a scientist I make the link between the genes of my ancestors and the masks."

NEWSROUND

Selected reports edited by Hannah Brown

Chemotherapy for rare childhood brain tumours

→ The Lancet Oncology

Intensive chemotherapy can be used to delay radiotherapy in children with ependymomas, a rare type of childhood brain tumour that is usually large and difficult to remove. These cancers arise mostly in children younger than five years, so delaying or eliminating the requirement for radiation treatment to the developing brain could reduce the risk of later cognitive problems.

Adjuvant chemotherapy is usually part of the treatment schedule for patients with these tumours, due to the difficulty of complete surgical excision. However, no standard regimen is universally used. Radiotherapy is effective, but its delivery is complicated by the fact that it may cause damage that leads to lower IQ, short-term memory problems and other cognitive defects.

To study maximally intensive chemotherapy strategies that could delay radiotherapy, the United Kingdom Children's Cancer Study Group/International Society of Paediatric Oncology undertook a study in children younger than three years. Radiotherapy was reserved only for those with resistant recurrent tumours.

Eighty-nine children with ependymomas were enrolled from 21 participating centres between 1 December 1992 and 31 April 2003. All patients were first treated with surgery before being given chemotherapy, comprising blocksof myelosuppressive treatment (carboplatin and cyclophosphamide) alternated with non-myelosuppressive treatment (cisplatin and high-dose methotrexate) at 14-day intervals.

After the treatment, 59 of the patients progressed and 37 of these subsequently died. Median time to progression was 1.6 years (range 0.1–10.2), but five-year overall survival was an encouraging 63.4%. "The median delay to radiotherapy was 20.3 months, and the median age at irradiation was 3.6 years," report the authors, adding, "The original aim of avoiding or delaying radiotherapy in these children without compromising outcome has been achieved. Our results confirm a role for primary chemotherapy in young children with intracranial ependymoma."

According to an accompanying commentary, however, these results are something of a surprise, given that other attempts at deferring radiotherapy have been less successful. What is more, the absence of data for response to chemotherapy is a major limitation in the interpretation of these promising results. "To justify the continuation of such a strategy, the study needs to prove that there are young children that will not be left with impaired neurocognitive abilities as a result of prolonged chemotherapy," the commentators write.

■ Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study. RG Grundy, SA Wilne, CL Weston et al, for the Children's Cancer and Leukaemia Group (formerly UKCCSG) Brain Tumour Committee. *Lancet Oncol* August 2007, 8:696–705

■ Paediatric ependymomas: should we avoid radiotherapy? [Editorial] E Bouffet, U Tabori, U Bartels. *ibid* pp 665–666

■ Primary radiotherapy for childhood ependymoma? [Editorial] DA Hamstra *Lancet Oncol* September 2007, 8:758–759

Immunotherapy no better than dacarbazine in melanoma

→ Annals of Oncology

Combined immunotherapy with histamine dihydrochloride, interleukin-2 and interferon-alpha 2b offers no significant benefit in terms of survival and extent and duration of tumour response over dacarbazine treatment for patients with stage IV melanoma.

In vitro and *in vivo* studies have previously suggested that the combination of dihydrochloride and interleukin-2 is more effective at destroying malignant cells than either compound individually. What is more, clinical studies in melanoma show that cytotoxic lymphocytes are more efficiently activated by systemic treatment with the combination than with interleukin-2 monotherapy.

To test this idea further, Middleton and colleagues recruited 241 patients over 18 years old who had histologically proven stage IV melanoma with a life expectancy greater than three months from 43 centres in Australia, Canada, Germany, Israel, Sweden and the UK. Between February 1998 and October 2000, patients were stratified on the basis of liver metastases at baseline (present or absent) and then randomised to either an immunotherapy combination of dihydrochloride, interleukin-2 and interferon-alpha 2b or to dacarbazine. Follow-up continued until June 2002.

Although the duration of response and survival were slightly longer in the combination group than in the dacarbazine group, these differences were not statistically significant. The results for other secondary endpoints were similar between groups.

"Immunotherapy regimens may yet provide treatment alternatives for patients with stage IV melanoma, but this immunotherapeutic regimen did not improve upon the response rate and overall survival seen with dacarbazine," the authors conclude.

■ Results of a multicenter randomized study to evaluate the safety and efficacy of combined immunotherapy with interleukin-2, interferon-α2b and histamine dihydrochloride versus dacarbazine in patients with stage IV melanoma. M Middleton, A Hauschild, D Thomson et al. *Ann Oncol* October 2007, 18:1691–1697

Radiofrequency ablation of liver metastases can extend survival

➔ Annals of Surgery

Radiofrequency ablation – a technique that involves inserting a special needle electrode into tumours to destroy them through heat from the inside – may help improve survival for patients with liver metastases from colorectal cancer whose lesions are unresponsive to chemotherapy and too widespread for surgery, according to an observational study.

Twenty-five percent of patients who present with colorectal cancer already have liver metastases and, within five years of diagnosis, 50% of those initially lacking obvious metastases will have evidence of cancer spread. Because this distant disease is associated with poor outcomes – less than 1% of patients with untreated liver metastases will be alive four years after diagnosis – and because in many patients the only site of metastases at death is the liver, effective treatment of these lesions could have substantial implications for survival.

Allan Siperstein and colleagues from San Francisco and Cleveland investigated the potential of this treatment in patients who were not candidates for surgery and in whom chemotherapy had failed. They designed a prospective study of 234 patients (81 women and 153 men) who were prescribed radiofrequency ablation for metastatic colorectal adenocarcinoma over a 10-year period beginning in May 1997. All of the patients involved in the study had failed chemotherapy and had an average of 2.8 liver lesions.

CT scans were done before and after the procedure and the patients were assessed for their number of lesions, size and location of defects, presence of disease outside the liver, and some liver function tests. Researchers followed the progress of the patients until the study came to an end in December 2006. They noted progression of disease in the treated areas of the liver, evidence of new disease either within or outside the liver, and death. The median follow-up was 24 months and 148 patients died during the study period.

For the whole group, three- and five-year survival data showed that radiofrequency ablation produced 20.2% and 18.4% survival rates, respectively. The number of liver lesions at diagnosis was found to be statistically linked to survival. Patients presenting with between one and three lesions had a median survival of 27 months versus 17 months in those presenting with more than three lesions. Lesion size was also found to be statistically significant: lesions smaller than 3 cm were associated with a median survival of 28 months compared with 20 months for lesions greater than 3 cm. One particularly interesting observation was the lack of a statistically significant difference in benefit from the treatment when the patients were divided up by stage of disease at presentation, leading the authors to conclude that "all patients despite initial stage derived survival benefit from RFA."

Overall, the authors say of their findings: "Previous to local therapies this subgroup of patients had virtually no survivors at five years, whereas our study demonstrates an 18.4% five-year survival rate."

■ Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. AE Siperstein, E Berber, N Ballem et al. *Ann Surg* October 2007, 246:559–567

CT versus colonoscopy for colon cancer screening

➔ New England Journal of Medicine

Computed tomography colonography may provide a more targeted screening approach for prevention of colorectal cancer than optical colonoscopy, according to the results of a prospective study.

Researchers from the University of Wisconsin analysed the clinical databases from parallel computed tomography and colonoscopy screening programmes at a single institution, which drew participants from the same geographical region, in order to evaluate the diagnostic yield of each approach. A total of 3,120 consecutive patients who were undergoing computed tomography during a 25-month period and 3,163 consecutive patients who had colonoscopy screening during a 17-month period were included in the analysis.

The researchers also identified all pathologically proven neoplasia that were detected by each screening method from the pool of resected polyps, and compared the prevalence of high-grade dysplasia, invasive adenocarcinoma and overall advanced neoplasia in each study group.

Similar diagnostic yields and detection rates for advanced adenomas were obtained in both programmes, and there was no statistical difference between the groups in terms of the num-

ber of large or small advanced adenomas that were removed. However, the number of polypectomies performed to achieve these similar outcomes differed significantly between the two groups, with more than four times as many polyps removed in the colonoscopy group as in the computed tomography group. Serious adverse events during primary colonoscopy screening included colonic perforation in seven patients (0.2%) and, in four of these, surgical repair was required. During primary computed tomography screening, there were no perforations or other serious complications.

"The marked decrease in the use of [optical colonoscopy; OC] and total rates of polypectomies in the [computed tomography] group suggests that this technique is a safe, clinically effective, and cost-effective filter for therapeutic OC. Furthermore, by combining primary CTC [computed tomography colonography] and primary OC screening efforts, with the choice between tests driven by patient preference, the overall screening compliance for total colonic examination could substantially increase."

■ CT colonography versus colonoscopy for the detection of advanced neoplasia. DH Kim, PJ Pickhardt, AJ Taylor et al. *N Engl J Med* 4 October 2007, 357:1403–1412

Probiotics improve chemotherapy tolerability

→ British Journal of Cancer

Dietary supplementation with probiotic bacteria and fibre can help improve the tolerability of chemotherapy for colorectal cancer, according to a recent prospective study.

Regimens containing fluorouracil and leucovorin have long been standard adjuvant chemotherapy agents in colorectal cancer but they cause diarrhoea, which is one of the most troublesome adverse effects related to cancer chemotherapy. Excessive bowel motility may be reduced using drugs such as loperamide and somatostatin analogues, but these treatments are associated with adverse effects, so safer interventions are needed.

Some studies have suggested that administration of micro-organisms such as *Lactobacillus rhamnosus GG* with standard rehydration therapy could reduce the duration of diarrhoea by stimulation of the proliferation of bowel epithelial cells, secretion of protective mucins, and stimulation of local and systemic immune response to pathogens.

This study assessed the efficacy of *L. rhamnosus GG* and guar gum supplementation in reducing fluorouracil-based chemotherapy toxicity. The researchers also compared frequency of diarrhoea related to two different chemotherapy schedules.

A total of 150 study participants who had undergone surgery for either Dukes' B or C colorectal cancer or metastatic colorectal cancer were involved. All patients received adjuvant chemotherapy following surgery and were randomised to either the Mayo regimen (where the drugs are given in bolus injections only) or the simplified de Gramont regimen (in which bolus injections are accompanied by a 48-hour continuous infusion). *L. rhamnosus GG* was administered orally as gelatine capsules twice daily during the 24 weeks of adjuvant cancer chemotherapy, and guar gum containing nutritional supplement was administered daily, on cycle days 7–14, for eight days per month.

The simplified de Gramont regimen was found to be better tolerated than the Mayo regimen, in line with previous findings. Patients who received *Lactobacillus* during chemotherapy reported less abdominal discomfort than those who did not receive it, and these subjects had also fewer chemotherapy-dose reductions, which might have an impact on chemotherapy efficacy. Since *Lactobacillus* supplementation appears to have few or no adverse effects, the capsules are simple to administer, and they are associated with low costs, the authors conclude that "daily oral administration of *L. rhamnosus GG* may reduce the frequency of severe 5-FU-based chemotherapy related diarrhoea, whereas fibre supplementation may be of little benefit."

■ *Lactobacillus* supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. P Österlund, T Ruotsalainen, R Korpela et al. *Br J Cancer* 16 October 2007, 97:1028–1034

Prophylactic mastectomy rates increasing

→ Journal of Clinical Oncology

More and more women diagnosed with breast cancer are opting for surgery to remove their non-cancerous breast to cut the risk of new cancers developing, according to an analysis of the prevalence of preventive mastectomy over time.

Todd Tuttle and colleagues from the University of Minnesota used the Surveillance, Epidemiology and End Results (SEER) cancer registry public-use database to examine rates and trends of prophylactic mastectomy of the non-involved breast in women with unilateral breast cancer from 1998 through 2003.

Over the six-year study period, 152,755 women registered in the SEER database were diagnosed with unilateral breast cancer and treated with surgery. Most underwent either breast conserving surgery (57.8%) or a unilateral mastectomy (38.9%), but 4,969 underwent a contralateral prophylactic mastectomy.

Young women were more likely than older ones to opt for this procedure: 6.7% of all surgically treated patients aged 39 or younger underwent non-cancerous breast removal, as compared with only 1.3% of women in their 70s.

Lower tumour grade and negative lymph node status were associated with a significantly higher rate of contralateral mastectomy. Rates increased by 150% for all stages of breast cancer over time, and these trends continued to the end of the study period with no plateau effect.

"These findings represent a dramatic change toward more aggressive breast cancer surgery in the United States," claim the authors. "Still, the rate of BCS [breast conserving surgery] also increased during our study period. Thus, patients are increasingly choosing between minimal surgery or more aggressive surgery (bilateral mastectomy) instead of unilateral mastectomy," they report.

"The decision to undergo [contralateral prophylactic mastectomy; CPM] is complex, and many factors are likely to contribute to its increased frequency. Nevertheless, patients with

unilateral breast cancer have options that are less extreme than CPM. Surveillance with clinical breast examination, mammography, and newer imaging modalities such as breast magnetic resonance imaging may detect cancers at earlier stages… Future prospective studies are critically needed to evaluate the decision-making processes leading to CPM," they conclude.

■ Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. TM Tuttle, EB Habermann, EH Grund et al. *J Clin Oncol* published online 22 October 2007, doi: 10.1200/JCO.2007.12.3141

Radiotherapy plus tamoxifen shows mixed results in breast cancer

→ European Journal of Cancer

Adding radiotherapy to tamoxifen treatment improves outcomes 5-10 years after treatment in women with stage II breast cancer, but late side-effects of radiation mean the combination does not significantly alter the incidence of systemic disease 20 years later, according to the long-term results of a trial first initiated in 1978, when the standard treatment for breast cancer was mastectomy and postoperative radiotherapy.

The original purpose of the study, part of a breast cancer care programme in southern Sweden, was to evaluate the effect of one year of tamoxifen treatment, both as an addition to radiotherapy and an alternative.

Postmenopausal women with stage II breast cancer who were younger than 71 years and had undergone modified radical mastectomy were offered inclusion in the trial. A total of 724 patients were randomised from 1978 to 1985 and, of these, 668 were fully evaluable. Women were randomised to three treatment alternatives: postoperative radiotherapy, radiotherapy and tamoxifen for one year, and tamoxifen alone.

Radiotherapy consisted of 45 Gy to the fossae, 48 Gy to the axilla and parasternal nodes and 38 Gy to the chest wall. All fields were treated once daily, split into two series, 12+8 fractions, with a three-week interval, commencing within four weeks after surgery. Ten milligrams of oral tamoxifen was given three times daily, starting at the same time as radiotherapy, for patients assigned to both treatments. According to the protocol from 1978, the study endpoints were time to recurrence, type of recurrence and overall survival.

For the long-term analysis, the researchers included additional endpoints of time to systemic disease, incidence of other events, and side-effects. After a median follow-up of 23 years, there was a very clear relative reduction in loco-regional recurrences of 71% for those undergoing radiotherapy, but no effect was evident in patients with no lymph-node metastases.

Radiotherapy as an adjunct to tamoxifen treatment did not significantly lower the cumulative incidence of systemic disease or survival at 20 years. However, the effect varied over the follow-up period: during the first 5–10 years, radiotherapy plus tamoxifen showed better outcomes than tamoxifen alone, but during the period 10–20 years, the survival curves merged and finally crossed over, suggesting radiotherapy influenced late mortality.

The authors speculate that modern radiotherapy techniques may decrease the associated late side-effects and conclude that, overall, the trial "strengthens the case for postmastectomy radiotherapy for breast cancer patients with 1–3 lymph node metastases."

■ Radiotherapy and tamoxifen after mastectomy in postmenopausal women – 20-year follow-up of the South Sweden Breast Cancer group randomised trial SSBCG II:I. F Killander, H Anderson, S Rydén et al. *Eur J Cancer* September 2007, 43:2100–2108

European Commission lifts threat over MRI

→ European Commission

The European Commission has proposed postponing, until 30 April 2012, the deadline for introducing legislation on workers' exposure to electromagnetic fields. The decision lifts a threat hanging over the use of MRI in Europe and comes in response to a year of heavy lobbying by the Alliance for MRI, a coalition of European parliamentarians, patient groups, leading European scientists and the medical community.

The EU Physical Agents (EMF) Directive was intended to protect the health and safety of people working in the vicinity of strong electromagnetic fields. The unintended effect, however, would have been to effectively end the use of MRI in the diagnosis and treatment of patients and for research. The Alliance had estimated this would affect some eight million patient examinations a year, resulting in unnecessary deaths.

Vladimír Špidla, EU Commissioner for Employment, Social Affairs and Equal Opportunities, said, "The Commission remains committed to the protection of the health and safety of workers. However, it was never the intention of this Directive to impede the practice of MRI. Obviously, the Commission recognises MRI as a technology offering clear benefits to patients, and continues to support MRI research financially. Postponement of the transposition will allow time to review the current Directive and amend those provisions which have been shown to be problematic by recent scientific studies."

Gabriel Krestin, a leading member of the Alliance for MRI and professor of radiology at the Erasmus University Medical Centre in Rotterdam, welcomed the decision. "We look forward to working with the European Commission prior to the proposal to amend the Directive," she said. "It is essential that the European Commission assesses closely the full impact the directive will have, taking into consideration the social, economic and environmental impact of the legislation. Any new legislation must be evidence-based and founded on sound science. There has been no proven harmful effect of MRI to either patients or workers over the past 25 years, during which time over 500 million examinations have been undertaken."

The Alliance for MRI has indicated that it will be seeking a derogation for MRI from the scope of the EU Physical Agents Directive to ensure the future unimpeded use of MRI, particularly for cutting-edge research and interventional MRI.

Does adjuvant radiotherapy increase survival in patients with Merkel cell carcinoma of the skin?

Marc Bischof

The findings of a large retrospective study show that postoperative radiotherapy is associated with a significant improvement in survival, and is indicated in all patients with local or locoregional Merkel cell carcinoma.

The aggressive nature of Merkel cell carcinoma (MCC), combined with high recurrence rates, frequent regional lymph-node metastases and the well-known radiosensitivity of this disease, indicate that a therapeutic regimen combining surgical excision and postoperative radiotherapy should be used to improve local control.

The optimum treatment regimen for MCC remains unclear, however, as the low worldwide incidence of this disease means that only small, retrospective series have been published.

The particular importance of the large series studied by Mojica et al. (see opposite) is that the analysis shows a significant improvement in survival after postoperative radiation therapy. The Surveillance, Epidemiology, and End Results (SEER) programme of the National Cancer Institute, from which data were obtained for this study, did not collect information about local recurrences, so the effect of radiation therapy on this outcome could not be studied. Local recurrence rates have been reported to be as high as 80% after surgical resection alone.[1] The superiority of adjuvant radiotherapy over surgery alone in preventing local recurrences is supported by the findings of various smaller series that each included up to 50 patients.[2] Medina-Franco et al. found a highly significant improvement in local control with adjuvant radiotherapy in a literature review of 1,024 cases.[3] Even the controversial study by Allen et al., who identified no significant improvement of locoregional control after adjuvant radiotherapy, showed nodal recurrence rates of 26% in the group treated with surgery alone, compared with 13% in the group with postoperative radiotherapy. It is possible that significance was not achieved because only a minority of patients (17%) received radiotherapy.[4] It can be supposed, however, that intensified local therapy consisting of surgical resection and postoperative radiotherapy results in better local control, which can be translated into better survival, as shown by Mojica et al.

Mojica et al. discuss the lack of information in the SEER programme

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Synopsis

Pablo Mojica, David Smith and Joshua DI Ellenhorn (2007) **Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin.** *J Clin Oncol 25:1043–1047*

Background. Merkel cell carcinoma (MCC) is a relatively rare, but aggressive, skin cancer, with a high propensity for local recurrence and regional and distant metastases. Most data on MCC are from single-institution retrospective analyses, making it difficult to assess the role of adjuvant radiation therapy in the treatment of this disease. Surgical resection of the primary tumour with extensive margins is the main form of therapy.

Objective. To analyse the role of adjuvant radiotherapy in patients undergoing surgical excision for MCC.

Design and intervention. Data extracted from the Surveillance, Epidemiology, and End Results (SEER) programme of the National Cancer Institute were used to identify patients diagnosed with MCC between 1973 and 2002. Information regarding patient demographics, treatment modalities and tumour characteristics was reviewed. Tumour characteristics documented included site of primary tumour, size at presentation, nodal status of the disease and whether distant metastases were present. Information was available on what surgery was performed at the primary site and lymph nodes, and on the use of adjuvant radiation therapy, but not on the use of chemotherapy or the use of sentinel node biopsy.

Outcome measure. The primary end point of the trial was overall survival.

Results. The SEER registry contained 1,665 cases of MCC over the time period reviewed, with surgery being a component of therapy in 89% of cases (n=1,487). The overall median follow-up was 40 months and the overall median survival was 49 months. Excision or re-excision or minor amputation without lymph-node dissection was performed in 82% of the surgical cohort (n=1,214), and extended surgery with lymph-node dissection or major amputations was performed in 10% of this cohort (n=135). External-beam radiation was the type of radiotherapy most frequently used (98%). Median overall survival was 63 months in patients who received adjuvant radiation therapy and 45 months in patients who did not (P=0.0002). On multivariate analysis, the association of adjuvant radiation therapy with survival was statistically significant (P=0.0122). The use of adjuvant radiation therapy was associated with improved overall median survival across all age groups. When the results were stratified by tumour size, adjuvant radiation therapy was associated with an improved overall median survival in patients with tumours <1 cm in size (from 48 to 93 months; P=0.0447), in patients with tumours 1–2 cm in size (from 52 to 86 months; P=0.0126) and in patients with tumours larger than 2 cm (from 21 to 50 months; P=0.0003).

Conclusion. There was a positive association between adjuvant radiation therapy and overall survival, which remained statistically significant on multivariate analysis.

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

regarding resection status, resection margins and the number of patients with lymph-node dissection. A majority of published series have the same limitations, because of the small numbers of patients and varying treatment paradigms used in different centres and regions and over long study periods. Additionally, because of problems in diagnosis of this rare tumour, patients are often administered adjuvant radiotherapy after excision of the first or second local recurrence.

The implementation of therapy standards for treatment of MCC is of even greater importance now than ever before, because the incidence of this tumour has tripled in the last 20 years. This increase is possibly related to an enhanced awareness of the diagnostic criteria of MCC, including immunohistochemical assessments, which allow a better distinction between MCC and other skin tumours.

Nevertheless, while there is no published evidence from randomised trials to suggest otherwise, postoperative radiotherapy, which is associated with a low risk of complications, is the suggested treatment for MMC. This recommendation is supported by the important findings of Mojica et al.

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Surviving childhood cancer

It's the journey of a lifetime

Peter McIntyre

Childhood cancer is increasingly about being cured. But developing bodies can suffer life-long damage from toxic treatments, and developing personalities become moulded by the experience of battling cancer and living with uncertainty. In the third part of our series on *Living with the consequences*, survivors and doctors talk about managing a journey that never ends.

First, there is the journey through cancer. Then, with luck and good treatment, the journey beyond cancer. Aemilia Tsirou was diagnosed with acute lymphoblastic leukaemia (ALL) at the age of eight, and 20 years later is helping to organise survivors of childhood cancer throughout Greece. She references a modern classic fantasy to illustrate their quest.

"In *Lord of the Rings*, Frodo had to take a bad thing, the ring, and carry it on a dangerous journey in order to destroy it. To get there he has to pass through many dangerous places, a forest of darkness, oceans, mountains, but he got there and he managed to destroy it.

"The majority of us who have survived realised that we could not do anything except live, and that the way to live is to fight it. After some days in the hospital you know that not everybody survives, but you try to have a very positive idea about life. This makes us stronger definitely, that we are survivors and winners."

Aemilia is a role model for children currently undergoing treatment who need to know that there is life after cancer and their lives can return to 'normal'. There is and they can, but their lives are always likely to be a bit different, even after the cancer is pronounced cured. For some there are long-term side-effects of surgery, radiotherapy or chemotherapy. For others there is the risk of the return of their cancer, or of a new cancer related to the treatment they received. Bad things happened before and could happen again.

As they grow into adulthood, some must overcome psychological barriers to becoming what a team of global experts set as a long-term aim: "a resilient, fully functioning, autonomous adult with an optimal health-related quality of life, accepted in the society at the same level of his/her age peers" (see the Erice statement, p 59).

The prospects for children with cancer have been revolutionised over the past 40 years. In the mid-1960s the five-year survival rate for children with ALL was under 5%. By the mid-1990s five-year survival was over 80% and still rising. For retinoblastoma and a few other childhood cancers five-year survival is around 96%. The rule of thumb is that more than two-thirds of childhood cancers (and in many places, more than 70%) can be cured with good-quality care at specialised cancer centres. Of course, this only applies in countries with well-developed health systems – which excludes 80% of the world's children.

PETER MCINTYRE

A role model. Twenty years after being treated for ALL, Aemilia Tsirou offers herself as living proof to young patients that there is life after cancer. She is pictured here at the Athens centre of the Floga parents' group, with a puzzle she made for young people undergoing treatment

About one in 500 children develop cancer. As more children survive, the number of survivors living as adults accumulates, and will exceed one in 700 adults. In the US alone, there are already more than 270,000 adult survivors of childhood cancer. The numbers in Europe also run into six figures.

According to the US Institute of Medicine, more than two-thirds of childhood cancer survivors experience some form of late effects, some of them serious or fatal. The largest study undertaken of five-year survivors showed a 10.8-fold increased risk of death in subsequent years covered by the study, which rose to 18-fold in females, although most of these deaths were from a recurrence of their original cancer rather than late effects related to treatment.

This US study (Mertens et al. *J Clin Oncol* 2001) looked retrospectively at what had happened to 20,000 people who had survived at least five years after diagnosis of childhood cancer. By the time of the study, 18,000 were still alive and 2,000 had died. Of these seven in ten had died from a recurrence, and two in ten had died because of late effects.

Another study on the same American cohort found that 73% of survivors had at least one chronic health condition, while 42% had a grade 3–5 chronic condition (severe, life-threatening or fatal). Long-term survivors were eight times more likely to have a severe or life-threatening condition than their siblings (Oeffinger et al. *NEJM* 2006).

These figures are alarming, but neither study is an accurate guide to current risks. Hamish Wallace, consultant paediatric oncologist at the Royal Hospital for Sick Children Edinburgh, points out that the US cohort was hospital-based and may over-represent problems. Moreover, all the survivors were diagnosed between 1970 and 1986, when chemotherapy and radiotherapy was used most intensively.

The prospects for children have been revolutionised over the past 40 years

LATE EFFECTS OF TREATMENT FOR CHILDHOOD CANCERS

Late effect	Probable treatment cause
Breast cancer	Radiation to chest exceeding 40 Gy
Thyroid and other cancers Hypothyroidism and other thyroid dysfunction Decline in cognitive function	Cranial radiotherapy; radiotherapy to the neck; chemotherapy; cranial radiotherapy
Congestive cardiac failure Cardiac disease	High doses of anthracyclines; irradiation at higher doses
Pulmonary fibrosis, pulmonary toxicity, restrictive lung disease	Chemotherapy or radiotherapy
Growth problems and obesity	Cranial radiotherapy; bone marrow transplant (with radiotherapy); chemotherapy
Orofacial and dental development problems	Radiotherapy to the head or neck
Delayed puberty in girls	Cranial irradiation
Incomplete development of breasts	Irradiation to pre-pubertal breast tissue
Incomplete uterine growth damage to ovaries Premature menopause	Chemotherapy or radiotherapy
Fertility problems in boys	Chemotherapy or radiotherapy

Wallace says that things have changed. "We have been working really hard to decrease the number of patients who get radiotherapy and – for those patients who have to have radiotherapy – decrease the dose."

Changes in treatment are not yet reflected in a reduction in late effects, because they take so long to show up. For example, in Hodgkin's lymphoma, second malignancies occurring within the radiation field are seen about 20 years after the original treatment. However, the incidence of second malignancies is related to dosage, so it is reasonable to assume that current treatments will produce fewer second malignancies.

A CHRONIC DISEASE?

Wallace chaired the development group that drew up Scottish national guidelines for long-term follow-up of survivors of childhood cancer. He says that rapid changes in treatment need to be matched by changes in attitude.

"Now what I am asking as an oncologist looking towards the future is, 'Is childhood cancer a chronic illness?' You have a cancer which is by and large cured, but it is not easy to say quite when you are cured. If you have Wilm's tumour at the age of five and you take it out and give some chemotherapy, it does not tend to relapse. But if you are female and you have radiation to the abdomen, then you are probably going to be infertile. So if you ask, 'Is this the treatment or the disease?' Well, she would not have got the treatment if she did not have the disease, so you are dealing with a long-term effect of the original disease."

Helen Kosmidis who pioneered paediatric oncology services in Athens, Greece, posed a similar question when she spoke at ECCO 14 in September 2007: "Is cancer in children an endless story for the survivor and the physician?"

She has been consultant paediatric oncologist at the A&K Kyriakou Children's Hospital in Athens since the oncology department took its first patient in 1979, and her unit treats almost one-third of the 250–270 new cases of childhood cancer each year in Greece. She goes to the weddings of many former patients and to the christenings of their children. But it is the occasional funerals that make her realise that there is still a long way to go.

"We have had 30 or 31 second cancers in the 28

"Survivors of childhood cancer need lifelong vigilance and some form of regular check-up"

years I have been here, and they hurt me more than the 1,800 newly diagnosed cancers."

She has opened a weekly 'late-effects clinic' to offer check-ups for former patients. But it is hard to organise a service of this sort. Paediatric oncologists are not trained for example to palpate an adult woman's breast and are not specialists in heart disease. "If children just needed to be followed up by the oncologist that would be fine, but you also need a whole bunch of people, the cardiologist, the endocrinologist, the radiologist, the social worker and the psychologist."

Kosmidis believes that current treatment regimens in protocols outlined by the International Society of Paediatric Oncology (SIOP) and others have reduced risks.

"Paediatric oncology has decided for many years that we will try to get a balance between cure and least possible late effects. This is not easy, but I believe in the protocols and I dare to call them wise. They use as much therapy needed to provide a cure with the least toxicity.

"In the past we used to give each and every child with acute leukaemia a set amount of anthracyclines, which is a potential hazard to the heart muscle. Now we decrease the total dose, especially in children who have good-risk disease.

"When I was in training in the United States, every patient with leukaemia received prophylactic radiation to the CNS [central nervous system]. We know that this cut down the number of relapses in the CNS, but there were too many late effects, especially in patients given radiation to the brain.

"We have cognitive problems, verbal IQ, memory, attention span, learning disabilities, especially in girls. The common age for ALL is three, four or five years. The female brain matures faster during those years than the male brain, so toxicity is greater.

"Nowadays we give high-dosage methotrexate which crosses the blood brain barrier, so we have better results and do not need to give every patient prophylactic radiation to the CNS, except to high-risk patients"

However, she learns to expect the unexpected. "You can give a drug to 200 patients and then get an adverse effect for the first time. Everyone handles a drug in a different way."

There is general agreement that survivors of childhood cancer need lifelong vigilance and some form of regular check-up.

The Erice statement (see box) says that children can be considered cured "when they have reached a time point at which the chance that they will die from their original disease is no greater than that of age peers in the general population of dying from any cause". This is usually reached 2–10 relapse-free years after diagnosis.

However, the Erice statement reflects the ambiguity of the term 'cure', and underlines the difficulties of explaining risks and uncertainties to young and vulnerable survivors. It says, "The term 'cured' should be used when discussing the survivors' status with them and in the larger society; vice versa, the term 'long-term survivor' should continue to be used in scientific research and related literature to alert professionals to sequelae which require care and attention."

THE ERICE STATEMENT

In October 2006, the International Berlin-Frankfurt-Munster (I-BMF) early and late toxicity educational committee invited 45 paediatric cancer experts to Erice in Sicily to discuss what constituted a 'cure' of childhood cancer and when follow-up care was required. The group comprised oncologists, psychologists, nurses, epidemiologists, parents and survivors from 13 European countries and from north America.

The Erice statement was published in May 2007, emphasising the need for information, communication, systematic follow-up, and research. It addressed the need to empower survivors and families, to better inform the general public and to address inequalities of treatment. The statement is online at http://www.icccpo.org/articles/general/erice_statement_2007.html

It adds, "Information about risk should be delivered to survivors and families in language that is easily understood and in a positive light. …Survivors and families have the right to be fully informed in person and in writing about being cured, as well as about the remaining risks of late effects, recurrence of the primary disease or second malignancies where applicable." This is a tall order, as the Erice statement acknowledges. "Communication of risk is difficult and challenging."

A dangerous journey ahead. Five-year-old Nikos at the K&A Kyriakou Children's Hospital in Athens is still being treated for his leukaemia. He is sitting with his doctor, Helen Kosmidis

Psychosocial effects

Some studies suggest that survivors of childhood cancer become vulnerable adults, but others indicate a resilience developed in childhood that continues into later life. A study of Greek survivors is the latest to demonstrate resilience, based on questionnaires and interviews with 103 childhood cancer survivors over the age of 15, whose mean age at diagnosis had been 8.8 years (Servitzoglou et al. *Support Care Cancer* 2007). One in three had mild to moderate late effects or side-effects, while 15 had severe effects.

The results show a reduced level of social functioning compared with other young people of a similar age. Female adults had higher levels of anxiety, especially those diagnosed at a younger age. There was also a tendency towards 'distancing', denial and wishful thinking. One-third regarded the future as uncertain and were more likely to expect to die young and for their own children to become seriously ill. However, in general they maintained a positive outlook on life, and were closer to their families and friends. They were less likely than the control group to blame themselves for bad events in their lives.

Lead researcher, Marina Servitzoglou, has since been working at Great Ormond Street Hospital in London, and is now on a one-year clinical fellowship at the Institut Gustave Roussy. She says that because stigma levels about cancer are still quite high in Greece, some young survivors only found out years later exactly what disease they had had.

"There are still parents who try to protect them from information, even now that they are adults. But that does not mean that they do not understand. If you talk to the children, they try to protect the parents in the same way as the parents try to protect them. Sometimes they do not want to discuss their feelings, or their fears because they don't want to affect their parents."

The psychological impact of cancer at a young age was very strong, partly perhaps because this is the period in a child's life where she or he develops identity, personality and character.

However, Servitzoglou says that many survivors develop an inner toughness. "I think they are much more mature and they have learned to fight. They are much stronger emotionally. They have learned a lesson that nobody knows what will happen tomorrow.

"They deal with their problems and have a positive attitude. In the back of their minds they still have fears about their health, but they say, 'I am grateful I am alive.' Their whole mentality, and priorities and outlook on life changes completely."

Aemilia Tsirou fits this positive pattern. "I was eight when I was diagnosed. I understood it was a really difficult situation. I did not know that I had leukaemia, but a very scary anaemia. My parents were

"They are much more mature and they have learned to fight. They are much stronger emotionally"

"If you don't say it, you don't admit its existence – even now, we don't discuss it with our parents"

really scared and we had to come three or four times a week for chemotherapy and radiation."

The real nature of her disease gradually became apparent to her later, when her parents became involved with the parents' group Floga (Flame), but she says that, deep down, she already knew. "At the hospital I saw many young children without hair. I knew children who the doctor said went back to the village, but I understood that they did not go back. There was no other reference to these children. You don't discuss this while you are under treatment, not with your parents and not with your doctors. If you don't say it, you don't admit its existence. Even now, survivors do not discuss this with our parents. Many parents are scared and say to their children, 'Just forget it'. This is problematic. We should know what we have gone through so we can take care of ourselves."

Far from forgetting about it, Tsirou, who works as an IT manager and teaches Greek literature and philosophy, has helped to create Kyttaro (the Greek for 'cell'), an organisation for survivors of childhood cancer. Their primary aim is mutual support, socially and practically, but the 30 members also visit children undergoing treatment to talk about films, music and life. "They have a different relationship with us because we are survivors. They are really open to us, because they feel comfortable. They take off their hats. They enjoy being with us."

Group members support the late-effects clinic and talk to family members. They have a commitment both to normal life and to each other. "Some members of Kyttaro have serious late effects but are still coming to the group. These people have had a relapse or second cancers. They have lived with more pain and suffering than me, but they come back to tell us that, 'OK it was bad, but you can live with this and you can win.'"

Survivor groups are being formed in an increasing number of countries. But if survivors and doctors are to better understand risks and monitor health, they need better data. Helen Kosmidis is president of the Hellenic Society of Paediatric Haematology Oncology, and expects the first Greek national registry of childhood cancer to be up and running by January 2008. Starting as a database of children undergoing treatment, it will in time also become a database of survivors.

The UK launched the British Childhood Cancer Survivors' Study in 1999, led by Mike Hawkins, professor of Epidemiology at Birmingham University. Although this study started years after the Childhood Cancer Survivors' Study in the US, it has the advantage of being population based, and therefore more representative, and includes children who have received more up-to-date treatments.

As a sign of the growing interest in this issue, in April 2007, Christian Moëll from Lund, Sweden, and Wallace from Edinburgh organised the first European Symposium on Late Complications after Childhood Cancer. A European late-effects group is being discussed.

Scottish guidelines (Scottish Intercollegiate Guidelines Network, 2004) recommend a range of follow-up regimens from an annual or two-yearly contact by phone or questionnaire, to an annual visit to a nurse or primary care physician. Where treatment has included high-dose radiotherapy, megatherapy (high-dose anti-blastic drugs, possibly with radiotherapy) or bone marrow transplant, a medically led long-term follow-up clinic three or four times a year is recommended until final height is achieved, and annually thereafter.

A LASTING RELATIONSHIP

Paediatric oncologists will be central to this work, because most want an ongoing relationship with their patients, and because survivors often prefer being seen by paediatric staff. Survivor Clare Dawson told the 2006 International Conference on Teenage and Young Adult Cancer Medicine, "When you have notes a foot high, going to someone who does not know you and knows nothing does not help. There is a real confidence from going back to see someone who does know you. You don't have to explain. He just knows."

"You can't talk to a 5-year-old about fertility, but you can talk about whether they'll be able to go to school"

Helen Kosmidis says that you have to learn to become a talking doctor to talk to children undergoing treatment and to survivors. She recently counselled a boy who had completed two years of treatment and three years of observation, but who was still pre-adolescent. "I tell him he will have to take care of himself. 'You are never going to smoke, promise me that.' I tell him that in future he will be checked by a heart doctor and a thyroid doctor. He says, 'Why? I have already had chest X-rays and heart examinations.' I said that the treatment he had could have caused some damage to those organs."

The ugly fact is that the risk of heart problems increases rather than decreases as the years since treatment pass. But Kosmidis does not think that the cold numbers are always helpful for parents or children. "The chances of them having childhood cancer in the first place were very low, but they had it. If we tell a parent your child has a 30% chance of being cured, and the child is cured, it is for them 100%. If we say your child has a 90% chance of being cured and the child dies, that is for them a 100% death rate. It is individual, and so you don't give them a number."

The same applies to survivors – the facts are given, but both doctor and patient recognise that this is an individual journey of absolutes.

Wallace agrees that you cannot talk to survivors unless you build trust with them as patients. "You cannot counsel the children once they have grown up and come to see you on their own, unless you made them the centre of their care as a child. It is the child that has the cancer. Often you see a tendency for doctors to ignore the child, and speak to the parents. Of course, the parents are very, very anxious, and often try to protect their children from the reality. But if you come to our ward and see these children running around, they could tell you exactly what they have got.

"My concept of leukaemia, the parent's concept and the child's concept are all different. Paediatricians have to understand the child's concept – what it means to them.

"You could not talk to a five-year-old about fertility, and they would not be interested. But you could talk to them about whether they will be able to go to school. You could talk about what they could do if their hair falls out. You have to try to get inside their world and find out what it is they are worried about.

Prepared for an uncertain future. This picture, by Aemelia Tsirou, was prompted by the discovery of a new tumour, 12 years after she had successfully beaten leukaemia

"Discussions can be very therapeutic with somebody at the right age. A 16-year-old girl I am treating has a sarcoma in her pelvis. Her major concern is fertility. I don't see how we can avoid giving her radiation to her pelvis, which will cause her ovaries to fail very early and will irradiate her womb. The fact that we say we could take a bit of your ovary and put it in the fridge for later on, gives her an inkling that someone believes that she is going to be alive later on."

After surviving cancer as a child, Aemilia Tsirou felt she was invulnerable. But in the year 2000, she found a new growth in her left ear. After months of tests, it was established that this was a benign tumour, and although it has left her deaf in one ear, she is still clear of cancer. It also made her realise she was not superwoman. She wrote in her diary, "After the malignancy came a new sense: I can win everything. After the benign tumour came a completely new truth: life can make anything happen. It is not the point to believe you can win everything. The point is to be prepared to meet anything that life serves you."

ECCO seeks healing touch for oncology's lost voice

Anna Wagstaff

It's been a frustrating couple of years for those anxious to see a single strong voice for oncology at a European level. But with the launch of the European CanCer Organisation at ECCO 14, things may be looking up.

ECCO 14, Europe's biennial cancer conference, held this September in Barcelona, was a success by any standards, attracting a record attendance of 13,200 – up almost 15% on Paris two years ago. The main programme included heavy-weight speakers addressing key topics across a broader range of oncology specialisms than ever before, and this was reflected in the number of surgical oncologists who attended – up by more than 250%.

When it was over, the people who had dedicated much of the last two years to get a unified European cancer show back on the road breathed a collective sigh of relief. A lot had been hanging on the success of that conference, and it could have been very different.

The ECCO conference is the symbol of multidisciplinary working in European oncology. But the organisation behind it was thrown into crisis at the Paris conference in 2005, when the six founding members of the Federation of European Cancer Societies (FECS) – cancer researchers, surgeons, radiation oncologists, medical oncologists, paediatricians and nurses – failed to agree on how to adapt their 25-year-old structure.

Medical oncologists felt that their discipline is where the most significant progress is happening in cancer care, and they wanted the sort of profile that ASCO offers medical oncology in the US. This, they argued, would be impossible within the existing federal structure. But smaller FECS societies felt that their voice and interests would be lost if they gave up a structure in which each society had equal weight. There was also a dispute over what to do with the organ specialisms – urology, gynaecology and so on. Medical oncologists felt they should be excluded because they are not primarily oncologists, but others wanted to include them because they treat large numbers of cancer patients in Europe and many organ-based societies have developed strong oncology sub-specialisms.

A FECS council held at the end of the Paris ECCO agreed to retain the federal structure and to invite the organ specialists in. A week later, the medical oncologists' society ESMO voted to pull out of FECS and establish their own multidisciplinary society. The resulting climate of confusion and demoralisation led to a haemorrhaging of FECS staff, including the top two positions, and the organisation went into nose dive. It was at this point that Michel Ballieu – now chief executive of FECS' successor organisation, the European CanCer Organisation (ECCO) – introduced himself. "I heard about the difficulties they were going through; it was a challenge. I thought this was something I could manage."

Ballieu knew nothing about cancer. But it turned out that he was perfectly suited to the job. He had long experience in managing associations; better still, he had experience of managing federations, "a very difficult format". Best of all, Ballieu could see that the faction fighting was a bad outcome of a fundamentally promising situation "Coming from outside the oncology world, as a federation manager, what I see is a mosaic of initiatives, very good missions, very good reasons to be active, a lot of commitment and energy – but it is a mosaic."

ALAIN DEREYMAEKER

Back on track. With a successful ECCO 14 behind them, president Lex Eggermont (left) and chief executive Michel Ballieu want to get to work expanding the organisation and pushing cancer up the political agenda in Europe

A RESCUE OPERATION

Ballieu believed his job was to get everyone pointing in the same direction. His priority, however, was to make a go of ECCO 14. He had nine months to pull it off, and only 3.2 full-time equivalent staff out of the original 14 – one about to go on maternity leave. Ballieu admits to a few sleepless nights trying to figure out how to extricate himself from this "catastrophe", but he applied himself to the task, aware of the obituary writers sharpening their pencils.

"People close to this internal politics were watching us with question marks in their eyes. I don't say people were expecting us to fail, but they thought there was a serious possibility." He attributes the success of ECCO 14 to the new staff – some had worked closely with him in previous jobs – to the remnants of the original staff who provided much needed continuity and indeed, to all the former FECS staff. "We feel so lucky to have inherited such a great conference as they built over 20 years."

After lengthy deliberations the five remaining societies of FECS decided that it should become more open in structure, add lobbying and advocacy work to its educational remit, and be rebranded as the European CanCer Organisation, ECCO – already the best-known acronym in European oncology. Each member organisation would pursue its own agenda within its professional field, but all would join forces in ECCO to develop common policy and a single voice on the wider issues, such as support for clinical research and the need for national cancer plans.

But will 'son-of-FECS' function any better than its predecessor? Lex Eggermont, incoming president, is convinced it will. The crucial difference, he argues, is an additional seven seats on the governing board. The FECS board consisted of six seats, one for each member society, with the presidency passing in rotation. Organ-based societies such as the European Society of Gynaecological Oncology and the European Association for NeuroOncology had the status of affiliates – as did groups such as the European Organisation for Research and Treatment of Cancer – but none had a say in the running of FECS.

Under the new structure, the six 'founding members' each get an automatic seat, but a further seven seats are elected by all ECCO members – the general assembly – which Eggermont believes will soon encompass representatives of every professional group that specialises in treating cancer in Europe.

Every member society will be able to vote, which is likely to result in a board that is more representative of all cancer professionals in Europe. And because each society can stand up to three candidates, anyone who feels they have something to contribute has a good chance of being able to stand for the board, and the larger societies will have the opportunity to increase their representation. "It is more of a break from the old FECS than you would think," says Eggermont. "Now it is in the hands of those who are there because they actually want to be part of oncology. Who was going to get in to the old FECS? Nobody – because it was introverted, closed and perceived as secretive, like an Old Boy's

"It is actually more of a break from the old FECS than you would think"

club. Every two years you would hear who had become the next president of FECS, because it was now 'turn' of the ESSO president or the EACR president. We couldn't go on like that."

Ready to go

Despite the decision two years ago to allow organ-based societies into full membership, so far only the gynae-oncologists and the neuro-oncologists have joined – and they had long been affiliates of FECS. However, as Eggermont points out, FECS/ECCO had a lot on its plate, and now that ECCO 14 is out of the way the organisation has both the time and the financial security to move forward.

The chief executive of ECCO shows sensitivity to avoiding the pitfalls of its predecessor. "In a direct membership organisation the decision-making power is diluted among several thousand members, whereas in a federation, there are only a few members and the smaller groups don't necessarily want to be overruled by the stronger ones. That brings management difficulties and requires a lot of understanding of diplomacy and service mindset to bring people to a consensus," says Ballieu.

Indeed, the smaller members look set to get a lot from the new ECCO. For the price of 1.2 full-time equivalent staff, for instance, the paediatricians in SIOPE now have time from ECCO's IT staff to help with their website, time from the finance people to keep their records straight, access to strategic advice from Ballieu, as well as their own part-timer to coordinate their clinical trials and another to run the organisation and support the public/EU affairs work of the SIOPE board. A huge improvement on hiring a single full-time person to work in isolation, as had first been envisaged.

The leaders. José Baselga, president of ESMO (left), at ECCO 14 with John Smyth (centre) past-president of FECS and Lex Eggermont, ECCO president

The new ECCO will be judged, however, not by whether it can serve the needs of its constituent members, but by its success in grabbing the attention of Europe's policy makers and getting its message understood and acted on. As president, Eggermont would like that message to be three-fold:

- Provide all cancer patients with equal access to high-quality cancer care
- Develop national cancer plans that reflect the needs and resources of your country, and
- Stop killing the academic research agenda – "nowhere does it hit as hard as in oncology."

Top priority

Given the expected increase in cancer incidence, especially among the elderly, and the rising costs and complexity of cancer treatment, failure to get these messages across to Europe's policy makers will have terrible consequences. But messages about cancer are complex and harder to deliver than those from other diseases. If professional oncologists fail to speak with a single voice, Eggermont knows that they don't stand a chance.

His number one priority now is to bring medical oncologists back into the fold – for ESMO to take its reserved seat on the board. "There cannot be anything successful without medical oncology. It would be so ridiculous to the outside world that nobody would ever understand what on earth we are doing. It's that simple. If I was a politician I would go with the Alzheimer's lobby and the diabetes lobby, and I would certainly not have a very high opinion of oncology."

The ESMO president, José Baselga, took a high profile alongside the FECS/ECCO leadership on the main stage of ECCO 14 – perhaps a signal that there is goodwill on both sides to resolve the split. The alternative, says Eggermont, does not bear thinking about. "If we cannot change the perception of oncology as not being able to create something united we would be permanently damaged. It will be a mediaeval situation, and everyone will lose out. We would be in such a sorry state that if I were a young oncologist I would lose interest in any oncology society in Europe and look to elsewhere for opportunities to contribute and to develop my career."

"The new ECCO will be judged by its success in grabbing the attention of Europe's policy makers"