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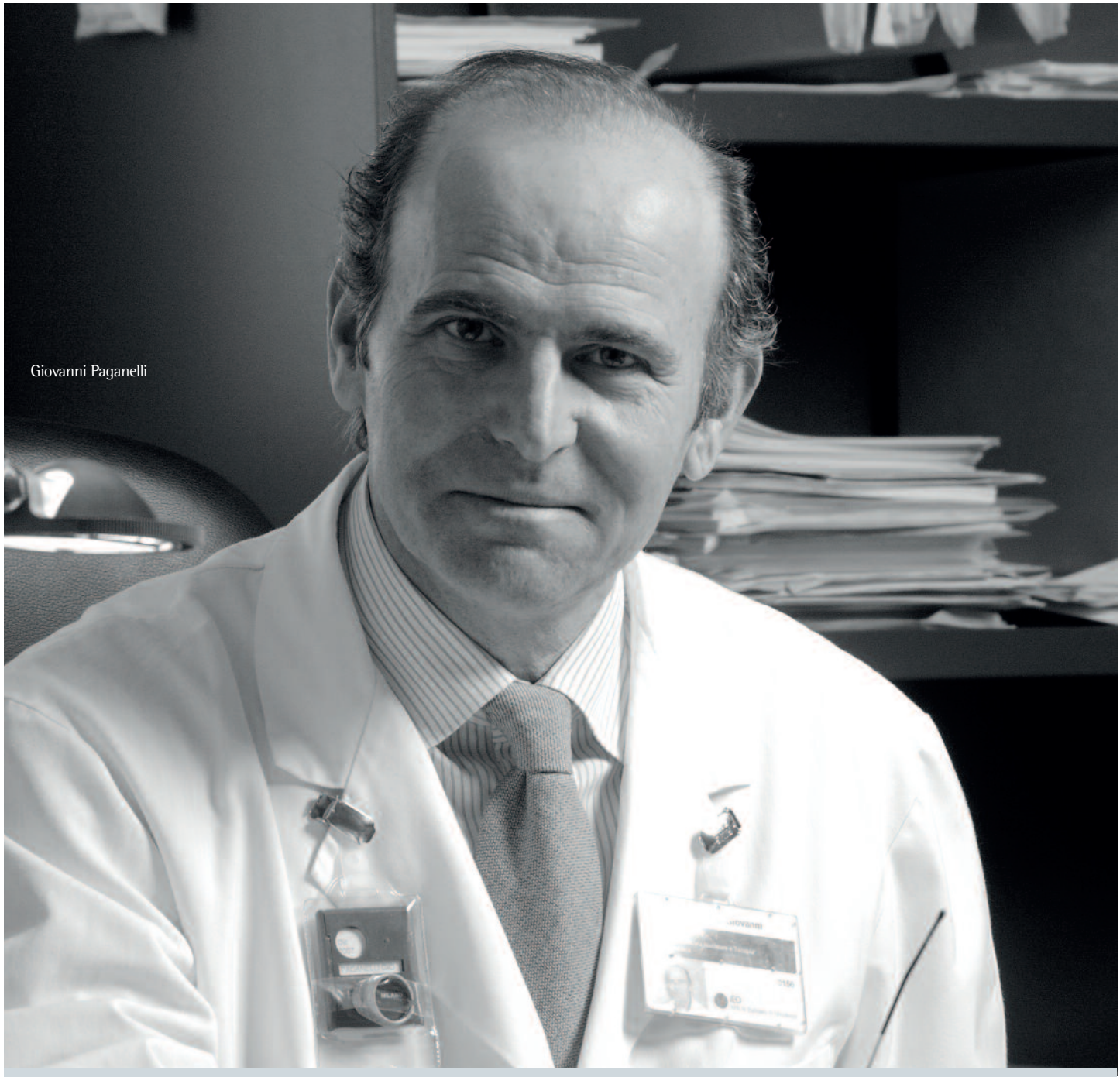

Giovanni Paganelli

➜ Giovanni Paganelli: nuclear medicine's enthusiastic ambassador ➜ Personalised therapies: who will champion the needs of patients? ➜ Scientific integrity must come first: the unique Baum brand of passion and perversity ➜ Helping survivors get their lives back

Make prevention easy

Czech journalist and colon cancer survivor pens a message to her country's health professionals

Had **Iva Skochová** been in her native Prague rather than New York when she went to the doctor complaining of stomach pains, her colon cancer may never have been discovered in time. A staff writer on the *Prague Post*, Skochová won a Best Cancer Reporter Award for a piece she wrote about the lessons to be learned from her experience, which is republished below.

It is no secret that the Czech Republic has the world's highest colon cancer rates per capita: every year 7,500 new patients are diagnosed, and every day 16 people die from it.

Anyone who has sampled traditional Czech food will be tempted to jump to conclusions and say "no wonder". On average, Czechs consume excessive amounts of animal fats and cured meats and prefer their vegetables pickled, if not fried. Cholesterol is a friend; fibre a foe.

Scientists, however, estimate that only about half of colon cancer rates are linked to lifestyle, and patients usually develop it later in life. The rest of cases may be purely genetic, and the cause is still unknown. Although poor diet certainly doesn't help, it appears that the gene pool of my countrymen may be partly to blame.

One aspect doctors agree on is that regular colonoscopies after the age of 40 dramatically increase survival rates. If doctors discover colon polyps before they turn cancerous or at least in the early stages of cancer, before they metastasise, it sharply decreases the premature mortality of patients.

Colonoscopies in the Czech Republic, however, are usually performed only when patients already show symptoms of colon cancer (indigestion, abdominal pain, anaemia, etc), not as a form of prevention. Since colon cancer often strikes without symptoms, taking preventive measures, especially for people with family histories of cancer, is essential.

I was diagnosed with colon cancer – completely asymptomatic – in October 2006 at the age of 29. For the record, my diet has consisted mainly of fruits and vegetables and other fibre-rich foods. I have always been thin and athletic and barely eat any meat. I don't smoke. Needless to say, the diagnosis was a shock.

Maybe it should not have been so surprising. My mother was diagnosed with the same disease

THE PRAGUE POST

Original article. This piece first appeared in the opinion pages of the Prague Post, the Czech Republic's leading English-language weekly, which reaches an estimated 40,000 readers, with a target audience that includes regional decision-makers in the business and political sphere

"The world we live in and the world around us"

THE PRAGUE POST

OPINION

January 3 – 9, 2007 A8

EDITORIAL REVIEW

From the opinion pages of the Czech press

PENETRATING MYTHS

Stigma and insensitive doctors make cancer prevention much harder than it needs to be

The year that wasn't; the year that could be

POSTVIEW

at the age of 40. My grandmother and great-grandmother both died from it. None of them was overweight. They were all too poor to eat foods rich in animal fat. Still, it seemed that I was too young and healthy to get caught.

Although I generally think highly of Czech doctors (that is, after all, why I decided to undergo surgery and chemo here, rather than in the United States), the healthcare system here severely underutilises prevention. My Czech doctors never asked me about a family history of disease, let alone suggested I needed to start going for check-ups 10–15 years earlier than the age at which my mother tested positive. It never really dawned on me that this disease can affect people younger than 30.

I was diagnosed in New York during one of my regular trips there. I went to see a doctor because my stomach was upset for several days after I took an aspirin for a headache. She thought I might have a stomach ulcer but an endoscopy showed that I didn't. My blood test, however, revealed I was anaemic.

The doctor suggested a colonoscopy only because she wisely linked my family history together with the anaemia. Iron-deficiency anaemia, or a shortage of red blood cells, often occurs as a result of internal chronic bleeding. The body essentially 'feeds the tumour' with blood.

It seemed a bit of a stretch at the time, since I only had a minor stomachache, but I will be grateful for the doctor's holistic approach for the rest of my life. I am certain that, given my age and overall health, a lot of doctors would have given me acid reducers for the stomach, suggested I take iron pills for the anaemia and sent me home until I could come back with 'real issues'.

For obvious reasons, I was nervous about having a colonoscopy. Getting a long object shoved where the sun doesn't shine is hardly anyone's idea of fun. I found that not only are people too ashamed to even talk about this procedure, but some find it extremely painful. I kept recalling my mother proclaiming for the past two decades she would rather die than have another colonoscopy.

A lot of doctors would have given me acid reducers, suggested I take iron pills, and sent me home

Special Merit Award. Iva Skochová received a special Best Cancer Reporter Award which is granted to journalists who are also cancer survivors, to acknowledge the valuable contribution they make to raising awareness when they write about their personal cancer experiences. The award was presented in October 2007 at the *Cancer World* Media Forum in Rome, by Franco Cavalli, co-chair of the scientific committee of the European School of Oncology

That is why, after her last chemo treatment 20 years ago, she never got tested again. My sisters, although they are older than I and also in a high-risk category, stubbornly feel the same way.

The good news is that colonoscopies are a lot easier than they used to be. The technology has got better and a lot of doctors have figured out that a little sedation goes a long way in making the procedure manageable.

My experience was good. It was actually easy; I did not feel a thing. My New York doctor put me under anaesthetic for the procedure. I couldn't understand what the big deal was until I found out that only a fraction of Czech hospitals use sufficient sedation for colonoscopies. Some put patients under as a matter of course, some of them only at patients' request, and some don't sedate at all.

It is almost too obvious: when a colonoscopy – the only reliable detection method in early colon cancer – is too difficult for people, they simply skip it until more serious problems arise. At that point, they have no choice. But it is often too late for effective treatment.

A friend who recently had an endoscopy in Prague asked about sedation, and a doctor told her they "only give sedation to hysterical women". Brave men and women apparently don't need it. In all truth, it was probably just easier and cheaper for the doctor to not have to deal with the procedures related to sedatives use. Since my friend did not want to appear hysterical, she agreed to try it without. She said it "wasn't too bad". But would she do it again? She's not sure.

In a country with essentially First World health care but sky-high rates of colon cancer, one would think that playing heroes for doctors would no longer be necessary. Making prevention easy is key.

This article was first published in the *Prague Post*, 3 January 2007

Colonoscopy is too difficult for people, they simply skip it until more serious problems arise

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Giovanni Paganelli:

nuclear medicine's enthusiastic ambassador

➜ Marc Beishon

Radioisotopes can be used to locate tumours and to deliver targeted therapeutic radiation internally. Sounds ideal for cancer, yet nuclear medicine remains an underdeveloped field, held back by irrational fears of all things nuclear, false perceptions of its potential, and bureaucratic and cost barriers to accessing agents. Giovanni Paganelli is a believer, and he is spreading the word.

It is a given that a complex field such as cancer spawns an increasing number of sub-specialities – and that there will inevitably be debates about which are most deserving of resources. Those working in fields that do not command much support can nevertheless spend many years quietly building a solid scientific and clinical reputation against the odds to emerge eventually with very important work – which arguably now applies to nuclear medicine, and in particular its application in therapeutic oncology.

Giovanni Paganelli, director of nuclear medicine at the European Institute of Oncology in Milan, describes what the specialty means for cancer. "It is the use of radioisotopes to both locate cancer cells for diagnosis and to deliver energy to the target cells to destroy them. I liken my field to an aircraft – to make it take off we need both diagnostic and therapeutic wings."

The problem for nuclear oncology, he adds, is that too many professionals – including oncologists – see mainly the diagnostic side of the subject, where practitioners often come from radiology, and not from internal medicine (as Paganelli himself does). This perception is reinforced by the fact that nuclear medicine departments are often located in the darkest bowels of hospitals – where large and possibly dangerous equipment often lurks – divorcing specialists from the multidisciplinary discussions taking place on the floors above.

Together with a public suspicion of anything 'nuclear' in some countries, the technical and bureaucratic difficulties of sourcing and preparing radioisotopes, the cost of equipment and agents, and to date fairly narrow progress in truly therapeutic applications, nuclear oncology has faced tough challenges. And as Paganelli notes, the specialists themselves are partly to blame. "We tend to spend most of our time talking to other colleagues in nuclear medicine – and not getting our messages across to medical oncologists and surgeons at the right meetings," he says.

"If you had talked to me 10 years ago I would have been quite depressed about our prospects. But in the last few years there has been much more progress." The arrival of PET (positron emission tomography) and SPECT (single photon emission computed tomography) as widespread techniques has triggered new awareness in the medical profession of the use of radioisotopes, says Paganelli, although again this is largely because of diagnostic potential. "What excites

LUIGI INNAMORATI

me – and what I consider true nuclear medicine – is the growing use of targeted diagnosis and therapy, and it is one of the few areas in oncology where we are really doing translational medicine from bench to bedside."

It is a bold claim, but Paganelli has a 20-year track record in researching the targeting potential of radioisotopes in combination with other agents, and while he concedes that clinical applications are currently limited, no one who visits his department in Milan could fail to be infected with his enthusiasm – and his persuasive arguments about the tremendous potential for tackling some of the most difficult oncology problems. Work on high-grade brain tumours, lymphoma and neuroendocrine treatments are in train, while a sequence of clinical research projects to aid breast-conserving surgery is a landmark at the Institute.

Paganelli always intended to become a doctor – "It was my dream as a boy to do research and understand why people get ill" – although he was later to discover that science does indeed follow Edison's famous maxim: 1% inspiration, 99% perspiration. He chose to pursue internal medicine while at the University of Bologna, and further selected geriatrics as a speciality – the growing 'market' of an aging population being a draw. He recognises a logical and philosophical link between aging and cancer – "After we have reproduced, maybe the DNA doesn't care

"Science does indeed follow Edison's famous maxim: 1% inspiration, 99% perspiration"

"One of the first examples of nuclear medicine was the use of radioactive iodine to treat thyroid cancer"

whether it's damaged or not" – but the move to nuclear medicine came about by chance when he was given an oncology research grant. He quickly embarked on his targeting research.

Leaving a permanent assistant's post in the nuclear medicine department at the Bufalini hospital in Cesena, near Bologna, Paganelli took up a fellowship to do basic research at London's Hammersmith Hospital. His Italian boss was none too pleased – but the opportunity to join a group working on new radioimmunotherapy targeting methods using monoclonal antibodies, under well-known medical oncologist Agamemnon Epenetos, was too good to pass up.

"The field started as a branch of pathophysiology," explains Paganelli, "and cardiology was the most important application 10–15 years ago. That's changed dramatically now. I estimate that about 80% of nuclear medicine is now focused on oncology, although heart and other organ functioning are still crucial areas." All told, there are now more than 100 procedures in regular use in nuclear medicine departments. However, as he adds, one of the first examples of nuclear medicine – and a truly targeted therapy and an oncology application to boot – was the use in 1946 of radioactive iodine to treat thyroid cancer, making use of the unique ability of the gland's cells to absorb iodine and so localise the killing effect of radiation. "A protein traps the iodine like a Trojan Horse," says Paganelli.

The first commercial radiopharmaceutical, based on iodine-131, went on sale in 1950; the scintillation (gamma) camera came out in 1958; cyclotrons to produce medical radioisotopes were introduced in the early 1960s (as was the forerunner of PET); and heart,

The nucleus. Paganelli with core members of his 40-strong department of nuclear medicine, including chemists, physicists, technicians, physicians, nurses and admin staff, grouped alongside one of their PET-CT scanners

lung and other organs became standard scanning targets for nuclear medicine, which was recognised as a speciality in the US, in 1971. But it was a demonstration by David Goldenberg, in 1973, of the targeting of tumour antigens by radiolabelled antibodies that set in train Paganelli's arrival at Hammersmith in the 1980s.

By then, melanoma patients had been treated with iodine-131-labelled monoclonal antibodies. But as Paganelli points out, while an excellent idea, this targeting had limitations – not least that the radiolabelled antibody went everywhere in the body. "The idea I had was to add a pretargeting stage. We first target the cancer cells with a non-radioactive antibody, which clears from the rest of the body. Then we deliver a second, radiolabelled molecule that is attracted by the antibody, and which is also cleared rapidly from the body." The aim is to deliver a more effective dose to the target, while minimising side-effects, and has been a plank of Paganelli's subsequent research and clinical practice; indeed it was the subject of a patent filed jointly with the Italian ministry of research in 1991.

The sheer amount of work – that perspiration — and multidisciplinary understanding is a feature of such research, says Paganelli. "Nuclear medicine is one of the few branches of medicine where you have to be on top of maths, physics and chemistry as well as the biology. If you want to know how to apply approaches such as pretargeting – the amount of agents, the timing of doses, the molecular operation and so on – you need to assemble a huge amount of information." His more than 40-strong department in Milan – comprising physicists, chemists and technicians as well as medical doctors – is testimony to the need for a multidisciplinary approach.

Paganelli first went to work in general nuclear medicine at the San Rafael hospital in Milan, with a licence to continue his research, before being asked by Umberto Veronesi to set up a fledgling department at the European Institute of Oncology in 1994. It has become the first and leading centre in Italy to carry out therapeutic targeting work, and his closest collaborators are now chemist Marco Chinol and physicist Marta Cremonesi, both based in his unit.

He had a window of opportunity at the start, as there were no regular patients for a few months, and he set about developing the pretargeting technique with high-grade brain tumours, which have a very poor outlook in the vast majority of cases. "I started with glioblastoma because it is an orphan disease with a suitable marker [the protein tenascin] and we could only have a few months to see if it worked or not – and if it did, it may then also work more easily in cancers such as lymphoma. We used the avidin biotin system and published some interesting results." His closest colleague on this work then was Antonio Siccardi, professor of biology and genetics at the University of Milan.

Paganelli describes avidin and biotin as a "fantastic natural system" (it's been described as nature's gift to molecular biology). Avidin – found in the egg whites of birds and in bird and reptile tissues – is a protein that binds to the much smaller biotin molecule (also known as vitamin H) with tremendous affinity. In his early work with brain tumour patients with grade III and IV astrocytoma, he employed a three-stage process – first injecting a monoclonal antibody tagged with biotin that binds to the tumour, then avidin, which binds to the antibody, and finally the radionuclide – in this case yttrium-90-labelled biotin. Although the number of patients was small, and the work took several years, a quarter (12 patients) showed a reduction in tumour size and three people had complete remission.

Now PAGRIT – pretargeted antibody guided radioimmunotherapy (and a trademark) – has entered the oncologist's lexicon, and is suitable for several other applications, notably in lymphoma, which is a cancer with good radiosensitivity and which also expresses tenascin. It also has potential in other cancers, according to Paganelli. A form of pretargeting is also now playing a role in his most important work to date, on breast cancer.

The complex nature of this work is obvious – and a further potential barrier is the availability of reagents.

The avidin biotin system has been described as nature's gift to molecular biology

"High costs should be defrayed by more competition and more centralised facilities to prepare reagents"

"When I started the work on glioblastoma there was a company that supplied the antibody for human injection – you need a lot of resources to prepare these agents, and now we also have to comply with European Good Manufacturing Practice regulation. But my supplier was sold to another company that was not interested in continuing production." It is only recently – after a gap of some 15 years – that he has found another company to step in (Sigma Tau, based in Rome), such that he is now in the registration process for the PAGRIT model for brain tumours with EMEA along with a phase I/II trial. He adds that there is – encouragingly – much more interest from commercial quarters in agents for nuclear medicine generally, from both smaller biotech firms and larger companies (one US commentator predicts a therapeutic market worth $1.9 billion by 2012, from just $71 million in 2005).

Two radioimmunotherapies of note for non-Hodgkin's lymphoma are now on the market – Bexxar (tositumomab and iodine-131 tositumomab) and Zevalin (90-ibritumomab tiuxetan). They hit the spotlight in the US recently when Medicare, the healthcare programme for older people, baulked at the very high reimbursement costs set by their makers – as much as $30,000 (€20,600) for one treatment.

These treatments are nothing new to Paganelli – he has been working with non-commercial versions of most nuclear agents for some time. Having prepared 90-ibritumomab tiuxetan himself at Milan, Paganelli comments that the costs could certainly be much lower, and argues that the high costs should be defrayed by more competition among biotech firms and more centralised facilities to prepare reagents for sharing among oncology centres.

"There is no central radiopharmacy in Europe for preparing monoclonal antibodies or peptides for therapeutic purposes," he says, adding that he is in discussion with colleagues to set up just such a facility at European level, and also at local level for the various clinics in and around Milan.

The short half-life of many medical radioisotopes does mean that supplies must be constantly on tap, and while medical cyclotrons can produce some isotopes, especially for glucose used in PET, others such as the widely used technetium-99 and iodine-131 are mainly produced in nuclear reactors (sometimes as longer lived 'parent' isotopes that are then used to generate 'daughters' locally). In Italy, nuclear reactors have been rejected by a referendum, so the country will always be dependent on outside supplies.

That nuclear medicine is dependent on a reliable commercial supply of radioisotopes was brought home very recently – a reactor in Canada that supplied a large proportion of the worldwide market was off-line longer than expected last December, leading some medical centres in North America to postpone procedures and to scramble around for alternative supplies.

Paganelli's most well-known work, in breast cancer, came in response to Veronesi's drive to cut unnecessary surgery. "In 1995 he asked me if I had anything that could avoid axillary dissection of lymph nodes, perhaps using PET. I said we could look at using blue dye to identify sentinel nodes, which was also being done with melanoma. Looking further, I realised we could optimise the approach, as blue dye can miss a lot of lymph nodes." The result was the first protocol for sentinel node lymphoscintigraphy in breast cancer, identifying the node using a radioactive marker injected into the tumour to see the extent of tumour spread. "I sent it to Veronesi, who was cautious, but we started to optimise the amount of radioactivity and size of particle we were injecting and we published in 1997.

"While I was doing this I realised that, after injecting the material into the tumour, sometimes it did not move from the cancer site and we were missing 30% of the nodes," he continues. Paganelli and colleagues found that injecting near the tumour instead found the sentinel node with much greater precision. "After now carrying out more than 12,000 sentinel node lymphoscintigraphies, we have missed the sentinel node in only 99 cases, which is a

Nuclear family. With his wife, Stefania, who also works at the Institute

sensitivity of more than 99%, and the technique is now routine for breast cancer." It is notable, though, that Europe differs in practice from the US. "The molecule we use is not authorised by the Food and Drug Administration, and is larger than the one used in America – and they see more lymph nodes as their molecule is not so easily trapped by the sentinel node. So our method is more precise."

This sparked off another innovation. Challenged in the coffee bar by a surgeon to solve with his 'high-tech methods' the growing problem of locating non-palpable lesions more precisely, Paganelli's immediate and not entirely serious response was, "Simple – inject a drop of radioactive material into the centre of the lesion and use a gamma probe to locate and remove it." But the idea became a study protocol within a few days and proved very effective – and has become known as ROLL (radioguided occult lesion localisation).

Now 'on a roll' with the work, Paganelli and his team have taken the elegant step of combining it with the pretargeting approach to add another option for eliminating residual cancer after a tumour has been removed in breast conserving surgery. Postoperative, partial breast irradiation using external beam technology is the standard treatment, but usually requires travelling to and from hospital for daily sessions over a period of six weeks. A technique now in phase II trial is to shorten this therapy with a radioisotope treatment, using the tried and tested avidin biotin system.

"The surgeon injects avidin into the tumour bed during the operation – no special skill is needed – then the day after, or when the patient has recovered, she receives an injection of radioactive biotin in the nuclear medicine department. It's very simple, very cheap and can be done anywhere, and I think we may be able to replace external beam radiotherapy altogether. There are many places where linear accelerators for radiotherapy are not available or not covered

"After more than 12,000 lymphoscintigraphies, we missed the sentinel node in only 99 cases"

Along with Veronesi, he knows only too well the struggle to get new therapeutic approaches accepted

by insurance – as many as half of women in the US still have a mastectomy instead of breast conserving treatment. I think this is the best idea I've had in my career so far."

The next step will be to add an antibody specific to breast cancer with the avidin, but this is not ready for trial yet. The technique without the antibody is known as IART – intraoperative avidination for radionuclide therapy – and Paganelli says, after successful completion of the present trial, it should go to a multicentre study this summer. There are several other techniques to accelerate breast irradiation currently in trial, but none that are as simple to apply as IART (see *Clin Cancer Res* 13:5646s–5651s), and he would like to extend the idea to other cancers where conventional radiotherapy can have major side-effects, such as in the head and neck.

It is another chapter in the now very lengthy story of breast conserving treatment, and Paganelli, along with Veronesi of course, knows only too well the struggle to get new therapeutic approaches accepted – and bureaucracy in Italy is a particularly tough nut to crack. He also anticipates running up against vested interests. "I'm sure the makers of linacs will not be so happy – but in fact if you cut the number of applications for them you can treat more patients."

One other notable area of therapeutic work at Milan is the treatment of neuroendocrine tumours with peptide receptor radionuclide therapy – Paganelli and colleagues have built on work pioneered in Rotterdam and Basel on this technique. "These are rare tumours, but not as rare as you think – and we can show a benefit in more than 70% of patients, with 20% in complete remission. It's attracted commercial interest and we are looking at peptides for other cancers." He says the peptide treatment has expanded around Italy, with about 50 patients seen each week. In Milan, quite a few come from abroad for this and other treatments such as for brain tumours.

All this is well known in the relatively small circle of nuclear oncologists, a profession that seems to have a number of entry points and patchy representation globally. Paganelli says there are more in Europe with a background in internal medicine, compared with the US, where he says nuclear medicine tends to be more a branch of radiology. The Netherlands and Germany are among the stronger countries, he adds, while pockets of excellence exist in several places – a case in point is in Nantes, France, where a high-intensity cyclotron is being built, and which is hosting a conference at the end of March: Nuclear Medicine Tomorrow (see www.arronax-nantes.fr).

The European Association of Nuclear Medicine – appropriately sited in Vienna, home to the International Atomic Energy Agency – is an active organisation, he notes. It established a school for continuing education in 1997 and is forging closer links with the European Society of Radiology as the crossover between imaging techniques becomes more pronounced (although this has courted opposition from some quarters, not least because nuclear medicine appears to be stronger in those countries where it has been allowed to flourish as a physician-led discipline). Paganelli is just keen to spread messages about nuclear oncology. "I'm more likely to attend meetings with surgeons and medical oncologists now than the nuclear medicine events," he says. He's also taken up teaching posts at the universities of Milan and Bologna, and is pleased to report that in Italy there are now at least 10 centres routinely doing work introduced at Milan.

Paganelli spends much time trying to convince companies to invest in the work. He also registered more patents recently – not for personal gain, "but because they are necessary to convince firms of commercial value."

Elsewhere there have been gloomy reports on prospects – in the US, federal cuts in 2006 led to "many important scientific projects related to nuclear medicine being abandoned", according to the Society of Nuclear Medicine. In the UK in 2003 nuclear medicine was said to be "close to collapse" – the country had just four PET scanners at the time, according to the *British Medical Journal*, and there

Enthusiast. Fishing is Paganelli's great passion

were concerns about a depleted workforce. Certainly a PET/CT set-up is costly – about €1.5 million – but as Paganelli notes, it should be justified as a front-line diagnostic tool and not shunted to the end of a queue of other techniques used for investigation.

Part of the debate about funding also revolves around the use of very costly external beam technologies. As Paganelli points out, there are different radioisotopes he can use internally that deliver not only beta particles (i.e. electrons/positrons) but also alpha particles comprising protons and neutrons (i.e. a type of hadrontherapy, and he's in a good place to monitor progress in the external use of ion beams, as the TERA Foundation, the Italian hadrontherapy project, is based in Milan). By and large, internal radionuclide approaches tend also to be safe and well-tolerated, he says, especially with pretargeting, while it is a myth that all such treatments need bunker-like facilities to be administered.

While the radionuclides show promise in a fairly limited number of treatments so far – bulky, solid tumours have been less amenable to the targeted approach – Paganelli is in no doubt that, given the right backing, they should remain at the forefront of translational research, including a growing use in studying the action of targeted drugs.

Apart from medicine and his family – four daughters and his wife Stefania, who works in administration at the institute – Paganelli's biggest passion is that ultimate in targeting, fly fishing (medicine is a hobby compared with this, apparently).

Nuclear medicine does, perhaps, need more high-profile leaders, but Paganelli is content to keep developing his base in Milan and doing some teaching, albeit with ongoing skirmishes with the Italian authorities. Heading a society, or following in the footsteps of that most famous Italian nuclear scientist, Enrico Fermi, to the US as so many other Italians have done, is not for him. "I'm happy to serve my country – but all the time trying to kill bureaucracy with evidence," he says, adding that he will be content if in 10 years' time targeted radionuclide therapy is mainstream in cancer centres. "Whenever you propose something new, people say it is not true. Then they say it doesn't work. And when you show it works, they say it's not new. Nobody will give you anything – you have to fight with great enthusiasm and work equally with your heart and brain."

And that is just what he is doing, forging new paths in search of innovative ways to put nuclear medicine to the service of cancer patients. Fourteen years after being diagnosed with a terminal brain tumour, his first patient at the Institute, now alive and well, and the thousands of women who have safely retained their healthy lymph nodes, are among the many who have reason to be glad of this spirit of innovation and enthusiasm.

Paganelli spends much time trying to convince companies to invest in the work

Diet and exercise: it's time to act on the evidence

Kathy Redmond ■ EDITOR

What if you could prescribe your patients a therapy that had proven powers to lift quality of life, boost psychological well-being, improve cardiorespiratory and physical fitness, and reduce fatigue?

Studies on exercise and diet have consistently shown that relatively small changes in lifestyle can achieve all these things. They can also improve the chance that your patients will complete their course of chemotherapy. And evidence is now mounting to show that eating healthily, avoiding weight gain and exercising regularly may reduce the risk of recurrence and death from certain cancers – breast and colon in particular.

Some studies estimate the risk reduction to be on a par with the benefit offered by a drug like trastuzumab (Herceptin).

Exercise and diet offer a way for patients to play an active part in fighting their disease – very important to many – without toxic side-effects. So why do we give so little priority to advising, helping and encouraging our patients to adopt a healthier lifestyle?

It is true that, while results from the studies are compelling, they are undermined somewhat by methodological difficulties such as a failure to control for a full range of prognostic factors. Yet the growing body of evidence is consistent, it points only one way, and so long as the advice is for moderate changes, patients have nothing to lose.

Wide variations in the dietary and exercise schedules studied have also confused the issue. In the absence of clear guidelines, the recommendations on cancer prevention made recently by the World Cancer Research Fund should be extended to cancer patients: try to be physically active for at least 30 minutes each day, keep as lean as possible and eat a healthy diet (five or more servings of fruit and vegetables a day, and keep off sugary drinks and energy-dense foods).

Another obstacle may be the time and effort required from health professionals as well as the patient. Making lifestyle changes isn't always easy; it may require experimentation, good advice and lots of encouragement, until patients find a way to modify their lifestyle that is compatible with their interests and everyday life – if it's too time-consuming, costly or inflexible it won't work. Providing aids such as pedometers or exercise guidebooks may be necessary.

Currently, not only do few patients receive such help and encouragement, but good advice is hard to find even when they look for it. Most well-known cancer websites require patients to dig deep to find fairly limited advice that could make an enormous difference to their quality of life and possibly mortality. This is a serious oversight. Rectifying it could be relatively cheap and easy, and it needs to be done now.

To avoid the Big C, stay small

The best ways to prevent cancer look remarkably like those needed to prevent obesity and heart disease as well.

JAMES NOBLE/CORBIS

Every day there are new stories in the tabloids about the latest link, sometimes tenuous, sometimes contradictory, between cancer and some aspect of lifestyle. If this is a recipe for confusion, then the antidote is probably a weighty new tome from the World Cancer Research Fund (WCRF). It is the most rigorous study so far on the links between food, physical activity and cancer – and sets out the important sources of risk.

Individually (except for smoking) these risks are quite small. However, many a mickle makes a muckle, and in total they add up to something significant. Roughly speaking, smoking is responsible for a third of cancers (smoking 20 cigarettes a day increases your risk of lung cancer 20-fold), poor food and lack of exercise result in another third, and other causes account for the rest. Some of this last third are known: genetic predisposition, ultraviolet sunlight, pollutants such as pesticides, and other factors including cosmic radiation and a naturally occurring radioactive gas called radon. But the picture is undoubtedly incomplete.

The research has taken six years, involved nine research institutes, and examined more than half a million publications – which were whittled down to

7,000 relevant ones. From these, the new guidelines spring. Few come as news (see box), but the most surprising is the degree to which even being a bit overweight is a risk. One of the most important things a person can do to avoid cancer is to maintain a body mass index (BMI) of between 21 and 23. According to the WCRF's medical and scientific adviser, Martin Wiseman, each five BMI points above this range doubles the risk of post-menopausal breast cancer and colorectal cancer.

For those unfamiliar with BMI, it is calculated by dividing a person's weight in kilograms by the square of his height in metres. Until now, a healthy BMI has been thought of as being between 18.5 and 24.9. The report implies that this range should be narrowed. It is not enough to avoid being clinically obese, or even just a bit overweight. To minimise your risk of cancer, you have to avoid getting fat at all.

Indeed, paying attention to what you eat and drink seems to be the report's watchword. The list is depressingly familiar from injunctions relating to what is coming to be known as metabolic syndrome (obesity, late-onset diabetes, high blood pressure, heart disease and kidney failure, which are starting to look like symptoms of a single, underlying problem).

Why cancer and metabolic syndrome might be connected is not yet clear. Cancer is caused by mutational damage to genes that otherwise hold a cell's reproductive cycle in check, and thus stop that cell proliferating. Metabolic syndrome, as its name suggests, seems to be related to the way cells process fats and sugars. There may be no direct link. But it may be that metabolic syndrome involves the production of growth-stimulating molecules that help cancers along.

On the matter of the miscellaneous final third, Devra Davis, an epidemiologist at the University of Pittsburgh and the author of a new book on cancer*, argues that more attention needs to be paid to pollutants and chemical hazards. Few Americans, she says, are aware that the roofs of 35 million homes may be insulated with material containing asbestos (which is linked to a cancer called mesothelioma). She observes that a forthcoming report from America's Government Accountability Office will criticise the government for its lack of public warnings about such risks.

There is also concern in America about the overuse of medical X-rays, especially in emergency rooms. Not many people, for example, are aware that computerised tomography (CT) scanning uses large doses of X-rays. A scan of a baby's head is equivalent to between 200 and 600 chest X-rays. However, Dr Wiseman says these risks account for a trivial number of cancers and guesses the remainder are also something to do with nutrition.

HOW TO REDUCE CANCER RISK (EXCLUDING SMOKING)

Body fatness	Be as lean as possible within the normal range of body weight, BMI 21–23
Physical activity	Be physically active, e.g. brisk walking at least 30 mins a day
Foods and drinks that promote weight gain	Limit consumption of energy-dense foods. Average energy intake should be 125 kcal/100 g of food. Avoid sugary drinks
Plant foods	Eat mostly foods of plant origin: fruits & non-starchy vegetables, at least 600 g a day
Animal foods	Limit intake of red meat, no more than 300g a week. Avoid processed meat including bacon and ham
Alcoholic drinks	Limit alcoholic drinks, two a day for men and one a day for women
Preservation, processing and preparation	Limit consumption of salt to less than 5g a day. Avoid mouldy cereals and pulses
Dietary supplements	Aim to meet nutritional needs through diet alone
Breastfeeding	Mothers to breastfeed; children to be breastfed
Cancer survivors	Follow the recommendations for cancer prevention

Source: World Cancer Research Fund

It's not enough to avoid being clinically obese, or even a bit overweight. You have to avoid getting fat at all

Risky business

With hazards everywhere, plus the complications of genetic predisposition and age, it is hard for someone to work out his actual risk of developing either cancer or metabolic syndrome. If that is a recipe for inaction – as it often is – there may be a solution in the form of a personalised health check-up called the PreventionCompass.

This system has been developed by the Institute for Prevention and Early Diagnostics (NIPED), a firm based in Amsterdam. It requires the customer to answer a detailed questionnaire about his way of life and to undergo a series of tests. It draws its conclusions by running the results through a 'knowledge system' – a database that pools expertise from many sources.

Coenraad van Kalken, NIPED's founder, says his scientists have programmed in risk factors for cancer, cardiovascular disease, diabetes, kidney disease, lung disease, 'burn-out', depression and other psychological disturbances. The system can, for example, use family history and elevated levels of a particular protein in the blood to work out who should undergo a biopsy to look for prostate cancer. And because it looks at lifestyle as well as biochemistry, it could similarly suggest lower alcohol consumption and a colonoscopy to someone at risk of colorectal cancer.

The way to go. For around EUR 100 a year NIPED's PreventionCompass can give you your risk profile for diseases including colorectal, breast and prostate cancer, together with advice on diagnostic tests and lifestyle changes

In the case of this disease, and also breast cancer, such early diagnosis prevents a serious and incurable condition. Bob Pinedo, the director of the Free University medical centre in Amsterdam, told a symposium held by the European School of Oncology in Rome on October 26th that it costs €250,000 ($360,000) to treat (not cure) a patient with late-stage colorectal cancer for 20 months. In the Netherlands, that would pay for 1,000 colonoscopies.

Given the rising costs of dealing with cancer alone – in America this is more than $100 billion a year – prevention and early detection look set to take off. In trials of the PreventionCompass that NIPED conducted [in 2006], more than 75% of the staff of four Dutch companies volunteered to join the scheme. Moreover, occupational-health officers in these companies claim that more than half their staff actually made changes to their way of life as a result. Not bad for a system that costs about €100 a year for each employee.

This year two large insurance companies, which provide corporate healthcare, income and disability insurance to employees, are offering to lower the premiums of customers who sign up to the PreventionCompass. Next year, the plan is to extend the scheme more widely, by recruiting Dutch GPs to offer it to people from lower-income groups who do not have such private health insurance.

The message, then, is prevention, not cure. And it is a message that needs to be heeded across the world as poor countries grow wealthier and adopt the eating habits and sedentary lives of the rich. It is an irony that evolution has shaped people to enjoy fat, sugar and indolence – things in short supply to man's hunter-gatherer ancestors, and desirable in the quantities then available. Wealth allows them to be indulged in abundance. Unfortunately, human bodies have evolved neither to cope nor, easily, to resist.

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* *The Secret History of the War on Cancer*, Basic Books, New York.

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Two large insurance firms are offering lower premiums to customers who sign up to the PreventionCompass

Personalised cancer therapies: why we may never reach the promised land

Anna Wagstaff

New technologies offer wonderful possibilities for cancer patients. But the development of personalised therapies is being squeezed between the priorities of industry and a regulatory system that offers poor value for money. Is there a champion to clear a route to this revolution in treatment?

If society continues to cede responsibility for developing new generations of drugs entirely to the private sector, there is a serious danger that the potential of modern medical science to tackle diseases like cancer will never be realised. The wonderful possibilities new technologies offer for knowledge-based drug development – investigating the biological mechanisms of cancer, exploring ways of intervening in those mechanisms and learning to identify which patients require which combinations of therapies – will remain untapped. At best, we will remain in the situation we are now, with a steady trickle of expensive new drugs entering the market, often aimed at similar targets, with hardly any of the information doctors need to use them effectively.

This is the message Larry Norton, breast cancer specialist, former president of ASCO and member of the President's Cancer Panel under President Clinton, brought to the *Cancer World* media forum in Rome last October. It was delivered with the sense of urgency of a doctor who knows that the answers he needs to treat his patients correctly are within reach if only the research is done. Detectable too was a slightly weary sense of frustration of someone who, for years, has used his public status to make the case for greater public support for developing effective cancer therapies, and is disappointed by the lack of response.

If it is public response he is after, Norton might do better to point the finger of blame at the pharmaceutical industry – a popular target. Indeed he does not gainsay the many charges commonly levelled against it:

- drugs companies often set their sights low, seeking to add minor benefit to existing drug concepts rather than trying something really innovative
- many are averse to the paradigm of personalised medicine because it reduces the size of the market for each drug they develop
- their competitive structure leads to the duplication of much research and hinders urgent investigations into the potential benefit of 'cocktails' of combinations of drugs,
- a hefty mark-up for 'risk' adds significantly to the price of the final product, and
- doctors cannot use the product to good effect because the research to show how it compares with similar drugs and who benefits most has often not been done.

"But you can't blame the pharmaceutical industry for doing their job, which is to maximise profits for shareholders," says Norton. "The problem is the rest of society is not taking responsibility for curing cancer. By shifting the burden entirely to corporations, we have got what we deserve."

What we have got is a system that takes up to 15 years (see p18) and costs more than $800 million[1] to deliver a single new drug to market.

With such sums and time-scales, it is understandable that drugs companies avoid taking a gamble on highly innovative treatments. It is also hard to see how

developing personalised therapies for small subsets of patients can ever be economically viable under such a system.

There are many who share Norton's concerns. In an article published in 2004 in *Nature Drug Discovery,* Mike Rawlins wrote, "It increasingly seems that [the hopes of personalised medicine] will not be realized without dramatic changes in the way that new medicines are discovered and developed. The cost of drug development is so great that medicines are in danger of becoming unaffordable for either manufacturers to develop or consumers to purchase."

As Rawlins is chairman of NICE, the UK body that advises government and health commissioners on the cost-effectiveness of new medicines, his opinion counts. Indeed NICE has ruled against reimbursing the cost of many of the latest cancer drugs for patients in England and Wales, including cetuximab (Erbitux) and bevacizumab (Avastin).

Four years on, however, there is little evidence of the dramatic changes for which Rawlins was calling.

Shift the burden of risk

The problem is that the new knowledge-based drug development is far more time-consuming and costly than the try-it-and-see 'black box' model of the past. Yet the risk of failure seems much the same – the paradigm still holds that from 10,000 molecules screened, only 250 enter preclinical trials, 10 enter clinical trials and only 1 reaches the market.

Norton believes that investing significantly more public funding in the very early part of the drug development process would dramatically cut the costs to industry and encourage greater innovation. The public sector would accept more of the risk in this critical stage – discovering targets, developing 'lead' compounds that can be shown to have the desired biological effect, and looking at drugs derived from these lead compounds

ILLUSTRATION: STEVE DELL

"By shifting the burden entirely to corporations, we have got what we deserve"

"Drug companies are often doing the exact same basic research, but not sharing the data"

that preserve their activity with manageable toxicity.

Drug companies could then do what they do best: turning promising compounds into marketable medicines – altering molecules so the drug is more effective, more stable, easier to administer and suitable for large-scale manufacture, taking it through the regulatory hurdles, and determining optimal dose/schedule and the disease setting it works best in. "That's where competition should start among corporations – at a much higher level than it does now."

Shifting more early research into the public setting, adds Norton, could also reduce duplication. "One of the things that makes drugs expensive is that drug companies are often doing the exact same basic research, but not sharing the data or even sharing the fact that this research is going on. Once you start to divulge information about your research, it becomes no longer profitable to do secret research."

For those who are sceptical about this public funding approach, Norton points to the electronics industry "where most fundamental research in terms of semiconductors and computer development is happening publicly and is shared by everybody and the competition starts after you have the transistors. Who can build the better computer? That is one reason why we are making so many advances in computer science, because the competition starts at a much higher level than it does in drug development."

Norton is calling for funding for this very early stage of drug development to be doubled or trebled. "Only around 10% of meritorious grants currently get funded, and what you see is a dramatic shift away from innovation towards much more predictable research. It didn't used to be that way. For many years it was 20%, and if you get into the range of 30% of meritorious grants being funded, that's when you get to see exciting science."

Reduce the regulatory burden

Rawlins agrees that increasing academic involvement in the early stage of drug discovery will result in greater innovation. However, he believes that the main cost problem lies in a regulatory system that imposes a huge economic burden and takes almost no account of the barriers this erects to the development of new therapies. He wants to focus attention on cutting costs at the stages of preclinical safety tests and clinical trials, which, according the Boston Consulting Group, account for around 10% and 30% respectively of the cost of developing a drug.

Rawlins is a pharmacologist, who spent 12 years as vice-chair and chair of the UK Committee on the Safety of Medicines before taking over the chair at NICE. He recognises and welcomes the contribution that drug regulation has made to protecting society from a repeat of the thalidomide disaster and from drugs that are ineffective or manufactured to a poor quality. But he also recognises that patient groups with rarer diseases – which will also include 'subgroups' of more common cancers – pay a heavy price for this protection, because the added cost burden makes it uneconomical to develop drugs that could benefit them. That price, says Rawlins, is not taken into account by the bodies responsible for drug regulation.

In his 2004 *Nature Drug Discovery* article, he calls for "a full analysis and assessment of the mass of data held in the vaults of US and EU drug regulatory authorities," to establish whether these studies add sufficient knowledge to justify the added time and expense. "There needs to be a rigorous examination of the 'rituals' associated with drug development. Every step in the drug development pathway should be tested against two separate criteria: is there a clear evidence-base to support the continuing inclusion of the measure in the requirements of regulatory authorities? and does each regulatory requirement offer value for money?"

Preclinical safety studies can take up to three years and involve four types of investigation:

- the pharmacalogical screen (exploring potential effects of the drug on biological processes other than those intended)
- pharmacokinetic investigations of the drug in the species to be used for formal toxicology testing
- acute- and repeat-dose toxicology studies
- special toxicity testing such as mutagenicity, carcinogenicity and reproductive toxicity tests.

Rawlins raises a number of questions about the evidence base for many of these studies (see box). He queries, in particular, the value of conducting *in vivo* carcinogenicity studies on compounds that have tested negative in short-term mutagenicity studies, arguing that this either results in findings irrelevant to humans or reveals a tumour type that could be predicted from the compound's pharmacological properties. "If it doesn't damage DNA *in vitro*, but produces cancers in

Preclinical Testing:

DOES THE EVIDENCE JUSTIFY THE EXPENSE?

The pharmacalogical screen

- How strong is its predictive power?
- What is the basis for the safety margins used?

Repeat-dose toxicology studies

- To what extent are current regulatory requirements based on biological plausibility, rather than formal evidence?
- To what extent does 'target organ' toxicity, as identified in experimental animals, reflect likely toxicity in humans? What are the predictive powers?
- What is the real predictive power of repeat-dose studies lasting more than three months?
- What is the evidence base for the 'safety margins' assumed by toxicologists?

Special toxicity testing

- What is the evidence base for conducting *in vivo* carcinogenicity studies on compounds that have tested negative in short-term mutagenicity studies?

Source: Rawlins (2004), Cutting the cost of drug development? *Nature Drug Discovery* 3:360–364

animals, then the company toxicologists spend the next two or three years working out the mechanism of toxicology in the animals, showing that it wouldn't happen in a human being, so the whole study was a waste of time," he commented to *Cancer World*.

Rawlins accepts that the evidence base for the regulatory requirements for clinical trials is a lot stronger, but given that trials can take more than seven years to complete and account for a third of drug development costs, he believes that there is still a public interest case to investigate cheaper and quicker alternatives.

The current regulatory requirements are based on randomised, controlled, blinded, parallel-group clinical trials. But the methodology of drug development has changed dramatically since these requirements were drawn up. Today, the skill lies in a seamless process of gathering information about the drug and its biological effects in a variety of patients, disease settings, doses and schedules, from preclinical studies onwards, adapting each stage of the trial protocol according to the information gained from previous stages.

A variety of statistical methodological approaches – sequential, adaptive, decision-based and risk-based designs, as well as Bayesian techniques – have been developed to guide this process of scientific exploration. If these could be shown to be sufficiently reliable to provide the basis for evaluation for marketing approval, says Rawlins, the time taken to conduct clinical trials could be cut dramatically.

"We need to say what we really want to happen, and then develop regulatory processes around it," Rawlins commented to *Cancer World*. "At present, we do phase I studies, then ponder the results. Then we go to the regulatory authorities and ask to do a phase II, which takes another two years, and we ponder the results. We then go back to the regulators and ask for a phase III. We should move almost seamlessly from phase I to phase II to phase III.

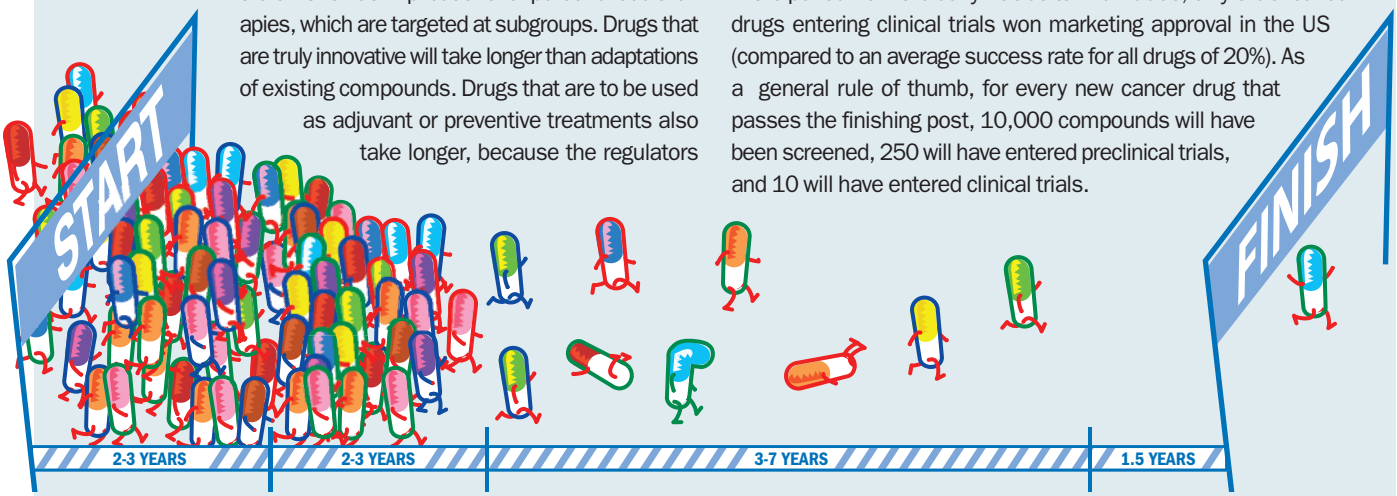
"Why not have real-time regulation saying, for instance, 'We want to carry on the comparator group and we will carry on the mid-dose group and we will drop the high-dose and the low-dose group because the low dose doesn't work well, and the high dose is too toxic, and we now want to include more patients for the phase III.' We need that sort of approach. Then we could concertina the current six or seven years – we could halve it, or at least reduce it by one-third. Even if you can reduce the time it takes, that itself saves a lot of money, because of the time companies are spending money and not getting any return."

EMEA, however, is resisting using these types of statistical approaches as a basis for market approval. After a two-year consultation, EMEA published in March 2007 a report, Innovative Drug Development Processes, making it clear that 'Bayesian' methodology does have a place in drug development, but only for "hypothesis generating in earlier phases" and "the assessment of futility". With the possible exception of drugs for small populations, where an adequately powered

"We need to say what we really want to happen, and then develop regulatory processes around it"

The long road to getting a new drug to market

It takes up to 15 years to get a new drug to market. Drugs intended for relatively small groups of patients tend to take longer than average, because it takes time to recruit sufficient volunteers to the clinical trials – this has implications for personalised therapies, which are targeted at subgroups. Drugs that are truly innovative will take longer than adaptations of existing compounds. Drugs that are to be used as adjuvant or preventive treatments also take longer, because the regulators require stronger data on safety where the drug is to be used in patients who may have no clinically evident disease. According to a report by the Tufts Center for the Study of Drug Development (2007), in the period from the early 1990s to mid-2000s, only 8% of cancer drugs entering clinical trials won marketing approval in the US (compared to an average success rate for all drugs of 20%). As a general rule of thumb, for every new cancer drug that passes the finishing post, 10,000 compounds will have been screened, 250 will have entered preclinical trials, and 10 will have entered clinical trials.



DRUG DISCOVERY	PRECLINICAL TESTING	SUBMIT CLINICAL TRIAL APPLICATION TO NATIONAL REGULATORY AUTHORITY	CLINICAL TRIALS			FILE MARKETING AUTHORISATION APPLICATION WITH EMEA	EMEA	
			Phase I	Phase II	Phase III			Phase IV
Cell lines	Laboratory and animal studies		20-80 patient volunteers	100–300 patient volunteers	1000–3000 patient volunteers			General patient population
Identify, prioritise and validate target. Select lead compound (compound believed to have potential to treat disease).	Does it reach the target? Does it have a biological effect? Is it safe? Can it be manufactured to a reliable quality – purity, stability, shelf-life?		What is the maximum tolerated dose of the drug? How does the body handle the drug? Are there any acute side-effects?	How effective is the drug in different cancers, used at the maximum tolerated dose? (Reject ineffective drugs at this stage.) What is the optimal dose? What side-effects?	Generate statistically significant data on efficacy and safety as the basis for applying for marketing approval.		Review process and approval.	Surveillance to keep a check on evidence of serious side-effects. Study new uses, patient types, long-term effects and different dosages.

"Those in charge of our public health cannot expect to get something for nothing"

phase III trial would be impossible, full phase III trials will continue to be compulsory, to "provide stand-alone confirmatory evidence of efficacy and safety".

Rawlins would like to see an international initiative to subject the whole issue to a 'value-for-money' analysis, based on retrospective reanalysis of a selection of past clinical trials, to see whether the approval decision would have come out any differently had a Bayesian approach been used. "It's perfectly feasible. It might cost a few million, and take two or three years, but that's nothing in the great scheme of things."

He believes the initiative would have to come from a European level, in conjunction with the US, and he has raised the general issue with the European Commission. He senses, however, that the Commission is reluctant to get involved in a major overhaul of the regulatory system, "because the next time a Vioxx happens – and it will happen – they would take the blame." (Merck's anti-inflammatory drug, Vioxx, had to be withdrawn from the market in 2004 after it was found to increase the risk of heart attack and stroke.)

But doing nothing to address the cost burden of regulation may kill off hopes of developing effective new personalised therapies. "If we do not work towards this goal, we will fail future patients, their families and society as a whole."

Regain control of clinical trials

Cost is not the only threat to developing effective personalised therapies. Perhaps the greater fear for Norton and his fellow oncologists is that they will never find out how to use the new drugs to greatest effect. Companies do not need to answer questions about which patients need what combinations of which therapies to get market approval for a new drug or to extend the indication for an existing one. Since the lion's share of funding for trials comes from the industry, industry can dictate the agenda. "It's the golden rule," says Norton, "The one with the gold makes the rule."

He says that the industry does not address the key questions that doctors want answered. "We are seeing an explosion of clinical trials that are company supported, and are designed to show that the drug has some merit, but not designed to try to influence in a productive way the standard of care."

These trials may, for instance, test a new drug A against existing drugs B and C, but not against the drug currently deemed to be the most appropriate for the relevant patient group, which is drug D.

"We call it a 'straw man' approach. We see dozens and dozens of trials like that, which are creating enormous confusion in my field, as important controls are being left out because they are not necessary to gaining regulatory approval. This is a tremendous dilemma for the practising cancer doctor. We are in a position where we have to make decisions about the treatment of patients where we don't know the answer. The thing that bothers me most is that we know the answer will never be found, because we know that the research needed to answer that question will never be done."

In fact, Norton is concerned that clinical trials are coming under increasing commercial pressure. In March 2007, he co-authored with Martine Piccart, Aron Goldhirsch and others, a Commentary in *Nature* entitled "Keeping faith with trial volunteers". They pointed to a growing trend for pharmaceutical companies to recruit academic investigators to conduct adjuvant trials in which the data will be controlled by the company outside the framework of a research cooperative group or a network of academic centres.

The authors warned of the dangers of allowing companies to control the research agenda in this way.

"First, if a trial is focused on answering a purely commercial question, vital opportunities to answer other important questions related to the care of patients and to biological understanding may be lost. Second, trial design can be distorted by commercial interest, for example, requiring an arbitrary duration of treatment, rather than focusing on the optimal treatment duration for patient benefit. We note an increasing tendency, especially in pharmaceutically controlled trials, to withdraw funding or cease follow-up studies after commercial endpoints have been satisfied...

"Data control entirely within a commercial organization may enhance the temptation to delay or suppress unwelcome findings. For example, large trials designed to define a subset of the patient population that benefit most from a treatment can run counter to the interests of a drug company wishing to maximize the number of potential patients for a new treatment. In such cases, control of data by the drug company would not be in the best interests of patients."

Returning to his earlier point, Norton emphasises that the pharmaceutical

industry cannot shoulder all the blame for this state of affairs. It is just another consequence of having shifted the burden of curing cancer entirely to corporations. He warns that a more equal partnership between the pharmaceutical trial sponsors and academic investigators will only happen if substantially more public money is made available.

An equal partnership

The industry itself is talking increasingly in terms of public–private partnership. The escalating cost of healthcare is prompting many European countries – and even the US – to look at ways of introducing some form of cost-benefit approach to reimbursement. Industry knows that what NICE has done in refusing reimbursement for many of its latest offerings, or at least severely restricting their use, is likely to spread. The companies have two options. They can work with academic researchers to demonstrate that their drugs really do represent value for money or accept that developing these drugs will become economically unviable. The pharmaceutical industry would prefer the former.

Most drugs companies now say they are keen to work in partnership with public health bodies to address the question of 'value in use'. Cynics may question their sincerity. They point to the failure of companies to carry out research to define which patient groups benefit most from new drugs, even when regulators specify this as a condition of conditional (early) approval – figures from the FDA show a compliance rate of less than 10%.

The industry attributes this largely to the difficulty in recruiting patients to trials of a drug that has already been approved.

Norton might add, however, that it is perfectly understandable that drugs companies may not want to sink resources into lengthy and costly studies that could well end up diminishing the market for their drug. Developing effective treatments for cancer is a public responsibility, and those in charge of our public health cannot expect to get something for nothing. If they want a say in how drugs are developed, they will have to pull their weight.

However, the industry also has a responsibility to make this partnership work. AstraZeneca's head of oncology, Brent Vose, accepts that companies have to change the way they work, and says he is sympathetic to criticisms of 'non-inferiority trials' (trials that seek only to demonstrate that a new drug is no worse than something already on the market).

He believes that patient stratification is very important here – breaking the trial population into groups to identify different levels of response according to, for instance, stage of disease or the presence/absence of a particular biomarker. "That is where this whole personalised healthcare, linking diagnostics with therapeutics starts to play out."

The key place to start doing this, he says, is in randomised phase II trials. "You have to come out of phase II with a hypothesis about the sorts of patients you want to take on. If you had choices you would obviously take those agents that did something better or in a different group than what already exists, because at the end of the day it is about patient benefit and about unmet clinical need."

He also accepts that companies need to take more responsibility for demonstrating the extent of benefit their drug offers across its intended patient population. Currently, formal assessment of what a new drug adds in terms of 'quality-adjusted life years' or similar measures of 'value in use' tends to be made after the drug has been approved. Vose would like to see data relevant to this collected within phase III of the clinical trial. "The whole quality of life agenda… probably needs to be played out in the trial design rather than as a retrospective data sweep up."

This is the point when doctors like Norton could start to get answers to questions about who really benefits from using the drug. And on this specific point too, Vose agrees that industry should do more. "When you start talking about targeted agents, the implication is that you target particular patients or particular stages of disease or particular combinations. The oncology community has to find out where that benefit is best placed. And it won't be sufficient for us to spend 30 years to find out how to use 5FU, because that is how long it took. That comes back to the need for close interaction between opinion leaders, investigators and companies about how we can find that benefit as quickly as possible."

Vose cites as one possible way forward a partnership approach in which conditional approval would allow the drug restricted use in certain public healthcare settings, where more could be found out about how many patients respond and who responds best, before the drug is allowed onto the market. "That would take you from hundreds of patients to thousands as quickly as possible, within a semi-trial situation. That seems to me to be a very good idea."

A proposal along these lines was made in the US during discussions about how to introduce the FDA's conditional approval procedure. The suggestion was that drugs approved this way would initially be used only in Medicare and Medicaid hospitals. But the idea was dropped and, currently, that research is simply not being done – as is evident from the 10% compliance rate with the post-approval studies demanded by the FDA as a condition of approval.

Who will champion drug development?

Norton, Rawlins and Vose come from the worlds of practising doctor and academic, drug regulator, reimbursement decision maker and industry. They may not agree about everything, but there is a

"A third or a half of us are going to die from cancer, but we are not acting that way"

shared understanding that drug development will have to change if it is to stand a chance of delivering on the great promise of personalised therapies. And there is clearly both the basis and the will for a constructive dialogue on how public and private players can work together to achieve that change. Yet there is also a real danger that the current unsatisfactory situation will just be allowed to drift, in the absence of leadership from government health departments, and the EU Directorate General for Health and Consumer Affairs (DG Sanco).

"We are dealing with a situation now when the funding available, compared to the opportunities, is grossly out of proportion," says Norton. Speaking to the situation in the US, where funding for cancer research has remained static for the last few years, he reels off figures to illustrate how little priority is given to finding ways to cure cancer. "The NCI funding, which is the entire funding for cancer research coming out of the US government, is a little above $4.5 bn. The total pharma investment for all diseases is about $50 bn, of which about 10% is cancer. US philanthropy is about another billion to billion and a half. Being generous, we are talking about $11.5 bn for all of cancer research for all cancers.

"In the same year, the American tobacco industry spent $16.1 bn on advertising and Americans spent $68 bn on soft drinks. If Americans didn't drink any soft drinks every Tuesday, and instead put that money in a pool for cancer research, we would be doubling the entire US budget for cancer research. If you go to any American and say: 'If I can dramatically accelerate the prevention and cure of cancer, would you be willing to give up drinking soft drinks one day a week?' they would say, 'Of course'. But we are not doing that."

The situation in Europe is worse. According to a report by the European Cancer Research Managers (ECRM) Forum published last September, Europe's per capita spend on cancer research from non-commercial organisations is only one-fifth of that in the US (up from one seventh, reported by the ECRM in 2005). Costs of clinical research, meanwhile, have escalated because of the badly thought out clinical trials directive.

More worrying, perhaps, is a trend for public funding for cancer research in Europe to speak primarily to the economic policy goal of making Europe a world leader in biopharmaceuticals, rather than the health policy goal of finding treatments for Europe's citizens. Instead of injecting a public interest goal into drug development, Europe's public money could instead be dragging existing academic research into the service of industry. This is a key concern flagged up in the ECRM report.

"EU money is often being partnered with industry and there is a real danger that if all increases in EU cancer research funding go this way, Europe's intrinsic creativity would be distorted by encouraging subsidy-seeking behaviour and essential areas of public health relevant to cancer, but not amenable to a business approach would remain orphans."

The ECRM warns against "priority-setting focused on predicted practical relevance, i.e. industrial utility."

The question is, who will champion prioritising a policy aimed at finding effective therapies for a disease that will kill one in every three European citizens? Who will argue the case for public money to be spent funding the sort of truly innovative approaches that could make a real difference in cancer treatment? Who will fight for the clinical research that may not deliver immediate economic growth and profit, but will give doctors the answers they need to treat the right patients with the right combinations of therapies – and will ultimately save vast sums that are currently wasted on treating patients with inappropriate therapies? Who will have the courage to initiate a review of the regulatory system that looks not only at the benefit of safety, but also at the obstacles the added costs pose to developing therapies for smaller groups of patients?

Norton tells an anecdote told him by an historian. "It's like the ancient Roman armourers saying to the ancient Roman senators: we know the Visigoths have burnt down the city and are about a block away from the palace, but how are you going to incentivise us to make swords?"

"The incentive," says Norton, "is that a third or a half of us are going to die from cancer. But we are not acting that way. We are acting as if this is a minor component of what we are doing."

1. The figure of $800 million to get one new drug to market is based on estimates developed by DiMasi et al. (2003) of the Tufts Center for the Study of Drug Development and a study conducted in 2001 by the Boston Consulting Group. Though the data behind these estimates are unverifiable, the figure is nonetheless widely used. The biggest criticism centres on the use of 'capitalised' costs, which include an estimate of what the money could have earned had it been invested elsewhere. It is, however, the capitalised cost that a company will consider when deciding whether or not to invest, particularly where the money is likely to be tied up for a very long time.

Are patients with multiple hepatic metastases from colorectal cancer candidates for surgery?

Michael D'Angelica

Results from a retrospective review of data from patients who underwent resection for colorectal liver metastases indicate that partial hepatectomy for four or more hepatic colorectal cancer metastases is no longer contraindicated and is associated with a five-year survival rate of 28–51%.

Partial hepatectomy is the only therapy associated with long-term survival in patients with resectable hepatic colorectal cancer metastases, and is the therapy of choice for these individuals. Although many factors have been shown to adversely affect outcome after partial hepatectomy, most do not preclude long-term survival. Historically, the presence of four or more metastases has been a contraindication to hepatectomy because of dismal five-year survival prospects. Publications condemning hepatectomy for patients with four or more metastases must be interpreted cautiously, however, since they are from an era of ineffective chemotherapy, poor imaging and poor staging.

In accordance with other recently published papers,[1–3] the report by Malik et al. (see opposite) has shown that, in well-selected patients, long-term survival is possible after hepatectomy for four or more metastases. The other papers are all retrospective reviews and reflect the selection bias of the treating physicians, who are able to choose for surgery the patients most likely to do well. Nonetheless, with five-year actuarial survival rates ranging from 28% to 51%,[1–3] surgery accomplishes an outcome that is probably not possible with chemotherapy alone. Malik et al. specifically analysed the number of tumours as a prognostic factor. Their major finding was that the presence of eight or more metastases was the only independent factor associated with poor survival. In fact, patients with four to seven metastases did no worse than those with fewer than four metastases. Patients with more than eight metastases had a median survival time of 21 months, but a five-year survival rate of 24%.

The era of four or more metastases being a contraindication to hepatectomy for metastatic colorectal cancer is over. Enough series have now shown, in patients with multiple metastases, long-term survival rates that cannot be attributed merely to selection bias. Most importantly, however, we have to interpret the results of these series thoughtfully and honestly, assessing what we are accomplishing with surgery. The issues of disease-free survival and of 'cure' after resection of multiple metastases are raised by these findings. Every series assessing resection for four or more metastases has shown at least an 80% recurrence rate on the basis of incomplete long-term

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follow-up.[1–3] Malik et al. reported an estimated five-year disease-free survival rate of 20% on the basis of a median follow-up of less than three years. My sense is that almost all the patients in this study will have recurrence of disease that would be observed if they were followed long enough, but only actual statistics after five years of follow-up will be able to definitively demonstrate this. Hepatectomy, therefore, seems to provide a chance of long-term survival, but rarely completely eliminates disease. We are probably not 'curing' patients with multiple liver metastases but, rather, prolonging survival by resetting their cancer timeline, altering disease patterns, or both. It is likely that chemotherapy, repeat surgery and ablation are also contributing considerably to long-term survival. Lastly, these resection outcomes have all been reported from tertiary referral hospitals with specialty hepatobiliary units, and the importance of evaluation and treatment at a specialty centre should be stressed.

It is an exciting time in which to treat metastatic colorectal cancer. Modern surgery and chemotherapy provide us with effective tools with which to treat a population of patients whose prognosis, until recently, was felt to be hopeless. We must now study novel combinations of surgery and chemotherapy for patients with extensive disease, and Malik et al. have provided us with more stimulating data to encourage such trials.

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

Synopsis

HZ Malik, ZZR Hamady, R Adair et al. (2007) **Prognostic influence of multiple hepatic metastases from colorectal cancer.** *Eur J Surg Oncol 33:468–473*

Background. The method of management of patients with multiple liver metastases is controversial.

Objective. To review 10 years of experience gained in a tertiary referral hepatobiliary unit in managing multiple liver metastases from colorectal cancer.

Design and intervention. This was a retrospective review of a prospectively collected data set from patients who underwent resection for colorectal liver metastases at a single specialist centre in the UK from 1993 to 2003. No ablative therapy was performed. To be accepted for treatment, patients were required to be fit for major surgery, and lack disseminated or nonresectable extrahepatic disease according to CT and MRI scans. The extent of resection performed was decided on the basis of the location and number of metastases, because underlying chronic hepatic disease was not usually present. Patients were permitted adjuvant therapy with fluorouracil and calcium folinate, unless they had received adjuvant therapy within the year previous to surgery. Patients received a minimum of two years' follow-up at specialist clinics (range 2–12 years; median 33 months for survivors).

Outcome measures. The endpoints of the trial were overall and disease-free survival, morbidity and mortality, and length of postoperative hospital stay.

Results. In all, 484 patients were included in the analysis (mean age 62 years; range 23–84 years), and 225 had synchronous disease. The number of liver metastases per patient ranged from 1 to 21 (median 2). Multiple metastases (≥4) were present in 136 patients, of whom 36 had numerous metastases (≥8). Individual metastatic deposits ranged in size from 3 mm to 200 mm (median 40 mm). Complete resection was achieved in 67% of patients. Postoperative hospital stay ranged from 3 days to 139 days (median 8 days). The in-hospital mortality rate was 3%; all the deaths were in patients who had undergone major resection. There was a postoperative morbidity rate of 26%. For the whole group, five-year and 10-year survival rates were 41.7% and 28.6%, respectively. Median survival was 50 months for patients with fewer than four metastases, but was 32 months for patients with multiple metastases (P=0.0072). Survival differences between patients with fewer than four metastases and those with multiple metastases were not significant. Patients with multiple metastases had poorer disease-free survival than those with fewer than four metastases (P=0.0142). Patients with numerous metastases had the worst survival outcome (five-year survival rate 24.2%; median survival 21 months, 95% CI 15–27 months; P=0.0245 for ≥8 tumours in comparison with 4–7 tumours). On multivariate analysis, only the presence of numerous (≥8) metastases predicted for poorer overall (P=0.047) and disease-free (P=0.015) survival. There was also an association between increasing number of metastases and worsening intrahepatic recurrence, with 74% of patients with numerous metastases having intrahepatic disease (P<0.001 vs both patients with <4 metastases and those with 4–7 metastases).

Conclusion. Significant numbers of patients who receive surgery for multiple metastases survive for five years or longer; therefore, resection is recommended for such patients.

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

Is drug treatment superior to allografting as first-line therapy in chronic myeloid leukaemia?

Timothy Hughes

A study comparing the survival times of patients who received allogeneic transplantation for early-stage CML with those of patients who received drug treatment showed that, with very few exceptions, drug treatment is the therapy of choice for this group of patients.

Since allografts for chronic-phase chronic myeloid leukaemia (CML) became an accepted therapy in the 1980s, the choice between drugs and allograft as first-line therapy has been actively debated.[1–3] The study by Hehlmann et al. (see opposite) is the first to compare these options in a randomised fashion, and reported drug therapy to be superior to allografting. The difference was impressive, particularly given that the drug therapy being compared with allograft was interferon alfa and hydroxyurea. The tyrosine kinase inhibitor imatinib has now replaced these drugs, leading to marked improvements in response rates and survival.[4] If this study was repeated today, the results would almost certainly demonstrate the superiority of drug treatment over allograft even more emphatically than do the present results.

The study by Hehlmann et al. shows similar patterns of survival to earlier comparisons.[2] Survival with drug therapy is clearly superior for the first five or more years, after which point, the two curves converge owing to the steady death rate from progression in the drug treatment arm. After convergence, survival with drug therapy falls more rapidly than that with allograft. This rapid drop in survival is unlikely to occur with imatinib treatment, as the annual risk of death beyond five years with imatinib therapy is <1% – similar to the rate for long-term allograft survivors.[5] Given this fact, the early survival benefit of drug treatment with imatinib will probably not be diminished by a more rapid decline in survival beyond five years.

One issue that is currently under debate is whether younger patients should still be considered for upfront allografts. The justification for carrying out such treatment is made on the basis that transplant-related mortality is lower in those less than 20 years old and because of concern about the possible life-long imatinib requirement for these young patients. In a review of outcomes for children (median age 14 years) with CML receiving matched sibling allografts that was conducted by the European Group for Blood and Marrow Transplantation, survival at three years was 73% in patients receiving allografts within six months of diagnosis. In the International Randomized Interferon versus STI-571 (IRIS) study, recipients of imatinib had a survival of 95% at three years and 89% at six years.[4] With annual rates of progression to acute phase of <1%, it is likely that survival on imatinib will remain

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Synopsis

Rüdiger Hehlmann, Ute Berger, Markus Pfirrmann et al. (2007) **Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia.** *Blood 109:4686–4692*

Background. For patients with chronic myeloid leukaemia (CML), allogeneic transplantation is considered the first-line treatment option; however, persistent transplantation mortality and the development of new drug therapies have challenged this concept. Until recently, there have been no randomised studies comparing the treatment outcomes of transplantation with those of drug therapy in patients with CML.

Objective. To compare the survival times of patients who received allogeneic transplantation for early-stage CML with those of patients who received drug treatment.

Design and intervention. Patients with Philadelphia chromosome and/or BCR-ABL-positive CML in chronic phase were enrolled in this study between January 1995 and December 2001. Randomisation was carried out according to the availability of a matched related donor. The patients eligible for allogeneic transplantation comprised two groups: those with, and those without a donor. The baseline characteristics of these two groups were similar. By contrast, there were significant differences in age, white blood cell count, symptoms due to organomegaly, and differential, haemoglobin, and prognostic score between patients who were eligible for transplantation and those who were not. Survival documentation was available for all but one patient.

Outcome measure. The primary endpoint of the trial was survival time.

Results. The study included 621 patients with chronic phase CML who were registered and stratified according to eligibility for primary allogeneic transplantation. Overall, 354 patients (62% male; median age 40 years) were randomised to receive either an allograft from a related donor (38%; n=135) or best available drug treatment (62%; n=219). Overall, 91% of the patients randomised to the allograft group received transplantation within a median of 10 months (range 2–106 months) from the time of diagnosis. The median observation time for living patients was 8.9 years (range 4.2–11.2 years). Patients who received drug treatment had a higher rate of survival than patients who received allografts, both until year eight and over the entire observation period up to year 11 (P=0.041 and P=0.049, respectively). Among patients with low-risk features at the time of diagnosis, those allocated to drug therapy had a higher rate of survival at both eight and 11 years' follow-up than did patients who received transplants (P=0.027 and P=0.032, respectively). The difference in survival between the two treatment arms was not significant for non-low-risk patients. At the time of evaluation, 55% of patients in the allograft group and 60% of patients in the drug-treatment group were alive. Analyses of their health status did not identify any differences between the two groups. Patients who survived at least five years were also analysed for cytogenetic and molecular responses. Patients who received transplantation had significantly higher rates of complete cytogenetic remissions than did patients who did not receive transplantation at any phase (91% and 48%, respectively; P=0.002). Major molecular responses were also more frequent in patients who underwent transplantation than in those who did not (81% and 45%, respectively; P=0.001).

Conclusion. Allogeneic transplantation should be recommended as a second-line rather than first-line treatment option in patients with chronic phase CML.

Acknowledgement: The synopsis was written by Eleftheria Rosmaraki, Assistant Editor, *Nature Clinical Practice.*

superior to survival with an allograft. The case for upfront allografts in young patients with CML is now difficult to sustain.

Patients defined as high risk by a high Sokal score might also have been considered suitable candidates for an upfront allograft. In the study by Hehlmann et al. there was no significant difference in the rate of survival between high-risk patients with a related donor and those without. In the IRIS study, survival for imatinib-treated patients at high risk as measured by Sokal score was 81% at 4.5 years, clearly superior to the survival of 52% at five years for high-risk patients with a matched donor in the study by Hehlmann et al.[6]

Is the debate now over? There have been innovations in allografting that may reduce early mortality, including the use of reduced-intensity conditioning. These innovations might increase survival of allografted patients. An increase in the progression rate in long-term imatinib recipients or emerging serious long-term toxicity with imatinib might also change the situation; however, for the foreseeable future, allografts should be considered a second-line option in chronic-phase CML.

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

Scientific integrity must always come first

Emma Mason

Challenging medical orthodoxies is essential in the interests of good science and improving patient care. All top-class doctors do it, but few enjoy the battle as much as breast cancer specialist **Michael Baum**. He has been called 'provocative' and 'perverse', but a career championing evidence-based patient-centred medicine has left him with huge respect among his colleagues.

Michael Baum attributes his willingness to take controversial standpoints and to challenge conventional wisdom and dogma to the experience of his childhood Friday night dinners.

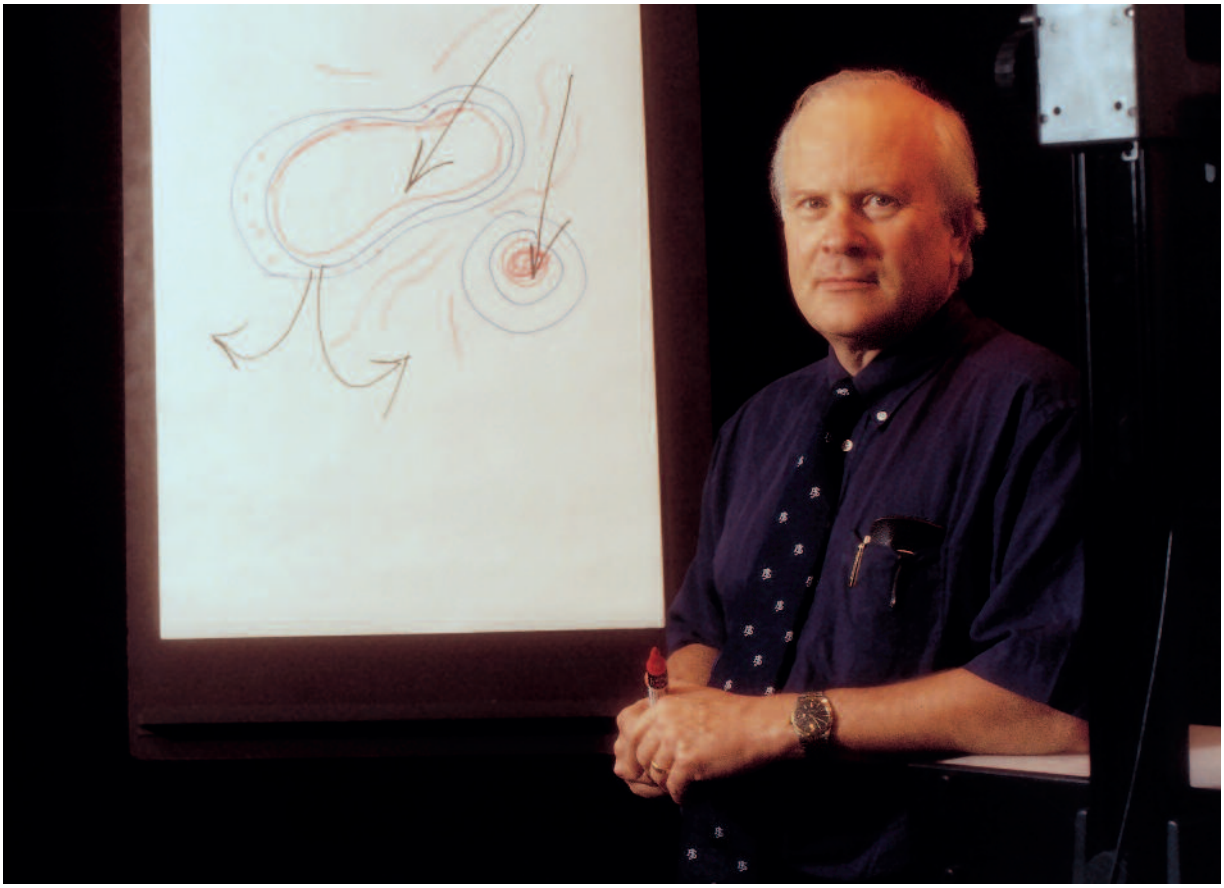
He was born into a large, boisterous Jewish family. Every Friday the family would gather together for dinner to celebrate the start of the Sabbath and to discuss the issues of the day. Having three brothers and a sister to compete with in the rowdy dinner-time discussions, he soon learned that, in order to make any impact at all, the best thing to do was to take the opposite view point to everyone else.

This trait has stayed with him ever since. His scientific training and his work to improve clinical trials taught him the importance of evidence-based medicine. He would argue with his friends and colleagues, but respect their point of view and, when confronted with convincing evidence, would be open-minded enough to change his mind. Sometimes he has found himself arguing vociferously against something that only a few years earlier he had been promoting just as strongly – such as the value of breast cancer screening.

Perhaps his most public disagreement has been with Prince Charles, heir to the British throne, over alternative medicine. In an open letter to the *British Medical Journal* he accused the prince of using the accident of his birth to promote unproven cures for cancer.

A deafening silence followed, and then slowly others emerged from behind the parapet to agree with him. "Well done Michael Baum, you deserve a knighthood at the very least for putting your head on the block yet again and having the courage to say what most of us believe, but usually feel too cowardly to express in the presence of the Royals. See you in the Tower. From your fellow heretic, Lesley J Fallowfield," wrote the professor of psycho-oncology at the Brighton and Sussex Medical School, Brighton, UK, three months later.

Baum, professor emeritus of surgery and visiting professor of medical humanities at University College London, is untroubled by this royal blight on his career. At a Festschrift held in his honour, he told *Cancer World*: "Without doubt the single most important thread running through my whole career is scientific integrity; that you don't spend your



career seeking popularity. You have to retain your intellectual and scientific integrity and everything follows from that. And it's been a hell of a lot of fun along the way."

The Festschrift (a tribute by admirers), held at the Wellcome Trust in London in November, saw friends and colleagues from all the different stages of his working life describe the man and his work in affectionate but robust terms.

A PASSIONATE MAN

"An extraordinary man," said Tony Howell (University of Manchester, UK). "A passionate man who often feels quite strongly about certain matters and feels he needs to do something," said Lord Turnberg (past president of the Royal College of Physicians) referring to Baum's spat with Prince Charles. "Working with Mike was totally harmonious – I always did what he told me!" said Terry Priestman (New Cross Hospital, Wolverhampton, UK), who then revealed that Baum had described the Baum/Priestman surgical team to an elderly patient as the "Starsky and Hutch of breast cancer". "He was mostly right, but sometimes wrong," said Hans-Jörg Senn (chairman of the St Gallen oncology conferences, Switzerland). Fallowfield compared him to George Orwell, whose book *Nineteen Eighty-Four* marked the year when she first started

"Well done Michael Baum, you deserve a knighthood at least for putting your head on the block yet again"

This was one of the first attempts to measure patients' subjective response to cancer and its treatment

collaborating with Baum, saying he was "erudite and prescient, but not right about everything," that he liked to "challenge individuals and the establishment," and that "Mike's views are provocative, occasionally perverse, even extreme, but he challenges us to think harder." David Berstock (Clatterbridge Hospital, UK) was more forthright: "He was prone to the odd bout of apoplexy."

Younger colleagues who had been helped and nurtured by him in later years spoke fondly of the advice he gave them (and others). Mohammed Keshtgar (Royal Free Hospital, London) said Baum's first advice to him was that "[I needed to] make up my mind whether I wanted to go for money and prestige or a spirit of enquiry. For money you need to go into private practice. Perhaps unwisely I chose a spirit of enquiry!" He recalled how Baum had decided to campaign for a breast cancer *un*-awareness week and issued the following advice to the "testicle squeezers of the men's health lobby", which was to "keep your nose out of my anus, your hands off my balls and stop interfering in my life."

Nick Ross, the UK television presenter with whom Baum set up *HealthWatch* to campaign against health fraud (the 'quackery' of alternative

The main man. Surrounded by colleagues at the Festschrift held in his honour last November

medicine), said in a recorded address, "It takes a good doctor to be evidence based in all he does. It takes a really good doctor to campaign wholeheartedly for clinical trials in his own field of expertise. It takes a *great* doctor to have a great skill and judgement and yet keep questioning his judgement in the open way you do."

The Festschrift covered Baum's career from his early days in medicine in Cardiff, Wales, through to chairs in surgery he held at King's College London, the Royal Marsden Hospital and University College London.

Championing quality of life

From the beginning Baum had an interest in quality-of-life issues and what is now called psychosocial oncology, after watching his mother, Mary, die from metastatic breast cancer in 1974, at a time when attempts to alleviate the pain from the disease and the toxic side-effects of the palliative chemotherapy were limited and largely ineffective.

While at Cardiff he developed the technique of linear analogue self-assessment, and he and Priestman modified it to develop a 10-point scale to give a global measure of quality of life. This was one of the first attempts to measure patients' subjective response to cancer and its treatment. "Now the floodgates were opened to exploring more holistic ways of looking at the subject," said Priestman.

Baum went on to establish the first nurse counselling service at King's College Hospital in 1981 and the first psychosocial oncology research team at the same time. He has had a long and productive working relationship with Fallowfield in which he has supported, encouraged and contributed to her work on psychosocial oncology – ensuring that patients were properly informed about their treatments and the choices available to them – and on improving the communication skills of the medical profession. His early work on advocating the use of lumpectomy and breast conservation (rather than mutilating mastectomy) was part of trying to improve the treatments and quality of life for his patients.

In 1970 he established the first UK multicentre collaborative group for trials of treatment for breast cancer and, in 1980, the first purpose-built clinical trials centre in the country. His early interest in the best ways to improve and run randomised clinical trials has formed the cornerstone of his belief in the importance of evidence-based medicine.

"Every single trial that I have been associated with, I have insisted that there has been a robust biological hypothesis that we were testing. That way… whatever the result is, that is valuable because you are learning more about the disease," said Baum.

This is at the centre of his argument with the alternative health lobby: that they can't and won't produce rigorously tested evidence to support their claims that their treatments provide benefit.

Challenging unproven therapies

"I'm against alternative medicine, not complementary medicine. When I'm asked what is alternative therapy, I say that it's treatment that doesn't work and I am against treatment that doesn't work. If anything can be shown to work, using the same scientific integrity that we apply to our study, we adopt it. There's no conspiracy. Complementary therapies that complement what we do and make patients feel better or live better is OK by me. But, again, you have got to be able to demonstrate that it does improve quality of life. My problem with the complementary and alternative fraternity is that they are too bloody lazy, they just want it to be received wisdom. They haven't got the guts, the courage, the integrity, or they're too bone idle, to actually test their beliefs.

"At the same time, I am knowledgeable about the subject. I was chosen to chair the EUSOMA [European Society of Breast Cancer Specialists] working party on complementary and alternative medicine. I was co-chairman of the EORTC [European Organisation for Research and Treatment of Cancer] working party on complementary and alternative medicine. I know what I am talking about. In the same way, Professor Edzard Ernst, a

"Every single trial I have been associated with, I insisted that there be a robust biological hypothesis"

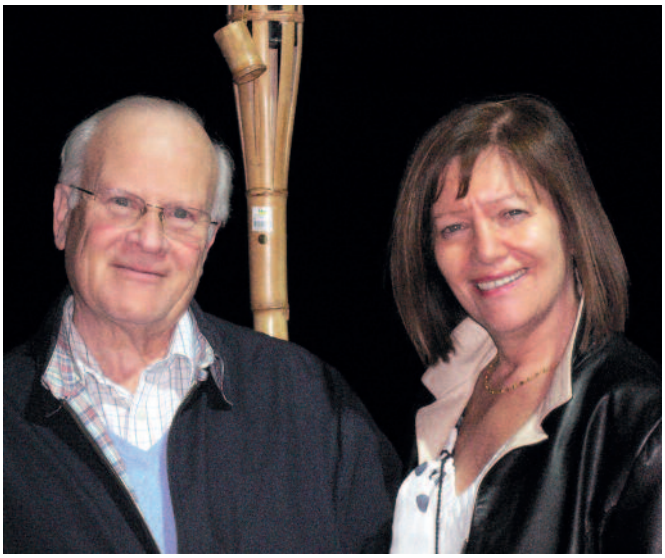
friend and colleague – we co-author stuff – is professor of complementary and alternative medicine and they [the CAM lobby] hate him. They hate him because he is unable to demonstrate that much of this stuff works."

During his time at King's he set up the National Health Service breast screening programme, establishing the first centre in the UK. Subsequently, he became so concerned about the effect that false-positive results were having on women's health and wellbeing that he changed his mind about the benefits of screening and has since argued against its widespread use.

Work on demonstrating a survival advantage of adjuvant tamoxifen for early breast cancer, which has contributed to a 30% fall in breast cancer mortality over the last 15 years, produced the interesting observation that the drug also reduced the incidence of subsequent contralateral breast cancer. This led Baum to collaborate with the statistician Jack Cuzick, now at the Wolfson Institute of Preventive Medicine, London, on the first IBIS trial, which investigated the use of tamoxifen to prevent breast cancer in women at high risk of developing the disease because of an inherited genetic susceptibility.

Baum's research interests then moved on to aromatase inhibitors, and, at the Royal Marsden Hospital, he and his colleagues established the ATAC trial – conducted by the biggest international cancer trials group in history – which demonstrated the superiority of anastrozole over tamoxifen for treating women with hormone-responsive disease. This trial is still continuing, and results from the first 100 months were reported at San Antonio in December.

Amongst his current interests is the international TARGIT trial (TARGeted Intra-operative radioTherapy), which delivers all the radiotherapy required during the surgery to remove the tumour. If it proves to be as effective as the early results suggest, it will save women weeks of daily travel to and from hospital, and resolve problems of adherence (when women can't or won't turn up for their follow-up radiotherapy).



Beside every successful man... With his wife Judy in Dubai, February 2007

"The other interest is mathematical modelling of breast cancer and the models that are being made for distant metastasis. I have written a lot on that." In a paper in December's *Nature Clinical Practice Oncology* (vol 4, pp 699–710), Romano Demichelli, Baum and others review the evidence on how removing a primary tumour can actually accelerate metastatic cancer. "People talk about enigmatic breast cancer, the enigmatic disease, we are saying that all the so-called enigmas, the outlying facts that cannot be incorporated into a model, can be explained by chaos theory."

Concerns over morale

When asked about future challenges in breast cancer, Baum said, "My current concern is the morale of the medical profession. I've just come back for a short contract with the National Health Service at University College Hospital and I'm finding the morale amongst the profession very low. Academic departments are closing. I cannot see where the new

"They haven't got the guts, the courage, the integrity, or they're too bone idle, to actually test their beliefs"

"There's absolutely no incentive now for young doctors to pursue an academic career"

generation of academic clinicians are coming from. There's absolutely no incentive now for young doctors to pursue an academic career. I think the greatest challenge to future success is to address the fundamental problem of medical training, academic training, governance and healthcare delivery. Everything is stacked up against academic excellence now.

"Even when you have a really important, innovative breakthrough, your masters in the health service aren't interested. I cannot interest anyone within the NHS to take intraoperative radiotherapy seriously. It's taken off all round the world, so we are in the very country where it was pioneered and we are having the greatest difficulty in getting it supported."

Baum has received numerous awards and honours during his career including the gold medal of the International College of Surgeons, the Miami breast cancer award, the San Antonio award and, most recently in March 2007, the prestigious Swiss St Gallen lifetime achievement award for the treatment of breast cancer. It is this award of which he is perhaps most proud. "You look back at the previous awardees and they are all men for whom I have the greatest respect and upon whose shoulders I have stood: Bernie Fisher, Gianni Bonadonna, Umberto Veronesi…To follow that, in a way that has to be the greatest honour. And I received an engraved Rolex watch and enough money to make a very nice party for my 70th birthday with all my family and friends."

When receiving the St Gallen award, Baum was able to announce that his sister had benefited from the past 30 years of clinical trials of breast cancer treatments. Diagnosed with the disease in the 1990s – Baum suspects there is a familial genetic predisposition – her treatment was completely different to that given to their mother, both in terms of its efficacy and its toxicity, and she is alive and well today.

As his family, friends and colleagues gathered for the Festschrift, many of them paid tribute to Judy, Baum's wife. "I believe that behind every successful man there is a most understanding, caring and supportive woman," said Keshtgar. Judy has brought up their family, played a full share in the areas where work and social events have overlapped, and fielded numerous evening phone calls from colleagues wanting advice or to share their latest exciting discovery.

At 70 there is not much sign of Baum slowing down, and nor would it appear that his colleagues want him to. Nick Ross said, "The trouble with a Festschrift like this is that it can sound a bit like an obituary or a wake. We expect a lot more of you in the future, Mike. This is just a half-way house."

Genetic testing. This painting is Baum's interpretation of Vermeer's "Girl weighing pearls". The importance of approaching patients on a human as well as a medical level has been a key theme throughout Baum's career

NEWSROUND

Selected reports edited by Hannah Brown

Preoperative RT can reduce recurrence in rectal cancer, but has little impact on survival

→ Annals of Surgery

A short, intense course of radiotherapy given before extensive surgery for rectal cancer does not significantly improve overall survival for patients, despite decreasing the likelihood of the cancer re-emerging in the same place, according to the long-term results of a randomised controlled trial.

The trial, which was conducted by a Dutch research group, involved 1,805 patients with clinically resectable adenocarcinoma recruited from all over Europe and one centre in Canada between January 1996 and December 1999. Patients with previous treatment for rectal cancer were excluded, as were those who had had previous radiation or drug therapy to the pelvis. The patients were randomly assigned to preoperative radiotherapy followed by total mesorectal excision (TME) – an extensive surgical procedure now considered the standard of care – or to TME alone. The radiotherapy consisted of 25 Gy delivered in five fractions to the primary tumour and surrounding tissue containing lymph nodes over 5–7 days. Surgery was scheduled to take place in the week after radiotherapy. The primary aim of the trial was to assess the rate of recurrence at the original cancer site (local control), but the researchers also had secondary endpoints including recurrence at distant sites and overall and cancer-specific survival.

An analysis of outcomes was done six years after the trial closed. Median follow-up of surviving patients was 6.1 years. Among the 1,748 patients in whom a total resection had been confirmed, local recurrence risk at five years was 5.6% in the group assigned to radiotherapy before surgery and 10.9% in TME alone patients, corresponding to a reduction in relative risk of almost 50% among patients assigned to preoperative radiotherapy. Distant recurrence risk at five years was 25.8% for patients assigned to radiotherapy plus surgery and 28.3% for surgery alone. None of the subgroup analyses, which included dividing patients by the site of recurrent lesion and the tumour stage as assessed during surgery, produced significant findings that could delineate between the radiotherapy and surgery alone groups. The authors caution, however, that the subgroups were probably too small to detect any outcome differences of statistical significance.

The researchers also looked at survival. As of 1 November 2005, 748 patients had died. Of these patients, 374 (50.2%) died with recurrent disease. At five years, the overall survival rate in irradiated patients was 64.2%, which did not differ significantly from the survival rate in patients who underwent TME alone (63.5%).

The authors conclude: "In our study, increased local control in irradiated patients does not lead to a detectable improved overall survival. Although local recurrences are known to be an important cause of death, an absolute difference in local recurrence rates of 5.3% is apparently too small to have a significant impact on survival."

■ KCMJ Peeters, CAM Marijnen, ID Nagtegaal et al, for the Dutch Colorectal Cancer Group. *Ann Surg* November 2007, 246:693–701

Obesity 'dilutes' prostate cancer marker

→ JAMA

Prostate cancer may be present in obese men even if they have low concentrations of prostate specific antigen (PSA), because the large volumes of plasma associated with being overweight mean PSA is diluted more in their circulation than in normal-weight men, according to a recent study.

Several studies have already found that obese men have lower PSA concentrations than non-obese men. But the mechanism that underlies this difference is unknown. Various theories have been put forward: obese men frequently show lower androgenic activity than normal-weight men, so they may simply be producing less of the substance, even if a cancer is present. But an alternative explanation is

that the larger plasma volumes in obese men actually dilute the serum components, thereby artificially lowering serum PSA levels.

To investigate whether large plasma volumes underlie obese men's lower PSA measurements, Lionel Bañez and colleagues from across Canada and the USA examined three cohorts of men with prostate cancer and looked at the relation between body mass index (BMI), PSA measurements, and plasma volume.

The researchers identified all men who had undergone radical prostatectomy for prostate adenocarcinoma over a period ranging from the mid-1990s to 2006 from the Shared Equal Access Regional Cancer Hospital database, Duke University's Prostate Center database, and the Brady Urological Institute at Johns Hopkins Hospital. Men with lymph-node-positive disease were excluded, as were those for whom no information on BMI was available.

Preoperative BMI was calculated and the researchers made estimates of body surface area and total circulating plasma volume for all patient records, adjusting for cancer-related variables that may affect PSA concentration. In the final study population of 13,734 men, it was established that men with a BMI of 35 or greater had 21%–23% larger plasma volumes relative to normal-weight men, and had lower preoperative PSA concentrations. Men in the most obese group had 11%–21% lower serum PSA concentrations than normal-weight men, in line with the 10%–32% decreased PSA concentration seen in population-based studies of men without prostate cancer.

Next, the researchers investigated whether this finding could be explained by the fact that obese men make less PSA or whether there are alternative explanations for the lower tests of these men. Overall, the PSA mass (the amount of PSA in the blood at the time the PSA measurement is done) did not change significantly with increasing BMI, suggesting that the lower PSA measurements in obese men were a result of the diluting effect of larger plasma volumes.

However, the researchers comment that, because obesity is associated with numerous changes in hormone production and effects, it remains possible that markers for several hormone-related tumours including prostate, endometrial, and breast cancer, "may be dually affected in obese individuals by both hemodilution and altered hormonal stimulation", although they concede that "in the case of PSA, the current data suggest that hemodilution predominates and that hormonal effects are rendered negligible."

Lower PSA values among obese men may have clinical relevance because they may result in fewer obese men undergoing prostate biopsy, leading to fewer cancers detected among this group.

■ Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. LL Bañez, RJ Hamilton, AW Partin et al. *JAMA* 21 November 2007, 98:2275–2280

Chemotherapy and radiotherapy should be standard for localised Hodgkin's lymphoma

➜ New England Journal of Medicine

A combination of chemotherapy and radiotherapy, rather than radiotherapy alone, should now be considered standard treatment for all patients with localised Hodgkin's lymphoma where the tumour is situated above the diaphragm, according to the results of a randomised controlled trial. The trial results further suggest that radiotherapy need only target areas directly involved in the cancer, sparing more extensive treatment of surrounding tissue.

These findings add clarity to speculation about the appropriate treatment of this cancer, after previous results from trials done during the late 1980s and early 1990s showed that clinical staging is sufficient for stratifying early stages of the disease; that chemotherapy followed by involved-field radiotherapy (limited to the areas of cancer, rather than extensive surrounding tissue) should be the standard treatment; and that duration of chemotherapy should be adapted to the severity of the disease.

Christophe Fermé and colleagues at the EORTC and the Groupe d'Études des Lymphomes de l'Adulte initiated the trial to further elucidate treatment options that might improve event-free survival in patients with Hodgkin's lymphoma. Using a set of prognostic factors previously published by the EORTC to stratify patients by severity of disease, the researchers compared subtotal nodal radiotherapy alone with a combination of chemotherapy and radiotherapy in patients preclassified as having good or poor prognosis.

A total of 1,538 patients between the ages of 15 and 70 were enrolled in the trial. All had untreated clinical stage I or II supradiaphragmatic Hodgkin's disease and were being treated at one of 91 centres in Belgium, France, Italy, the Netherlands, Poland, Portugal, Slovenia and Spain.

Of the total patient population, 542 (35%) were categorised as having favourable prognostic factors and 996 (65%) as having unfavourable prognostic factors. Patients in the favourable prognostic factor arm were randomly assigned to receive either subtotal nodal radiotherapy or combination therapy consisting of three cycles of chemotherapy plus involved-field radiotherapy. Patients in the unfavourable prognostic factor arm were randomly assigned to one of three regimens: six or four cycles of chemotherapy plus involved-field radiotherapy or four cycles of drugs plus subtotal nodal radiotherapy.

The chemotherapy regimen used for all the groups was mechlorethamine, vincristine, procarbazine and prednisone in combination with doxorubicin, bleomycin and vinblastine. Taking event-free survival as a primary endpoint, the researchers found that, in the group with favourable prognostic features, response rates to the two treatment regimens were similar. However, among the 446 patients from both groups who had a complete remission, there was a significant difference in rates between the combination group and the radiotherapy alone group: five had a relapse after combination therapy and 61 after subtotal nodal radiotherapy. This equated to a difference in the estimated five-year event-free survival rate of 24%, favouring the combination-therapy group.

For patients with unfavourable prognostic factors, complete remission rates were 83% in the group receiving six cycles of chemotherapy plus involved-field radiotherapy, 85% in the group receiving four cycles plus involved-field

radiotherapy, and 86% in the group receiving four cycles plus subtotal nodal radiotherapy. However, there were no significant differences in the five-year event-free survival estimates or in estimated overall survival.

The researchers conclude from their findings that four courses of a doxorubicin-containing regimen and involved-field radiotherapy should be the standard treatment for this tumour type. Furthermore, they note, in patients with risk factors, four cycles of a doxorubicin-containing regimen are as effective as six cycles, and involved-field radiotherapy yields a disease control rate similar to that with subtotal nodal radiotherapy. "Our study showed that a combination of chemotherapy and radiotherapy should now be considered the standard treatment for all patients with localized stage supradiaphragmatic Hodgkin's disease and that subtotal nodal radiotherapy alone can no longer be recommended," summarise the authors. "The results of our trial show that it is possible to tailor the duration of chemotherapy according to risk factors. Moreover, our findings point to a new role for adjuvant radiotherapy with smaller radiation fields, allowing for the reduction of toxic effects associated with large fields. A remaining question now under investigation is whether patients with early-stage Hodgkin's disease can be cured with chemotherapy alone," they conclude.

■ Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. C Fermé, H Eghbali, JH Meerwaldt et al for the EORTC–GELA trial. *N Engl J Med* 8 November 2007, 357:1916–1927

Thalidomide analogue beats standard multiple myeloma treatment

➔ New England Journal of Medicine

Two clinical trials published side by side in the *New England Journal of Medicine* show that lenalidomide – an oral immunomodulatory drug that is similar to thalidomide but has a different safety profile and more potent biological activity – used in combination with dexamethasone is better than dexamethasone plus placebo for treatment for multiple myeloma.

The two trials, one from Europe and the other from North America, which together provided the evidence base for the Food and Drug Administration's 2006 approval of this combination, investigated the efficacy of lenalidomide plus dexamethasone in the treatment of relapsed or refractory multiple myeloma. In the European trial, 351 patients who had received at least one previous antimyeloma therapy were randomly assigned to receive 25 mg of oral lenalidomide (n=176) or placebo (n=175) plus a course of oral dexamethasone administered in 40 mg doses. In the American trial, 177 patients were assigned to lenalidomide and 176 to placebo, again with 40 mg of oral dexamethasone.

Time to progression was similar in the two trials, and was significantly longer in patients taking lenalidomide versus those on placebo: 11.3 vs 4.7 months and 11.1 vs 4.7 months in the European and American trials, respectively. Median overall survival times were significantly better in patients taking lenalidomide, although in the European trial the median overall survival had not yet been reached at the time of publication. In both trials, grade 3 or 4 adverse events, including neutropenia and venous thromboembolism, were more common in the lenalidomide group than in the placebo group.

The authors of both trials conclude that lenalidomide plus dexamethasone is more effective than placebo plus dexamethasone in relapsed or refractory multiple myeloma. In an accompanying comment, Alan List asserts that the duality of the actions of immunomodulatory drugs on both the malignant clone and the surrounding microenvironment set them apart from more selective drugs, and most likely account for the unanticipated breadth of activity of this class of agents. "Lenalidomide and the immunomodulatory drugs stand as prime examples of potentially dangerous chemical compounds that have been granted a second life with powerful therapeutic applicability," he says.

■ Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. M Dimopoulos, A Spencer, M Attal et al, for the Multiple Myeloma (010) Study Investigators. *N Engl J Med* 22 November 2007, 357:2123–2132

■ Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. DM Weber, C Chen, R Niesvizky et al, for the Multiple Myeloma (009) Study Investigators. *ibid*, pp 2133–2142

■ Lenalidomide – the phoenix rises. AF List. *ibid*, pp 2183–2186

Ten years' survival signals cure in colorectal cancer

➔ Journal of Clinical Oncology

Ten years of survival after resection of colorectal liver metastases can be defined as 'cure' – the time point from hepatectomy after which disease-specific death becomes an extremely rare event – according to a detailed analysis of single-institution experience with this intervention.

In 20%–35% of patients with metastatic colorectal cancer, the liver is the sole site of disease. This makes it possible to attempt curative resection, and this procedure is now considered the standard of care. Five-year survival rates of nearly 40% have been reported with this procedure, compared with a median survival of just 6–12 months in patients with potentially resectable tumours who do not have surgery, or 21 months with chemotherapy. However, these survival estimates are based on retrospective studies.

To counteract weaknesses in previously published estimates of cure-rate, James Tomlinson and colleagues report a large, single-institutional experience with at least 10 years' follow-up. Data on 612 patients who underwent resection of colorectal liver metastases at Memorial Sloan-Kettering Cancer Center in New York, from 1985 to 1994, were used. Of these patients, 132 had no evidence of disease at last follow-up, 24 were alive with disease, 466 were dead, and 73 patients were lost to follow-up.

Analysing survival data, the researchers

established that median survival was 44 months and that the survival curve reached a plateau after 10 years from the time of hepatic resection – demonstrating a minimum cure rate of 17% from this procedure.

Because the enrolled patients underwent resection of their metastases before the introduction of modern chemotherapeutic agents, this was a unique opportunity to investigate the independent therapeutic benefit of surgical resection. There were no preoperative factors that were sufficiently discriminatory to negate the potential for attaining a cure after resection. "A positive margin, however, negated the potential for long-term survival. Identification of novel predictive factors that define tumor biology associated with curable regionally confined metastases clearly is necessary in future attempts to predict outcomes in patients who present with CLM [colorectal liver metastases]," note the authors.

■ Actual 10-year survival after resection of colorectal liver metastases defines cure. JS Tomlinson, WR Jarnagin, RP DeMatteo et al. *J Clin Oncol* 10 October 2007, 25:4575–4580

New drugs can transform patients with liver metastases into surgery candidates

➜ Journal of Clinical Oncology

Patients with liver metastases from colorectal cancer who are initially assessed as being unsuitable for surgery because of the extent of their disease and unresponsiveness to standard chemotherapy can be transformed into surgical candidates after treatment with the biological agent cetuximab [Erbitux], according to a recent study.

The vast majority of colorectal cancer patients who present with liver metastases are not initially candidates for hepatic resection, either because of the distribution of tumours within the liver or because of the presence of disease in other locations. Use of chemotherapy can reduce the burden of disease to an extent where surgery is possible. However, most patients who are classed as having initially unresectable liver metastases do not respond sufficiently well to chemotherapy to become resectable – and this poor first-line response often means these patients are also unlikely to respond well to additional drug treatment.

Combining newer biological agents with cytotoxic chemotherapy might increase response rates and therefore improve resectability in patients in whom chemotherapy alone did not work. To test this idea, René Adam and colleagues chose to investigate systemic chemotherapy with cetuximab in patients unresponsive to first-line chemotherapy to convert patients to resectable status.

A total of 151 patients were switched to receive cetuximab-containing systemic therapy after becoming refractory to their first-line treatment. They were imaged with computed tomography or magnetic resonance scans of the chest, abdomen and pelvis every two months to evaluate tumour responses. Eighteen of the 151 patients (14%) met the criteria for resection of their liver metastases after treatment, although no complete clinical responses were observed. Two of the patients were found, during surgery, to have unresectable disease.

The median follow-up from the initiation of cetuximab therapy was 16.4 months (range 6–31 months). At the most recent follow-up, 25 of the treated patients were alive, including 10 patients who were free of disease. Median overall and progression-free survival from initiation of cetuximab therapy were 20 and 13 months, respectively.

"We have demonstrated the ability to convert 14% of patients from an unresectable status to a resectable situation, with a postoperative five-year survival rate of 33%," comment the authors.

■ Hepatic resection after rescue cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic therapy. R Adam, T Aloia, F Lévi et al. *J Clin Oncol* 10 October 2007, 25:4593–4602

HER2 amplification linked to survival after trastuzumab

➜ Clinical Cancer Research

Patients with locally advanced breast cancers whose tumours contain high numbers of copies of the gene for the human epidermal growth factor receptor 2 (HER2), as assessed by fluorescence in situ hybridisation (FISH), are more likely to have a complete response to treatment with an antibody to the receptor than patients with fewer copies of the gene in their tumours.

Around 20%–30% of breast tumours contain several copies of the HER2 gene, and patients affected by this genetic lesion are more likely to relapse quickly and die sooner than non-affected women. Treatment with trastuzumab (Herceptin), a recombinant monoclonal antibody against HER2, can significantly improve survival and reduce the risk of recurrence in women with various stages of HER2-positive breast cancer, but it is not clear exactly how the extent of overexpression of this gene relates to the survival benefit of treatment.

In a study to ascertain whether there is a relationship between the specific level of HER2 amplification, as assessed by FISH, and the rate of pathological complete response, 93 women diagnosed with HER2-positive locally advanced breast cancer who were treated preoperatively with a combination of trastuzumab plus chemotherapy underwent breast biopsies which were tested for HER2 expression using two methods: immunohistochemistry (IHC) and FISH. The HER2 scores obtained by FISH were subsequently compared with several variables including treatment regimen, patient age, tumour staging, and pathological complete response rates, to determine whether FISH testing could predict response to treatment more accurately than current methods.

Pathological complete response was seen significantly more frequently in high-amplification FISH tumours than in low-amplification tumours – a degree of subclassification that would not have been possible using IHC. "Therefore," the researchers conclude, "FISH may be a

more accurate HER-2 testing method to predict pathologic complete response in the neoadjuvant setting [than IHC]." This technique may also help select those patients for whom trastuzumab confers the greatest clinical benefit, they add.

■ Pathologic complete response to trastuzumab-based neoadjuvant therapy is related to the level of HER-2 amplification. L Arnould, P Arveux, J Couturier et al. *Clin Cancer Res* 1 November 2007, 13:6404–6409

Patients and physicians anxious about opioids

➜ Annals of Oncology

Patients with cancer have concerns about tolerance, addiction and side-effects that limit their uptake of opioid analgesics, according to the results of a qualitative study into patient and physician attitudes to opioids.

It has been documented that health professionals' belief in the inevitability of cancer pain, and fear of hastening death, distract them from using sufficient opioid analgesics to relieve discomfort. To examine patients' views about commencing opioids, a qualitative in-depth interview study was done, focusing on the reasons patients make their initial decision to receive or refuse opioid-based pain relief.

Participants were recruited from a pain management trial that took place in a UK oncology centre during which they were randomised to either cocodamol or the opioid oxycodone, described in the patient information sheet as being similar to morphine.

Twenty-nine patients were approached about the study and 18 took part. Of these 18, six had refused to participate in the drug comparison trial. Interviews took place within two weeks of recruitment to the trial.

Participants described their views about opioid analgesics in detail. For most of them, uncontrolled pain served as a constant reminder of their cancer and caused them to reflect on their anticipated death. Participants viewed morphine as the last resort. This association had led some of them to become frightened when morphine had been discussed in the context of the clinical trial. They anticipated the inevitable consequences of sedation and then death. Thus, pain relief was traded-off against further loss of function and hastened death, and this trade-off was only acceptable when death was imminent.

In conclusion, the authors state, "We found that patients with cancer who were offered morphine for pain relief interpreted this as a signal that their health professional thought they were dying, because opioids were interventions used only as a 'last resort'.

Because participants themselves were not ready to die, they rejected morphine and other opioids as analgesics despite the pain experienced as a consequence."

■ Opioid analgesics for cancer pain: symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. CM Reid, R Gooberman-Hill and GW Hanks. *Ann Oncol* January 2008, 19:5–7

Combined adjuvant treatment best for endometrial cancer

➜ Gynecologic Oncology

According to a retrospective analysis of patients with advanced endometrial cancer, combined adjuvant treatment involving both chemotherapy and radiotherapy gives better outcomes than when either modality is used alone after surgery.

Optimal management for advanced endometrial cancer has yet to be defined and there is an urgent need for new treatment regimens after surgery that can improve survival with acceptable toxicity. While chemotherapy is thought to control distant disease better than radiation therapy, it may not be adequate to achieve local control. Therefore, combined modality therapy with chemotherapy and radiation might give better results than either used alone. Several studies have reported improved clinical outcomes with combined modality therapy; however, there remains some uncertainty about the optimum regimen.

A multicentre retrospective analysis of patients with advanced surgically staged endometrial cancer was done to investigate this issue. Angeles Alvarez Secord and colleagues identified all patients with stage III or IV endometrial cancer who received primary surgical treatment followed by adjuvant therapy with chemotherapy, radiation therapy, or both, at Duke University and the University of North Carolina between 1975 and 2006.

In all, 356 patients with advanced surgically staged endometrial cancer were identified. Adjuvant therapy had been administered to all patients, with 48% receiving radiotherapy alone, 29% chemotherapy alone, and 23% chemotherapy plus radiation. Median follow-up time was 38 months, and 202 patients were alive at last follow-up. Of patients treated with chemotherapy alone, 63% had a documented recurrence or progression compared with 37% for those treated with radiation alone and 31% treated with combined chemotherapy and radiation. Those receiving chemotherapy alone had significantly poorer three-year overall survival and progression-free survival than those who received either radiotherapy alone or combination therapy.

"We believe our study is the largest retrospective series to date to explore the clinical outcome of patients with advanced endometrial cancer treated with adjuvant radiation, chemotherapy, or combination chemotherapy and radiation, following comprehensive surgical staging and cytoreductive surgery," note the authors. "Consistent with other studies in the literature, our findings suggest that combined multi-modality therapy with adjuvant chemotherapy and radiation may improve survival in patients with advanced stage disease compared to either modality alone."

■ The role of multi-modality adjuvant chemotherapy and radiation in women with advanced stage endometrial cancer. A Alvarez Secord, LJ Havrilesky, V Bae-Jump et al. *Gynecol Oncol* November 2007, 107:285–291

It's not just about surviving, it's about getting your life back

Peter McIntyre

Recent issues of *Cancer World* have looked at the physical and psychosocial damage than can be inflicted by radiotherapy, chemotherapy and surgical cancer treatments. The final part of our series on *Living with the consequences* looks at the transition from patient to survivor and the sort of tailored support survivors need to help them live their lives as fully as possible.

The International Agency for Research on Cancer estimates that around 20 million Europeans alive today have had a cancer diagnosis – more than 8.3 million of them within the past five years. This number is set to rise significantly as cancer survival rates and general life expectancy increase.

Cancer treatment has become a priority in many European countries, while the campaign against tobacco and for improved diet has raised the profile of prevention policies.

Now the need for better rehabilitation and long-term support for cancer survivors is forcing its way onto the agenda, as the long-term effects of living with cancer are better understood and as patient support groups become better organised. This complex area covers a huge range of needs, a long time scale and requires an interdisciplinary approach within and outside the healthcare system.

Many cancer patients make a good recovery and return to a fulfilling life. But millions more could live like them if support services were more available and better joined up. There is a clear need for more comprehensive rehabilitation and long-term support.

Each survivor has different needs. Some require short-term rehabilitation to recover strength and function. Others suffer long-term fatigue, heart problems, lymphoedema, incontinence, loss of sexual function or infertility. The problems may result from the effects of the disease or the treatment. Sometimes they do not become apparent for many years after the treatment has ended – particularly in the case of cardiac damage or new cancers arising from radiotherapy. The worry of what might happen in the future can be an additional burden for cancer survivors.

At this most vulnerable of times many survivors lose their jobs – despite anti-discrimination legislation. Loss of self-esteem, social isolation and loss of income can contribute to a cycle of physical, emotional and psychological decline with a substantial impact on quality of life.

According to a report by the US Institute of Medicine, up to 30% of women treated for breast cancer experience episodes of persistent psychological distress that interfere with their ability to cope with cancer treatment. At worst, feelings of depression, anxiety, panic and isolation can become disabling. Following treatment, women's concerns include fear

of recurrence, physical symptoms of fatigue or pain, changed body image, sexual dysfunction, persistent anxiety and fear of death, relationship problems and feelings of vulnerability.

The Institute recommends that each cancer patient receive a 'survivorship care plan' which should summarise all the information they need for their long-term care, and also include legal rights affecting employment and insurance, and the availability of psychological and support services.

What should rehabilitation include?

Rehabilitation should focus on the needs of patients. For most patients this will include physical exercise to regain strength, movement and confidence, and psychosocial support. There is increasing evidence that physical and emotional confidence feed off each other.

The Department of Health Education and Promotion at Maastricht University and the Limburg Comprehensive Cancer Centre in the Netherlands have spent a decade trialling a combination of physical and psychosocial support. Groups of 12–16 cancer patients visited the rehabilitation centre for twice weekly physical training and for psychoeducation aimed at enhancing quality of life.

As measured by physical, emotional and social function, quality of life improved significantly, with lower rates of fatigue by the end of the 12-week course, and the researchers concluded that "a rehabilitation programme for a mixed group of cancer patients is both beneficial and feasible," (*Eur J Cancer Prev* 15:541–547)

The trial is continuing to define the best interventions and timing. But already the programme is running in 60 centres in the Netherlands and in some parts of Belgium.

Fit for life. These patients are taking part in a rehabilitation programme at one of the centres that took part in the follow-up trial of the Maastricht study. They had completed their primary medical treatment at least three months previously but had been experiencing physical and/or psychosocial problems before the programme began

THE LANGUAGE OF SURVIVAL

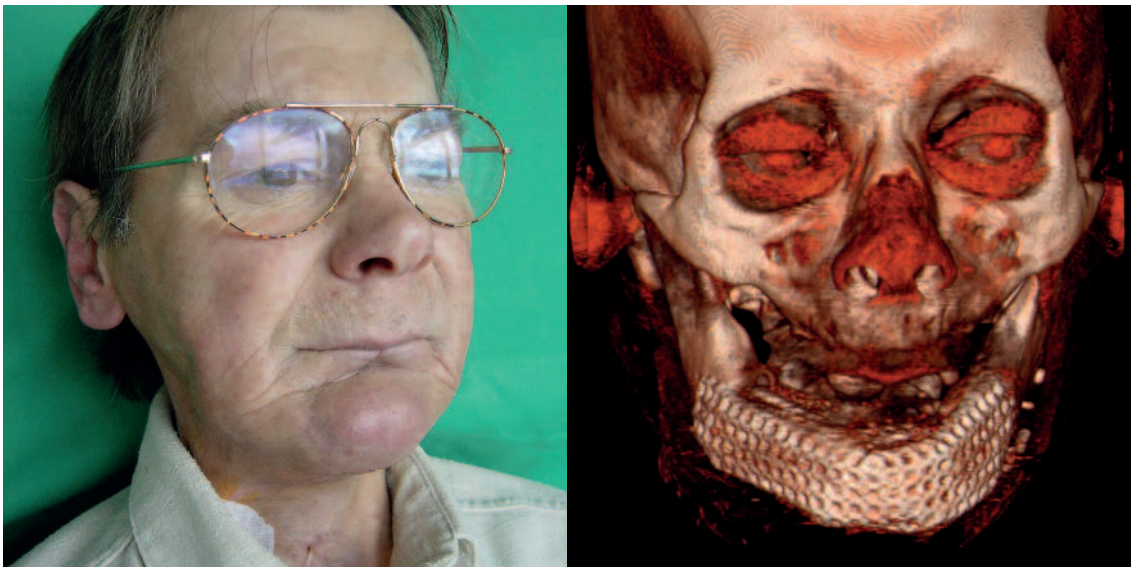
The term 'cancer survivor' can mean different things to different people. The US National Cancer Institute suggests the following definition: "an individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life."

Cancer survivors may have many years of life ahead of them but can face physical, psychosocial and financial problems, which can be hard to deal with alone.

Rehabilitation has been defined as a process that assists the cancer survivors to obtain maximal physical, social, psychological and vocational functioning within the limits created by the disease and its resulting treatment*.

** Robert Kaplan, Cancer and Rehabilitation, http://www.emedicine.com/PMR/topic226.htm*

Concerns include fatigue or pain, sexual dysfunction, persistent anxiety and relationship problems



Embarrassed no longer. Treatment for a head and neck cancer left this patient isolated and suicidal because he could neither eat nor speak properly. His life was transformed by a novel bone replacement that was grown in the patient's right-side latimus dorsi muscle and transplanted into his jaw. The right-hand image shows a CT scan taken after the transplantation

Irene Korstjens, from the Department of Health Education and Promotion at Maastricht University, says that physical confidence in patients boosts psychological confidence: "As their physical condition improves their social and psychological functioning improves too. Because they can do more, they get more self-assured and a feeling of control. Rehabilitation enhances self-confidence and autonomy. I think that is the way it works. Performing within a group stimulates people. They dare more."

Today, what began as a research project is becoming part of routine care in some centres and some health insurance companies are already paying for the programme. "The main issue now is to get the programme better known," she said.

In a sense, however, rehabilitation starts with treatments that minimise risk of side-effects, late effects, damage and mutilation. Less invasive surgery, lower doses of radiotherapy better targeted on the tumour, and targeted drugs which do less systemic damage, put patients on course for a better and more complete recovery.

New techniques, such as tissue engineering to provide reconstructive surgery, are increasingly focused on quality-of-life outcomes. In 2004, doctors at Kiel University in Germany succeeded in growing a new jaw bone with a healthy blood supply for a man who had undergone an extensive tumour surgery and radiotherapy, using bone mineral blocks, recombinant human bone morphogenic protein (BMP) and liquid bone marrow containing stem cells. After eight years of eating soup and soft food, the 56-year-old man was able to tuck into sausage and bread for the first time.

Surgeons used computer-aided design to build the new mandible and then grew it inside the patient's right-side latimus dorsi muscle, his body serving as a living bioreactor. When it was ready, the surgeons transplanted the jawbone, bridging a gap in his mandible of more than seven centimetres. Bone formation continued for eight months and the graft

"As their physical condition improves their social and psychological functioning improves too"

There is a backlog of 'legacy' damage suffered by people who were treated 20 years ago or more

remained in place until the patient's death from a heart attack 15 months later.

In a commentary in *Biomaterials*, Warnke and his team said, "The patient reported an improvement in both quality of life and self-confidence. He raised his body weight from 60 to 65 kg and he took part in family functions again. Prior to our reconstruction he had isolated himself out of embarrassment due to his inability to chew solid meals and socially inappropriate noises and mess due to anaesthesia of his lower lip. …Following transplantation his speech and tongue mobility improved and he found pleasure again in talking to friends on the phone. His mood turned from one previously of depression and suicidality to one of excitement and optimism."

Similar techniques are being used to rebuild noses after surgery, and hold great hopes for facial reconstruction, and for reconstructing palates after surgery.

Frans Hilgers and Annemieke Ackerstaff from the Netherlands Cancer Institute, carried out a review of patients who had had their larynx removed during cancer treatment. They found that rehabilitation focused almost exclusively on regaining speech. However, laryngectomy removes not only the 'voice box' but part of the respiratory system connecting the upper and lower airways, so that patients lose the ability to breathe through the nose. This leads to shortness of breath, coughing, excessive sputum production and loss of a sense of smell.

They concluded (*Folia Phoniatr Logop* 52:65–73) that prosthesis combined with good rehabilitation allowed patients to recover better speech and addressed their other problems. "The three main adverse side-effects of the surgical procedure, i.e. loss of natural voice, loss of the protective function of the larynx for the respiratory system and the loss of olfactory acuity due to the absence of a nasal air stream, should all be addressed in a complete rehabilitation program."

High-tech interventions will prevent and resolve some long-term problems. But there is also growing concern about former patients who were damaged by radiation therapy and who suffer pain, restricted movement and exhaustion many years after treatment. Rehabilitation cannot therefore be seen simply as a short-term intervention following treatment. Indeed, there is a backlog of 'legacy' damage suffered by people who were treated 20 years ago or more, for whom a long-term rehabilitation programme is desperately needed. Few in Europe have access to such services, and this will become an increasing challenge for policy makers.

When should rehabilitation begin?

Göran Laurell, head of the ear, nose and throat clinic at the Karolinska University Hospital, Sweden, believes there may be advantages in involving patients in their own physical rehabilitation almost as soon as they receive their diagnosis. His department piloted a trial in Stockholm, which is now being evaluated.

In an article in the Swedish Cancer Foundation magazine *Rädda Livet* Laurell says, "We teach patients to take responsibility for their rehabilitation from the start. It is our hope that some of them will achieve better function in the gullet, jaw and neck and shoulder muscles. We also hope that this will help them get their strength back more quickly."

This rehabilitation team includes a physiotherapist, psychologist, dietician and speech therapist and social worker as well as the medical team.

Polly Nikolaidis, the physiotherapist, teaches patients to strengthen the back of their throat and to look out for signs of problems in the jaw joint, which can often follow radiotherapy.

Speech therapist Therese Engström deals with voice, speech and swallowing. She meets patients before they are treated with radiotherapy or surgery. "I prepare them for the sort of problems that can arise during their treatment and I give them information and exercises that can pre-empt a lot of problems."

Laurell says patients have different needs and getting to know them is part of the art of providing care. He anticipates that the pilot may show that, for

"It is important to have an individual approach to the rehabilitation of each patient"

some patients, starting rehabilitation this early could prove too demanding. "It is important to have an individual approach to the rehabilitation of each patient. They have got tough treatment to go through and there are loads of people around them all the time. Some patients get too little space for themselves."

Irene Korstjens believes that the timing should depend on the patient and the state they are at. The best time for the programme she started is two to three months after treatment ends. This rehabilitation builds on the natural recovery process.

But there is also a need for a second line of support. After the immediate treatment and recovery period, patients often emerge from a period of intense activity into a landscape where they seem to be facing the future alone.

Ciarán Devane, chief executive Macmillan Cancer Support, points out that in the UK the average cancer patient makes 53 visits to a health facility during their treatment, but this activity can stop very suddenly. "Six months after the end of treatment people tend to feel abandoned. What is the intervention that will help with that?"

Certainly women who have been treated for breast cancer need ongoing support, says Stella Kyriakides, President of Europa Donna Cyprus. "The level of anxiety does seem to increase as women finish treatment and move away from frequent contact with their breast team. While you are in treatment and you are the centre of attention, you have plenty of opportunities to voice your anxieties. As you are over the treatment and left on your own, the levels of anxiety seem to go up.

"We need to think of follow-up as an ongoing process for patients and their families. We need to address quality-of-life issues and side-effects, not only in the acute treatment phase. Often they are not addressed to the extent we would want, especially in some groups of patients, such as older patients."

Heinz Ludwig, head of the Department of Medicine and Medical Oncology at Wilhelminen Hospital, Vienna, says that some long-term problems only emerge after the priority – to guarantee survival – appears to have been achieved.

"As we learn more about the late consequences of treatment, there are secondary cancers but also several other delayed consequences like sexual dysfunction. This is a major concern in patients with breast cancer, which is frequently not adequately addressed. It is something that is still taboo, so patients are afraid to discuss it with their physicians and care givers. In my opinion, support for this problem is part of the service that we need to provide. It is not essential to have this service in the oncology centre – it could be somewhere else – but it is essential to offer it."

The policy challenge

Post-treatment plans, link nurses and support groups all play a vital role in the longer term follow-up of cancer patients. Survivors also need a proactive way back into the system if new problems emerge or symptoms do not improve. One of the key messages that emerges from the testimony of people who have suffered late effects is that many feel cut off from avenues of support.

But if health rehabilitation requires interdisciplinary teamwork within the health system, it is a still greater challenge to include social care, housing, employment rights and to challenge stigma. Despite many countries passing laws to try to prevent disability discrimination at work, it is clear that many people with cancer lose their jobs or unnecessarily give up their jobs. This can be a huge blow, because, in addition to providing an income, work also offers security, normality and self-esteem – issues often mentioned as important by cancer patients.

Increasingly, these broader issues are being taken up at policy level. In 2003, the French National Cancer Plan pioneered legal measures to give people with cancer better access to loans and insurance and more time to return to work.

The new Cancer Reform Strategy for England, launched in December 2007, includes a National

Cancer Survivorship Initiative designed to improve services for those who have finished their treatment. Mike Richards, National Cancer Director for England, and Macmillan Cancer Support, the charity that employs Macmillan nurse specialists, will jointly launch the initiative in March 2008.

Although this is still a paper policy, it has been endorsed by the British Prime Minister, Gordon Brown, and is expected to include:

- Follow-up by hospital doctors, nurses and general practitioners to check for recurrence or any late effects of treatment
- Education, self care and expert patient programmes
- Proactive case management, with patients using electronic technology to report on their wellbeing, and automated surveillance systems to ensure that tests are done at the right times
- Drop-in centres for peer support
- Rehabilitation programmes
- Psychological and spiritual support
- Back to work support and access to financial and benefits advice
- Nutritional advice
- Support for carers

ROLF LARSSON

Expert hands. After finishing her medical treatment, this lung cancer patient spent time in Fenix, a specialist establishment in the south of Sweden, which provides a variety of physical and psychosocial support to cancer survivors

Devane, of Macmillan Cancer Support, characterises the Cancer Reform Strategy as 'groundbreaking'.

"We use the word groundbreaking because we really do believe that the Cancer Reform Strategy, as an evolution of the original Cancer Plan, has made it clear that we are talking about holistic cancer support along the whole journey, not just clinical and medical. For example, if we have a care pathway to cover the clinical side, what is the care pathway to cover the emotional support as somebody moves through the cancer journey?"

Funding on a sizable scale will be needed to provide a long-term survivorship plan for each patient that includes social as well as clinical care. However, the fact that survivors merit a whole section in the reform plan represents a shift in the thinking of policy makers.

The challenge will be to turn these aspirations into reality.

A key message from people who have suffered late effects is they feel cut off from avenues of support