

Cancerworld

Education & knowledge through people & facts

Number 13, July-August 2006



David Khayat

→ David Khayat: driving the French cancer plan → Are you feeling lucky? Top tips on explaining risk and exploring options → Moscow's smokebuster: fighting cancer in an era of political change → Has the TNM system been overtaken by science?

**Editor**

Kathy Redmond
editor@esoncology.org

Assistant Editor

Anna Wagstaff

Editorial Assistant

Mariarita Casese

Editorial Board

Mariano Barbacid, Franco Cavalli
Alberto Costa (chair)
Lev Demidov, Mario Dicato
Gordon McVie, Nicolas Pavlidis
Hans-Jörg Senn, Antonella Surbone

Board of Advisors

Jan Betka, Jacques Bernier
Vincent T. DeVita, Lex Eggermont
Jan Foubert, Lynn Faulds Wood
Neel Mittra, Santiago Pavlovsky
Bob Pinedo, Mike Richards
Maurice Schneider, Tom Voûte
Umberto Veronesi (chair)

Contributing Writers

Marc Beishon, Raphaël Brenner
Patrick Lynch, Emma Mason
Keith McCullagh, Peter McIntyre
Michael Pfreundschuh, Anna Wagstaff

Publishing Advisors

Gillian Griffith, Fedele Gubitosi

Website Liaison

Chatrina Melcher

Project Designer

Andrea Mattoni

Graphic and Layout Designers

Pier Paolo Puxeddu+Francesca Vitale

Production Manager

Gianfranco Bangone

Published by

Editoriale Darwin srl
Piazza Antonio Mancini, 4 - 00196 Rome

Printed by

IGER Istituto Grafico
Editoriale Romano s.r.l.
Viale C.T. Odescalchi, 67 - 00147 Rome

Cover photograph

Hamilton / REA

Registrazione Tribunale di Roma

Decreto n. 436 del 8.11.2004

Direttore responsabile

Emanuele Bevilacqua

All enquiries about *Cancer World*

should be made to:

ESO Editorial Office

Viale Beatrice D'Este 37

20122 Milan, Italy

e-mail: magazine@esoncology.org

Fax: +39 02 8546 4545

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

Copyright ©2006 European School of Oncology.
All rights reserved

Contents

3 Editorial

UICC – taking on mission impossible

4 Cover Story

David Khayat: driving the French cancer plan

14 Grand Round

Are you feeling lucky? Discussing risk and treatment options with patients

26 Drug Watch

RNA-bound: the future of antisense drugs

32 Forum

Has TNM been overtaken by science?

40 Masterpiece

The Moscow smokebuster

48 Impact Factor

Does regular use of aspirin reduce the risk of colorectal cancer?
Factors predictive for response of follicular and mantle cell lymphoma to rituximab
Newsround

60 Bookcase

Cancer World is published six times per year by the European School of Oncology with an average print run of 10,000 copies. It is distributed at major conferences, mailed to subscribers and to European opinion leaders, and is available on-line at www.cancerworld.org



UICC - taking on mission impossible

→ Franco Cavalli* ■ GUEST EDITOR

For almost 75 years the International Union Against Cancer (UICC) has been the only international non-governmental organisation dedicated exclusively to the global control of cancer. But with many societies currently 'going global', including ASCO and the American Association for Cancer Research, questions could be raised about whether the UICC is really needed anymore. I'm convinced it is.

We need the UICC to ensure that cancer achieves and retains priority status on the agenda of the main political bodies including the UN, G8, and the World Bank.

It was thanks in large part to sustained pressure from the UICC that last year the general assembly of the World Health Organization finally declared the fight against cancer as a priority. But despite this resolution, and despite cancer being a bigger killer than tuberculosis, malaria and HIV together, experience shows that governments won't act unless forced to by pressure of public opinion.

On a global scale, this level of pressure can be organised and channelled only through an established and representative non-governmental organisation (NGO) like the UICC.

People who are living in countries with more limited resources need the UICC today more than ever.

On top of the toll of poverty-related cancers, demographic changes are now leading to an upsurge in cancers related to western lifestyles. As a result, while globally cancer incidence is expected to increase by 50% over the next 15 years, most of that rise will be in the developing world, which by 2020 is expected to account for almost two-thirds of all new cases.

And because most of these people will have no access to screening, early diagnosis and appropriate treatments, they stand less chance of surviving. By 2020, for every one cancer death in an affluent country, three people will die in the developing world.

Finding ways to avert a catastrophic cancer epidemic may seem like an impossible mission, but having worked with the UICC for many years, I know that great things can be achieved when the whole oncology community pulls together. As incoming president, I accepted the heavy responsibility of leading this huge NGO, because I believe the UICC is the only body that can coordinate a successful global fight for cancer control. I see no reason why 'mission impossible' should be confined to the movie screen.

*Franco Cavalli is Director of the Oncology Institute of Southern Switzerland, and will take on the presidency of the UICC at the World Cancer Conference, Washington, 8-12 July

David Khayat: driving the French cancer plan

→ Marc Beishon

A committed medical oncologist, David Khayat reluctantly dragged himself away from his patients in 2003 to oversee the implementation of the French cancer plan. This grand and sweeping venture exercises huge control over cancer services, education and research. But its real value, says Khayat, is that it treats cancer patients as normal human beings.

What does it take to kick-start a national cancer plan that will deliver fast and sustainable improvements in cancer care, prevention and research? Such plans are badly needed – as John Seffrin, president of the International Union against Cancer, says: “We know that every country needs to develop a cancer plan. If you’re not planning, you’re planning to fail.”

In the UK, the shame of long waiting times and one of the worst treatment records in Europe led to the NHS Cancer Plan in 2000; Australia, Canada and New Zealand also have plans in place. In the US, politicians attempted but failed to pass a national cancer act in 2003 to re-energise the famous ‘war on cancer’ launched by President Richard Nixon in 1971. Indeed, it is similar top-level backing that has seen the successful launch of arguably the most complete and rapid initiative yet seen – France’s national cancer plan, which is one of the legacies chosen by President Jacques Chirac for his second term in high office.

France’s plan was announced in 2003, three years after another landmark cancer occasion in the country – the Paris Charter, to which countries and agencies have been signing up, pledging their commitment to the cancer effort. Both the plan and the charter have one thing in common – the pivotal figure of David Khayat, a medical oncologist who has been rather reluctant to spend time away from clinical work, but who undoubtedly possesses the charisma and contacts to lead sweeping changes in France’s cancer care and research provision, and to engage international colleagues in wider collaborative initiatives.

As he points out, France actually has a very good record in cancer treatment compared with most other European countries. “But while we had the best survival after diagnosis on average, there were major discrepancies in outcomes depending on where you lived – by a factor of six. For a country that has made equality the basis of its constitution, that’s unacceptable.” Other major issues were too many research institutions, diluting the research effort, and a



HAMILTON / REA / CONTRASTO

It would take another law to abolish INCa, and it's hard to imagine that any government would do that

drop-off in the French contribution to seminal findings in recent years; a lack of diagnostic equipment such as CT scanners; not to mention France's major consumption of cheap tobacco.

"That is to name just a few issues – the cancer plan has a total of 70 key areas, and while very ambitious they are all being precisely funded and evaluated," says Khayat. The engine room of the plan is the organisation over which Khayat currently presides – the National Cancer Institute (known as INCa) – without which it is highly unlikely that much 'joined-up' progress would have been made.

Khayat says the institute has been set up as a legal entity – "It would take another law to abolish it and it's hard to imagine that any government would vote to stop fighting cancer." While the initial cancer plan runs for five years, from 2003 to 2007, the idea is that INCa will continue to coordinate improvements, and it has been invested with considerable power. "For example, we have the responsibility to authorise how cancer is treated across France – it is not open anymore to individual doctors either in public or private practice to treat patients without specific approval for their hospital. We can also authorise

En famille. With his wife, Jocelyne, and daughters Julie (left), Cecile (centre) and Barbara (right)



interim approval of drug treatments before they have been passed at European and national level, as we did last year with Herceptin for people with early-stage HER-2 positive breast cancer.”

Such powers might seem authoritarian, but Khayat is quick to point out that decisions are reached collaboratively with other agencies, and while raising standards will always make waves, no doubt many of its primary functions – such as uniting fragmented research efforts and leading investment in diagnostic equipment – are broadly welcomed. And in Khayat, the institute has a leader who has been plucked somewhat against his will from the coalface of patient care, and so knows first hand the day-to-day issues of practitioners. He is also head of medical oncology at Pitié-Salpêtrière hospital in Paris, one of the largest public hospitals in Europe, and professor of medicine at the Pierre and Marie Curie University. He insisted when he took on the institute’s presidency that he retained these posts, and that he would return later this year, once his work in establishing INCa was done.

Khayat was born in Tunisia into a Jewish family, and came to France after Tunisian inde-

pendence when he was four. Living in Nice, his family were fairly poor, and they were fortunate to benefit from good medical treatment when Khayat became seriously ill with rheumatic fever at the age of eight. “I had to take steroids and penicillin for five years, but I was struck by this general practitioner who came to our little apartment, wrote out the prescriptions and made everyone smile. I decided then I would become a doctor, and I never change my mind – just as I said to my parents there was a certain girl I was going to marry.”

It was the young wife of a best friend, however, who was to profoundly influence Khayat in his career. By now a medical student, he saw this young woman diagnosed with metastatic cancer and enduring two years of surgery and chemotherapy of the 1970s – and surviving. “I thought it was amazing that she could be cured – and I knew then that I wanted to be part of this revolution.”

Khayat became an ‘intern’ – a competitive position attained by the top 5% of medical students in France – and moved to Pitié-Salpêtrière, where he worked with some of the

best oncologists of the time. Among them was Claude Jacquillat, a pioneer in treating Hodgkin's, who taught him his clinical craft, and another who advised him to carry out some basic research. While doing his military service as a civil placement in a research laboratory in Israel, he worked on a mouse serum discovery, and learned to appreciate the controlled conditions for basic research, as compared with the variability in clinical conditions.

"In France we have a good history of encouraging doctors to do basic research – it's not mandatory but you can't move up the professorial scale if you don't do it for some years. But only a few people can continue with such research, as there is just too much clinical and teaching work to do. In any case, it has become more evident that having small labs attached to departments is not viable – you need large research establishments to have a critical mass of people and equipment. Today, I think it is a good thing that doctors collaborate with large research units rather than doing things themselves."

He also went to the Mount Sinai hospital in New York where he purified the soluble Fc receptor in mouse serum, and back in Paris did the same in human blood, demonstrated its pathology and duly got a PhD in tumour immunology and went on to become full professor at the early age of 34. "This should have been a unique period, when I was set up with a good salary and conditions for the rest of my life and not that much responsibility – but unfortunately Claude Jacquillat, my head of department, died and I was asked to take over."

While such responsibility has no doubt made Khayat the organiser he is now, the early days as head of medical oncology at Pitié-Salpêtrière were very tough. "I had to fight other department heads for resources, manage some difficult older colleagues and I also found out my boss had been raising a lot of money from



charities to fund the department. Almost half the doctors around me were paid for by charity – I had no idea about this, and I was soon asked how I was going to continue to raise funds."

Jacquillat, who died of cancer, had been well known and was a hard act to follow. Khayat worked round the clock to build the department and meet fundraisers. He's especially proud of continuing to put the hospital on the map for innovative clinical work. "We introduced neoadjuvant chemotherapy for breast cancer which, while quite normal now, was a huge struggle back then, as if you delayed surgery you were considered a potential murderer. But we showed that with a combination of chemo- and radiotherapy you could avoid surgery altogether, and it stimulated the work of famous oncologists such as Tom Frie and Bernie Fisher."

Great minds think alike. Gabriel Hortobagyi (right) is a close associate and was part of the gathering that dreamt up the idea of the Paris Charter Against Cancer

INCa is promoting itself as a key player and mover in all manner of European initiatives

Other achievements include the introduction of what is now called biochemotherapy for the treatment of melanoma, and generally the establishment of the hospital as one of the most important centres for phase I and II trials in France.

That said, Khayat says French clinical trials have only been running at about the European average for some time. “It’s been very unsatisfactory – apart from a few large phase III randomised studies, the average patient population involved in trials has been less than 2%. This is partly because a majority are treated in the private sector, which has no incentive to run trials. Further, most of the protocols are funded by pharmaceutical firms, so there has also been a lack of independence.”

Several aspects of the cancer plan deal with this. “We ran hearings from experts around the world about what they’ve done to improve the quality and quantity of clinical research, and we chose to model our approach on England’s National Cancer Research Network, but adapted a bit.” Both the English and French approach have area-based research networks, but Khayat explains that the French system is funding research units not on a population basis, as in England, but on the number of patients entered in trials. “This year we will have set up 28 expert groups, covering topics such as lung, breast, psycho-oncology, surgery and so on – and we will produce a set of clinical research protocols. We have divided France up into 35 territories, each receiving a budget to recruit clinical research assistants and data managers. Each doctor that enters patients into the protocols will receive payment.” The goal is to recruit 10% of new patients into trials.

The relationship between France and England/UK is becoming quite intimate on the cancer front – if less so on other issues – following the centennial of the Entente Cordiale in 2004. As Khayat notes, the countries have agreed to cooperate on developing their cancer plans, with specific reference to joint work on all type of research, including epidemiology, and training. But as he adds, France is also keen to collaborate with other countries and INCa is promoting itself as a key player and mover in all

manner of European initiatives, including a virtual tumour bank and a fledgling European alliance against cancer, which looks to be growing out of a meeting of European health ministers, and which Khayat says could produce backing for large-scale clinical research such as a major lung cancer screening study. INCa is also helping other countries as far afield as the Ukraine and Tunisia with cancer plans.

Khayat has also helped to build a multi-disciplinary cancer centre at Pitié-Salpêtrière, and it is his strong interest in holistic issues that brought him to prominence in France as a cancer commentator and set in train his involvement with the cancer plan. “What gives us the value of what we do is looking at someone affected by cancer as a normal human being – reflecting their identity back to you like a mirror,” he says. “I’ve been talking about this for 10 years in the media now – I believe it was the fact that we had to start considering the patient beyond the disease that convinced Chirac we needed to do something.”

A journalist included Khayat as one of 10 profiles in a book on the work of doctors, and it was his story of fighting cancer with his boss at Pitié-Salpêtrière, who was fighting cancer himself, that attracted media interest and led to him being perceived as “the doctor who talks about cancer on TV”.

At the same time, he made several major contributions to the profession. He says he was instrumental in founding the French federation of medical oncologists, a union of Parisian oncologists, a Paris oncologists’ club and a master’s diploma in oncology. These initiatives were fairly straightforward in the latter half of the 1990s, as medical oncology had been recognised in France as a speciality in 1989 – that though had been a battle against vested interests, comments Khayat.

Naturally, Khayat would like to see more consistency around Europe in the recognition of medical oncology, and he is concerned that oncologists are not always taking the lead in teaching their subject, with organ specialists filling the gap. “The knowledge you have to acquire and maintain in oncology means you have to do only that,” he comments. A battle he’s still fighting today at the hospital, however, is the funding



HAMILTON / REA / CONTRASTO

of extra resources and staff such as psycho-oncologists. If anything, charitable donations have been harder to attract since France's major cancer charity, ARC, was victim to a major financial scandal in the 1990s, for which its director was jailed. Khayat eventually had to change the name of a charity he inherited from his department head – CRAC has become AVEC to avoid association in the public mind.

The Paris Charter Against Cancer came about in 1999 when Khayat and close oncologist friends and colleagues were discussing how best to raise awareness of cancer for the new millennium. Khayat has an enviable network of international colleagues, and has a particularly close

association with Gabriel Hortobagyi, head of breast oncology at the MD Anderson in the US, with whom he has organised an educational conference that now takes place each year in Paris (the International Congress on Anti-Cancer Treatment). It was with Hortobagyi and other senior oncologists such as Peter Harper and Martine Piccart, in the famous Guy Savoy restaurant in Paris, that the charter idea came up for the year 2000.

“We wanted to declare war on cancer like Nixon did in 1971, and for support I wrote to UNESCO, the then French minister of health and President Chirac [who was on the opposite political wing to the minister]. UNESCO said

“The value of what we do is looking at someone affected by cancer as a normal human being”

“We calculated how much the 70 measures would cost, and asked for 1.7 billion euros – and we got it”

‘yes’, the minister said ‘no’, and Chirac asked me to explain further. He said that if we called it a charter, not a war, we had his support – and when the president supports something in France, it opens a lot of doors.”

The Paris Charter was duly signed on TV by Chirac and others on 4 February 2000 at an event called the World Cancer Summit, and that date is now World Cancer Day each year. So far more than 15 nations are on the signatory list. “The idea is to remind governments about the basic rights of cancer patients through its 10 articles,” says Khayat. “We were amazed that the idea of a group of friends should turn into a global story.”

Khayat had the ear of Chirac now, and in 2002 when Chirac was re-elected as President, along with a government of his own complexion this time, there was an opportunity to put weight behind a cancer plan. There had been a plan on the stocks since the late 1990s, but Khayat says there “wasn’t a single euro behind it”. With Chirac making the cancer plan, the rights of the disabled and a cut in traffic accidents his triple legacy for his second term – in preference to building another arts project, which many presidents favour – Khayat and colleagues set up an expert committee that suggested several routes for the plan, with Chirac selecting the 70 steps now in play, plus of course the founding of INCa.

“We calculated how much the 70 measures would cost, and asked for 1.7 billion euros – and we got it,” says Khayat. There is a lot of substance to the plan, which has the great merit of having very visible measures – in the two reports issued so far, there is clear indication of progress on each and well-written discussions on rationale, with case studies to illustrate.

About half the plan had been completed by early 2006, says Khayat, and he expects everything to be in place by the end of 2007.

There are 11 departments at INCa focusing on various aspects of the plan – Khayat says it was decided not to focus on a few priority areas but to do all elements of the plan together. Commenting on a few items, he says the waiting times for CT/MRI/PET scans have been cut greatly by investment in new machinery (the number of PET scanners has gone up to 72 from just five in 2002). Over 100 psycho-oncology positions have been created – “There was a huge lack here – there was a time in France when we really didn’t listen to the patient.”

Other notable parts of the plan include an information disclosure procedure for all patients, coordinated care programmes, the setting up of seven regional cancer research hubs, and a ramp-up of screening programmes for breast and colorectal cancers.

He’s particularly pleased with INCa’s role in the interim funding of Herceptin in the early-stage setting – “This cost 80 million euros and could save 2,000 lives over 9 months,” he reckons, adding that if the drug had not been approved eventually by the regulatory agencies, only then would INCa have withdrawn the drug.

There has been some criticism that not enough emphasis has been placed on prevention – for which about 13% of the budget has been allocated – but Khayat says that given France’s previous record, notable progress has been made. “The government has increased the price of cigarettes by 45% in the first two years – and we have 1.8 million fewer smokers as a result,” he says. “It was courageous – we had a revolt of tobacco sellers and had to buy them off.” Recently, the French government seems to have backed down on plans for a smoking ban in public places, but Khayat is confident it will come to pass before the end of this year.

“We also did a big campaign on TV about the dangers of sun exposure – it has been new in France to do so much on prevention,” he says.

Work on alcohol, diet and occupational exposure is also included in the plan, although not as much as some critics would like.

As president of INCa, Khayat's role has been very much hands on – he says it's more of a CEO's role (despite there also being a CEO) – but he's still been putting two half days a week in at the hospital. He can be justifiably proud of getting INCa off the ground from nothing to a staff of 185 in just six months, and he reckons its research programme and budget can pass muster with other agencies, notably the US National Cancer Institute (NCI). "If you compare the NCI's extra-mural activities – take away the researchers and labs – with us, we are fairly similar in budget, and our funding goes directly on research not on salaries, as most French researchers are existing public servants, and we already have enough labs and beds."

While the cancer plan is going well, Khayat recognises that progress also throws up other problems. "As soon as you share information with patients you share power. And when you share power you share decisions and need to respect the patient's right to choose." A health-care system that builds large centres of excellence will inevitably take people further away from home – and with the growing backdrop of chronic degenerative illness, the existing 'operate or die' model of acute care may well need to be radically rethought. Balancing such ethical and economic arguments has been a preoccupation for Khayat in various talks and writing.

Although he's cut out much international travel while at INCa, Khayat admits he's often late home to see his wife, Jocelyne, a pharmacist turned art historian, and his three daughters, none of whom are turned on by medicine. His two great hobbies are food (and it has to be worth asking for an oncologist's discount at Guy Savoy) and writing. He is a prolific author of medical fiction and non-fiction, and also



Friends in high places. President Jacques Chirac chose cancer as a defining issue of his presidency, and his personal backing was key to getting the French cancer plan approved. In the foreground are Bernadette Chirac (right) and Jocelyne Khayat (left)

screenplays; two of his medical dramas have been recorded for French television, one only last April.

At just 50, Khayat has a huge collection of awards and positions, both real and honorary, to his name – he's even a Commander of the British Empire, an honour rather lost on him. The one he values above all else, however, is an adjunct breast cancer professorship at the MD Anderson, an institution he considers "a dream – it's by far the best in oncology."

He is stepping down from INCa this year, once a successor is found, to return full time to Pitié-Salpêtrière to focus on his patients. He also intends to go back to the lecture circuit and perhaps to industry consultancy, which he was obliged to set aside owing to conflict of interest with INCa. It is hard to imagine that Khayat will sink out of either the public or professional spotlight, however. As he says: "My secretary is always afraid when I come in on Monday morning with yet another idea such as a charter or a federation." The next idea will no doubt not be long in coming – and will be well worth the short wait.

“The government hiked the price of cigarettes by 45% – and we have 1.8 million fewer smokers”

Are you feeling lucky?

Discussing risk and treatment options with patients

→ Anna Wagstaff

Doctors use trial-based evidence and years of experience to assess risks of treatment and relapse. But patients make choices based on their own experiences and priorities. How can doctors best explore treatment options with patients? *CancerWorld* asked the experts and offers Ten Tips for Effective Communication About Risk.

Cancer is beset by uncertainty. Despite dramatic increases in the amount of information from clinical trials and translational research, doctors are still unable to accurately predict who will suffer recurrence or relapse or who will respond to a particular therapy. Patients often have to decide whether to opt for adjuvant chemotherapy, radiation therapy or hormone therapy to protect themselves from something that may never happen. Treatments can expose the patient to serious risks, and may make them feel worse than the disease. People at high familial risk may decide to take radical preventive measures such as having ovaries or breasts removed, without any certainty that they would ever develop cancer. Patients with metastatic disease have to understand the trade-off between treatment and

side-effects, and decide whether to sacrifice quality of life for the chance of extra months of life.

Not only must patients make choices that could save their lives or mean damaging treatment for no benefit, but no-one can ever be sure before or after the decision whether it is, or was, the best decision for them. So it is very important that these decisions on treatment options should be made jointly by the doctor and patient in partnership.

This is easy to say, but not so easy to do, because doctors reach decisions on treatment options through a process which is alien to the way most patients approach the same decisions. Most patients are ill-equipped to grapple with statistics and science; while many doctors have trouble seeing beyond the disease and its epidemiology. It is easy to overlook what the diagnosis and treatment

options might mean for the patient's work life, family life, social life and sex life.

Doctors base their knowledge on evidence-based medicine, which is often derived from trials involving thousands of individual patients, who have been stripped of personal characteristics and reduced to a selection of potential prognostic and predictive factors, from which appropriate guidelines and protocols are derived.

Deciding on the best treatment for an individual patient involves matching them up with the relevant prognostic and predictive factors, and throwing in data on comorbidity. These calculations become increasingly complex as research uncovers new biological and molecular markers. Nowadays, doctors often make use of nomograms to make risk-benefit calculations, to support their own clinical judgement.



PHILIP HARVEY / CORBIS

A partnership. The doctor knows more about the disease and treatment options, the patient knows more about how these may affect his life

Evidence-based medicine is not under question. However, nomograms do not provide data about any individual patient, all they do is offer values for the apocryphal 'average' patient with a defined set of prognostic and predictive factors. Drawing up guidelines involves value judgements about relative costs and benefits, which can lead in different directions. There is, for example, a greater use of adjuvant chemotherapy for early breast cancer patients in the US than in Europe, while UK paediatricians have tended to opt for less intensive use of radiotherapy in young rhabdomyosarcoma patients compared with their US counterparts.

Prostate cancer most clearly illustrates the catastrophic results that can occur when treatment options are not informed by the priorities and values of the patient. The introduction of PSA screening led to a generation of men having their lives blighted by incontinence and impotence because a generation of urologists

failed to understand or communicate the true risk associated with more slow-growing or indolent prostate cancers, or to explore with patients the effect of treatment on quality of life. As a result, it is estimated that at least one-third of patients with good prognostic signs treated with radical prostatectomy in the previous two to three decades never would have needed it. Today, a doctor is much more likely to recommend intensive monitoring, than plunging in with the knife.

Patients often have huge faith in their doctors, and sometimes want to pass on the responsibility of taking the decision. "What would you do in my shoes, doctor?" is a question that is often asked, but no doctor is in a position definitively to answer it.

Presenting information to patients in a way they can understand and act on is a high-level skill. Yet many oncologists finish their training inadequately equipped to communicate effectively with their patients.

He or she has to understand how the patient perceives their diagnosis, their hopes and fears, their background and responsibilities, their preferences and their level of knowledge. To help the patient to make a decision, a doctor requires listening skills, time with the patient, opportunities for repetition, endless patience and the ability to call on other means of support.

But circumstances are stacked against this. The medical setting in which the consultation takes place tends to undermine the patient's sense of identity, individuality and autonomy, and time is at a premium. As Louis Denis, Director of the Antwerp Oncology Centre, says: "The doctor is in a hurry, the patient is panicking."

CancerWorld has talked to patients, oncologists, cancer nurses and a genetic counsellor and distilled their knowledge into Ten Tips for Effective Communication About Risk.

Tip 1

It takes two

Effective communication requires *Equal status* for what the doctor and patient bring to the consulting room. Too often authority wears a white coat, while the patient feels like a number or a bundle of case notes.

Both sides can do something to change this. The patient can bring a family member or trusted friend to the consultation as a way of retaining their personal identity, and for practical back-up (see Tip 6). The doctor can involve other health professionals, such as specialist cancer nurses or psycho-oncologists (Tip 7), who are able to spend more time getting to know the patient in advance and talking things through later on.

Having a row of medical students observing the consultation can feel very intrusive. Medical students have to learn, but the patient should be given the option to refuse their presence *before* inviting them into the room, numbers should be limited to one or two, they should be properly introduced.

Terms of address should reinforce a sense of equality. Patient and doctor

should either both use first names or both adopt a more formal 'Mr' and 'Dr'. If possible, avoid carrying out a physical examination at the consultation session, particularly if this involves undressing or wearing a hospital gown. It is hard to feel equal without clothes.

Make it clear that there is no rush to reach a decision, and that the patient will have time to absorb the information and, if need be, come back and discuss it further. Be aware that patients often pick up a sense that the doctor's time is short while they are sitting in the waiting room. Patients who feel under time pressure will be inhibited from asking questions or expressing their concerns.

Many patients are torn between wanting to know, and fear of hearing something they cannot cope with. If a doctor launches into a routine explanation, the patient is unlikely to enter a dialogue. Doctors can ask the patient what they understand is the purpose of the consultation, giving them an early opportunity to talk about what they hope, fear and feel about what they are going through.

"It is a dialogue. Not, 'here are the facts, now make a decision,' but being able to establish a rapport. Let them talk a bit about how they feel, and where they are at, and that will help you tailor the information to them."

Clara Gaff genetic counselor

"It's so important to encourage the initiative of the patient, so they are not automatically led into something they have not had the chance to absorb, never mind consent to... Listen, listen and listen again to the patient. What is the patient saying between the lines?"

Rita Pilbrow Carlsson breast cancer patient

Tip 2

Keep language simple

Make an effort to use language that is easy for non-medical people to understand, and explain words that carry a different meaning in everyday language. For instance, "response" means that a tumour shrinks or grows less quickly – but patients may assume it means "cure". "Aggressive" means the cancer is fast-growing or will spread quickly, but it carries other connotations in daily language. Avoid euphemisms like "lump" or "tumour" or "neoplasia", at least until the patient understands that these words relate to cancer. Patients are not stupid and most will suspect they might have cancer. Until they are clear about whether or not they do, it will not be possible to move on to focus on examining options.

"My consultant [specialist], I think was frightened of my response and said something like: 'On a scale of cars, you have a 2CV as opposed to a Ferrari,' and didn't mention the word cancer. My GP (family doctor) drew me a diagram, explained it to me and gave it a name."

Eve Setch haemangioendothelioma patient

"Generally speaking the patient asks the nurse for more explanation or clarification, because the nurse usually speaks in simpler terms."

Kath MacLachlan and Lynn Dowde specialist breast nurses

Kath MacLachlan and Lynn Dowde work for Breast Cancer Care, UK: www.breastcancercare.org.uk

Tip 3

Side-effects: keep it personal

It is important to consider how each potential side-effect might impact on each individual patient.

The doctor needs to understand the patient's lifestyle, priorities and preferences and be willing to have a meaningful dialogue exploring what each option could mean. Care should be taken to *avoid making assumptions* about, for example, who will be most concerned about possible impotence. The side-effects of treatment may damage someone's self-image, self-

esteem and self-confidence, just when they need those things most.

A doctor understands infertility, early menopause, incontinence, impotence, neutropoenia, fatigue and neuropathy, but not what each of these means to the patient.

Mastectomy, hair loss, hot flushes, incontinence or impotence can each have a devastating effect on one patient, while others may find them easier to cope with. Fatigue may be less important to a patient who can

take time out to look after themselves, than to a patient who feels obliged to keep working, or to continue 'normal' family life. Some people will be desperate to avoid the risk of becoming infertile, while for others this could be a minor issue. Neuropathy may mean trouble with buttons for some people but loss of a job for others.

"Some oncologists do tend to assume that a patient with a disability, perhaps in a wheelchair, won't want to attend daily radiotherapy. But some people want treatment to minimise the risk, no matter how old they are. And we know from experience that any woman, regardless of her age, can be devastated at the thought of losing a breast."

Kath MacLachlan and Lynn Dowde specialist breast nurses

Tip 4

Statistics: explaining the figures

Deciding on the best treatment often involves complex trade-offs between alternative risks or combinations of risks. For instance, adjuvant therapy becomes more attractive the higher the risk of recurrence, the more serious that recurrence would be, the greater the effect of therapy in reducing a risk, and the less serious the risk of side-effects and their consequences.

Although not all patients want to explore statistics, doctors need to be able to help them navigate their way through choices by explaining numbers in the simplest possible way. A great deal of research has been done on how to do this most effectively.

THE PERCENTAGE GAME

A survey asked respondents how many people out of 100 would develop a disease if the chance of getting it was 10%. One person in five could not work it out. People are most proficient at comparing two risks and indicating which one is larger. They are less proficient at adding risks, interpreting a trade-off in risks (e.g. a drug cuts one risk in half but doubles another) or understanding a sequence of risks (the probability of a side-effect occurring, and the probability that if it occurs it will be serious).

Risk factors and probabilities can be presented in a variety of ways: 20% is 1 in 5, or 20 in 100, or a ratio of 1:4. *Try to stick to one system.*

Patients find it easier to interpret trade-offs when risks are presented in the form of 'N in base' comparisons (20 in 1000 compared with 70 in 1000).

However, they understand percentages best when interpreting a sequence of risks (for instance a 70% risk of relapse and a 20% risk that any relapse will be fatal). Any percentage smaller than 1 is poorly understood.

Studies also show that some people understand 1 in 10 as a higher >>>

risk than 1 in 5, simply because they associate the higher number (10) with higher probability. This can be avoided by using *the same denominator*: i.e. compare '2 in 10', '5 in 10' '1 in 10', in preference to '1 in 5', '1 in 2' and '1 in 10'.

Some people find *graphical presentations* easier to understand than figures. Decision trees (see opposite) can be helpful for evaluating options that involve a number of successive risks (e.g. risk that you will survive the transplant, risk that having survived you may go onto relapse, etc.). Bar charts and line graphs can help explain benefits in survival over time. However, they can also be misleading. For instance, graphs that show only the top half of the survival curve (i.e. from 50% to 100% of the patient sample) can make the increase in survival offered by a particular therapy look twice as great as it really is.

Relative risk is frequently a source of confusion for doctors and patients, and can magnify perceived levels of risk or risk reduction. Clearly if the risk of an adverse side-effect rises from 1 in 1000 to 2 in 1000, the risk has doubled, but the odds remain extremely favourable. To give a real life example, for women with Her2+ early breast cancer, adjuvant Herceptin can decrease the relative risk of recurrence in the first few years by around 50% – i.e. it halves the risk of recurrence. But that risk without Herceptin is only about 20% in the first few years, so the absolute risk reduction is only 10 percentage points. The patient is much more likely to focus on the 50% ("my risk is halved") than on the 10% that is relevant to her decision.

Avoid the abstract. People may understand statistics better if they are put in human terms. "In a group of 100

women with your type of diagnosis, the chances are that 20 will have a recurrence within 5 years, and 80 will not. We don't know whether you will be one of the 20 or one of the 80. If all the women took adjuvant hormonal therapy, it is likely that only 10 will have a recurrence and 90 will not."

Using *comparisons* such as "as likely as being struck by lightning" or "you are more likely to be run over by a bus" may be less informative than they sound (patients will have their own ideas about how likely these may be, and anyway both depend heavily on circumstances), and may be misleading. The odds of a big win on a national lottery are said to be smaller than the risk of being murdered, but every week millions of people confi-

dently predict that their numbers will come up on the lottery, without worrying about murder.

Many of the above findings are contradictory (or true within some contexts and not others), and they mainly relate to written presentations. A doctor–patient consultation gives an opportunity to discuss the risk, in a situation where the doctor can assess how well the patient understands these concepts, and can tailor their approach. The examples of Roger Wilson, a leiomyosarcoma survivor, and Jan G, a CML patient, shown below, show how differently patients approach the question of risk, and how important it is to be able to tailor the information and the discussion to the particular patient.

APPLIED STATISTICS 1

Roger Wilson: "You either will or you won't survive"

Roger Wilson is a leiomyosarcoma survivor with a background in the media. When diagnosed with cancer his response was to look for as much information as possible. However, he did not find statistical data very helpful in deciding what to do. Roger is 1 of 4 complete remissions out of 322 patients who participated in a trial six years ago comparing doxorubicin with two experimental schedules of ifosfamide for metastatic leiomyosarcoma. The odds against him were 80–1, but as far as he is concerned, the success of the treatment in his case was the statistic that really mattered. "In your mind, whether the odds are 30:70 or 70:30, for you it is still 1:1. It is a binary issue. You either will or you won't."



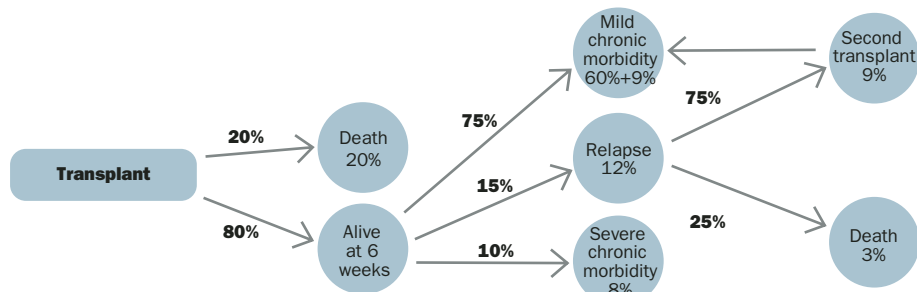
APPLIED STATISTICS 2

Jan G: "I calculated the odds and used a decision tree"

Jan G is a chronic myeloid leukaemia (CML) patient with a background in information technology. When he was diagnosed in 2001, at the age of 28, his response was to turn to the statistics for guidance: "I got the figures from medical reports, Internet discussion forums and various doctors – I took the median of those." Jan had two options: immediate bone marrow transplant, or joining a phase II trial of STI-571 – now Glivec (imatinib) – and interferon. He drew up a decision tree (see opposite) to show the likelihood of dying associated with the two options, and decided to opt for the Glivec. So far, the decision has served him well, but he recognises that many patients find this highly objective approach "too rational", and that many would not have the statistical skills to do this for themselves.



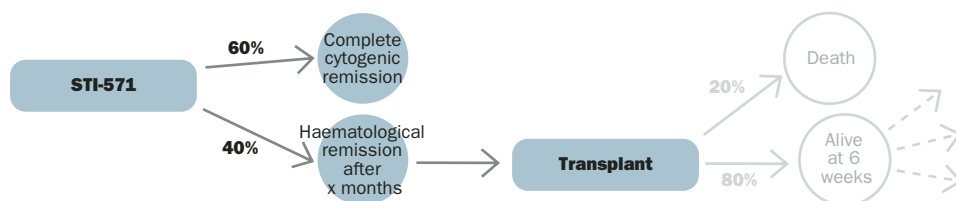
JAN'S DECISION TREE: STEM CELL TRANSPLANT VS STI-571 PLUS INTERFERON



Probability of death **23%**
(20%+3%)

probability of a desirable outcome **69%**
(60%+9%)

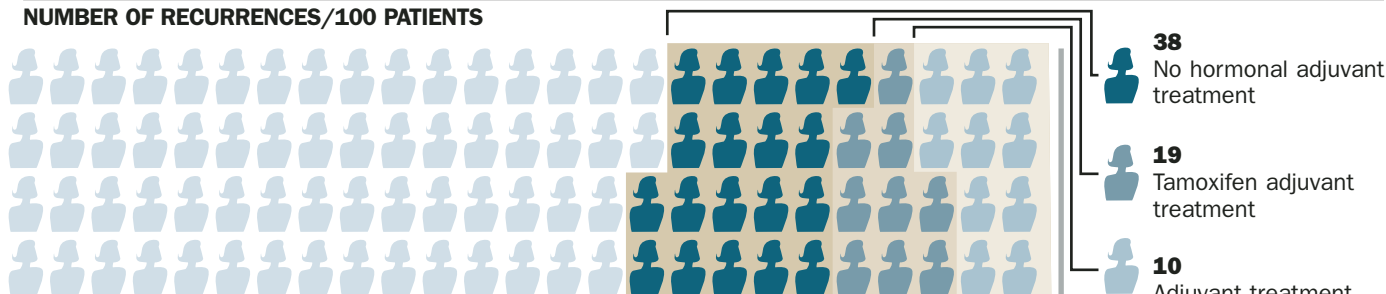
Decision trees can be helpful for exploring complex options such as this comparison between two alternative series of risks. The figures were best guesses on the information available in 2001. Survival rates for both options are higher now



Probability of death **9.2%**
(40% \times 23%)

probability of a desirable outcome **87.6%**
(60%+27.6%[40% \times 69%])

NUMBER OF RECURRENCES/100 PATIENTS



Many patients find visual information easier to relate to than numbers. This image shows how hormonal treatments can affect the risk of breast cancer recurrence

Tip 5

Statistics: keep it personal

Statistics can seem a welcome oasis of hard information, but even patients who understand the figures often find them unhelpful when interpreting their own situation. Tailoring information to the individual can make a big difference. The doctor may view risk factors as per-

“Patients cannot and do not want to see themselves in statistical terms, and probably find it very unpleasant and unconstructive to have to discuss their treatment options with a doctor who talks like that.”

Rita Pilbrow Carlsson breast cancer patient

centages, but the patient may find it easier to consider ‘real-life’ risk factors

rather than figures, such as what was found at surgery, various >>>

“What does help is to assist the patient to understand that the treatment they are recommended is tailored specifically to them as an actual person.”

Kath MacLachlan and Lynn Dowde specialist breast nurses

pathological reports and scans, and relevant medical history.

Some doctors find *Adjuvant! online* (www.adjuvantonline.com) useful. This is an Internet programme for breast cancer assessment, which draws on information from various databases and the literature. Available to health professionals (and designed to be used by the health professional and patient together), it calculates the risk of negative outcomes, the reduction of risks afforded by therapy, and the risks of side-effects, once a doctor (or nurse) feeds in data from the patient's pathology reports and medical history. Estimates are printed out in graphical and text formats, for discussion with patients.

It can be helpful to *use words as well as numbers* to indicate risk levels. Although phrases such as “highly unlikely”, “not very likely” or “fairly likely” are unspecific and open to interpretation, studies have found that they actually do a better job of representing true feelings than numeric scales using odds or percentages, due to the way most people process information.

It is also important to recognise that patients interpret statistical risk according to their own preconceptions,

“Asking survey respondents to place a numeric probability on the occurrence of a health outcome and then comparing their answers with objective data is one of the least meaningful and least reliable measures of risk understanding.”

Neil Weinstein (*JNCI* 25:15–20)

experiences, emotions and so on.

Events that are more serious are often perceived as being more likely to happen. Thus a chance of 1 in 8 seems objective, but feels more likely to a patient when applied to more serious outcomes, such as metastases, than to less serious outcomes such as neuropathy.

People also think that something that has already happened to someone they know is more likely to happen to them. Thus, two women with identical breast cancers may have very different views about probable outcome, if one had a mother who died from the disease, while the other has two friends who both survived it.

Doctors should therefore be aware that the statistical message they are giving may be different from the one the patient receives. This is why it is helpful early in the discussion to *talk about what experiences and prior information the patient already has*. Asking, “What do you know about the

cancer/proposed treatment?” is one way of doing this. This can help the patient to reveal the experience that is influencing their judgment. The doctor may then have an opportunity to explain: “From what you say it sounds as if your mother was diagnosed when the cancer was already quite advanced. Luckily your cancer has been picked up quite early, which means there is a much better chance the treatment will be successful.”

The immediacy of the risk can also affect perception. Faced with a cancer diagnosis, a patient may panic and only be able to think about the risk of the disease and getting rid of it as soon as possible. They may find it impossible to focus on the longer-term implications of treatment options. *Encouraging a patient to take time to talk through the risk of side-effects may help them to balance one risk against another*. For example they might consider how a risk such as infertility or impotence would impact on their mental health, their relationships and their plans for the future. Patients may later become very bitter about such outcomes if they feel they had no opportunity to discuss them when they were deciding on treatment.

FROM MORE THAN ONE ANGLE

Genetic counselors tend to use absolute figures (e.g. your risk of developing colorectal cancer during your lifetime) and relative figures (e.g. you are three times more likely to develop colorectal cancer than an average person of your age). They may also offer 5- and 10-year probability figures (your risk of developing colorectal cancer within the next 5/10 years). Giving data that present a different angle on the same issue may confuse some patients, but will help others to formulate a more complete picture in their mind.

Tip 6

Take enough time – use it well

Lack of time is the single constraint mentioned most often by doctors as hampering communication with their patients. But time has to be taken. The issues are complex, and the patient can be overwhelmed by the situation and the amount of information. Faced with a cancer diagnosis, patients can panic and reach for a snap decision. In most cases, the patient loses nothing by giving themselves a week or two to decide how to proceed. They stand to gain a great deal by taking stock of their situation, and talking through options with their doctor, friends and family. *Trying to rush a consultation can be a false saving.*

Make best use of time with the patient. A lot of time in consultations is wasted going over information the patient already knows, while things they need to talk about are barely touched on. Asking patients what they already know saves time. *Reading the patient's notes* avoids asking the same questions two or three times (a common complaint from patients). *Focus on the information most relevant* to the decision that has to be made.

Around 70% of information provided when the patient is first given a

cancer diagnosis is not retained. Retention can be improved if the patient *brings a member of the family or close friend* as a second pair of ears,

and if they take notes. See also the advice under Tip 8 (Signposting the patient) about how to reinforce information.

“I tell the young urologists that you need to give more time in the first consultation and you will gain it back in all the subsequent consultations.”

Louis Denis urologist

“Take time for explanations after the diagnosis. Re-explain if the patient doesn't understand. Give them the impression there are no silly questions. Offer them the chance to come back after they have made up their mind, and ask questions again. If this time is invested in the beginning, it will make things much easier in the course of the treatment.”

Jan G CML patient

LISTENING SAVES TIME

“One of the feelings some doctors have is that consultations will take much longer if they have to do all this touchy feely stuff, but an Australian study looking at oncologists' reactions to cancer patients' verbal cues (Butow et al. *Psycho-oncology* 11:47–58) has shown that this isn't the case. What can happen when people aren't really getting what they want or when they don't feel they've been heard or understood is they start asking the same question over and over again, sometimes in slightly different ways, and the doctor can get quite frustrated thinking: 'I've already given them the information, why are they asking again?' It tends to be an indication that some underlying emotion is not being recognised.”

Clara Gaff Genetic Counselor

Tip 7

A team approach

It is hard for one doctor to fulfil all a patient's needs for information and for discussion. Patient and doctor can both benefit from the involvement of specialist cancer nurses, psycho-oncol-

ogists and other members of a team. There is great scope in much of Europe for *making better use of nurses and other health professionals*. Nurses who are part of a cancer team normal-

ly have more contact with the patient, and know more about the family situation and their emotional state, and may be better placed to talk things through with a patient at his or her own >>>

pace. Patients often feel more relaxed with nurses, and it is common for patients to open up and ask more questions after the doctor has left the room. However, it must be the doctor who plays the critical role in discussing and helping the patient decide on treatment options.

“Doctors often feel they have to provide every bit of support and information to a patient. They don’t have to do it all themselves. They need to be aware of who is around and who can help.”

Kath MacLachlan and Lynn Dowde specialist breast nurses

Tip 8

Signposting the patient

There are many avenues to helping patients to take in information, understand their condition and judge available options. Some doctors encourage their patients to *tape the consultation*, so they can listen to it again where and when they want. *Written information* should be provided from the start, and the patient should be asked to read it before they attend their next consultation. Patient groups are very willing to check written information to ensure that it is appropriate, relevant and easy to understand.

Doctors can supply their patients with a short list of the clearest and more accurate *resources on the Internet* that are designed for patients. This will help them to access good-quality information and make it less likely that they will visit sites with poor-quality or misleading advice.

There are many *independent sources of support and information* to help a patient build a picture of their disease and treatment options. Many countries have support agencies with free help lines staffed by health profes-

sionals who can be an additional source of information and advice. Some hospitals have a cancer information centre or a psycho-oncology service that takes referrals.

All these options provide sources of support and information, which patients can access in their own time.

Cancer units should *compile a list of all these resources* and should make them available to patients. Though this might seem an obvious point, doctors are not always natural networkers, and often omit to mention patient groups or cancer information centres, even those attached to the same hospital!

Doctors can also *encourage a patient to seek a second opinion*. It can be reassuring for a patient to hear another specialist talking in similar terms, even if the second opinion varies slightly from the first. Suggesting a second opinion and offering a list of names gives an important signal that the patient is being encouraged to make an informed decision, rather than following recommendations out of blind faith.

“It is extremely important that doctors do not work against the patient’s request for a second opinion. It should be encouraged and not met with the arrogance I received from one consultant [specialist] in a UK hospital. His exact words were: You can either believe me or choose another consultant.”

Rita Pilbrow Carlsson breast cancer patient



Doctors should offer their patients a list of good-quality relevant Internet sites. This comprehensive list of French-language sites was compiled on the initiative of Rouen University Hospital

Tip 9

Patient groups

Many patients say that the insights and information they found most useful came from other patients. It can be easier to discuss painful and frightening issues with someone in the same situation, who talks from personal experience. Patients in patient

groups are often also experts – and have good reason to be.

Most European countries have patient groups for many cancers, local or national or attached to a particular hospital. Patient websites and chat groups can also provide information and put patients in touch with people

facing similar situations, although language may be a limiting factor for non-English speakers.

Working with patients to *set up a patient group* where they do not already exist is an important way that specialists can help patients learn what they need to know.

“If you really do believe in partnership with patients and joint decision making, I cannot see how you can work effectively without a patient group. [Helping set up a group for stoma patients] was the best thing I ever did in my life. It takes a lot of patience and time to get them organised. But once they are organised, if you are lucky they work on their own and are certainly not dependent on your opinion, they form their own opinion, because then they have contacts.”

Louis Denis urologist

“I think quite often one of the biggest influences on a patient’s decision is another patient who has been through that decision before. You get some sort of ‘decision inheritance’ that works in an untraceable way.”

Roger Wilson leiomyosarcoma patient

Tip 10

The right decision?

Doctors have a responsibility to ensure, to the best of their ability, that a patient’s decision is based on an accurate picture of the medical facts. *Talking through with the patient how they reached their decision* may reveal misunderstandings or logical flaws that need to be explored further. However, afterwards, it is never possible to say whether a decision was right or wrong. There is no telling whether a recurrence might have happened with or without adjuvant chemotherapy.

“Some patients have said ‘no thank you’ to a recommendation of anti-hormonal medications such as tamoxifen or aromatase inhibitors. Others have refused chemotherapy. These patients should be informed fully about the statistics and treatment guidelines, with material they can take home to read, but most of all their decision should be respected. Some patients have felt threatened into having the recommended treatment, although their inner voice says something quite different.”

Rita Pilbrow Carlsson breast cancer patient

There is no knowing which patients gained tremendous benefits from treatment, and who suffered side-effects needlessly. Patients with similar diagnoses make different decisions based on a myriad of factors, including different priorities

and preferences, and differing feelings about their chance of being one of the lucky (or unlucky) ones.

The patient lives or dies with the consequences of a decision, and it is not for a doctor to say whether it was right or wrong.

RNA-bound: the future of antisense drugs

→ Keith McCullagh*

The use of nucleic acid therapies to block RNA function was first described in 1978. The latest generation of these compounds, LNA antagonists, is now overcoming the main obstacle to the success of its predecessors, through a greater ability to bind to RNA.

Innovative approaches to drug discovery and disease treatment are the basis of the biotechnology industry. However, it is a rare event when a new technological approach leaps straight from the lab bench into the market. Invariably, by a process of iterative refinement, a concept evolves through multiple generations before a marketable product is created. A prime and well-recognised example is monoclonal antibody technology, which is in its third and fourth generations. There are now over 100 potential antibody products in clinical development.

A similar evolution is emerging with the development of nucleic acid therapies. The use of a string of DNA nucleotides to bind and block messenger RNA function was first reported in 1978 and, since then, many companies have applied the antisense principle to make oligonucleotide drugs with the aim of switching off the expression of a specific disease-associated protein – the drug blocking or destroying the messenger RNA responsible for the protein's synthesis. The first such

drug to be marketed was Isis Pharmaceuticals' Vitravene, a topical treatment for human CMV (cytomegalovirus) retinitis, which was approved by the European Medicines Agency (EMA) in 1999 and the US Food and Drug Administration (FDA) in 1998. Through a series of chemical improvements, antisense drugs have been refined substantially since then and breakthroughs have been made by a number of companies.

In particular, the discovery of RNA interference – a natural antisense mechanism in plants and animals – has led to the emergence of companies such as Alnylam Pharmaceuticals and Sirna Therapeutics, who are developing synthetic double-stranded RNA as high-potency antisense drugs known as short interfering RNA (siRNA). More recently, the recognition that siRNAs are unwound within the cell by a mechanism known as RNA-induced silencing complex (RISC), and that only one of their two RNA chains (the antisense strand) binds and inactivates the target mRNA, has

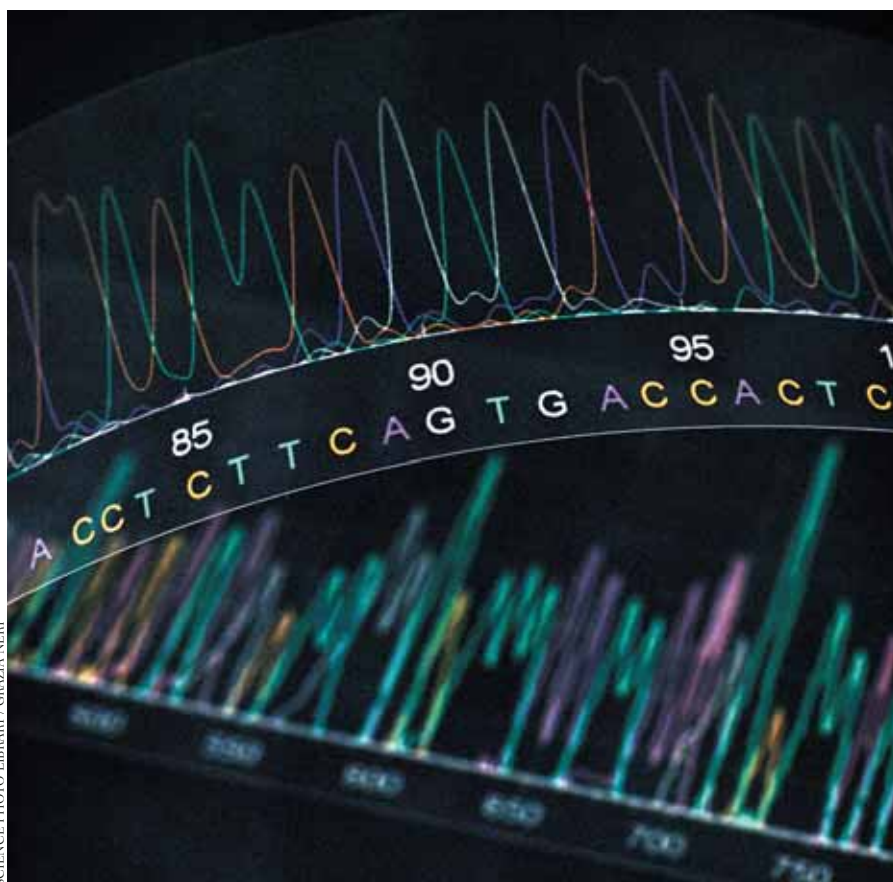
swung the pendulum back to the potential potency of RNA analogues, such as locked nucleic acid (LNA) as single-stranded high-affinity antisense drugs. The latest generation of nucleic acid therapeutics in the clinic therefore encompasses both double (siRNA) and single (LNA) oligonucleotide compounds.

FIRST GENERATION OF RNA INHIBITORS

The first generation of antisense compounds were made from synthetic DNA monomers, modified only in so far as they contain a sulphur substitution in place of oxygen in the phosphate linkages between nucleotides. This so-called phosphorothioate modification has been used in most clinical oligonucleotides to date, since it goes some way towards enhancing the stability of the drug in the presence of tissue nucleases, and also improves plasma half-life. Both Vitravene and the Genta drug, Genasense – currently the subject of a re-submitted NDA – are DNA phosphorothioates. The main problem for such drugs is their relative

* Keith McCullagh is CEO of Santaris Pharma, based in Hørsholm, Denmark

This article was first published in the March 2006 issue of *Scrip Magazine* (issue 154). It is republished with permission from Informa Healthcare, a division of Informa UK.
© 2006 Informa



SCIENCE PHOTO LIBRARY / GRAZIA NERI

tissue breakdown. Isis is applying this technology in several areas, including diabetes and cardiovascular disease, and has sub-licensed development of further 2'MOE drugs to Oncogenex and Antisense Therapeutics. However, although they have improved stability over DNA oligonucleotides, 2'MOE compounds show only marginal improvements in the affinity with which they bind RNA.

Other second-generation modifications, such as 2'OMe (pioneered by Hybridon, now Idera Pharmaceuticals) or morpholino-compounds, developed by AVI BioPharma, appear to have no greater potency or benefit than 2'MOE. This lack of potency, particularly when phosphorothioated, is likely to restrict the use of the second-generation antisense compounds to diseases of the liver or kidney, where they achieve relatively high tissue concentrations.

ENTER THE THIRD GENERATION

There is current excitement in the RNA inhibition field because it is now possible to synthesise compounds with two-to-three orders of magnitude greater RNA-binding affinity. These third-generation antisense drugs fall into two categories: double-stranded siRNA and single-stranded LNA oligonucleotides. In the presence of transfection reagents in cell cultures, both of these third-generation compounds produce significant reductions in target mRNA and proteins at concentrations below one nanomolar. This is dramatically higher than any previous antisense

lack of potency because of weak binding affinity to their target RNA and continuing inadequate resistance to nuclease digestion. Acute toxicities of DNA phosphorothioates reported in primates have also limited the doses at which such drugs can be administered systemically to human patients.

Most experts in the field agree that the first-generation antisense drugs are simply not potent enough to achieve statistically robust efficacy. To date, phase III trials of six separate DNA phosphorothioates have failed to meet their primary endpoint.

Only the seventh – Genta's Genasense in a chronic lymphocytic leukaemia (CLL) phase III trial – met its primary endpoint and the drug is being reviewed by US regulators. In the face of such poor results, many companies have sought to develop improved products.

Thus evolved the second generation of antisense compounds, also pioneered by Isis, which acquired a licence for Novartis' 2'-O-methoxyethyl (2'MOE) chemistry. Oligonucleotides consisting wholly or partially of 2'MOE-derivatised monomers have increased resistance to plasma and

To date, phase III trials of six DNA phosphorothioates
have failed to meet their primary endpoint

OVERVIEW OF OLIGONUCLEOTIDE COMPOUNDS IN DEVELOPMENT IN 2005

Name of compound	Target	Indication	Phase	Nucleotide chemistry	Company
First generation antisense: DNA phosphorothioates (low metabolic stability, low potency)					
Vitravene	CMV	CMV retinitis	Approved	DNA	ISIS
Genasense	Bcl-2	Malignant melanoma	III (NDA withdrawn)	DNA	Genta
	Bcl-2	Chronic lymphocytic leukaemia	III	DNA	Genta
Alicaforsen/2302	ICAM-1	Ulcerative colitis	II	DNA	ISIS
GTI 2040	RNR R2	Renal cell carcinoma	II	DNA	Lorus Therapeutics
GTI 2501	RNR R1	Prostate cancer	II	DNA	Lorus Therapeutics
Second generation antisense: 2'-O-methoxyethyl phosphorothioates (high metabolic stability, moderate potency)					
ISIS 113715	PTP-1B	Diabetes	II	MOE	ISIS
ISIS 301012	ApoB-100	Cardiovascular	II	MOE	ISIS
ATL-1102	VLA-4	Multiple sclerosis	II	MOE	Antisense Therapeutics – licence from ISIS
ATL-1101	IGF-1R	Psoriasis	I	MOE	Antisense Therapeutics – licence from ISIS
OGX-011	Clusterin	Prostate/breast/non-small-cell lung cancer	II	MOE	Oncogenex – licence from ISIS
LY 2181308	Survivin	Cancer	I	MOE	Lilly – licence from ISIS
Other second generation antisense: 2'-O-methyl, and morpholino analogues (high metabolic stability, moderate potency)					
AEG35156	XIAP	Local and metastatic solid tumours	I	2'OMe	Aegera – licence from Hybridon
Resten-NG	C-myc	Cardiovascular restenosis	I/II	Morpholino	AVI Biopharma
Resten-MP	C-myc	Cardiovascular restenosis	I/II	Morpholino	AVI Biopharma
AVi-4020	West Nile virus	West Nile virus	I	Morpholino	AVI Biopharma
AVI-4126	C-myc	Bladder cancer	I	Morpholino	AVI Biopharma
PD3	Multitargeted?	Chronic obstructive pulmonary disease (COPD)	Preclinical	FANA	Topigen
Third generation – double stranded: siRNA (low metabolic stability, very high potency)					
Cand5	VEGF	Wet AMD	II	siRNA	Acuity Pharmaceuticals
		Diabetic retinopathy	Preclinical	siRNA	Acuity Pharmaceuticals
		Diabetic retinopathy	Preclinical		

Continued on page 29

LNA oligonucleotides bind to RNA

with extraordinarily high affinity

technology and predicts enormous clinical potential, provided the drugs can get to their site of action in vivo.

Unfortunately, unmodified siRNAs are inherently unstable in the body, with the duplexes unwinding and being degraded by nucleases in the circulation. This may be less of a problem for topical applications and, indeed, Acuity Pharmaceuticals has the most advanced siRNA clinical programme with Cand5 – a local ophthalmic drug to treat wet age-related macular degeneration (AMD), which is in phase II. The product is designed to silence the vascular endothelial growth factor (VEGF) genes that promote the retinal neovascularisation that leads to

loss of vision in AMD. Similarly, Alnylam's siRNA drug ALN-RSV01, currently in phase I studies for the treatment of respiratory syncytial virus (RSV) infection, is delivered directly into the lungs.

By contrast, the RNA analogue, LNA, when coupled by phosphorothioate linkages, is remarkably resistant to nuclease cleavage and has a prolonged tissue half-life. In addition, LNA oligonucleotides bind to RNA with extraordinarily high affinity. These characteristics are critical, and result in substantial increases in potency in vivo compared to first- or second-generation oligonucleotides. Santaris Pharma reported data at the American Society of Hematology meeting last December

showing that an LNA drug directed against HIF-1 α (hypoxia-inducible factor 1) mRNA appeared significantly more effective in reducing tissue hypoxia and VEGF protein levels after systemic administration to mice than the best siRNA directed against the same gene – the comparison was made using the siRNA against HIF-1 α described by Yu et al (*Lab Invest* 2004). HIF-1 is a transcription factor that functions as a key regulator of VEGF and VEGF receptor expression and is therefore important in tumour angiogenesis. Additionally, HIF-1 α also plays important roles in other cancer processes, such as cell proliferation, apoptosis and cell invasion.

A daunting technical hurdle for

Name of compound	Target	Indication	Phase	Nucleotide chemistry	Company
Sirna-027	VEGF	Age-related macular degeneration (AMD)	I	siRNA	Sirna Therapeutics/partnered with Allergan
	IL4/IL4R	Asthma	Preclinical		
	IL13/IL13R	Asthma	Preclinical		Partnered with Lilly
	VEGF	Solid tumours	Preclinical		
	HBV/HCV	Hepatitis	Preclinical		
ALN-RSV0	RSV	Respiratory syncytial virus (RSV) infection	I	siRNA	Alnylam
NN	HVC	Hepatitis C virus	Preclinical		Benitec
NN	HIV	AIDS lymphoma	Preclinical		
Third generation – single stranded: LNA-based RNA antagonists – LNA phosphorothioates (high metabolic stability, very high potency)					
SPC2996	Bcl-2	Chronic leukaemia	I/II	LNA	Santaris Pharma
SPC2968	HIF-1 α	Renal cancer & myeloma	Preclinical	LNA	Santaris Pharma
SPC3042	Survivin	Chemotherapy in cancer	Preclinical	LNA	Santaris Pharma

The evolution of nucleic acid therapies has much in common with the antibody market

siRNA is uptake into cells in the body. SiRNAs are large double-stranded molecules which do not pass readily across cell membranes. Alnylam reported in 2004 that liver uptake, at least, could be enhanced by conjugation of the siRNA with cholesterol. Santaris has matched that by data, presented at a recent Keystone science conference, showing that unconjugated LNA oligonucleotides directed against ApoB100 in the liver are effective in reducing ApoB synthesis and plasma cholesterol levels in mice at doses eight times lower than those required by Alnylam's cholesterol-conjugated siRNA, synthesised as described by Soutschek et al (*Nature* 2004). LNA may transform the opportunity for oligonucleotides as drugs. The much higher binding constants of LNA to complementary

RNA sequences, compared to conventional DNA analogues, is such that LNA oligonucleotides can be considered a new class of drug. Santaris has coined the term 'RNA antagonists' to describe such drugs in recognition of their high-affinity binding and target specificity.

NUCLEIC ACID THERAPIES THE FUTURE

As is clearly demonstrated in the field of antibodies, the early murine antibodies showed great promise, and some progressed onto the market. However, a rapid evolution of the technology followed. Murine antibodies soon became chimeric (part mouse, part human). The second generation of antibodies were described as humanised – in effect recombinant mouse antibodies

tweaked to closely resemble human antibodies. The third generation of antibodies were fully human, and now we have further developments into antibody fragments, domain antibodies and nanobodies.

In addition to the 100 in development, this class of compounds now has 20 products on the market.

The evolution of nucleic acid therapies has much in common with the antibody market. Few of the early generation of drugs reached the market, but these are being closely followed by the next generations. Third-generation products based on LNA and siRNA are now in the clinic. As these progress, much will be learned and, before too long, we are likely to see a burgeoning series of more effective nucleic acid-based targeted therapeutics hit the market.

LNA-based RNA antagonists

Locked nucleic acid (LNA) drugs appear to be well tolerated in animals. Santaris has completed GLP (good laboratory practice) toxicology studies with three separate LNA compounds and has observed no clinical, haematological or pathological adverse effects in either rodents or monkeys at clinically relevant doses. Santaris' lead product, SPC2996, is being developed to treat chronic lymphocytic leukaemia (CLL) – the second most common type of cancer of the blood, characterised by a progressive accumulation of long-lived, functionally incompetent lymphocytes.

SPC2996 acts by inhibiting the synthesis of Bcl-2, a key sensor protein that protects cells against apoptosis. The protein is expressed in most cancers but is especially high in CLL where the level of over-expression also correlates with poor outcome. In primate pharmacology studies, SPC2996 has been shown to effectively down-regulate Bcl-2 mRNA and protein when injected intravenously at low doses. The compound is currently being evaluated in an international phase I/II multicentre clinical study at haematology centres in Denmark, France, the UK and the US.

Santaris has two further preclinical candidates in development. The first, SPC2968, was selected from a small library of LNA-based RNA antagonists of HIF-1 α mRNA. The other compound, SPC3042, is a potent LNA-based RNA antagonist of survivin mRNA. The latter plays a vital regulatory role in apoptosis, by inhibiting activation of lethal caspases.

In addition, survivin plays a pivotal role in normal mitotic progression and cell division. Survivin is over-expressed in many cancers and in endothelial cells engaged in angiogenesis. However, it is almost absent in normal adult differentiated tissue, thus making it a prime target for cancer therapy.

Has TNM been overtaken by science?

→ Emma Mason

The biology of a cancer is a key factor determining prognosis and prediction of response. So should we still be characterising it by the size of the tumour and spread of the disease? In a debate at the European Breast Cancer Conference in Nice, a packed hall of delegates was, reportedly, evenly split on the question.

The international system for classifying cancer by tumour size and location, regional lymph node involvement and distant metastases (the TNM staging system) has served oncologists well for more than 50 years. But now questions are being asked about its usefulness in the 21st century. While some people believe that it can and should survive, albeit with some adaptations, others are already writing its obituary.

Chief amongst its critics is Harry Burke, Associate Professor of Biochemistry and Molecular Biology at the George Washington University School of Medicine, Washington DC, USA. In 1993, when he was a consultant to the American Joint Committee on Cancer (AJCC), he proposed that a computer-based system for cancer prognosis should

replace TNM. His reasoning was that such a system could include molecular factors, such as oestrogen and progesterone receptor and HER2 status, and it could provide individual patient recurrence and survival predictions for specific therapies. His idea was rejected, but since then he has kept up the pressure with various articles on the subject, and most recently he participated in a debate at the European Breast Cancer Conference 5 (EBCC-5) in March this year, entitled “This house believes that TNM is a waste of time”.

The TNM system is a cancer staging classification system that is used around the world as a common language to classify anatomic disease extent in tumours and give indications as to the course of the disease. The French surgeon, Pierre Denoix, developed the TNM Classification of Cancer Stage at the Institut Gustave-

Roussy, France, and proposed it to the International Union Against Cancer (UICC), which adopted it in 1953, with the AJCC following suit in 1959.

Since then there has been an explosion in knowledge about cancer. TNM was created before any of the genes implicated in the onset of various cancers had been discovered, before the role of hormones had been revealed, before routine screening had been introduced which enables cancers to be discovered at much earlier stages in their development, and before the introduction of neoadjuvant and molecular therapies. Biomarkers have been discovered for cancers such as breast and prostate, which enable physicians to have a more detailed view about what treatments would be best for a particular cancer sub-type and the likely course of the disease, yet they are not

“TNM is basically dead... it is clinically misleading rather than informative”

incorporated into TNM and are not predicted by it.

Burke argues that, in an age of increasingly personalised medicine, TNM is unwieldy, outdated and should be replaced by a system that includes tumour size, lymph node status, metastases, and other predictors of outcome, including powerful new biomarkers, in order to provide the most accurate predictions of which therapy would be best for an individual patient. Other oncologists point out that, while TNM may no longer provide all the information that needs to be known about some cancers such as breast and prostate, there are still many cancers where biomarkers have not been discovered or developed, and where cancer staging gives valuable information about not only the extent, but also the likely course of the disease. In addition, they argue that the developed world owes a duty to the developing world to maintain an international classification system that is simple to understand and to use.

Burke told *CancerWorld*: “TNM is basically dead. It cannot take account of the fact that screening is now detecting cancers at much earlier stages when they are smaller; it cannot incorporate new biomarkers; and it cannot incorporate new thera-

pies. So it is clinically misleading rather than informative.”

When the TNM system started, all that was known about a cancer was the size of the tumour and the extent of its spread; the existence of clinical symptoms was the only way of detecting it. The system was based on the fact that the larger the tumour and the greater the extent of the spread, the less likely the patient was to survive the disease. TNM organised this spread into ‘stages’ of the disease, with a higher stage having a poorer prognosis.

However, in October 2004 a paper published in the *Journal of the National Cancer Institute* on colon cancer survival rates revealed that there was an outcome cross-over between stage IIIa and IIb patients, with the IIIa patients, who according to the TNM system should have a worse prognosis, having better survival rates than the IIb patients. The likely reason for this cross-over was that the IIIa patients had received an effective chemotherapy that the IIb patients had not received and this therapy resulted in improved survival – survival that was not taken into account by TNM.

In an accompanying editorial, Burke stated that this proved that TNM was not taking account of new

treatments, nor was it taking into account the biology of the disease, and that this was the final nail in the coffin of the TNM staging system.

Burke explained: “The TNM staging system relies on the surgical removal and pathologic description of the anatomic characteristics of the tumour and of any associated lymph node involvement, so that it tells you the prognosis of patients if they receive surgery (whereas some cancers only receive radiation therapy, for example, prostate cancer). Further, what if patients receive other treatments such as chemotherapy or molecular therapy (e.g. Herceptin)? How does it take these factors into account in terms of its prediction of prognosis? It is clear that, today, the staging system is making predictions that are not accurate because other treatments are changing the patient’s survival and the staging system doesn’t tell you about that. That’s a fatal flaw in the TNM staging system.”

Supporters of TNM responded to the cross-over in a way that Burke says has shocked many clinicians. “The leaders of the AJCC and UICC, in response to my editorial, wrote that it was all right to have outcome cross-over in the staging system, because it’s not a prognostic system,

“Let’s base prognosis on the biology of the disease, not on how big it is when it is discovered”

it's an anatomic, extent-of-disease system," said Burke. "But once you disconnect prognosis from the staging system, that's the end of the system. Clinicians are totally shocked when I tell them that the staging system is nothing to do with prognosis now." He said most clinicians did not know of the disconnection between stage and outcome and continue using TNM. Yet this approach, using the stages to determine therapy, could mean that some patients were being denied an effective therapy they needed, while others were being treated unnecessarily.

While supporters of TNM say that it is possible to adjust the system so that it can either take account of new developments or can be used to complement prognostic tools such as molecular biomarkers, Burke says that this is impossible because you would end up with hundreds, if not thousands, of different categories that cross over each other, thus defeating the main purpose of TNM – that it is a simple, easy to understand and use, outcome system.

However, Burke feels that the real issue with the use of TNM is what he calls "biological determinism". "The essential question is: are we going to continue to treat our patients based on an anatomic extent-of-disease approach, or are we going to use what we have learned about the biology of the cancer to defeat the tumour that is growing in the patient?"

Seconding Burke at the EBCC-5 debate was Frédérique Penalut-Llorca, a pathologist at the Centre



Harry Burke: TNM is unwieldy, outdated and should be replaced by a system that includes biomarkers and other predictors of outcome

Jean Perrin, Clermont-Ferrand, France. She highlighted the irrelevance of TNM in breast cancer compared with the far more relevant information that is now known about the role of oestrogen and progesterone positive and negative markers (ER and PR), and HER2 status.

"We need prognostic and predictive intrinsic tumour parameters of response to treatment that can be obtained by understanding the tumour biology. These are not in the TNM!" she said.

While not all cancers are as far advanced as breast cancer with the identification and use of biomarkers, Burke says that there needs to be a paradigm shift.

"We need to recognise that can-



Frédérique Penalut-Llorca: oestrogen and progesterone receptors and HER2 status are all far more relevant than TNM stage in breast cancer

cer is a biological disease and let's base prognosis on the biology of the disease, not on how big it is when it is discovered. If we know about ER, PR, HER2 and p53 status, then we know about the prognosis. And survival is very different, even for patients within the same TNM stage of disease. Your destiny is determined by the biology of your disease. This is the definition of biological determinism."

He believes that a computer-based prognostic system, such as the one that he developed for the AJCC, that can take account of all the patient's biomarkers is still the best way forward, and he has established a model for this at www.cancerhome.com.

Mary Gospodarowicz, Professor

“Clinicians are shocked when I tell them that the staging system is nothing to do with prognosis now”



Mary Gospodarowicz: The TNM system is under continuous review by several expert groups and is able to respond to the challenges of the 21st century

and Chair at the Department of Radiation Oncology, University of Toronto, Canada, and Medical Director at Princess Margaret Hospital, Toronto, disagrees with Burke and opposed him in the EBCC-5 debate.

She is a member of the UICC Core Committee of the UICC TNM Project, which maintains the TNM classification and has introduced a rigorous process for continuous improvement of the TNM system.

She told *CancerWorld* that nobody was pretending that TNM was a perfect system. “We live in a world that is imperfect. What is important is that we understand the principles of what we are doing, observing and reporting.”



Lars Holmberg: Lymph node status is still the major prognostic divider. Even if another system is developed, we still could not abandon TNM

The importance of the basic principles of the TNM staging system still remained, she said. “In order to make decisions in cancer you always need to know the anatomic extent of the disease and it always has diagnostic importance. It may be that in selected cancer centres where all the patients have very small tumours (stage I disease), other tumour characteristics are more important than the disease extent for making treatment decisions. But TNM provides a world-wide framework for considering the extent of the disease across all cancer sites.”

Although other prognostic markers, such as molecular biomarkers, were constantly being developed, these tools should be used in addi-

tion to, not instead of, TNM, she argued. “TNM is useful whether or not you have access to biomarkers. It’s not perfect, but it’s useful.”

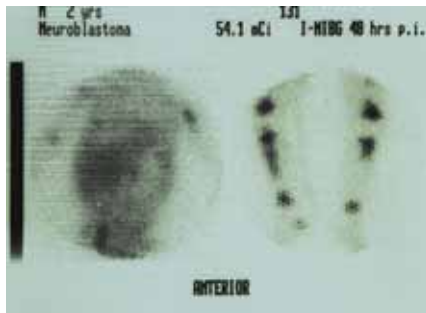
The basis for making decisions in cancer rests on several factors:

- the tumour
- the type of cancer (i.e. site, histology, genetic, phenotypic and molecular characteristics) and the extent of the disease (i.e. stage, size, number of lesions, sites of metastasis)
- the patient (i.e. age, race, general health, etc)
- the environment (i.e. what tools and treatments are available for the physician to use, quality of care, and access to appropriate care)

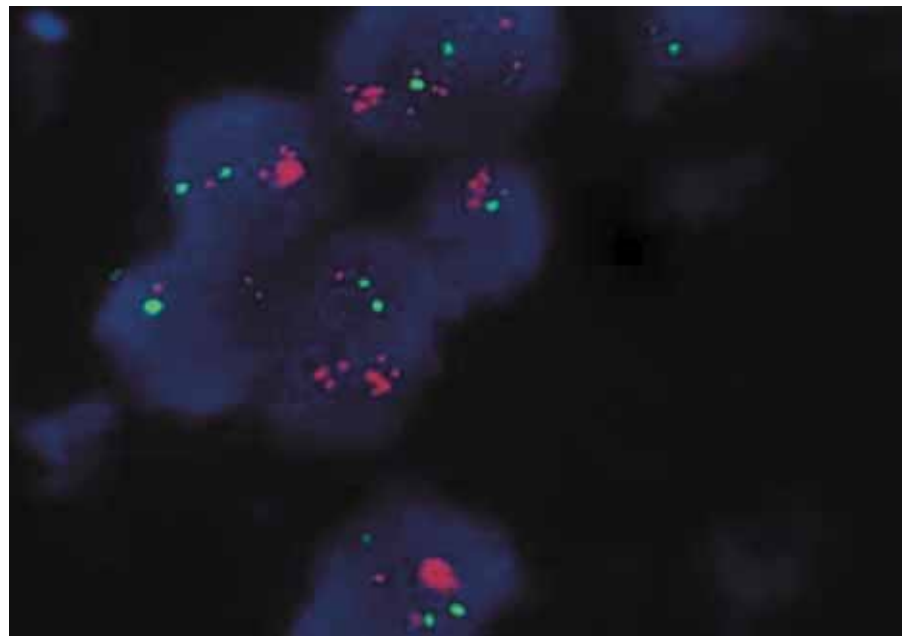
and TNM gives valuable information on several of these. “Everyone in oncology in the world uses the extent of the disease as the main part of their prognostic design,” said Gospodarowicz. “Even in breast cancer, if you have a small cancer, with no lymph node involvement and no metastasis, you know that the patient may not need to have chemotherapy or radiotherapy. On the other hand, if the tumour has spread then you know that the patient does need more treatment.”

The aims of the TNM staging system, she argued, were to aid the clinician in planning treatment, to give some indication of prognosis, to assist in the evaluation of the results of the treatment, to facilitate the exchange of information between treatment centres and to contribute to the continuing investigation of human cancer.

“Other prognostic markers should be used
in addition to, not instead of, TNM”



Partial pictures. Proponents of TNM say it is simple, provides vital epidemiological information, and requires relatively low-tech imaging techniques, such as bone scan (above). Opponents argue that information on molecular biology, such as HER2 status as revealed by the FISH test (right), should be at the heart of any modern staging system



Because TNM had been running as a uniform system for more than 50 years, it was now possible to track changes in cancers over a long period of time, even though some details of staging classification had altered to keep track with developments (Burke disputes this). This, said Gospodarowicz, made it possible to conduct epidemiology studies, investigate the natural history of cancer, and share information from clinical trials.

“Cancer registries need a system that provides a framework for recording and considering all cancers. They need the uniformity provided by TNM,” she said.

TNM is subject to a process of continuous review and improvement by several groups of experts around

the world. Gospodarowicz believes that this system is capable of responding to the challenges that TNM faces in the 21st century.

“TNM provides a common language for classifying cancer so that people know what they are talking about. There would be total chaos if everyone used different methods for describing different cancers,” she said.

Lars Holmberg, Professor of Clinical Cancer Epidemiology at the Regional Oncologic Centre in Uppsala, Sweden, also spoke in favour of TNM at the EBCC-5 debate.

“TNM needs to be maintained for epidemiological cancer surveillance,” he told *CancerWorld*. “It is important to know how many people have localised cancer, cancer with

regional metastases and cancer with distant metastases. World-wide it has large public health implications. In many parts of the developing world, cancer is becoming the most important disease, once other causes of death such as starvation, infections, malaria and tuberculosis have been dealt with. It’s very important to have the TNM system to record and classify the cancer burden here.

“There’s the issue of public health planning. TNM is an indicator of the scale of resources that countries will need for cancer treatment, because if you have a large proportion of patients diagnosed when they have distant metastases, that’s quite different to people diagnosed with local tumours in terms of the resources needed to treat them.

“TNM is simple and affordable. The developed world has a responsibility to keep the system in operation”

“It is a naïve over-estimation of our progress to believe that traditional staging rapidly will be outdated”

“The developing world will not be able to afford modern, elaborate systems of surveillance of cancer epidemiology and cancer management for a long time to come. TNM is simple and affordable. The developed world has a great responsibility towards developing countries to keep the TNM system in operation.”

However, Burke argues that TNM has become extremely complex (for example, the determination of sentinel lymph node involvement) and is itself too complicated for developing countries to use. He mentioned a much simpler system, which predated TNM and is still being used by the US National Cancer Institute, of “local, regional and distant disease spread”, and suggested this would be a better system for developing countries to use, especially where patients might not even be able to have surgery.

Holmberg said: “TNM reflects tumour-host balance and tumour burden, none of which is well captured by known biological tumour markers. The cancer burden in one patient is still biologically important and relevant. The surgeon has to know what size a tumour is and whether there is lymph node involvement.

“It is a naïve over-estimation of our progress to believe that traditional staging rapidly will be outdated. Lymph node status is still the major prognostic divider. Even if another system is developed, we still could not abandon TNM.”

Although molecular biomarkers are being developed for cancers such as breast, prostate and testicular cancer, there are many other cancers with no known biomarkers as yet. “Breast cancer has been at the forefront for many years in terms of biological markers. But if you look at lung cancer, bowel cancer and gastric cancer for instance, it’s more obvious that TNM is still needed,” said Holmberg.

While he conceded that there was some validity in the argument that increasingly tumours were being detected earlier, at stage I, and that this consequently affected prognosis, he pointed out that this was far from the norm. “This is a correct argument when we get to the stage where everyone has a small localised tumour, but we are not even there in breast cancer. We still need to know in different countries how many people have what stage of tumour, and there are still many countries, even in Europe, such as Eastern Europe, Turkey, Croatia, where a significant proportion of patients have distant metastases.

“When you look at sophisticated markers that show how a tumour will progress, the actual anatomic burden in one patient at the time of diagnosis is reflecting something of the biology. You need to know the tumour burden to know how much the disease has over-powered the patient, as well as a number of other factors, and TNM reflects this.”

Medicine tends to be a conservative field and there is always resistance to change. While this can be

good in that it reduces the risk of fads and transient phenomena, it can stand in the way of progress. The crux of the debate at EBCC-5 was: do we determine prognosis and therapy based on the biology of the disease or do we remain with the anatomic extent-of-disease system, perhaps with some adaptations? In the event, the chair, Aron Goldhirsch, declared the vote to be split down the middle. There is no doubt that the debate will continue, which is good for science and for patients.

Further reading, listed by date of publication

- HB Burke, DE Henson (1993) Criteria for prognostic factors and for an enhanced prognostic system. *Cancer* 72:3131–35
- FL Greene, LH Sobin (2002) The TNM system: our language for cancer care. *J Surg Oncol* 80:119–120
- J Benson (2003) Overview of the TNM system. *Lancet Oncology* 4:56–57
- I Mittra (2003) Failure of the TNM System. *Lancet Oncology* 4:59
- HB Burke (2004) Outcome prediction and the future of the TNM staging system. *J Natl Cancer Inst* 96:1408–09
- MK Gospodarowicz, D Miller, et al (2004) The process for continuous improvement of the TNM classification. *Cancer* 100:1–5
- JB O’Connell, MA Maggard, CY Ko (2004) Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst* 96:1420–25
- SB Edge, LH Sobin, DL Page, MK Gospodarowicz, FL Greene, DP Winchester (2005) Re: Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst* 97:463–464
- HB Burke (2005) Re: Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst* 97:464–465
- S-Y Jeong, DB Chessin, D Schrag, WD Riedel, JG Guillem (2005) Re: Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst* 97:1705–06
- HB Burke (2005) Re: Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst* 97:1707
- D Weaver (2005) Benefits of the revised TNM system. *Lancet Oncology* 4:57–58
- U Veronesi, G Viale, N Rotmensz, A Goldhirsch (2006) Rethinking TNM: Breast cancer TNM classification for treatment decision-making and research. *The Breast* 15:3–8

The Moscow smokebuster

→ Peter McIntyre

There are smokers in Russia alive today thanks to **David Zaridze** and the lead he took in halving tar levels 20 years ago. He has a long history in cancer prevention, but believes the biggest gains may lie in early detection. Will the country that discovered the first liver cancer marker give the world the first proteomic marker for lung cancer?

Lung cancer deaths have been in decline in Russia since the mid 1990s, which is perhaps surprising given that 35 million Russians smoke and show few signs of giving up the habit (70% of young men and 25–30% of young women are current smokers).

Mortality from all cancers in Russia is still higher than in the US and other Western countries. Lung cancer deaths in Russian men are a third higher than in Western Europe.

Yet after rising steadily between 1965 and the early 1990s, the age-standardised death rates from lung cancer levelled out and then began to fall. David Zaridze, Deputy Director of the N N Blokhin Cancer Research Centre in Moscow and Director of the Institute of Carcinogenesis, traces the turning point to the first meeting on smoking prevention in what was then the Soviet Union, in 1985.

Zaridze organised the meeting in conjunction with the International Agency for Research on Cancer (IARC) and the renowned Oxford University epidemiologists Richard Doll and Richard Peto. The meeting was attended by influ-

ential Russian doctors and senior officials from the Ministry of Public Health and other agencies.

Behind the scenes, there was a dispute. Zaridze and Peto both saw the high levels of tar in Russian cigarettes as being the priority. Lorenzo Tomatis, then director of IARC, believed that this should be secondary to a “stop smoking” message.

The Moscow–Oxford alliance held. The conference adopted a resolution which said: “although elimination of tobacco consumption should be the final goal, an upper limit such as, perhaps, 15 mg, on cigarette tar deliveries should be introduced as quickly as possible.”

Zaridze believes that was right. “At that time Soviet cigarettes had tar levels of 30 plus, so this was a proposal to reduce the tar levels by half. We have seen since the middle of the 1990s a reduction in the incidence and mortality of lung cancer. The only explanation of this decline is that measure we took in the middle of the 1980s, because smoking levels in Russia have not changed.”

The Soviet Union introduced tobacco regulations within three years of the meeting. Since the state had a monopoly on cigarette production,



putting it into effect was easy. The reduction in lung cancer mortality will continue for many years because of the effect on lifetime smokers. More recently, the International Cigarette Variation Group compared packets of Camel, Lucky Strike, and Marlboro cigarettes purchased in 29 countries. The cigarettes were analysed in Moscow where they found similar amounts of tar and nicotine, but great variations in the amounts of two nitrosamines, NNK and NNN, carcinogens which are probably responsible for the increase in adenocarcinoma of the lung.

Zaridze has written to the chief physician at the Ministry of Public Health to call for regulations to reduce the level of these carcinogens in cigarettes on the market. But he recognises that in the market economy of modern Russia, this time there will be a fight with the tobacco companies.

“The high content of nitrosamines in these tobaccos has different causes, but the tobacco companies don’t care and they don’t want to invest.”

Some campaigners fear that if cigarettes become “safer” that will dilute the “stop smoking” message. Zaridze does not see these policies as mutually exclusive. “The main slogan of anti-smoking campaigners, myself included, is that there are no safe cigarettes. Safe cigarettes don’t exist and never will be produced. But if we can make cigarettes less carcinogenic, less harmful, less noxious, we have to do this.”

Zaridze does not seem perturbed at the prospect of having to take on the tobacco companies while keeping anti-tobacco campaigners united. In the course of his career, he has promoted public health within a variety of political systems and social policies, while keeping strong international contacts. He has learned to respect the data, rather than the current orthodoxy.

In 1969, Zaridze was accepted as a postgraduate fellow in pathology at what was then the Institute of Experimental and Clinical Oncology, headed by Nicolai Krayevsky. As chief pathologist of the Soviet Army during World War 2, Krayevsky had been responsible for identifying the remains of Hitler and Eva Braun in Berlin. Zaridze says he was “a very nice man and a first class pathologist”.

And this was what Zaridze himself wanted to be. Over the next decade, he carried out hundreds of autopsies and biopsies on all kinds of tumours, with a special interest in thyroid cancers and morphological peculiarities. This hands-on approach, examining tumours

“Safe cigarettes don’t exist. But if we can make cigarettes less carcinogenic, we have to do this”



PETER MCINTYRE

Lighting up. Zaridze and his assistant Olga Gorbacheva at the tobacco smoke analysis kit in the Institute of Carcinogenesis in Moscow. This machine can 'smoke' 20 cigarettes at once – and it doesn't like what it finds in any of them

physically, gave Zaridze a grounding. “Knowledge of the body is essential and I had ten years of very valuable experience. I do not want to insult modern pathologists, but in recent years there are fewer and fewer autopsies. And some molecular biologists for example have no idea what happens above molecular level.”

Nikolai Blokhin, a former wartime surgeon and a leading traumatologist, became the first Director of the Cancer Research Centre in Moscow. “He was really a brilliant personality. The cancer institute was just a hospital before he took over and the research part was really his child, based on his interests. He was interested in basic science, and understood and took part in discussions and arguments in this field. He was fascinated by basic research into cancer and by epidemiology which was a very new, young discipline for chronic disease.”

When Blokhin met Richard Doll – the pioneer on work relating smoking to lung cancer – something clicked. He was determined that his centre would base research and treatment on the best epidemiological evidence. He looked for someone to train in this new art. Of his team,

Zaridze had the best English.

Zaridze went to Oxford in 1977 on a fellowship from IARC. “I joined the department where Richard Doll was Regis Professor. This was a brilliant team. Doll himself, Richard Peto (today Professor of Medical Statistics & Epidemiology at Oxford University), and his brother Julian Peto (now Cancer Research UK Chair of Epidemiology) and many other brilliant people.”

He was only in Oxford for 10 months but his collaboration and friendship with Doll and Richard Peto has been lifelong. After a crash-course in epidemiology and statistics at the London School of

Hygiene and Tropical Medicine, Zaridze was appointed to work at IARC in Lyon.

For six years, he headed the group on diet and cancer. He also worked on colorectal and prostate cancer. In the early 1980s Zaridze and Peter Boyle (now Director of IARC) published the first paper that explained the rise in incidence of prostate cancer in the US.

“Today, what we said is commonplace. PSA screening was discovering a lot of indolent carcinomas which, thank god, the urologists have now understood should be followed, not treated. Urologists in the United States pushed this test into the screening programmes without testing it as an instrument for screening. It was misused.”

In 1985, Blokhin invited Zaridze back to Moscow to head the unit of epidemiology, a small group who did not then even have a computer.

One of his early efforts was on diet and cancer. It was becoming obvious that diets rich in green vegetables are protective against cancer. Zaridze had been instrumental in setting up an intervention trial in Uzbekistan, where a study group was encouraged to take vitamin supplements in the form of pills – beta-carotene for vitamin A, riboflavin (vitamin B2) and vitamin E. However, the results were disappointing, as were trials in other parts of the world. Vitamin supplements appear to offer no protection.

“Empirically we could see the beneficial

“The day was devoted to visiting the barricades in Moscow, and we worked at night-time”

effects of beta-carotene, vitamins B, C & E and ascorbic acid, but we do not know their complex interactions. Twenty years ago, we were sure about the story of diet and cancer; we knew more then than we know now! Today, we know the beneficial role of a diet low in calories and high in fruit and vegetables, but it is a complex interaction.”

By the time Zaridze returned to Russia, Gorbachev was President and social and political life was beginning to loosen up. However, a party apparatchik from the central committee was still in charge of the Institute of Carcinogenesis.

Zaridze says: “People started to say what they thought and they were fed up with this guy. Finally, he was sacked. Then the staff met and everybody voted – not a scientific council but all 350 people who worked here. I was probably the first and the last director of a research institute who was elected by popular vote.”

Zaridze was a member of the executive board of the Organization of European Cancer Institutes, and he helped its chairman, Walter Bodmer, to plan a meeting in Moscow on Cancer Prevention in Central and Eastern Europe. The date was set for 2 September, 1991. On 19 August, a group calling itself the State Emergency Committee launched a coup, holding Gorbachev in the Crimea and surrounding the Parliament with tanks.

Zaridze recalls how nervous they all felt that the old guard would return. His staff took their photocopiers and paper to the Parliament, so that the anti-coup forces could print out their own leaflets and orders. After a week, the coup collapsed and Gorbachev was back, although now Yeltsin was effectively in power.

Despite the crisis, Zaridze decided to go ahead with the meeting, warning those coming that they had better bring their own paper. “We had a beautiful meeting here – a historic meeting. Everybody arrived with a pack of paper. The day was devoted to visiting the barricades in Moscow,

and we worked at night-time. I have a lot of memories of this meeting because people who were coming from the West were delighted to visit barricades in central Moscow.”

The economic crisis in the former Soviet Union coincided with a fall in life expectancy. From 1991 to 1995, premature mortality rose steadily. In 1998 a further economic crisis saw the death rate climb again.

Zaridze and his colleagues worked on a hypothesis that the high background mortality rate in Russia was mainly to do with smoking, while fluctuations in the 1990s were mainly to do with high levels of alcohol consumption.

At the close of the decade the Institute of Carcinogenesis in cooperation with Oxford University and IARC set up a huge two-part study in three Russian cities – Tomsk, Barnaul and Novgorod – a retrospective mortality study and a longitudinal study, following the lifestyle and health status of 200,000 healthy people.

Results from the mortality study are not yet published, but will show a much greater than expected role of alcohol. In Barnaul, researchers examined records of 25,000 forensic autopsies carried out on those who died outside hospital or the home. They found that an incredibly high proportion of men had high levels of alcohol in their blood.

“About 20% of those people who had a post-mortem diagnosis of cardiovascular disease in fact died from alcohol poisoning. Russia in general is a very heavy drinking country and all negative situations are washed down by vodka. There is also a lot of spirit that people make themselves. With the fake product on the market, even lower levels of alcohol may be lethal.”

Alcohol and smoking together multiply the risk of cancers of the pharynx, larynx, oesophagus and stomach. Surveys show an interrelation between habits that can damage the health of young people. A teenager who smokes has a



The famous 1991 meeting in Moscow that took place amidst the barricades. Amongst the audience are (foreground from left), Maurice Tubiana from Paris, Richard Peto from Oxford, IARC editor Elizabeth Heseltine and Rodolfo Saracci, director of epidemiology in Pisa

greater chance of drinking alcohol, taking drugs and becoming involved in crime.

Zaridze believes there should be stronger public policy to alert the public to the dangers of hard drinking and illegal spirits, but policy is currently poorly related to evidence. In April 2006, Russia banned imports of wine from two neighbouring republics, Georgia and Moldavia, with whom it is having political disputes, on “health grounds”. No action was taken against home-brewed vodka.

The Institute of Carcinogenesis is responsible for basic research as well as population-based studies. Its current focus is on the need for early detection of lung cancer.

Zaridze points out that even countries with screening programmes really only succeed in preventing cervical cancer, while mammography prevents only 25% – 30% of deaths in the screening group. He believes they can do better and that the most urgent need is for early

detection of lung cancer.

“Screening means that you discover the disease before symptoms, before clinical manifestation of cancer. Lung cancer is different because people who smoke have a lot of problems like coughing, bronchitis, emphysema and so on. We need early biological markers that can help us to detect disease at an early stage, because disease detected at early stage is curable.”

“I am working for the development of highly sensitive and highly specific cancer markers. We have collected a huge database, epidemiological database and blood serum bank for about 1,000 cases of lung cancer and 1,000 controls. All these cases are very well documented. We know the type of cancer, squamous, adenocarcinoma, small cell and so on.

“Using mass spectrometry, we are looking for proteomic patterns in blood which distinguish the plasma serum of lung cancer patients from the plasma of healthy individuals. When these proteins are discovered and characterised we will produce diagnostic chips that can be used for early detection of lung cancer, and for monitoring, before and after an operation.

“We have seen four or five peaks which distinguish the blood from lung cancer from the blood of healthy people. We don’t know what these proteins are; we have not characterised them yet, but sensitivity is about 96% and specificity is about 94% and this is already quite good. We are going to try to make them more sensitive and more specific, and to identify the proteins.

“The next step will be to test it in epidemiological studies as a screening tool for lung cancer. You screen heavy smokers – those who smoke one

Neither he nor Russian science ever made
a penny out of their discovery

“They started earlier in the US, but they made a lot of mistakes, which we learned from”

pack plus, because you know that in this high-risk group, 17% develop lung cancer in their lifetime.

“We have only a small group interested in proteomic patterns but I don’t think that we are much behind internationally. They started earlier in the US, but they made a lot of mistakes which we learned from.”

Keeping up with cutting edge research is difficult when so much talent is lost.

“A lot of young people go to the US. We lose a terrible amount both in molecular biology and in epidemiology. We just cannot keep the best young people. This is not a question of personal income, but mainly of being able to do something good. When you are young, you have to work and have facilities. I don’t know if I would come back myself, if I were their age.

“Frankly if I did not have a lot of grants from different parts of the world I would not be able to do anything.

“Now, like the Americans, I spend half of my working time writing up grant applications. I hope from next year we will have quite reasonable grants for different bits of research.”

One research gap he would like to plug is to investigate what makes some cancers indolent while others progress rapidly. “That has fascinated me for several years. Prostate cancer is probably the best example, but breast cancer incidence is increasing partly because indolent breast cancers are discovered by mammography. They are probably different. If not discovered on screening, they would not manifest themselves clinically during the person’s life span.”

Perhaps it would help the research programme if Russian researchers could exploit their developments as their US and European counterparts do. But there is no tradition of taking their work to market. The liver cancer marker, alpha-feto protein, was discovered in the Institute of Carcinogenesis by Gary Abelev 35-years ago. Abelev still works at the Institute. Neither he nor

Russian science ever made a penny out of their discovery.

Nor is there a tradition in Russia of those who have made money putting something back into research. Zaridze compares unfavourably the Russian billionaires who made their money by taking over the assets of the old Soviet state, with Bill Gates, whose foundation now funds research all over the world.

As President of the Russian Cancer Society, Zaridze sees how the money trickles in. “Contributions are mainly very small sums offered by old people from their pensions, 10, 20, or 30 roubles – less than US\$ 1. These people feel something and want to do something. They are different from those billionaires.”

In all the changes in Russia there have been gains and losses – wealth for some, poverty for others. Few want to turn back the clock, but some services have been abandoned in a rather shocking manner. The former screening system for cervical cancer (based on check-ups every two years) was cancelled in the early 1990s, since when deaths of young and middle-aged women from cervical cancer have been on the increase.

The role of Zaridze’s institute is partly to provide evidence to help policy makers protect the population – by curbing smoking, reducing alcohol intake and appropriate screening. But Zaridze is frustrated that cancer is still not being given the priority it deserves. AIDS and avian ‘flu, he says, are the subject of intense debate at high-level political meetings, while cancer, which kills 300,000 people a year in Russia, is scarcely mentioned.

“Our duty is to inform people that if cancer is discovered at an early stage you are saved. For example if breast cancer is discovered at an early stage, a small operation is done which is not mutilating. The main message should be that cancer, if discovered at an early stage, is a curable disease.”

Does regular use of aspirin reduce the risk of colorectal cancer?

→ Patrick M Lynch*

Use of at least two standard aspirin weekly, for 10 years or more, reduces colon cancer risk in women. Subject to certain caveats, aspirin should be considered for colon cancer prophylaxis.

The recent update of the Nurses' Health Study (see opposite) provides data on the relationship between aspirin use and colorectal cancer occurrence. In this report, a lower risk of colon cancer was observed in regular aspirin users ($\leq 2 \times$ standard 325 mg tablets per week) than in women who did not regularly use aspirin. Dose and duration of use were important; if a woman consumed 2–5 standard aspirin per week, the RR was modestly reduced, while at higher doses (>14 tablets per week) the risk reduction after 10 years was highly significant ($P < 0.001$). The aspirin protection was limited to the colon and was seen for early-stage (stage I and II) but not for later-stage (stage III and IV) colorectal cancers. Non-aspirin NSAIDs were also associated with dose-dependent cancer risk reduction in the colon, but not in the rectum. No protection was afforded by regular use of paracetamol.

The greatest potential impact on colorectal cancer incidence and mor-

tality so far appears to have come from screening measures, with colonoscopic polypectomy preventing cancer in some individuals undergoing aggressive screening.¹ Economic models have suggested colonoscopy alone to be more cost-effective than most other cancer screening measures, and have found lower efficacy and higher costs for aspirin chemoprevention compared with endoscopic screening, mainly because of the need to treat complications of its use. If aspirin were already in use, for example for cardiovascular protection, then the addition of colonoscopy would yield a life-years saving greater than either measure alone.² The field of colorectal cancer chemoprevention has become very active in recent years, with much interest in NSAIDs, including aspirin.³

A key question is whether the benefit of long-term aspirin, high-dose aspirin, or both warrants recommendation for its use as prophylaxis against colon cancer. Randomised prospective trials utilising aspirin have demonstrated a reduction in

adenoma recurrence in subjects with a previous adenoma or cancer.^{4,5} Interestingly, despite the major differences in endpoints and study design, the magnitude of risk reduction in these studies is very similar to that seen in the study of Chan et al. Taken together, these studies provide a consistent body of evidence in favour of a protective effect of aspirin.

Of course a number of questions remain unanswered. Why is a protective effect not seen in the rectum? Why is there a reduction in early-stage but not later-stage colon cancers? Is at least some of the risk reduction related to bleeding from tumours induced by the anti-platelet effect of aspirin? Is the protective effect of non-aspirin NSAIDs global or are there differences in magnitude of benefit gained depending on which agent is taken? Do we sufficiently understand the biochemical pathways by which aspirin exerts its protective effect? Might further work enable more-effective, less-risky agents or combinations of agents to be developed? Notwithstanding the

*Patrick Lynch is Associate Professor of Medicine at the Department of Gastrointestinal Medicine and Nutrition, the University of Texas MD Anderson Cancer Center, Houston, Texas, USA. This article was first published in *Nature Clinical Practice Oncology* 2006 vol. 3 no. 4, and is reproduced with permission. www.nature.com/clinicalpractice doi:10.1038/ncponc0459, ©2006 Nature Publishing Group

need for further study, it must be concluded that aspirin reduces risk of incident and recurrent colon neoplasia. Whether the individual clinicians are willing to prescribe aspirin prophylactically will depend on whether they believe, in the absence of a specific indication from the FDA, that such use is warranted, and on the potential cardiovascular risks and benefits for the individual. Subjects prescribed aspirin prophylaxis would have to be monitored carefully for other adverse events, especially gastrointestinal

bleeding, and appropriate colorectal cancer screening examinations should still be performed. This study, although not really designed to rigorously address such matters, did not show any substantial excess in bleeds among the long-term or high-dose aspirin users.

References

1. SJ Winawer, et al. (1993) Prevention of colorectal cancer by colonoscopic polypectomy: the National Polyp Study Workgroup. *N Engl J Med* 329:1977–1981
2. A Sonnenberg (2002) Cost-effectiveness in the prevention of colorectal cancer. *Gastroenterol Clin North Am* 31:1069–1091
3. E Hawk, et al. (2004) Colorectal cancer chemoprevention – an overview of the science. *Gastroenterology* 126:1423–1447
4. JA Baron, et al. (2003) A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 348:891–899
5. RS Sandler, et al. (2003) A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* 348:883–890

Synopsis

A Chan, E Giovannucci, JA Meyerhardt, et al. (2005) **Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer.** *JAMA* 294:914–923

Background. Regular aspirin use for 1–3 years reduces the risk of recurrent adenoma in patients with a history of colorectal adenoma or cancer, but it is unclear whether aspirin similarly reduces risk of incident colorectal cancer and whether nonsteroidal anti-inflammatory drugs (NSAIDs) have similar anticancer effects in these patients.

Objective. To prospectively examine whether long-term use of aspirin and NSAIDs might prevent the development of colorectal cancer.

Design and intervention. Women participating in the Nurses' Health Study were prospectively studied biennially for medication use from 1980 to 2000, using self-completed questionnaires, the content of which was adjusted with time to reflect changes in lifestyle, diet and medications. The questionnaire included a validated assessment of diet and patterns of use of aspirin and NSAIDs. Participants were requested to record the weekly number of pills taken and the number of years of use. Reports of cancer were confirmed by medical records and by death reports from the National Death Index, and cancer stage was classified according to the sixth edition of the American Joint Committee on Cancer's *Cancer Staging Handbook*. Individuals with a history of inflammatory bowel disease, cancer, familial polyposis syndrome or hereditary non-polyposis colorectal cancer were excluded from analysis.

Outcome measures. Incident colorectal cancer was the primary outcome measure.

Results. During 1,592,017 person-years, there were 962 cases of colorectal cancer among the 82,911 eligible women. After controlling for other potential risk factors, the risk of colon cancer was lower in regular aspirin users (≤ 2 x standard 325 mg tablets per week) than in women who were not regular aspirin users (< 2 standard tablets per week; multivariate relative risk [RR] 0.77; 95% CI 0.67–0.88). A reduction in risk did not occur until at least 5 years of use, and this effect strengthened after 10 years of use (multivariate RR 0.67; 95% CI 0.54–0.85; $P < 0.001$). The effect of aspirin was dose-dependent, with the greatest reduction in risk achieved with cumulative doses of more than 14 standard tablets per week (multivariate RR 0.68; 95% CI 0.49–0.95; $P < 0.001$). The relative risk was modestly reduced in women taking 2–5 standard aspirin tablets per week (RR 0.89; 95% CI 0.73–1.10). A protective effect of aspirin was seen for early-stage cancers (stage I and II; multivariate RR 0.67; 95% CI 0.55–0.82), but not for later-stage colorectal cancers (stage III and IV; multivariate RR 0.86; 0.71–1.05), or for rectal cancers (multivariate RR 0.94, 95% CI 0.72–1.23). Other, non-aspirin NSAIDs were also associated with a dose-dependent risk reduction for colon cancer but not for rectal cancer. Regular use of paracetamol had no protective effect.

Conclusions. Long-term, regular use of aspirin or NSAIDs was associated with a significant reduction in the risk of incident colorectal cancer in an average-risk population.

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

Factors predictive for response of follicular and mantle cell lymphoma to rituximab

→ Michael Pfreundschuh*

A recent analysis of prognostic factors may help identify which follicular and mantle cell lymphoma patients should be excluded from trials of single-agent rituximab therapy.

The major merit of a recent study of Ghielmini et al. (see opposite) is that it provides the first evaluation of prognostic factors emerging after rituximab monotherapy. Moreover, it is reassuring that, while prolonged rituximab therapy results in sustained immune suppression, it does not cause an increased rate of infections. There are, however, considerable problems with the interpretation of the study. The study population included both untreated and pretreated patients, and the current analysis of predictive factors combined the results from two subtrials in follicular lymphoma (FL) and mantle cell lymphoma (MCL).^{1,2} Quite importantly, it is unclear how many patients who really needed therapy were included in the trial.

The results of the univariate analysis of prognostic factors must be interpreted with caution. With 33 factors included in the analysis and with no adjustment made for multiple testing, some factors might have emerged as having prognostic value merely by chance.

These shortcomings might also explain some puzzling results. For example, histology (follicular vs mantle cell) did not emerge as a factor prognostic for event-free survival (EFS). Similarly, it is unclear why a lower baseline lymphocyte count predicted good response, but a higher lymphocyte count after induction therapy was associated with a better EFS. Whether this result is due to the smaller number of patients included in the EFS analysis, or the different processes used for patient selection, remains open to speculation.

For patients with indolent lymphoma, for whom an aggressive treatment would not be suitable, single-agent rituximab might be a valid option. This study shows that rituximab might be particularly worthwhile in patients with a low tumour load and normal blood counts; however, it is exactly this patient population that might as well be followed using a 'wait-and-watch therapy'. Indeed, studies comparing the single-agent rituximab and watch-and-wait treatment strategies in this

favourable subpopulation of patients are ongoing. The prediction score suggested by Ghielmini et al. might be useful for identifying patients who should not be treated with single-agent rituximab, but it does not provide information on how to treat symptom-free patients who have low tumour burden.

While the results obtained with prolonged treatment with rituximab are regarded by the authors as promising, the interpretation of the clinical relevance of the study is difficult. Early treatment with single-agent rituximab aims to delay the time until chemotherapy is required, and possibly to lengthen overall survival time; however, it is unclear whether either of these goals can be achieved by prolonged rituximab treatment. Most importantly, from a clinical point of view, both the previous^{1,2} and current paper on the two subtrials suffer from a relatively short observation time and a lack of data reported regarding overall survival.

*Michael Pfreundschuh is Professor of Internal Medicine at Saarland University Medical School, Homburg, Germany. *Competing interests:* Pfreundschuh is a member of the advisory board for Mabthera (Roche). This article was first published in *Nature Clinical Practice Oncology* 2006 vol. 3 no. 4, and is reproduced with permission. www.nature.com/clinicalpractice doi:10.1038/ncponc0457, ©2006 Nature Publishing Group

In conclusion, while adding rituximab to conventional chemotherapy resulted in a significant increase in remission rates, remission duration and, in some trials,^{3,4} lengthened overall survival, the value of single-

agent rituximab with respect to these endpoints remains to be determined. Currently, the most urgent clinical dilemmas relating to FL are whether we can prolong survival further, and whether we can do so by earlier or

more aggressive treatment, or both? Unfortunately, none of these issues are answered by this paper.

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

Synopsis

M Ghielmini, K Rufibach, G Salles, et al. (2005) **Single agent rituximab in patients with follicular or mantle cell lymphoma: clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: a study of the Swiss Group for Clinical Cancer Research (SAKK)**. *Ann Oncol* 16:1675–1682

Background. Follicular lymphoma (FL) and mantle cell lymphoma (MCL) are generally considered incurable, so treatment is aimed at improving symptoms in most cases. Single-agent rituximab is an option in this setting, because it causes little toxicity and with prolonged treatment produces remissions in some patients. Factors predictive of response of FL and MCL to single-agent rituximab are ill-defined.

Objective. To identify characteristics potentially associated with event-free survival (EFS), response and toxicity of therapy among patients receiving single-agent rituximab for FL or MCL.

Design and intervention. This randomised trial used data from two subtrials, one for FL patients and one for MCL. Between January 1998 and January 2002, 29 institutions enrolled adult patients for induction therapy with rituximab for 4 weeks (375 mg/m² weekly). Patients who had partial or complete response or stable disease at week 12 were randomised to no further treatment (standard treatment) or treatment with infusions of rituximab (375 mg/m²) at week 12 and months 5, 7 and 9 (prolonged treatment).

Outcome measures. Factors predictive of response rate and EFS were identified using preliminary univariate analyses (logistic regression for response and Cox regression for EFS), followed by a stepwise regression and multivariate analysis without adjustment for multiple testing. A scoring system to predict benefit of therapy was constructed and tested.

Results. At a median follow-up of 4.5 years, patients who received maintenance rituximab therapy had a significantly longer EFS than those who received no further treatment (17.9 months vs 11.2 months; $P=0.005$). Independent predictive factors for response were disease bulk <5 cm, follicular histology, normal haemoglobin and low lymphocyte count. Factors predicting prolonged EFS were response to induction therapy, a maximum of one previous cycle of chemotherapy, Ann Arbor stage* I–III, high lymphocyte count, disease bulk <5 cm, Fc γ receptor genotype VV and prolonged rituximab treatment. Using a prediction score constructed on the basis of MCL histology, bulky disease, previous chemotherapy and low haemoglobin, patients could be divided into groups expected to experience high, intermediate and low benefit of therapy, according to the number of predictive factors they presented with (0–1, 2–3 and 4–5, respectively). Median levels of circulating B lymphocytes were reduced to 20% of baseline during treatment ($P<0.0001$), but their numbers partially recovered after a median of 12 and 18 months following standard and prolonged treatment, respectively. More prolonged suppression of serum IgM occurred with extended as opposed to standard rituximab treatment. Incidences of adverse effects were similar in the two arms of the study. Serious adverse events considered to be related to rituximab included 13 infections, six cardiac events and five intestinal complications. There were seven deaths due to adverse events, consisting of four cardiac, two infectious and one intestinal event.

Conclusions. Clinical baseline characteristics that predicted response to single-agent rituximab therapy in FL and MCL were defined.

Acknowledgement: The synopsis was written by Michael Pfreundschuh, Professor of Internal Medicine at Saarland University Medical School, Homburg, Germany

* Classification of lymphoma into four stages based on the involvement of anatomic groups of lymph nodes; stage I indicates localised nodal involvement and stage IV indicates disseminated disease

NEWS ROUND

Selected press reports compiled by the ESO Cancer Media Centre

New surgical technique for malignant glioma

→ **Lancet Oncology**

A novel technique that uses a fluorescent marker to guide surgery in malignant gliomas has been shown to enable surgeons to remove more of the tumour and improve progression-free survival.

Malignant gliomas have a poor prognosis. This may be because surgeons often have difficulty in seeing exactly where the tumour stops and healthy tissue starts, making complete removal difficult. Numerous new techniques have been developed to try and solve this problem; however, they have not fulfilled expectations – frameless stereotaxy (image-guided surgery) is too expensive and intraoperative MRI is too cumbersome to use in every case.

Researchers from the ALA-Glioma Study Group investigated a new way to detect the tumours during surgery, by using a drug called 5-aminolevulinic acid, which causes fluorescent compounds to accumulate in cancerous tissue. The tumour can then be seen with a modified microscope during neurosurgery, in a simple, economical procedure.

The study compared two groups of patients; one group was operated on with fluorescence-guided surgery and the other group received the usual surgical procedure under white light. They found that after a median follow-up of 35.4 months, the percentage of patients who had their

tumours removed completely was higher in the group that received fluorescence-guided surgery than in those who received usual surgery (65% vs 36%).

In the fluorescence-guided surgery group, more people survived to 6 months without progression of their tumour (41% vs 21%). Furthermore, there was no difference in serious side-effects between the groups.

"This technique is an advance over older, traditional methods, because it is simple, cheap, can be performed in real-time, and has now been put to a truly prospective test," claims coordinating investigator Walter Stummer.

In an accompanying article, Fred Barker, of the Massachusetts General Hospital, Boston, USA, welcomed the trial, but added that, "this study alone cannot definitively establish that the more extensive removal, and not some other unanticipated effect of the drug, led to the improved clinical results."

Although the drug is not yet available commercially worldwide, he concludes that the trial is likely to "encourage surgeons in pressing for more complete resections of malignant gliomas using the various technological adjuncts that have become widespread over the last 10-15 years, such as intraoperative MRI and frameless image-guided surgery."

■ Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. W Stummer, U Pichlmeie, T Meinel, et al for the ALA-Glioma Study Group. *Lancet Oncology* 7: 392–401, published online 13 April

Alcohol blamed for a large part of cancer deaths

→ **International Journal of Cancer**

New research carried out by the International Agency for Research on Cancer (IARC), based in Lyon, France, shows that alcohol-related cancers are responsible for around 1 in 30 cancer deaths worldwide each year.

The researchers analysed data from 2002 on the prevalence of drinkers obtained from the World Health Organization Global Burden of Disease. The information based on relative risks of cancers of the oral cavity, pharynx, oesophagus, liver, colon, rectum, larynx and female breast was examined and the researchers estimated the number of cancer cases and deaths attributable to alcohol drinking.

The study found that, worldwide, almost 390,000 cases of cancer are attributable to alcohol drinking, this represents almost 4% of all cancers. Among women, breast cancer appeared to make up 60% of alcohol-attributable cancers.

The authors cautioned that the estimates were based on simplified assumptions; however, they highlight the need for alcohol-associated cancer to be taken seriously, and raise questions about whether public health recommendations on alcohol drinking need to be reviewed.

■ The burden of cancer attributable to alcohol drinking. P Boffetta, M Hashibe, C La Vecchia, et al. *Int J Cancer*, published online 23 March, doi: 10.1002/ijc.21903

New hand-held device to detect oral cancers

→ Journal of Biomedical Optics

A new, simple, hand-held device may help dentists detect high-risk precancerous and early cancerous lesions by shining a light that causes fluorescence in oral tissue.

Tumours developing in the mouth are often easily visible; however, determining whether a sore is benign or potentially cancerous has remained scientifically problematic. Early identification of high-risk disease could greatly reduce both mortality and morbidity due to oral cancer. This new device can help dentists tell whether a lesion is likely to become cancerous and thus avoid needless biopsies. Oral cancers are particularly prevalent in India, where the technology to perform biopsies is expensive and impractical in rural villages.

The Visually Enhanced Lesion Scope (VELScope), which was developed with support from the National Institute of Dental and Craniofacial Research, emits a cone of blue light into the mouth that excites various molecules within the cells, causing them to absorb the light energy and re-emit it as visible fluorescence.

Changes in the natural fluorescence of healthy tissue are generally caused by light-scattering biochemical or structural changes indicative of developing tumour cells. The VELScope allows dentists to shine a light onto a suspicious sore in the mouth and watch directly for changes in colour through an attached eye piece. Normal oral tissue emits a pale green fluorescence, while potentially early tumour, or dysplastic, cells appear dark green to black.

The device was tested in 44 people, and in 43 of them it was found to distinguish correctly between normal and abnormal tissue, classified on the basis of biopsy and standard pathology.

"The natural fluorescence of the mouth is invisible to the naked eye," said Miriam

Rosin, a senior author on the paper. The VELScope literally brings this natural fluorescence to light, helping dentists to answer in a more informed way a common question in daily practices: To biopsy or not to biopsy."

Rosin said her group is now engaged in a larger follow-up study in Vancouver that will further evaluate the VELScope. "Laboratories are developing similar devices to detect lung and cervical cancer," said Rosin. "That means that the same basic technology is now being used to evaluate three tumour sites, and we can begin hopefully to pool our data and fine-tune the characteristics and meaning of the changes in fluorescence."

■ Simple device for the direct visualization of oral-cavity tissue fluorescence. PM Lane, T Gilhuly, P Whitehead, et al. *J Biomed Optics* 10 April, 11:024006

Children need more information to deal with cancer in the family

→ British Medical Journal

Children whose mothers have been recently diagnosed with breast cancer need more age-appropriate information about the disease to cope better, according to a recently published study. More than a quarter of women in the Western world will have children living at home when they are diagnosed with breast cancer. It is important for a child's psychological wellbeing to understand their mother's diagnosis and treatment.

British researchers separately interviewed 37 mothers and 31 of their children aged between 6 and 18 years to find out about their attitudes to the mother's recent breast cancer diagnosis. The study found that parents may underestimate their children's needs for information in order to

protect them. Evidence from paediatric cancer shows that giving children appropriate information about diagnosis and treatment reduces anxiety. The more children are prepared and informed, as appropriate for their age and development, the more it seems to help them cope.

Even before their mother's diagnosis, children from seven years old were more aware of the life-threatening nature of cancer than their parents and other adults realised. Talking about cancer and death may help relieve children's apprehension. Children had sometimes picked up skewed information about cancer through the media, including TV adverts and soap operas. For example, many children linked smoking to all kinds of cancers, including breast cancer, and were troubled when family members continued to smoke.

Many of the children said they were unprepared for the consequences of their mother's treatment – particularly the side-effects of chemotherapy, such as the loss of their mother's hair, and the length of treatment. Visits after surgery were also an area of anxiety.

Children were unprepared for their mother's drowsiness, the number of tubes around the bed and even the blood on the sheets and in the drainage tubes. Children who had visited their mothers before the operation in hospital and then at least two days after the operation seemed to cope better with visiting times.

Some of the older children expressed a desire to talk to a health professional so that they could learn more about their mother's disease, and a few also expressed a desire to talk to their mother's doctor. Older children wanted a list of websites to look at for more information.

The study recommends that parents with newly diagnosed cancer need to be supported to think about how they will talk to their children. Some families may need their doctor and nurses to take part in the discussions with the children. Families should be routinely offered age-appropriate

information, and more literature needs to be developed for younger children.

■ Breast cancer in the family – children's perceptions of their mother's cancer and its initial treatment: qualitative study. G Forrest, C Plumb, S Ziebland. *BMJ* 29 April, 332:998–1003

Potential new target to prevent metastasis

→ Nature

Researchers from Stanford University School of Medicine, USA, have identified a protein vital for the spread of cancer from one part of the body to another. The research may help scientists develop new targeted anti-cancer drugs.

Most deaths from cancer occur from metastasis. Scientists have been trying to find out what makes cancer cells spread to help develop targets for anti-cancer therapies.

Cancerous tumours contain areas low in oxygen. This seems to make the cells particularly prone to metastatic growth, although scientists are unsure why. The new research shows that the enzyme lysyl oxidase (LOX) is produced at high levels in oxygen-starved human breast, head and neck tumours.

They found that patients with tumours producing high levels of LOX are more likely to suffer metastases and tend to have poorer survival.

The research demonstrated that LOX promoted the spread of cancer cells by helping cells invade new tissue. In a mouse model, it was also found that inhibiting the LOX enzyme blocked the spread of breast cancer. Further research is needed to see whether inhibiting the LOX enzyme in humans would prevent the spread of cancer cells.

■ Lysyl oxidase is essential for hypoxia-induced metastasis. JT Erler, KL Bennewith, M Nicolau, et al. *Nature* 27 April, 440:1222

EMA gives positive opinion for Herceptin

→ European Medicines Agency

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has given a positive opinion to extending the use of Herceptin (trastuzumab) to include adjuvant treatment of early breast cancer (invasive, non-metastatic) over-expressing HER2 following surgery, chemotherapy (neo-adjuvant or adjuvant) and radiotherapy (if applicable).

This was the first accelerated assessment by EMA under new EU legislation introduced in November 2005. The application was submitted in February 2006 and a decision made at the end of April. Also for the first time, EMA supplied a separate question-and-answer document relating to the extension of Herceptin's indication.

Manufacturers Roche will be asked to perform further studies on the long-term effects of treatment with the product, particularly its cardiovascular risk. Efforts will also be made to identify patients at higher risk of cardiotoxicity and define monitoring requirements. A final decision on extending Herceptin's indication now has to be made by the European Commission. Normally this takes a further 1–2 months.

Other decisions of the CHMP include a positive opinion on Bayer Healthcare's Nexavar (sorafenib tosylate) for the treatment of advanced renal cell cancer in patients who have failed to respond to prior interferon- α or interleukin-2 based therapy or are considered unsuitable for such therapy. The CHMP also adopted the first positive opinion on the granting of a conditional marketing authorisation under new EU rules on conditional approvals that came into force at the beginning of April 2006. It recommended that Pfizer's Sutent (sunitinib malate) should be approved for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumours

(GIST) after failure of imatinib mesylate treatment due to resistance or intolerance, and for advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon- α or interleukin-2 therapy. A marketing authorisation under conditional approval means that further evidence on the medicinal product is awaited. In the case of Sutent, this relates to the product's effect in terms of progression-free survival in patients with MRCC, for which a study is being conducted. EMA will review new information within one year and update the product information as necessary. The European Commission will now consider these recommendations and should make a decision on the marketing authorisation of both products within two months.

Stopping chemo early halves survival time in colon cancer

→ Journal of Clinical Oncology

New research from Columbia University Medical Center in New York has found that as many as 30% of patients with stage III colon cancer who were prescribed six months of chemotherapy with a combination of 5-fluorouracil and leucovorin stop their treatment prematurely. Early termination of chemotherapy for colon cancer was shown to be equivalent to receiving no treatment at all. The findings add to the arsenal of reasons why colon cancer patients, and all cancer patients, need to complete their chemotherapy regimens whenever possible.

Previous studies have shown that not completing chemotherapy regimens for breast cancer is associated with shorter survival. This is the first study to look at a link between mortality rates from colon cancer and treatment adherence.

"The intuitive thinking is that if you complete most of a treatment regimen, you should get most of the treatment benefit. But these findings are significant because

they indicate that completing treatment is as critical for colon cancer as it is for breast cancer – and we need to do better to ensure that patients who can, complete treatment as intended," said Alfred Neugut, one of the leaders of the study.

The research team used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to identify stage III colon cancer patients who were at least 65 years of age or older, and who received between one and seven months of fluorouracil-based adjuvant chemotherapy treatment.

Among the 1,579 patients who survived eight months or longer, the 1,091 (69.1%) who underwent five to seven months of treatment survived nearly twice as long as the 488 (30.9%) who received only one to four months of treatment. Patients who were older, unmarried and had co-morbid conditions, were more likely to receive less than five months of treatment.

■ Duration of adjuvant chemotherapy for colon cancer and survival among the elderly. Al Neugut, M Matasar, X Wang. *J Clin Oncol*, published online 17 April, doi: 10.1200/JCO.2005.04.5005

Some melanoma patients at risk of additional tumour within two years

→ Archives of Dermatology

Approximately 8% of patients with melanoma may develop an additional melanoma within two years of their initial diagnosis, and those with atypical moles appear to be at higher risk, according to a recent study.

Cutaneous (skin) melanoma begins in cells known as melanocytes, which produce the pigment that gives skin its colour. Previous studies have evaluated the recurrence of melanoma among patients already diagnosed with the disease; most have estimated that less than 4% of them will develop additional tumours in the year following diagnosis.

Linda Titus-Ernstoff, of the Dartmouth Medical School, New Hampshire, USA, and colleagues, assessed the frequency of and risk factors for recurring cancer among 354 New Hampshire residents with a first diagnosis of cutaneous melanoma. Participants completed a 40-minute telephone interview, during which they answered questions about medical history, demographics, eye and hair colour, sun exposure and whether their skin tanned, burned or freckled in the sun.

They then underwent a skin examination, during which a physician identified and catalogued benign and atypical moles. Atypical moles have at least three of the following features: a diameter larger than 5 mm, redness, an irregular or ill-defined border, a variety of colours or a portion that is flat.

By examining pathology records, the researchers found that 20 (6%) of the participants developed an additional melanoma within one year of diagnosis and 27 (8%) developed an additional melanoma within two years. Sixty-three percent of those who developed additional tumours and 37% of those who did not had at least one atypical mole. The more atypical moles an individual had, the more likely he or she was to develop additional melanomas – three or more atypical moles indicated four times the risk. Lifetime history of sun exposure did not appear to influence the risk of recurring melanoma.

"The importance of studying risk for additional primary tumours within a defined population-based study group is underscored by our findings," they conclude. "These findings, which indicate a higher frequency of second primary melanomas than suggested by previous studies, also underscore the importance of close surveillance of patients with melanoma."

■ Multiple primary melanoma: two-year results from a population-based study. L Titus-Ernstoff, AE Perry, SK Spencer, et al. *Arch Dermatol*, April 2006, 142:433–438

WHO announces new standards for clinical trial registration

→ World Health Organization

The World Health Organization (WHO) is urging research institutions and companies to register all clinical trials, including phase I trials, whether they involve patients or healthy volunteers. As part of the International Clinical Trials Registry Platform, a major initiative aimed at standardising the way information on medical studies is made available to the public, WHO is also recommending that 20 key details be disclosed at the time studies are begun.

Before making the recommendations, the Registry Platform initiative consulted with all concerned stakeholders, including representatives from the pharmaceutical, biotechnology and device industries, patient and consumer groups, governments, medical journal editors, ethics committees, and academia over a period of nearly two years.

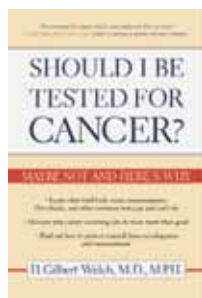
Currently, there are several hundred registers of clinical trials around the world. The planned Registry Platform will not be a register itself, but rather will provide a set of standards for all registers. It has not only standardised what must be reported to register a trial but is creating a global trial identification system that will confer a unique reference number on every qualified trial.

"Registration of all clinical trials and full disclosure of key information at the time of registration are fundamental to ensuring transparency in medical research and fulfilling ethical responsibilities to patients and study participants," said Timothy Evans, Assistant Director-General of the WHO.

Later this year, the WHO Registry Platform will launch a web-based search portal where scientists, patients, doctors and anyone else who is interested can search among participating registers for clinical trials taking place or completed throughout the world.

To screen or not to screen?

→ Raphaël Brenner



Screening healthy people for cancer is a double-edged sword: while tests may help, disadvantages can often outweigh the benefits. Eminent physician Gilbert Welch argues forcibly for a less test-oriented, more human approach.

Conventional wisdom about cancer screening is that all screening is good. After all, patients and health providers alike have been infused with the notion that the earlier cancer is diagnosed, the better for all. But reality is not so simple, asserts Gilbert Welch, professor of Community and Family Medicine at Dartmouth Medical School in New Hampshire, USA. In his thought-provoking book, Welch urges caution on the matter and contends that forgoing cancer screening can sometimes be a reasonable option. Screening, that is, testing asymptomatic people at regular intervals, is now a well-established practice in the field of cancer prevention. Mammograms, blood tests for PSA (prostate specific antigen) and faecal occult blood testing (for colon cancer) are among the most frequently given tests. However, as Welch points out, cancers that grow fast (interval cancers) are the type of cancers which tests are most likely to miss, since they appear in between tests. Few randomised trials have been carried out for cancer tests, and when they have, proof of effectiveness was minimal. A detailed analysis of randomised trials comparing groups screened with groups not screened by mammography

or faecal occult blood testing shows only a tiny reduction or none at all in the overall mortality of the screened group. The statistics are also misleading, particularly regarding five-year

Should I be Tested for Cancer? Maybe Not and Here's Why

H. Gilbert Welch

University of California Press, 234 pp, £12.95

Prédisposition génétique aux cancers: questions psychologiques et débats de société

Coordinated by C. Julian-Reynier, J. Pierret and F. Eisinger

John Libbey Eurotext, 128 pp, euro 30

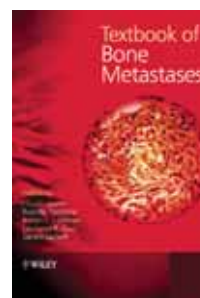
survival rates for cancer screening. In his fascinating chapter on the subject, Welch points out that the apparent improvement in five-year survival rates is often the result of diagnoses being made earlier. What really matter are mortality rates, and these have not improved, at least for some cancers. Welch does not try to dissuade the public from screening for cancer. He acknowledges that tests may greatly benefit a few people, but he objects to “the emerging mindset that patients should be persuaded into undergoing

tests” and to the prevailing “medical correctness” regarding the subject.

For the vast majority of people, even with the most sophisticated screening tests, the benefit is limited, and contrary to the prevailing presumption that “it can’t hurt just to gather a little information”, screening for cancer can be detrimental. Tests are imperfect and the chances of a false-positive result over time are quite high – around 10% for mammograms. False-positive tests and ambiguous results not only cause anxiety for patients, they can also trap them into an endless cycle of testing and potentially risky biopsies.

The truth is that some cancers – collectively referred to as pseudo-disease – do not progress, or progress so slowly that they will never produce symptoms or require treatment. This is the case with certain neuroblastoma, small kidney cancers, small prostate cancers in older men and even, says the author, early forms of breast cancer (ductal carcinoma in situ). For such cancers, watchful waiting, says Welch, can be a reasonable strategy, because “the risks of treatment are greater than the risks of inaction.”

As it happens, screening and pseudo-



Textbook of Bone Metastases

Edited by Claude Jasmin, Robert E. Coleman, Lawrence R. Coia, Rodolfo Capanna and Gérard Saillant
Wiley, 582 pp, £195

Although metastases represent the most serious complication in cancer and most metastatic cancers are considered incurable, quite remarkable progress has been made in the quality of life of cancer patients with bone metastases – and in our understanding of the bone molecular and cellular mechanisms involved in osteogenesis and osteolysis and their development for therapeutic purposes. This fact and the optimism it has generated is the *raison d'être* of the *Textbook of Bone Metastases*, by Claude Jasmin et al, which highlights recent advances in all fields related to bone metastases and provides physicians with the elements needed in the clinical and therapeutic management of patients with bone metastases.

Accordingly, the first part of the book focuses on metastatic disease and covers biology, epidemiology, clinical aspects and assessment of patients. More than two thirds of this part is devoted to the different types of therapy available: surgery, interventional radiology, endocrine treatment, chemotherapy, plus an excellent review of the direct and indirect anti-tumour effects of bisphosphonates.

disease go hand in hand: the harder one looks for cancer, the more one is likely to find it. The problem, as Welch illustrates through numerous case histories and studies, is that “the more we find, the more likely it is that what we find is a pseudodisease. A downside of testing is that you might find a cancer you would rather not know about.”

Beyond establishing concretely that screening is a thorny and complex issue, Welch is to be praised for questioning the ethos of modern medical practice. In what is probably the most provocative chapter in his book, “Understand the Culture of Medicine”, Welch graphically demonstrates to what extent cancer screening is promoted by the medical world: by physicians, (because of their fear of malpractice suits, because of financial incentives, etc.), by the managerial health providers, and by medical researchers who have vested interests in ‘proving’ the effectiveness of new tests. Alas the culture of medicine is also a culture of pride and prejudice: no matter the evidence-based facts, when it comes to cancer screening, there are forces at play that preclude rational discourse on the subject.

Practically, Welch urges patients to develop a healthy scepticism and participate more in decision-making: he urges them to ask questions, particularly whether it is worthwhile undergoing screening. Even if for most people, the most likely outcome of cancer screening will be neither beneficial nor harmful, Welch argues that “it is still important to think about the decision, because not every choice will necessarily be right *for you*.”

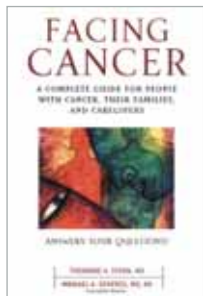
In addition to explaining clearly the pros and cons of cancer screening, Welch has produced an indispensable book that injects good sense and a human dimension into a field of medical decision-making that is dominat-

ed by hype. In daring to question the *doxa* of modern medicine, he has shown that not everything that is possible should be done and not everything that is new is beneficial. All patients intending to undergo specific cancer screening tests should read this book beforehand. So should their physicians, for it will permanently change their views on testing.

Genetic testing for cancer even more dramatically raises the question: “What should one do if a test proves positive?” The problem, as Julian-Reynier and her colleagues point out in their book, is that in the case of BRCA mutations (in breast cancer) as in other mutations, science has outpaced clinical understanding of what to do with the data. Since there are no clear-cut medical recommendations, once a test proves positive, genetic testing simply opens up a Pandora’s box. Nonetheless Julian-Reynier’s book strongly supports genetic testing for high-risk groups. It specifically focuses on the societal, psychological and economic issues connected with genetic testing for breast and ovary cancer susceptibility and stresses the importance of psychological support for patients testing positive. Interestingly, it emerges, from studies on how people at risk deal with the issue when a cancer gene has been identified in a member of their family, that more than 20% choose not to undergo genetic testing, preferring to stay in the dark and live their lives freely.

As for broad-based genetic testing for low-risk groups, given the uncertainty and fear associated with a cancer diagnosis, testing here can be more detrimental than beneficial. The risk, as Welch notes in his book, is that “testing further distracts from the practice of medicine: rather than making sick people well, we end up making well people sick.”

The chapters on the biology of bone metastases are of particular interest. They show that the detection and treatment of micrometastatic disease still represent major challenges in oncology. The second part of the book offers a global approach to the treatment of patients, including management of pain, psychological and social aspects and the special attention needed for treating the elderly and children. A third section covers specific tumours, notably breast and prostate cancer, the two solid tumours which most often give rise to bone metastases.



Facing Cancer: a Complete Guide for People with Cancer, their Families, and Caregivers

Edited by Theodore A. Stern and Mikkael A. Sekeres
McGraw-Hill, 474 pp, \$19.95

I like to be surprised. “Another guide for people with cancer!” I thought as I began to peruse this book, but quickly discovered that my initial assumption was altogether unfounded. The first reassuring fact which sets this book apart is that the two editors consist of an oncologist and a psychiatrist, and roughly half of the 38 co-authors are psychiatrists. This may seem strange, but it reflects precisely the ethos that underscores the book, which is the inexorable

inter-connection between body and mind.

Practically speaking, *Facing Cancer* combines top-tier medical information on cancer and its causes (including a comprehensive glossary), with compassionate counselling and attention to the emotional aspects of dealing with the illness. The book explores the various aspects of cancer – epidemiology, screening, diagnosis, and treatment (including alternative and complementary therapies), taking into account not only patients, but also their families and caregivers. “Families experience the same level of distress as do people with cancer,” notes Erika Ryst, who argues that cancer, as such, should be considered more of a “familial disease” than an individual problem. For this reason, the book deals extensively with the impact of cancer on families and how to help children cope with a parent’s cancer. The guide is organised in short easily readable chapters (written in plain English but never overly simplistic or patronising), in which issues are formulated as questions posed by patients. The chapter on new therapies and protocols includes, for instance, sections titled “What are the phases of clinical trials?” “What is informed consent?” and “What is a placebo and could I receive one?”

But the originality of this book lies mainly in the emphasis it places on psychological issues and on developing coping strategies for all those involved and at every stage – from the point of receiving a diagnosis of cancer to the stage of loss and bereavement. Attention is also given to understanding the meaning of cancer for children, stress reactions in caregivers, psychological interventions and support groups. There are also original chapters on

how cancer is portrayed in the media and on the role of faith in the lives of patients with cancer. Through its holistic, humane and sensitive approach to the disease, this truly original guide for patients and their families will help to fulfil the editors’ aim “to make the [cancer] journey less frightening, less painful, and less lonely.”



Looking Forward...

The Speech and Swallowing Guidebook for People with Cancer of the Larynx or Tongue

4th edition

Jack E. Thomas and Robert L. Keith
Thieme, 138 pp, euro 12.95

Patients diagnosed with cancer of the larynx or tongue often feel so overwhelmed by what may lie ahead for them, they are unable to absorb all the information provided by their healthcare professionals. This guidebook steps in to fill the gap. It offers accurate, practical data, with many precise illustrations (about anatomy, equipment and processes), on the various treatments for cancer of the mouth and throat and therapies for speech and swallowing impairments caused by cancer and cancer-fighting treatments. A highly useful book which may help patients with this type of cancer feel more able to cope.