European School of Oncology
Learning to care

Cancerworld

Number 37, July-August 2010

Education & knowledge through people & facts

Serigne Magueye Gueye

➜ Serigne Magueye Gueye: an agent for change ➜ Yes we can treat cancer, even in the poorest countries ➜ How do we avoid dangerous interactions if we don't know what patients are taking or whether it matters? ➜ Damaged sex lives: the unspoken side-effect

Contents

3 **Editorial**
Turning the World Cancer Declaration into action

4 **Cover Story**
Serigne Magueye Gueye: an agent for change

15 **e-Grand Round**
Pitfalls and uncommon problems in thyroid cancer management

24 **Cutting Edge**
Grapefruit juice and St John's Wort are just the tip of the iceberg: how can we prevent damaging interactions in this era of long-term oral cancer therapies?

32 **Masterpiece**
Yes we can treat cancer – even in the poorest countries: so says Ian Magrath and his INCTR partners, and they have the evidence to prove it

42 **Impact Factor**
Chemoradiation in head-and-neck cancer – are we any closer?
Preoperative biliary drainage – better stents in specialised centres are needed
Newsround

56 **Patient Voice**
When sex lives suffer: what some cancer patients go through and how oncology teams can help

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Grafiche Porpora

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Published by
European School of Oncology

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Registrazione Tribunale di Roma
Decreto n. 436 del 8.11.2004

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Cancer World is published six times per year by the European School of Oncology. It is distributed at major conferences, mailed to subscribers and to European opinion leaders, and is available online at www.cancerworld.org

Turning the World Cancer Declaration into action

Franco Cavalli ■ GUEST EDITOR

Cancer kills more people than does AIDS, tuberculosis and malaria combined. Going by recent global health trends, this year will see cancer emerge as the world's single leading cause of death. In an effort to focus the minds of international bodies and national governments on the gravity of the situation, the World Cancer Congress issued a World Cancer Declaration four years ago, which called for urgent action to deal with the worldwide crisis. It set 11 targets that need to be reached by 2020 in order to avoid a disastrous escalation in new cancers and to significantly improve cancer survival in all countries. These ambitious goals were based on growing evidence that concerted action can make a big difference, even over a short period of time.

The 2010 World Cancer Congress, gathering this August in Shenzhen, China, will offer the first opportunity to review progress towards meeting the 11 targets. The picture is likely to offer cause for both hope and disappointment. The Declaration has certainly elicited great interest: so far, more than 177,000 people have signed up, promising to help achieve its goals. Many influential associations, from LiveStrong to the World Economic Forum, have taken measures that contribute to achieving many of the targets. Universal access to effective pain control – target 8 – for instance, is now a step closer with the launch of the UICC Global Access to Pain Relief Initiative (GAPRI). The intention is to engage with international bodies – including the relevant UN agencies – and to stimulate action on pain at a national level in key countries.

More disappointing is the impression that, over the last two years, efforts to use the Declaration as a template for developing regional or national targets have tailed off, without which it is very difficult to measure progress – or lack of it – on the ground. Whether the Declaration has stimulated a significant increase in the number of national cancer control plans, which still represent the most powerful method for realising the 11 targets, is also far from clear.

The World Cancer Congress in Shenzhen will look at ways to strengthen and further coordinate efforts towards achieving the World Cancer Declaration goals by the target date of 2020. Central to this will be rolling out UICC pilot projects on childhood cancers, cervical cancer and more, which have so far been limited to only a few countries.

With the United Nations General Assembly having belatedly recognised the urgent need for tackling non-communicable diseases like cancer, in a resolution passed a few weeks ago, we now have a window of opportunity to regalvanise efforts where they are flagging, and prompt action where nothing has yet been done. The World Cancer Declaration will remain a vital roadmap to direct these efforts.

Franco Cavalli is the immediate past president of the UICC

Serigne Magueye Gueye:

an agent for change

➜ Marc Beishon

After years of international declarations and pilot projects, Africa is starting to take control of its efforts to tackle cancer. At the helm is Serigne Gueye, professor of Urology at Senegal's Cheikh Anta Diop university and president of Africa's cancer research and training body AORTIC, which is now in a race against time to get cancer up the agenda of national governments and the African Union.

When people think of Africa's illness burden, the major communicable diseases such as malaria, tuberculosis, HIV/AIDS and others come to mind as the big killers and causes of chronic conditions. This perception has been outdated for years, if not decades, and it has hampered efforts to prepare the developing world for the explosion in non-communicable diseases such as cancer that we know is coming.

Cancer already kills more people than AIDS, malaria and tuberculosis combined, in all but the very poorest countries, and it is rising rapidly as progress is made in controlling infectious diseases, and people live longer and start adopting western lifestyles. But the world missed an opportunity to galvanise efforts to meet this challenge when it left cancer off the targets for the Millenium Development Goals – an omission that has only just begun to be redressed this May, with the United Nations General Assembly resolution on non-communicable diseases.

According to Serigne Gueye, president of the African Organisation for Research and Training in Cancer (AORTIC), and a urologist based in Dakar, Senegal, the most damaging omissions, however, have been not so much in the agendas of international organisations, but in Africa itself.

"The problem has been a lack of awareness of cancer among Africans and lack of action by governments, but it is also the case that international agencies have mostly lacked practical strategies for tackling cancer as the focus has been on communicable diseases.

"Cancer in Africa will become a huge problem in the next ten years or so as people live longer, while other diseases common in developed countries will also be major issues, such as diabetes and cardiovascular disease. But we can do much now to prevent many cancers, as in Africa up to 40% are caused by infections. We need to start now with training and research networks across Africa that will address the different needs of the regions — and we must have Africans setting the agenda, not outside agencies.

"We have not lost the battle against cancer yet – there is time to get it on government agendas although of course we still have major communicable disease problems."

The reason he stresses prevention is simple –

NIC BOTHMA

there is a massive lack of resources to detect and treat cancer in Africa, as revealed in stark data from the International Agency for Research on Cancer (IARC). It has found, for example, that breast cancer survival five years after diagnosis has ranged from just 12% in the Gambia to nearly 80% in countries such as South Korea, while bowel cancer survival is even lower, at 10% in the Gambia and Uganda. The vast majority of patients present with late stage disease.

As Gueye says, the lack of infrastructure will not change dramatically without concerted action by governments. For example, a country as large as Nigeria has only 40 urologists to serve the entire population of 140 million, and many of the continent's 53 countries have no or maybe a single radiotherapy machine, while cancer drugs are simply unaffordable and not yet part of widespread international aid. The epidemic of cancer that is on its way will surely overwhelm already badly stretched healthcare systems.

"We can though prevent cervical cancer, hepatocellular cancer and HIV-related malignancies, which are all caused by infections, and we can also introduce more effective tobacco and environmental pollution control," says Gueye. "And one of our key goals at AORTIC is to urge governments to establish national cancer control programmes that will start to address resourcing issues, such as reversing the brain drain of doctors and scientists away from Africa and putting in place more training and treatment facilities."

Gueye and colleagues also aim to build on research into the characteristics of cancer among Africans, such as why prostate and breast tumours tend to be more common and aggressive among black people not just in Sub-Saharan Africa but also in the Caribbean and North America.

A particular priority, however, is filling in major knowledge gaps in the incidence of cancer in Africa – there are few registries that are gathering sufficient data. The IARC notes that there is a "dire need for population-based cancer survival information from

THE STATISTICS

- One fifth of all cancers worldwide are caused by a chronic infection, and up to one third of cancers in the developing world are curable if caught early
- 100,000 children die unnecessarily each year from cancer
- Only 5% of global resources for cancer are spent in the developing world
- African states will account for a million new cases a year out of 16 million worldwide by 2020
- Low- and middle-income countries account for only 6% of world morphine consumption
- In Ethiopia, 85% of the population have never seen a healthcare worker
- Uganda has one cancer unit for 32 million people

developing countries", and Gueye says that of all the actions in AORTIC's strategic plan for 2010–2015 (subtitled 'Working together to prevent and control cancer in Africa') improving data collection is the first and most important measure.

Gueye's own position as AORTIC president is also a sign that cancer has more chance of being a serious proposition for national governments on the continent. Until fairly recently, he says, the organisation was not an effective force, as it had been set up and run mainly by expatriate Africans in the US (it was founded as far back as 1983). Now Gueye and colleagues in Africa who have become involved recently have managed to revitalise the organisation, such that last November in Tanzania its biennial conference attracted some 700 delegates, and a call was made by Tanzanian president Jakaya Kikwete for African leaders to include cancer control in national health plans.

"What is also helping is that people are becoming better informed about cancer thanks to the Internet and programmes on the BBC and CNN, and stories in local media, while prominent people who have cancer have been speaking out, such as Desmond Tutu in South Africa," says Gueye. Events such as World Cancer Day (4 February, led by the UICC, the International Union Against Cancer) also contribute – this year the focus was on prevention, including tackling the infections that can cause cancer.

Uniting a continent as large and diverse as Africa around cancer is a daunting task, but Gueye feels that getting the messages across about what is most appropriate for African countries offers considerable hope in the years ahead. "The critical force is the African Union – the highest level meeting of nations – to which we aim to take our strategic plan. If we can engage all political leaders we can make similar progress to that in HIV/AIDS, such as opening up channels for cheap or free generic drugs."

Gueye's reason for pursuing a medical career is rooted in personal tragedy. "I lost my father when I was just 11 – he went into the medical centre in Thies and didn't come back. I don't know why he died, but it was probably related to malaria. I thought then I wanted to go into medicine to do what I could."

He was the first in his family to go to college, let alone medical school, and was attracted to urology while on rotation by one of his key mentors, Aristide Mensah, the professor of urology. He was fortunate, he adds, that Senegal has a long tradition of investing in training. "The first medical school in Francophone Africa was in Senegal and the country has had a stable democratic culture since its independence 50 years ago."

He trained as a urological surgeon and with the country's links with France did more than three years of fellowships in Bordeaux and Paris, learning the then latest techniques such as radical prostatectomy and bladder replacement surgery. He is also a master trainer in reconstructive urology, such as repairing uro-genital fistula, and continues to play an important role in healing the scars left by the widespread rape that has been a feature of many wars in the region. Today he is not only head of urology at Grand Yoff general hospital in Dakar, but also the chief medical officer at the hospital, and professor of surgery and urology at Dakar's Cheikh Anta Diop University. What's more, he is also still the president of the Pan-African Urological Surgeon's Association – but as he says, in Africa it is not unusual to find doctors performing multiple jobs.

"But we are fortunate in my hospital that we

The reason he stresses prevention is simple – there is a massive lack of resources to detect and treat cancer

NIC BOTHMA

With members of his urology department, at the Grand Yoff general hospital, Dakar

have multidisciplinary teams in urology and other specialties, which is not the case of course for many African surgeons. At present I do mainly surgery and hormone therapy for prostate cancer, which is my main specialty, and I have colleagues who specialise in other operations and who administer chemotherapy. We are also able to carry out procedures such as radical prostatectomy that are not available in many places in Africa owing to a lack of trained surgeons and resources. Before we introduced the latest surgical techniques, people just came to the hospital and received palliation and died. Now we are able to track cases earlier and people are more confident about undergoing surgery and we carry out radical procedures on a daily basis."

That said, Senegal has just one radiotherapy machine for the whole country – it is based in another hospital in Dakar – and it is only recently that planning for cancer has become more organised. "It was when we held the AORTIC conference in Dakar in 2005 that our minister of health and prevention made cancer a focal point for the first time, and we now have a national cancer plan that includes activities such as outreach and education work, early detection for cervical cancer and mammography in some places, and it is now much easier for people to see doctors about cancer."

The country is one of the few in Sub-Saharan Africa with a cancer plan, he adds – others that do, at least in draft form, are Ghana, Nigeria and Tanzania; the Nigerian plan was launched this year to coincide with World Cancer Day.

But Senegal, he adds, does not yet have a population cancer registry, and with most data about cancer in Africa coming only from hospitals, there is gross underreporting of cancer incidence and countries tend to focus on what doctors see in practice, and the true scale of the problem is hidden.

"That is why I see developing population-based cancer registries as so important, and I think the best route to achieve this more consistently is through the World Health Organization, as it has an office in each country and already collects data on malaria and TB and other diseases from health ministries, and has influence

with governments. In fact the WHO regional office for Sub-Saharan Africa in Brazzaville, Republic of the Congo, has started to train people in cancer registration, but rolling this out will take five years or more."

There are differences in the types of cancer most common in different parts of Africa, adds Gueye. North Africa has obvious differences with Sub-Saharan Africa, as the people in the north are mainly from Arabic inheritance. A striking difference is, for example, the high incidence of bladder cancer in Egypt, which is linked to schistosomiasis, a parasitic disease, although Gueye notes that there is now a shift to tobacco-related bladder tumours in the country (and inevitably, smoking is becoming an increasing problem throughout Africa).

Regions in Sub-Saharan Africa show some patterns, such as prostate cancer being more common in West Africa, and Kaposi's sarcoma, the cancer related to HIV infection, reported more in Central and East Africa. "Breast and cervical cancers are common everywhere, with cervical being the most common female cancer, while hepatocellular cancer is the most commonly diagnosed cancer overall, when you combine data from both men and women, and it is the most common cancer in men and by far the major male cancer killer."

Hepatocellular carcinoma – liver cancer – is a deadly disease that can be caused by chronic infections with hepatitis B and C viruses (especially B), and also by concurrent exposure to alfatoxins, produced by funguses that infect crops and which are extremely carcinogenic. Clearly, halting transmission of hepatitis B can greatly help cut the incidence of the disease, and a vaccine for the virus has been available for 20 years. But Gueye says that, given the high prevalence of infection, especially in East and West Africa, much research remains to be done on how the disease develops and on appropriate antiviral treatments for carriers, in a similar way to the development of HIV drug treatments.

While liver cancer is very much a disease of the developing world, so too are HIV/AIDS-related malignancies, which include not only Kaposi's sarcoma, but also increased susceptibility to cervical cancer and non-Hodgkin's lymphoma. "Kaposi's sarcoma is a particular problem in Central and East Africa where the HIV infection rate is high and people do not get early anti-retroviral treatment, which increases the prevalence of Kaposi's, although we do not know the full natural history of this disease. Some countries are reporting that 25% of new cancer cases are HIV/AIDS-related so we urgently need to develop better treatment programmes for these patients," says Gueye.

Senegal, he adds, has a relatively low HIV incidence – about 1% of the population – and has taken a hard line with HIV carriers, passing a law that allows doctors to inform patients' partners of their infection status. "I did a study with a colleague where we found that 25% of men didn't change their behaviour when they knew they were HIV positive – they didn't tell their wife and didn't use a condom," says Gueye.

While Senegal does not see much HIV/AIDS-related cancer, Gueye says he saw many Kaposi's sarcomas when he worked as a United Nations surgeon in Rwanda towards the end of the genocidal conflict there. His humanitarian work there won him several honours, including a UN Peace Medal.

At least generic drugs for the major communicable diseases such as HIV/AIDS are now available to many Africans free of charge, he notes, although not without a considerable struggle with patent holders. But that is not the case for most cancer drugs. With increasing numbers of standard chemotherapy drugs coming out of patent, more low-cost anti-cancer agents could be available, but the latest targeted therapies will be way out of reach for most – not to mention the lack of medical oncologists, who are much rarer than surgeons.

Vaccines are another class of drug where price is an issue, he adds, with vaccines against human papillomavirus (HPV – the cause of cervical cancer) currently unaffordable for most countries. Attempts to introduce HPV vaccines are now being made by organisations such as the GAVI Alliance – it aims to bring the costs down greatly with its large purchasing power. The vaccines do not, however, protect against

"We now have a cancer plan that includes education, early detection for cervical cancer and mammography"

all strains of HPV, and are not a substitute for screening (see also cover story on Vesna Kesic, *Cancer World* Nov–Dec 2009) and Gueye adds that some Africans can reject vaccines, fearing that HPV shots, for example, could render girls infertile.

In turn, screening has major drawbacks in Africa, says Gueye, apart from the huge logistical issues that entails. "It is simply that it is unethical to screen everyone and then not be able to offer treatment to all for diseases we detect," he says. "The day we have mass treatment for everyone is the day we start talking about mass screening." Instead, as in Senegal presently, the approach should be one of raising awareness and carrying out examinations when, for example, women attend a family planning clinic. "We need to target certain groups instead," he says, adding that it is especially important to head off the growth of controversial screening tests such as PSA for prostate cancer.

NIC BOTHMA

Best practice. With its multidisciplinary approach to treatment and emphasis on in-country training and research, Dakar's Grand Yoff general hospital offers an example of the sort of sustainable cancer service that can be achieved in all but the poorest countries, if only the political backing is there

Gueye became involved in international prostate cancer research in the late 1990s, notably on a programme that is looking at the reasons why black people, particularly of West African origin, have the world's highest incidence and mortality from the disease. He has been working with colleagues at the University of Pennsylvania on some of the first studies to examine the risk factors for prostate cancer outcomes for African-American and West African men, and also European Americans, who have lower incidence. Now under the umbrella programme title of MADCaP (Men of African Descent and Carcinoma of the Prostate), there were initial parallel studies in Dakar and Philadelphia that have gathered data on incidence, genetic differences (and possible candidate genes) and environmental factors such as diet, revealing, says Gueye, that African men seem to be at higher risk than their African-American counterparts, which may be partly explained by Caucasian genes mixed in as the diaspora expanded to North America.

What especially interests Gueye as a clinician is that this research could lead to better targeting of men most at risk, and also the opportunities it is bringing for capacity building for researchers and infrastructure for carrying out such studies, not only in Dakar but in the other African sites that are interested in participating alongside a growing number of American centres in MADCaP, such as in Nigeria, Ghana, Zambia and Uganda.

However, this type of research – which is also being conducted with women to find out why African American women are more likely to suffer from aggressive 'triple negative' breast cancer – is not without possible controversy. Gueye says there is a danger of black Africans being used as guinea pigs for trials, with rich countries leaving research sites behind with little support once trials are complete (and he goes as far as mentioning the infamous Tuskegee syphilis experiment in the US, where poor African-Americans were left untreated after the discovery of penicillin). "We have to be very careful about collaboration – it must be an equal partnership," he says.

For his own part, Gueye has organised several successful collaborations, not just in research but also in training, which he sees as particularly vital to building capacity and keeping young African doctors in their countries. "For example we have had paediatric urologists from Pittsburgh, Pennsylvania, here in Dakar at a workshop on paediatric urology, attended by more than 50 people. And every year, for more than five years, residents and staff from surrounding countries have received training in radical prostatectomy with the help of Albert Ruenes, a urologist from Doylestown,

"It is simply unethical to screen everyone and then not be able to offer treatment to all for diseases we detect"

Pennsylvania. I see onsite training as the key – we can't go on sending doctors to train abroad, otherwise we will continue to lose some. Also, if you send someone away for training there is no guarantee they will teach others when they return.

"I could easily have stayed in France – indeed, I was advised to – and I chose to come back. But we must also put in infrastructure for people to work and train with." As he says, it is pointless sending a state of the art scanner to a site where it will fall into disuse if no one can use and maintain it, while a surgeon will not be able to work on prostate cancer if they can't request scan to determine if a tumour is localised or not.

NIC BOTHMA

"And maintaining skills is vital to carrying out radical procedures such as prostatectomy and nephrectomy, otherwise urologists and other surgeons will fall back to late management of cases and palliation only. Then when a patient comes in presenting early they can't provide a service."

Other important topics in the AORTIC strategic plan, says Gueye, include paediatric cancers such as Wilm's tumour and Burkitt's lymphoma. While relatively rare, although undoubtedly under-reported in Africa, the cure rates for African children are shockingly low – about 5% compared with some 80% in the developed world. The UICC with pharmaceutical company Sanofi-Aventis, is having some success with raising the profile of childhood cancers in poor countries with the My Child Matters programme, notes Gueye, and it is now running in 26 countries including several in Africa.

Given the late presentation of far too many cancer patients, pain and palliative care are other big issues, not least for children, says Gueye. Morphine availability and use is particularly poor in Francophone countries, he says, and he would like to see more local facilities to manufacture drugs. "And palliative care must be a priority in any national cancer plan."

There is, he adds, the African Palliative Care Association, and other bodies on the continent working in various aspects of cancer control, so it is not the case that there is little support for AORTIC's agenda (there is also a pan-African radiotherapy group – even though the vast majority of machines are in South Africa and the North African countries).

"One of AORTIC's tasks at present is building a database of organisations in Africa – that's almost done now," says Gueye. "And of course we also need international collaboration with agencies such as the International Cancer Registry Association and IARC, US bodies like ASCO, AACR, NCI/NIH, ACS and so on, and also the UN agencies."

There are certainly many organisations outside Africa with interests in supporting cancer work on the

continent, and no shortage of declarations of intent, such as the London Declaration on Cancer Control in Africa, adopted at a conference in London in 2007 and put forward by AfrOx (Africa Oxford Cancer Foundation – now working in Ghana, and established by David Kerr, who has helped with cancer plans for Ghana and other African countries). This built on a flurry of developing world conferences and declarations, including the Cape Town Declaration on Cancer Control in Africa.

For Gueye, the test is whether such initiatives are progressing beyond talk to action, and action determined by Africans, and not by agendas set from afar. "We call it NATO – no action, talk only – but as we refine the AORTIC strategic plan to make it more practical we hope organisations will be able to integrate more with what Africa needs."

Of all the many programmes that are making some headway on the ground, he picks out the IAEA (International Atomic Energy Agency) Programme of Action for Cancer Therapy (PACT), which was set up in 2004 and which partners with the WHO and a range of other organisations to build public–private partnerships and mobilise resources for cancer control in the developing world. One of its six demonstration pilot projects is in Tanzania, and the IAEA is challenging companies to produce equipment suitable for use in poorer countries.

Certainly, Gueye has extensive contacts with many organisations now, which he can bring to bear to further AORTIC's mission, though moving the organisation forward has required overcoming opposition from long-standing interests, he says, while bridging the language barrier that divides French-speaking from English-speaking countries is always a challenge.

Gueye certainly seems to have what it takes to meet the challenge. Tim Rebbeck, professor of epidemiology at the University of Pennsylvania's School of Medicine, who co-leads the US/Africa prostate risk factors study with Gueye and others, comments particularly on his leadership skills, and the great respect he commands among those he works with. "He has an exceptional way of dealing with people. He seems to have no ego to get in the way of his work, but nurtures and motivates those around him to get things done."

Gueye is a family man – his wife Ramatulaye is a language specialist and teacher, and he has three children, two now grown up, so the extensive travel he undertakes now may not be so disruptive.

"My aim now, along with the AORTIC executive council, is to finish the strategic planning for AORTIC and then build capacity for research and training by establishing regional centres of excellence that will cover all aspects of the cancers we see in Africa, and we have plans for this. We must have research infrastructure that promotes capacity building, such as helping young researchers to apply for grants and write protocols.

"We can't tell countries what to do – just help shape policies at national and pan-African level. But if we don't lobby for our strategic plan we will deserve to disappear as an agent of change."

Gueye himself seems determined to continue as an agent for change at this critical period, helping Africa meet the challenge of its rising tide of cancer.

GLOBAL AND AFRICAN EFFORTS

The World Cancer Congress – held every two years – will be highlighting system changes at the 2010 event in Shenzhen, China, in August. Topics such as cancer registries as a basis for cancer prevention and control, the untapped potential of public health law and policy in cancer control, and 'ending the pain' – what has to be done for 5 million sufferers – are central to the World Cancer Declaration road map and of crucial importance to AORTIC's agenda in Africa.

The UN General Assembly recently adopted a resolution calling for the curbing of premature deaths from non-communicable diseases, and for a high-level meeting on the issue, with the participation of heads of state, to take place in New York in September 2011.

Apart from AORTIC, and major organisations such as the WHO and the IAEA (International Atomic Energy Agency), agencies and projects seeking to improve cancer control within Africa include the Pan-African Clinical Trials Registry (www.pactr.org), the African Radiation Oncology Group, the African Tobacco Control Alliance, the African Palliative Care Association, the African Cancer Network, Cancer-Africa, AfrOx and EDUCARE (EDUcation for Cancer in African Regions).

The test is whether such initiatives are progressing beyond talk to action, and action determined by Africans

Pitfalls and uncommon problems in thyroid cancer management

Thyroid cancers are fairly common, but medical oncology departments will generally come across only the small minority of patients with advanced or recurrent disease that responds poorly to standard treatments. These patients require comprehensive oncological management, including radiotherapy and medical oncology as well as supportive care.

Thyroid cancers are quite common cancers and they can generally be cured. They are managed primarily by endocrinologists, surgeons specialised in endocrine surgery and specialists in nuclear medicine. A small proportion of patients, no more than 1 in 20, experience a poor outcome. Drawing on our experience of managing more than 250 cases of this kind at the Centre Léon-Bérard at Lyon, this e-grandround explores the different types of thyroid cancer and their diagnosis, behaviour and management, as well as key challenges such as loss of radio iodine uptake and the management of bulky metastases and metastases that have mutated from the primary cancer. It also looks at the potential of new drugs developed in this setting, several of which are also being studied in more common cancers.

Differentiated thyroid cancer

There are two histological subtypes of differentiated thyroid cancer: papillary thyroid carcinoma (PTC) and PTC

European School of Oncology
e-grandround

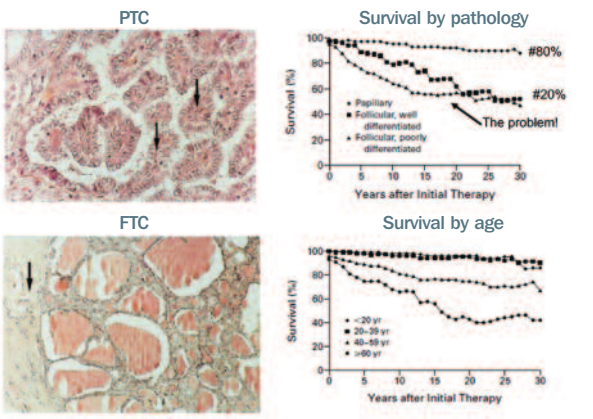
The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these is selected for publication in each issue of *Cancer World*.

In this issue, Jean-Pierre Droz, Professor Emeritus of Medical Oncology at the Centre Léon-Bérard, Lyon, France, reviews the medical treatment of advanced disease in patients with thyroid cancers that pose particular challenges, drawing on the centre's experience in the management of approximately 250 patients.

Christelle de la Fouchardière, also of the Centre Léon-Bérard, poses questions that explore the issue further. The presentation is summarised by Susan Mayor.

The recorded version of this and other e-grandrounds is available at www.e-eso.net/home.do

PAPILLARY AND FOLLICULAR THYROID CARCINOMA



Survival rates are poorer for follicular than papillary thyroid carcinoma, and they worsen with patient age

Source: © 1998 Massachusetts Medical Society. All rights reserved. MJ Schlumberger. Papillary and follicular thyroid carcinoma. *NEJM* 1998; 338:297–306

with follicular differentiation (FTC). A good review by Martin Jean Schlumberger published ten years ago in the *New England Journal of Medicine* (*NEJM* 1998, 338:297–306) showed that patients with PTC had a better prognosis than those with FTC, particularly those with poorly differentiated FTC. Age is also an adverse prognostic factor (see figure above).

In general, the guidelines for the treatment of differentiated thyroid cancer recommend initial management with a total thyroidectomy and radioactive iodine (I^{131}) therapy. Patients then have a good inhibition of thyroid stimulating hormone (TSH) production and their thyroglobulin is followed. In cases of recurrence, the standard treatment is radioactive iodine therapy (*Eur J Endocrinol* 2006, 154:787–803)

The first challenging issue in differentiated thyroid cancer is that there are patients with metastatic disease with radio iodine uptake who can lose their uptake. For example, the CT scans for a patient with differentiated thyroid cancer lung metastases, shown in the figure below, show an initially strong uptake of radio iodine. However, five years later, after four applications of radio iodine, there was no more uptake of radio iodine in the lungs.

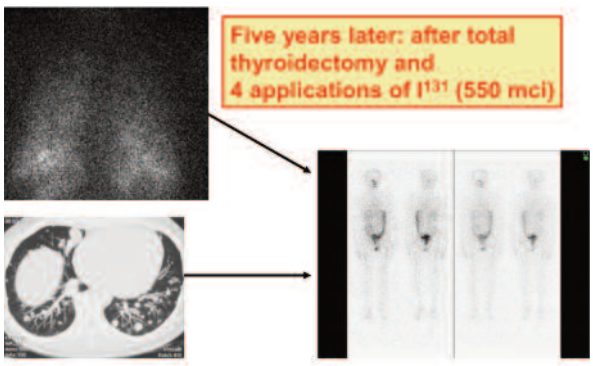
There are two explanations for this observation. The first is that the disease is still differentiated – papillary or follicular thyroid carcinoma – but it becomes functionally different with the loss of radio iodine uptake. The other possibility is that the disease becomes poorly differentiated. This is the problem of pathological switch. Poorly differentiated carcinoma is often called 'insular carcinoma'.

A case study that illustrates this was that of a 40-year-old woman who had initially multiple bulky bone metastases without lung metastases. In 1999, she had a thyroidectomy for papillary + follicular thyroid carcinoma without any undifferentiated components within the thyroid. She received several radio iodine applications and then had surgery to treat spinal cord compression and hip fracture with hip replacement. In 2002, she had a bulky iliac metastasis, which grew. A biopsy showed poorly differentiated carcinoma.

One year later, this woman had multiple lung micronodules without I^{131} uptake. Histology showed both solid and insular patterns. Iodine scintigraphy showed absolutely no uptake of iodine. We can assume that in this patient the development of lung metastases may have been linked to the switch from differentiated carcinoma to poorly differentiated carcinoma.

Another possible scenario is the coexistence of both histological patterns. For example, a 48-year-old woman had a thyroidectomy in 2000 for the combination of papillary thyroid carcinoma and poorly differentiated thyroid cancer. At the same time, she had lung and right shoulder/arm bone metastases. She received several applications of radio iodine, but despite a good iodine uptake she had growing shoulder metastases with fracture. The decision was made to perform surgery, with the upper part of the humerus being replaced. The figure opposite shows the humeral metastasis, the presence of lung metastasis and very good iodine uptake on the scintigraphy both

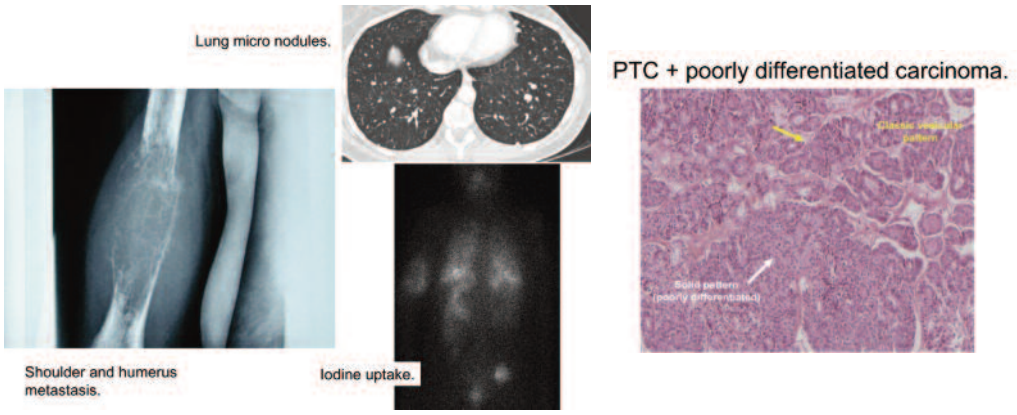
LOSS OF RADIO IODINE UPTAKE



Initially the radio iodine treatment was taken up in the lung metastases of this patient (top left). Five years later, however, there is no evidence of radio iodine uptake in the lungs (right-hand image) despite lung metastases being clearly revealed on CT scan (bottom left)

Source: Slides courtesy of Centre Léon-Bérard, Lyon

TWO HISTOLOGIES CAN COEXIST



At initial diagnosis, this patient had a papillary thyroid carcinoma with undifferentiated areas and multiple bulky bone metastases. The slide of a humeral metastasis, taken three years later, shows the cancer has areas of poor differentiation, which was associated with the development of lung metastases a year later

Source: Slides courtesy of Centre Léon-Bérard, Lyon

in the lung and in the arm. Histology showed a classic vesicular pattern and a solid pattern of poorly differentiated carcinoma.

There is growing interest in functional imaging with PET scans in patients with differentiated thyroid cancer. A case study illustrating its value is that of a 41-year-old woman who underwent a thyroidectomy for papillary thyroid carcinoma in 1995. Her thyroglobulin increased despite several administrations of radio iodine. She had absolutely no uptake. Eleven years later, a PET scan showed the presence of bone metastases in the pelvis (see top figure overleaf). This patient was managed with a RANK-ligand inhibitor.

A scan several months later showed extension of bone metastases. The thyroglobulin level increased despite the presence of good inhibition of thyroid-stimulating factor. There was no more iodine uptake, and the FDG radiotracer uptake showed metastases in the adrenal gland and extended metastases within the bone. As at the start, the use of functional imaging was interesting, but the metastases could also be seen on anatomical imaging in a CT scan.

The problem of bulky metastases

Bulky metastases pose a very difficult problem and there is no consensus on management. The challenge is illustrated by the case of a 50-year-old man with no known history of thyroid problems. In 2005, he felt pain in his spine, and was found to have a large-volume iliac metastasis and thyroid cancer. A biopsy of the metastasis showed the presence of follicular thyroid carcinoma. Shortly after, he had a thyroidectomy for a combination of papillary thyroid carcinoma and poorly differentiated thyroid cancer. He had major iodine uptake of I^{131}, and a decision was made to proceed with debulking surgery of the unique iliac bone metastasis.

The huge uptake of I^{131} on the right part of the pelvis can be seen in the bottom figure overleaf. There is residual uptake after thyroidectomy, although this is common. The original CT scan shows a huge metastasis within the bone, and also within the muscle. It is very unlikely that this patient could be managed only with I^{131}, because the activity would be small in this large tumour.

After debulking surgery, the PET scan shows there is still uptake of the FDG radiotracer, and this area is clearly tumoural, so there is a need to perform additional treatment with radio iodine.

Medullary carcinoma

Medullary carcinoma is not really cancer of the thyroid because it is derived from normal C cells.

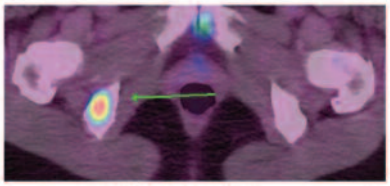
There are three main points in the recommendations for management:

- It is important to determine information on the genetics of the disease, and particularly the possibility of a hereditary medullary cancer or even a mutation in the RET gene.
- It is important to look for adrenal gland abnormality, and particularly a phaeochromocytoma, as well as hyperparathyroidy.
- Surgery is clearly the standard treatment. Patients must have thyroidectomy plus level VI compartmental lymph node resection. This is the only curative treatment.

A patient's calcitonin level, as well as carcinoembryonic antigen (CEA), must be followed carefully. If calcitonin is raised, imaging should be used for further investigation. A solitary metastasis should be managed with surgery, while a patient found to have extensive

THE VALUE OF PET SCANS

- Woman, 41 years; thyroid familial antecedents: goitre in father, mother, brother.
- 1995 thyroidectomy for goitre. PTC stage pT3b.
- Thyroglobulin increases despite 400 mci I^{131}. NO UPTAKE.
- 2006: FDG-PET scan=



- Inclusion in a RANK-L inhibitor protocol.

This PET scan picked up very clearly a bone metastasis in the pelvis of a woman who had undergone a thyroidectomy for papillary thyroid carcinoma 11 years earlier

PTC – papillary thyroid carcinoma, FDG – fluorodeoxyglucose radiotracer
Source: Slide courtesy of Centre Léon-Bérard, Lyon

metastases should be considered for a clinical trial.

Differential diagnosis of medullary carcinoma can be challenging. We have observed two patients where this has been a problem. The first was a 55-year-old man, who had backbone metastases with muscle invasion. He underwent a thyroidectomy and the initial diagnosis was differentiated carcinoma (papillary thyroid carcinoma). There was absolutely no radio iodine uptake and his thyroglobulin levels were low (0.3 ng/ml) without antibodies. Scintigraphy showed no radio iodine uptake on the bone metastases and MRI showed cervical and lumbar metastases, muscle invasion and spinal cord compression (see lower figure, p19).

What were the hypotheses? The first was dedifferentiation, with the possibility that it was a papillary thyroid carcinoma that may have switched to an insular or poorly differentiated carcinoma. An alternative possibility was metastatic disease of other origin. The most likely possibility, however, was medullary carcinoma. The serum tumour marker profile was strongly in favour of this diagnosis, with a slight elevation of carcinoembryonic antigen (20 ug/L), elevation of the NSE (neuro-specific enolase) biomarker (68 ng/ml) and elevation of calcitonin (800 ng/ml), which was very significant. Review of the pathology slides showed an immunohistochemistry profile that strongly supported a diagnosis of medullary carcinoma, with no uptake of thyroglobulin, staining with calcitonin and carcinoembryonic antigen.

IMAGING MEDULLARY THYROID CANCER

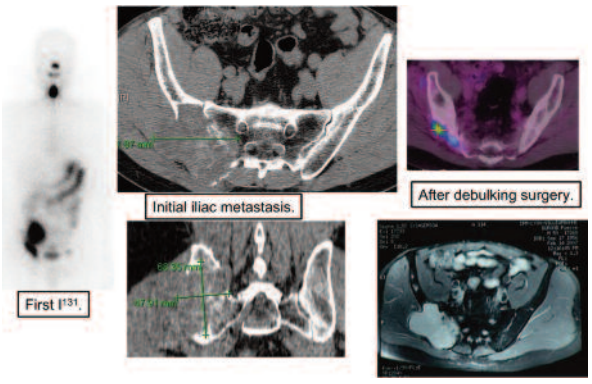
When a patient undergoes surgery and has increased serum calcitonin levels, a range of different imaging techniques are indicated. These included ultrasound to explore the neck, CT scan for the liver (but this can be difficult to interpret, MRI is also useful for the liver imaging), functional imaging with FDG-PET scan, octreoscan, MIBG-I^{131} scanning, an Indium scan and laparoscopy.

What about liver metastases? In medullary thyroid carcinoma, liver metastases are sometimes difficult to see; for example, some metastases are more visible on the portal phase of a CT scan than on the arterial phase. In these cases MRI may be more accurate, particularly with the use of gadolinium enhancement. Injection of gadolinium is the best method to visualise liver metastases in such a patient.

THE POTENTIAL OF TARGETED DRUGS

There are several different targets in thyroid cancers. These include the angiogenesis receptors, such as VEGF-R; PDGF-R, C-KIT and, more importantly RET, particularly in medullary carcinoma, and fusion genes RET/PTC in PTC, and BRAF in papillary thyroid carcinoma. A study with sorafenib suggested there is a relationship between the drug's activity and particular mutations of BRAF (MS Brose et al., abstract A6002, ASCO 2009). Other receptors are EGF-R and c-MET. RET is a transmembrane receptor, which is a tyrosine kinase. It needs dimerisation for activity.

BULKY METASTASES



There is no consensus on managing bulky metastases. This very large pelvic metastasis was debulked and the residual tumour – visualised on a PET scan – was then treated with radio iodine

Source: Slides courtesy of Centre Léon-Bérard, Lyon

Trials in differentiated thyroid cancer

Published phase II trials

There are three important trials in differentiated thyroid cancer. The first is a trial with motesanib, with the targets of VEGF-R, PDGF-R and C-KIT. The trial included 93 patients and showed a partial response rate of 14%, with 33% of patients having stable disease at more than six months (*NEJM* 359:31–42). More than 50% of patients had clinical benefit – a combination of partial response plus stable disease for more than six months.

The second trial is with sorafenib. Clinical benefit in a fairly large series was found to be around 70%.

The third trial is with axitinib, which acts on VEGF-R. This resulted in a 30% partial response rate and a 70% clinical benefit in total.

Published abstracts of phase II trials

Abstracts of early trials in differentiated thyroid cancer treated with sunitinib published in 2008 showed clinical benefit of around 80%. There is now an ongoing phase II randomised trial of vandetanib versus placebo.

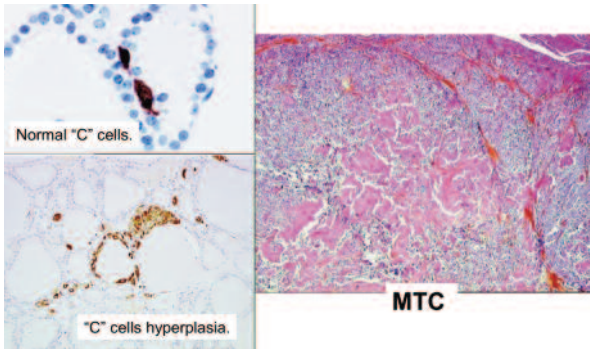
The results from trials with sorafenib in differentiated thyroid cancer show a good proportion of patients achieving partial response and stable disease, but anaplastic or poorly differentiated carcinoma does not respond.

However, there are adverse events with sorafenib, such as hand foot syndrome, which affects 90% of patients, as well as diarrhoea and hypertension. Dose reduction is required in 50% of patients treated with the drug, and 20% of patients came off the drug due to its toxicity.

Future trials

A randomised trial is planned of sorafenib versus placebo with crossover in patients with differentiated thyroid cancer. A phase II trial is also planned of the new drug E7080, which acts on PDGF-R, VEGF-R and EGF-R, in 104 patients with differentiated thyroid cancer who are refractory to I^{131}, either upfront or further down the line.

MEDULLARY CARCINOMA



Medullary cancer is derived from normal C cells

Source: Slides courtesy of Centre Léon-Bérard, Lyon

Trials in medullary carcinoma

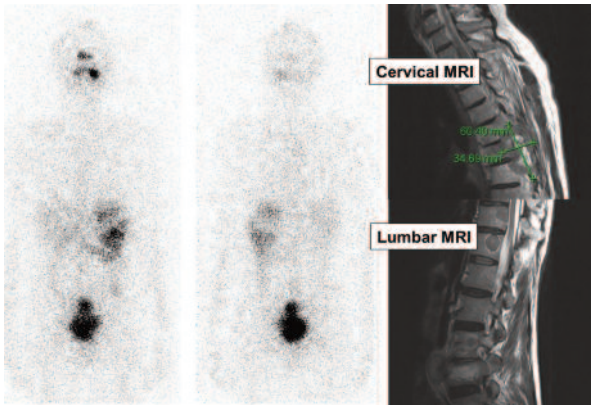
Published phase II trials

There is a very good study with motesanib where the rate of clinical benefit – mainly stable disease at more than six months – is around 80% (*JCO* 27:3794–3801).

Vandetanib, which acts on RET, EGF-R and VEGF-R, has been studied specifically in hereditary medullary carcinoma, showing a partial response rate of 20% and an overall clinical benefit of 70% (*JCO* 28:767–772).

Very small trials have also been conducted with gefitinib and axitinib.

PROBLEMS OF DIAGNOSIS



The two MRI images on the right show cervical and lumbar vertebral metastases and epidural involvement with medullar compression, yet scintigraphy shows no iodine uptake on the bone metastases

Source: Slides courtesy of Centre Léon-Bérard, Lyon

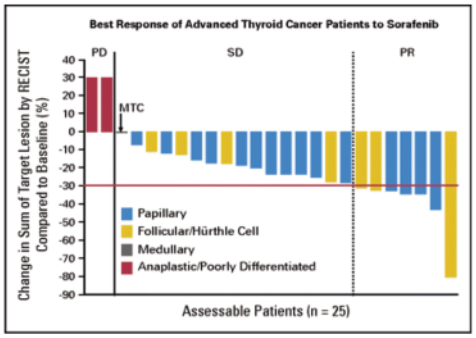
Published abstracts of phase II trials

There is a very interesting study of XL184, which acts on VEGF-R2 and RET and c-MET, with a response rate of 40% and clinical benefit of 80% (Kurzrock 2008, Proc 20th EORTC–NCI symposium on Molecular Targets and Cancer Therapeutics, abstract 379).

Future trials

The most important trial planned for medullary carcinoma is a study randomising to XL-184 versus placebo without crossover. There is also a phase II trial of E7080 planned in patients with progressive medullary carcinoma.

THE POTENTIAL OF TKIs



The tyrosine kinase inhibitor sorafenib induced disease stabilisation and partial response in a good proportion of thyroid cancer patients, but was ineffective in anaplastic or poorly differentiated thyroid cancers. Motesanib, axitinib and sunitinib have also shown some promise, and more TKIs, such as E7080 are in the pipeline for use in this setting

Source: Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved. V Gupta-Abramson et al. Phase II trial of sorafenib in advanced thyroid cancer. *JCO* 2008; 26:4714–4719

Drugs available in clinical practice

At the moment, no drug has been registered for the treatment of differentiated thyroid carcinoma or medullary carcinoma. In differentiated thyroid cancer, we consider that sorafenib is likely to be used in the future. There is interest in sunitinib, although efficacy has yet to be demonstrated. There is clearly uncertainty around the development of motesanib, and it is too early for vandetanib. In medullary carcinoma, the early results of new drugs are promising but it is too early to draw any conclusions for vandetanib and XL-184.

Metastatic sites

There are some surprising observations regarding the sites where metastasis occurs. The most common metastatic site is the cervical lymph nodes, followed by the mediastinal lymph nodes and lungs.

Bone metastases are also observed commonly. The main problem for bone metastasis is fracture, but spinal cord compression can also occur.

Uncommon metastatic sites

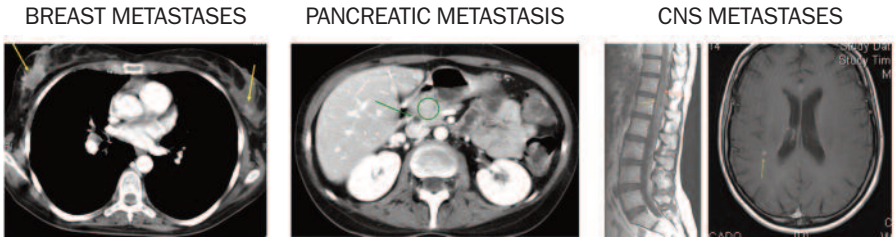
Metastases sometimes occur at very uncommon sites, which can complicate differential diagnoses. This is illustrated by the case history of a 35-year-old woman with no familial history who underwent a thyroidectomy for her thyroid tumour. The tumour was a locally involved, poorly differentiated medullary carcinoma, which was absolutely typical. She had elevated calcitonin after surgery, but no metastases at that time. Five months later, her calcitonin had increased, but, more importantly, CT scans showed uncommon metastatic disease. She had two metastases in the breast, which were confirmed by microbiopsy, and a pancreatic metastasis with dilatation of the biliary tract. The patient was treated with etoposide and cisplatin, but this failed. She then developed epidural and CNS involvement (see figure below).

Another patient had involvement of the bronchus, which could be differentiated from a primary lung cancer. This proved to be a thyroid tumour. A further patient had a kidney metastasis, with a solid tumour on the left kidney. It is important to remember that there are patients with kidney metastases whose primary tumour is thyroid, underlining the need to perform a biopsy to be certain of the diagnosis. We have also seen metastasis in the adrenal gland in a patient with differentiated thyroid cancer. In the case of medullary carcinoma, the problem is a differential diagnosis with phaeochromocytoma.

Another case showed a leukaemic reaction – a frail woman, aged 83 years, who had a huge thyroid cancer, which on biopsy proved to be an anaplastic thyroid carcinoma. She had hyperleukocytosis with leukaemoid reaction in both the blood and marrow smear. The possible mechanism for this may be hypersecretion of G-CSF and GM-CSF.

Another uncommon presentation

UNUSUAL METASTATIC SITES



It is unusual for thyroid carcinomas to metastasise to the breast, pancreas or central nervous system. These ones developed in a woman who had been diagnosed with a seemingly typical poorly differentiated medullary thyroid carcinoma

Source: Slides courtesy of Centre Léon-Bérard, Lyon

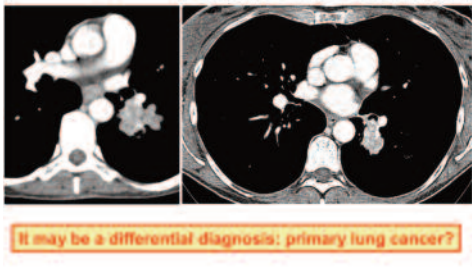
we have observed is paraneoplastic syndrome. This was found in a 40-year-old man who in 2000 had a thyroidectomy for locally advanced disease, which was found to be medullary carcinoma. His calcitonin level was greatly increased, but he had no metastases on CT scan at that time. One year later, he developed a neuropathy, and five years later he developed metastatic disease in the mediastinal lymph node and in the liver.

Paraneoplastic neuropathy developed as increasing sensitive neuropathy in the foot, leg, thigh and elbows, with pain and no paresthesia. There was slight hypoesthesia, but no other clinical abnormality. The diagnosis was neuronal sensitive neuropathy on EMG. We found no antineuronal antibodies. We know that subacute sensitive neuropathy is paraneoplastic in half (47%) of patients, and the majority have antibodies, although this was not the case in this patient.

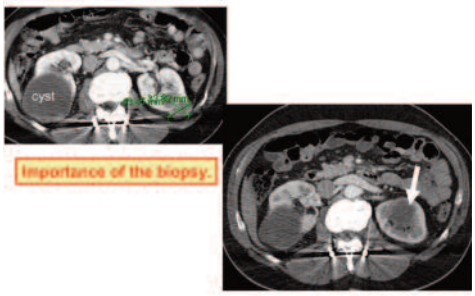
Question: *In the results from clinical trials, the majority of differentiated thyroid cancer patients show a very slow progression and maintain a good quality of life for months or years, even without any specific treatment. Is six months follow-up really appropriate to evaluate the response in new drug trials? And is a stable disease response really due to therapy, or the natural history of the disease?*

Answer: *I am also involved in renal cancer, which is treated with the same drugs, and there we have the same problem. In medullary cancer, the randomised trial that is comparing XL-184 against placebo without any crossover should be able to answer the question of whether there is an impact on survival. In trials, six months is generally considered to be a good surrogate for activity.*

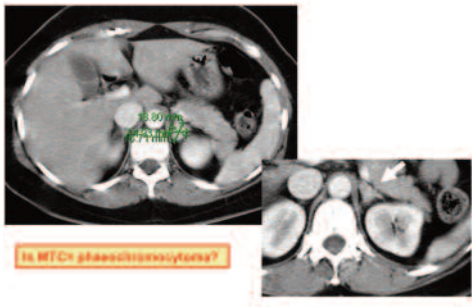
DIAGNOSTIC PITFALLS



(b) Kidney metastases



(c) Adrenal gland metastases



These lesions are all metastases from thyroid cancers, but without a careful differential diagnosis, they could mistakenly be identified as (a) originating from a lung cancer, (b) a primary kidney cancer, and (c) a phaeochromocytoma

Source: Slides courtesy of Centre Léon-Bérard, Lyon

I should mention that some trials have required evidence that a patient had progressive disease during the six months before starting the treatment as a condition for them joining the trial. This could be a good way to approach this problem.

To conclude, the question is well put, but I think the effect of these treatments is completely different from what we saw in the past with chemotherapy. It may be the beginning of a great story of the use of these treatments in patients who are not likely to receive standard treatment – surgery, radio iodine and even radiotherapy.

Uncommon pathologies

There are several variants or uncommon pathologies, including: poorly differentiated carcinoma (insular), Hürthle cell carcinoma, tall-cell carcinoma and diffuse sclerosing papillary thyroid carcinoma. In general, they have a worse prognosis than standard papillary, or even follicular, thyroid carcinoma.

Anaplastic thyroid carcinoma

Anaplastic thyroid carcinoma (ATC) is a rare tumour, accounting for less than 2% of thyroid cancers. It occurs in patients aged over 65 years. The origin is differentiated thyroid cancer or goitre. There are specific mutations, including RAS, BRAF and p53, and the diagnosis is generally made under a huge cervical mass (see figure overleaf). Approximately 40% of patients have metastases at diagnosis.

The pathology shows aspects of both papillary and anaplastic thyroid carcinoma. On immunochemistry, anaplastic thyroid carcinoma shows no staining for TTF-1 (thyroid transcription factor-1) or for thyroglobulin, as is shown with papillary thyroid carcinoma.

An example of anaplastic thyroid cancer is shown in the case of a 50-year-old woman, who presented with a huge ATC. In 1996, she had total thyroidectomy plus cutaneous cervical reconstruction. She received chemotherapy with doxorubicin 50 mg/m² + cisplatin 50 mg/m², with supportive care

(G-CSF + erythropoietin + nutritional supplementation) and radiotherapy (total dose around 60 Gy). The treatment schedule was two cycles of chemotherapy and then radiotherapy, followed by four cycles of chemotherapy. She completed the therapy and recovered very well and was followed by CT scan until 2006.

The patient's post-radiotherapy fibrosis was very limited, but there were several, very limited lung metastases. We administered radio iodine, and there was absolutely no uptake, but then this patient had a positive PET scan. We decided to perform a surgical excision of all metastases and we observed that the recurrence was due to a papillary differentiated tumour. She was treated four years ago and is currently in complete remission and very well.

Question: *Why did you decide to administer radio iodine in the patient who had an anaplastic thyroid carcinoma?*
Answer: *The initial diagnosis was anaplastic thyroid carcinoma plus a small proportion of papillary thyroid carcinoma. We took the chance. Ten years later, she had lung metastases we wanted to know whether radio iodine could be active. There was no uptake, so we then decided to operate. Fortunately, it was papillary thyroid carcinoma.*

TAKE HOME MESSAGES

- Careful pathological diagnosis is the cornerstone of decision making in thyroid cancer management.
- Total thyroidectomy remains the only curative treatment for thyroid cancer in general. It is added to radio iodine in differentiated cancer, but is the only curative treatment in medullary carcinoma.
- The majority of patients are cured by surgery and radio iodine.
- In progressive disease, it is important to control serum tumour markers, and to combine morphological and functional imaging.
- Targeted drugs become important in the clinical management of these rare cases, at least in the setting of clinical trials.

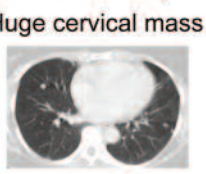
Question: *We have a 38-year-old man with papillary and follicular thyroid carcinoma, maybe in a mixed pattern, who has lung metastases but who is asymptomatic. He has received seven doses of radio iodine and has shown no radiological response but remains asymptomatic. How long should you continue with radio iodine treatment?*
Answer: *What is important is the patient's benefit. This patient is not curable, but while he is asymptomatic you can wait, you can observe and make decisions depending on progression. Sometimes, you can observe progression with imaging, such as a CT scan. It is important also to check for uptake. At some time, you must decide to include the patient in a trial, when he requests to do so or when there is progression or a symptom. It is a palliative treatment, and what you have to do is achieve the best quality of life for the patient. These new treatments are very interesting, but they are toxic.*

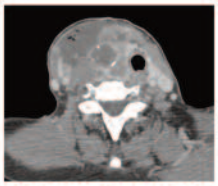
Question: *Are there any validated immunochemistry markers for premalignant thyroid lesions?*
Answer: *This is not my field of expertise. What I would say is that there is an evolution from an atypical adenoma, but there is no immunochemistry staining that is useful here. There are, however, interesting studies that look at the differences in gene expression between true differentiated carcinoma and suspected adenoma.*

The presenter, Jean-Pierre Droz, would like to thank Martin Schlumberger (Institut Gustave-Roussy, Villejuif) for his mentorship and Christelle de la Fouchardière, Claire Bournaud, Françoise Borson-Chazot and Jean-Louis Peix, at the Thyroid Cancer Consortium Hospices Civils-Centre Léon-Bérard and Department of Endocrinology and Nuclear Medicine, Hospices Civils, Lyon, France.

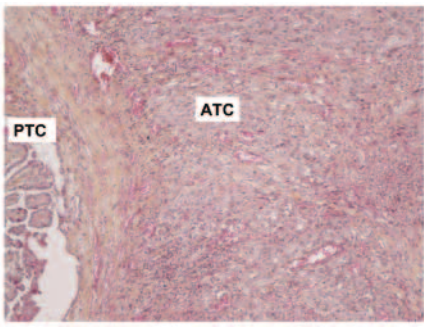
ANAPLASTIC THYROID CARCINOMA

- Incidence: 1.6% of TC, M/F 1:1 age > 65y
- Origin in DTC and goitre
- Mutations: RAS, BRAF, p53+++
- Huge cervical mass





- Metastases: 40% at diagnosis (lung, liver, CNS)



These cancers are very rare and only occur in older age groups

TC – thyroid cancer, DTC – differentiated thyroid cancer, CNS – central nervous system, PTC – papillary thyroid cancer, ATC – anaplastic thyroid cancer
Source: Slides courtesy of Centre Léon-Bérard, Lyon

Grapefruit juice and St John's Wort are just the tip of the iceberg

How can we prevent damaging interactions in this era of long-term oral cancer therapies?

Anna Wagstaff

Certain foods, prescription drugs and complementary remedies interact with cancer therapies, altering the effective dose and putting patients at risk. Yet there is scant clinical evidence on which interactions are dangerous, and many doctors are unaware of what their patients may be taking. Calls are now growing for a strategy to get to grips with this hidden problem.

One of the biggest hurdles in bringing a new cancer drug to market is turning a promising molecule into something that actually works therapeutically in the human body. The active compound has to be absorbed by the body and reach the parts that matter so that it acts before it is flushed from the system or broken down in a way that deprives it of its cancer fighting properties. The drug has to be effective at strengths that don't put a patient's life and long-term health at risk from heart failure, stroke, or attacks on the liver or other organs. Tolerability is also important, particularly for long-term therapies – no patient wants a life blighted by diarrhoea, vomiting or a facial acneiform rash.

If cancer patients were more aware of the delicate balance, they might think twice before casually reaching for a new health supplement from their local supermarket, or embarking on a course of an additional prescription medicine that could radically alter the way their body deals with their cancer drugs.

If doctors, nurses and pharmacists were more alert to the possibilities, they might make more effort to ask what other substances their cancer patients might be taking that could interact with their therapy, and be quicker to explore interaction as a possible factor if patients fail to respond to a drug or experience unexpected side-effects.

It has long been known that medicines can interact with other prescription drugs, with complementary/alternative medicines (CAM), or even with certain items of food or drink. But this poses particular problems for cancer patients – problems that are likely to get worse as new agents come onto the market, and as management of the disease moves towards long-term control with oral therapies.

Because of the toxic nature of many cancer drugs, interactions that increase the amount of the active drug circulating in the body can have fatal consequences. Even where the consequences are less dramatic, if they are not properly explored, they can lead to patients being taken off a beneficial drug on the grounds that they are 'intolerant'.

Interactions that lower the level of active drug in the body, on the other hand, render the therapy less effective. Again, without proper investigation, it can be easy to assume the patient is just one of the unlucky ones whose disease is resist-

ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

ant to the therapy. The problem is particularly acute with adjuvant treatments, where evidence of response or resistance may not become apparent for many years.

How serious is this problem?

The behaviour of cytochrome P450 3A4 (CYP3A4) offers a useful starting point for exploring the significance of the interaction problem. This enzyme plays a greater or lesser role in metabolising the tyrosine kinase inhibitors (TKIs) dasatinib (Sprycel), erlotinib (Tarceva), gefitinib (Iressa), imatinib (Glivec), lapatinib (Tyverb), nilotinib (Tasigna), sorafenib (Nexavar) and sunitinib (Sutent), and indeed some non-TKI anti-cancer drugs such as docetaxel, irinotecan, taxol, vincristine, etoposide, ifosfamide and tamoxifen.

If a patient's CYP3A4 levels increase above the range considered normal, these drugs are likely to be broken down into inactive compounds and flushed from the system too quickly, giving them less chance to do their anti-cancer work – effectively an underdose. If levels of the same enzyme are too low, however, more of the drug remains active in the body for longer than intended – effectively an overdose that could lead to very serious side-effects.

CYP3A4 levels seem to be affected by a wide spectrum of substances. The United States National Library of Medicine lists 38 prescription drugs – including antifungals, antibiotics and antidepressants – that inhibit CYP3A4 (making the cancer drug more toxic). It lists a further 20 drugs that induce CYP3A4 (reducing the efficacy of the cancer drug). Added to this are many CAM products and common foods known or suspected to interact with the enzyme – including grapefruit, starfruit, St John's Wort, kava-kava, cat's claw, valerian root, milk thistle, goldenseal, black cohosh, many herbal teas, ginseng, and genistein (found in soy products). The potential for problems is clear.

Some of these interactions pose a very serious threat (see table overleaf). The antifungal drug ketoconazole, for instance, can lead to a five-fold increase in serum concentrations of dasatinib, and a three-fold increase with nilotinib and lapatinib. While serum concentrations of many of the TKIs are reduced by more than 80% in the presence of the bactericidal antibiotic rifampin. St John's Wort, known as the 'sunshine herb', and commonly used in many countries as a natural remedy to treat insomnia, sadness and depression, is known to reduce serum concentrations of imatinib by 30%, and is likely to have a similar effect in other TKIs.

Interactions that are flagged up as potentially dangerous by preclinical pharmacological data do not always play out in the clinic, however, as can be seen from the clinical data on sorafenib (see table), where ketoconazole shows no effect on serum concentration levels. It is therefore difficult to tell which of the substances featured on lists of inhibitors or inducers actually do pose a danger for

which cancer drugs, as only a minority have been studied in a clinical setting. Indeed, many potential interactions would be unlikely to occur in practice – perhaps because the interacting drug is taken at a different time of day, or prescribed for too short a time, or the dose is too low to have a serious impact.

More of a worry, perhaps, are the hundreds of non-prescription products that cancer patients take of their own volition and that have never been subjected to pharmacological scrutiny.

How widespread is this problem?

Drug interactions cannot always be avoided, but so long as they are identified, they can at least be managed. The danger lies in interactions that are not being identified, and by their very nature it is difficult to know how widely this is happening.

Research by Molassiotis et al. (*Ann Oncol* 16:655-663) showed that around 35% of Europe's cancer patients use some form of CAM, with rates in some countries as high as 73%. Not every CAM is biologically active, but a lot are, and very little is known about how these products may interact with cancer medication. Molassiotis found that herbal medicine was the most used CAM in the majority of countries and was in the top five CAM types used in every country bar one. Megavitamins/vitamins/minerals, homeopathy, and medicinal teas were also all in the top five in at least half of the countries surveyed.

Studies confirm what is already well known among patient advocacy groups – that doctors are often unaware of what additional substances their patients are taking. They seldom ask and patients can be reluctant to reveal the information, perhaps for fear of being ridiculed or told to stop, or simply because they don't perceive 'natural' remedies as relevant.

There is less excuse for such communication failures with prescription medicines. General practitioners wanting to prescribe an antibiotic will usually ask their patients if they are taking any other prescription medicines and in most cases they know if their patient is being treated for cancer. Community pharmacists who provide the antibiotics should be aware of what other prescription drugs that patient is taking. However, they may not, if those drugs are delivered by the hospital, which is usually the case with chemotherapy and, in many countries, with oral cancer therapies.

In the absence of computerised medical records and automatic interaction alerts, the system relies on professional vigilance, and there are many opportunities for potential problems to be overlooked.

A study of the literature on the frequency of drug–drug interactions (DDIs) in cancer published in the *Annals of Oncology* last year (vol 20, pp1907–1912), found

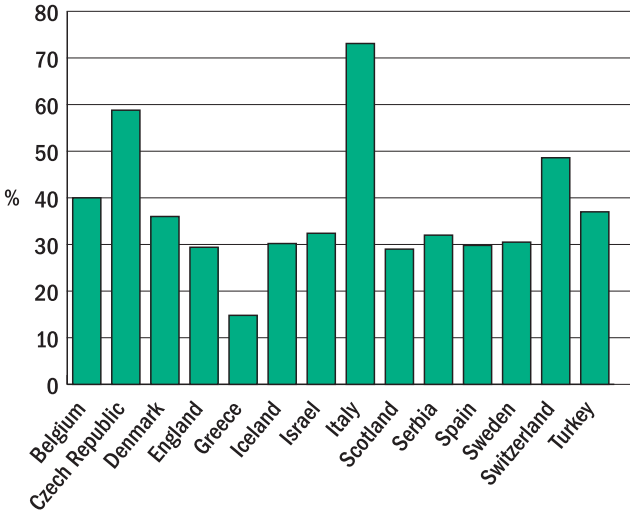
SOME INTERACTIONS CAN HAVE A MAJOR IMPACT

Object Drug	Inhibitor	Inducer	Comments
Dasatinib	Ketoconazole		5-fold ↑ AUC
		Rifampin	>80% ↓ AUC
Erlotinib	Ketoconazole		>85% ↑ AUC
		Rifampin	>80% ↓ AUC
		Smoking	Smokers have 65% lower AUC than nonsmokers
Gefitinib	Itraconazole		60%–80% ↑ AUC
		Rifampin	>80% ↓ AUC
Imatinib	Ketoconazole		80% ↑ AUC
		Rifampin	75% ↓ AUC
		St John's Wort	30% ↓ AUC
Lapatinib	Ketoconazole		3.6-fold ↓ AUC
		Carbamazepine	75% ↓ AUC
Nilotinib	Ketoconazole		3-fold ↑ AUC
		Rifampin	80% ↓ AUC
Pazopanib	Ketoconazole		3-fold ↑ AUC of pazopanib eye drops
Sorafenib	Ketoconazole		No change in AUC
		Rifampin	37% ↓ AUC
Sunitinib	Ketoconazole		50% ↓ AUC
		Rifampin	45% ↓ AUC

AUC – area under the curve (effective concentration of the drug)

Source: J Horn and Philip Hansten, *Pharmacy Times* April 2010 (http://www.pharmacytimes.com/issue/pharmacy/2010/April2010/DrugInteractions-0410)

Use of CAM in cancer across Europe



Around 35% of Europe's cancer patients are thought to use some type of CAM – much of it biologically active. Herbal medicine was in the top five most popular types of CAM in every country surveyed bar one. Megavitamins/vitamins/minerals, homeopathy, and medicinal teas were in the top five in at least half of the countries

Source: Molassiotis et al. (2005) *Ann Oncol* 16:655–663

only eight publications, six of which reported on potential interactions, with only two trying to estimate the frequency of actual interactions. It concluded that "although it seems that one-third of cancer outpatients are at risk of DDI, the proportion of them who actually suffer from DDIs remains unknown." They advise caution, in particular, in prescribing warfarin, anticonvulsants and antihypertensives.

Warnings have also been sounded about the risk of interactions between tamoxifen and antidepressants. Estimates (Horn and Hansten, *Pharmacy Times*, March 2009) suggest that almost a third of patients on tamoxifen are taking antidepressants. But many antidepressants – particularly fluoxetine (Prozac), paroxetine (Paxil), bupropion (Wellbutrin) and duloxetine (Cymbalta) – are known to significantly inhibit the enzyme CYP2D6, which is needed to make tamoxifen do its job.

A recent retrospective clinical study did not find evidence that all these drugs reduced the effectiveness of tamoxifen in clinical practice, but it did find almost double the risk of death (91% increase) among women taking paroxetine for at least 75% of the time they were on tamoxifen. Excess mortality was reduced to 24% increased risk if the overlap was only for 25% of their time on tamoxifen (Kelly et al. 2010, *BMJ* 340:c693).

It is difficult to know how many of the doctors who prescribe antidepressants, the pharmacists who administer them and the breast cancer patients who take them are aware of these dangers. There is anecdotal evidence that awareness is not as high as it should be even among psycho-oncologists. And while some breast cancer advocacy organisations such as Mamazone in Germany cover this issue in their national and regional education days and provide information and advice on their website, the UK advocacy organisation Breast Cancer Care makes no mention of it in their patient leaflet on tamoxifen, and nor does the website of the Macmillan Cancer Support.

A GROWING CONCERN

Jutta Hübner, a medical oncologist specialising in the use of CAM, who heads the department of Palliative, Supportive and Complementary Therapy at the University Cancer Centre in Frankfurt, is reluctant to hazard a guess at the scale of the interaction problems among cancer patients. She is convinced, however, that it is steadily growing. "The problem with TKIs and drugs like that is they are for the long term. Chemotherapy lasts for about three months, and in most cases it is only the day of therapy itself that is the really sensitive period. TKIs, or even oral chemotherapy, is something patients take at home, so the possibility of interactions is much greater."

She points to the steady rise in the number of CAM substances now available on the Internet, including a lot of traditional Chinese and Ayurvedic medicines which are often biologically highly active, but in ways that have never been pharmacologically investigated. Compounding the effects of this rise in supply is a parallel rise in demand, with the trend for patients to want to know more and take more personal responsibility for their own health. "Our patients learn that they have to look for themselves in the system. And when you look for yourself, you find some things that are good and some things that are problematic. It is very hard for the patients to know which way to go."

Hübner offers a couple of examples from her own recent experience to illustrate how various and unpredictable are the potential problems. One patient on chemotherapy had come in after suffering very serious side-effects. It turned out that she had been drinking her own urine, having read that this could help fight the cancer. As her urine contained large quantities of the metabolites of the chemotherapy drug that had been flushed from her system, she was in effect giving herself a second dose.

Another patient who had been doing very well on chemotherapy recently turned up at clinic, also suffering very serious side-effects. This wasn't a problem with interaction. It was simply that since starting a 'cancer diet', she had lost so much weight that the chemotherapy dose she had started on

"Some things are good and some things are problematic – it is very hard for patients to know which way to go"

was now too big for her reduced body mass, and the change had gone unnoticed. Hübner says, "She could have had very, very serious consequences, but fortunately they stopped the chemotherapy. This is an example that shows we really should be careful to ask our patients what they are doing." .

Doctors are aware that interactions can be a problem, she adds, but they don't really know what to look for. "Most of our data about interactions are derived from preclinical experiments in laboratories and animal experiments, whereas most interactions that really happen are not reported." She worries that there is too much hype around some of the pharmacological data on interactions, and cites the recent flurry of articles around green tea and bortezomib (Velcade) as a case in point.

"There are pretty few data, and I've had so much discussion with patients: 'Can we drink one cup of green tea a day or not?' I think we need to calm down. There is even a new paper saying green tea extract and Velcade go very well together." If you create too much hype over very uncertain data, you end up with a confused picture that can make life very stressful for patients and very difficult for oncologists when they are asked for advice.

"The question always for a doctor is what to tell the patients. We can't say, 'Don't use all these things', because, using the example of green tea and Velcade, the problem is not just green tea; any antioxidant will do exactly the same. So if you want to say 'no green tea', you also have to tell the patient: 'Don't eat any fruit, don't drink any tea, drink water and eat bread and that's all.'" Which, as she points out, is pretty much the advice some patients are given. "I have seen some sheets for patients telling them what they should not eat, and sometimes I'm asking, 'For heavens sake what do you eat if you have to be careful of all these things?'"

Hübner, who chairs the CAM working party of the German Cancer Society (Deutsche Krebsgesellschaft), wants to see a whole new approach to dealing with this issue, based on:

- regular communication with patients
- a more open-minded approach to CAM, based on seeking expert advice rather than always advising against, and
- a systematic effort to build up an evidence base about which substances present significant interaction problems with which therapies in clinical practice.

With her colleagues on the CAM working party, she is recommending the use of a questionnaire that could be used in outpatient clinics and hospitals to regularly screen patients about what they are doing. This would be backed up by an expert advice centre that doctors could turn to for advice on interactions, This would allow the patient to 'own up' to taking something without feeling they will be punished by their oncologist.

They also want to set up a register where doctors can report interactions or unexpected side-effects, in order to compile information and to allow doctors to swap notes with colleagues elsewhere whose patients are taking similar compounds.

Hübner herself has been arguing for many years about the need for guidelines on CAM, including simple and clinically relevant information on interactions, to replace the current reliance on lengthy lists of hypothetical dangers. This would be helpful for doctors and for pharmacists, she suggests, but also for patients, many of whom are currently well aware of the dangers of interactions, but hazy on details. "Nearly everyone seems to have heard of St John's Wort and grapefruit," she says, "but often they assume that if they stay away from these two products then everything else is OK."

As so often happens, however, the clinical studies needed to draw up these guidelines and develop knowledge and expertise in this area are being held up by lack of funding. "We have many interesting projects, but no funding. We are waiting for a response from the Deutsche Krebshilfe, (German Cancer Aid) which gives support to research, and I am talking to many other people who may give some money to some of our projects. This is a big difference to the US system where the cancer centres get public funding for their complementary activities as well."

A role for pharmacists

Hübner and her colleagues can expect support for their efforts from one key group of professionals, who 10 years ago joined together to form the European Society of Oncology Pharmacy. ESOP believes oncology pharmacists are perfectly positioned to play a key role in communicating with patients about interactions, side-effects and adherence, as the trend towards long-term oral therapies reduces the contact

between patients and their cancer clinic.

At a European level they are still trying to identify the role currently played by ESOP members in their contact with cancer patients in different countries, to which end they conducted a survey, published last year in the *European Journal of Oncology Pharmacy* (vol 3, p 25). This asked a number of general questions, but also looked specifically at how well equipped they are to advise patients with CML (chronic myeloid leukaemia) – a particularly relevant group because of the long-term nature of their treatment and the variety of oral therapies.

At the same time, ESOP's German affiliate is forging ahead with proposals designed to significantly step up the contribution pharmacies play in the long-term management of cancer patients. If successful, it could provide a template that could be adjusted for use elsewhere.

These proposals seek to:

- Ensure every patient on oral cancer therapies receives accurate, relevant and concise information
- Provide for regular consultations where the pharmacists get feedback on side-effects, adherence and about what else the patient is doing that might affect their therapy, and can offer advice

Klaus Meier, the president of ESOP, has been at the forefront of developing and pushing forward these proposals on behalf of its German affiliate, the Deutsche Gesellschaft für Onkologische Pharmazie (DGOP). Like Hübner, he feels the currently available interaction lists are of little use in advising patients, and together with the German Cancer Society, the DGOP has started consulting with pharmaceutical companies and others with a view to drawing up patient-friendly leaflets for use in pharmacies.

"If you tell patients 20 topics, they will have forgotten 18 when they leave," says Meier. "We want to focus on just, for instance, the three main drugs and the three main non-prescription drugs with which it will not work. We will choose those that do the main harm, and those that may not be quite so harmful, but are most widely used."

This would be supplemented by a questionnaire. Part would be filled out by the patient at home, to record for instance when they take their drug and what side-effects they experience. The rest would be filled in at a monthly consultation with the pharmacist, including a question about what else the patient is using to promote their health. Such a system would allow pharmacists to individualise their advice, says Meier. "We want to know what really is going on with the patient, and not just fill them up with general stuff. What really is the problem?"

If successful, such procedures should not only help improve patient outcomes, but could also provide a goldmine of information on adherence, side-effects, what CAM patients are using, and symptomatic interactions. But Meier knows that getting pharmacies to expand their role in this way will be neither cheap nor easy. As a means of enforcement, the DGOP is actually proposing to extend to all oral cancer drugs the conditions demanded by the European regulatory body, EMEA, for the administration of thalidomide – the drug that caused a wave of birth deformities when it was first introduced in the 1960s, which was recently given approval for use in patients with multiple myeloma. Should these proposals be accepted, both doctors and pharmacists would be required to sign on the prescription for any oral cancer medicine that they have given key information to their patients and asked certain mandatory questions.

"There's also the question of financial support, if you ask pharmacists to have more time and space in their pharmacy for private consultations," adds Meier – not to mention the cost of the additional training, which the DGOP has already started, with a series of courses running across Germany's 16 regions.

German pharmacies are under pressure in today's cost-conscious environment to justify the monopoly position they hold, and this may be part of the motivation behind the DGOP's bid to step up the value-added they can offer for cancer patients. But it is hard to deny the need for the sort of systematic, individualised and informed follow-up of patients on oral therapies that they are proposing, whether this is done in pharmacies, or in out-patient clinics, as Hübner suggests, or by cancer nurses over the phone.

Meier argues that you not only benefit from a reduction in the likelihood of potentially fatal interactions, but also maximise the value for money from very expensive cancer drugs. With some oral therapies costing tens of thousands of euros per patient per year, it would surely be worth a little investment to ensure that their effects are not largely wiped out by a bottle of sunshine herb purchased at €12.95 from the local corner shop.

"We want to know what is really going on with the patient, not just fill them up with general stuff"

Yes we can treat cancer – even in the poorest countries

So says Ian Magrath and his INCTR partners, and they have the evidence to prove it

➜ Simon Crompton

Ian Magrath has spent more than a decade helping develop strategies and build capacity for treating cancer and researching new protocols in low- and middle-income countries, including in areas that had no facilities at all. The foundations built over these years, and the experience gained, will be crucial to the success of current efforts to stem the rising tide of cancer in the developing world.

Upstairs in the Brussels offices of the International Network for Cancer Treatment and Research (INCTR) are shelves packed with colour-coded box files. They contain data from clinical trials conducted all over the world, and each has a story to tell. Ian Magrath, president of the network, points to the navy blue, sky blue, green and red files containing data about INCTR research on breast cancer.

The story he tells about the blue file from a cancer institute in India is that 40% of women diagnosed with breast cancer never get treatment – it's either too advanced, or the women simply can't afford the time away from family responsibilities. In Pakistan, many of the information forms were chewed by rats. In Egypt, many records weren't available because some departments were reluctant to share information.

This is a world of cancer that few of us in higher-income countries encounter. But it's a world with which Magrath, at the helm of the network for 10 years, is intimately familiar. He's at pains to point out the statistics that should make the rest of us sit up and think. "85% of the world's population lives in low- and middle-income countries, but there are far fewer cancer facilities in these countries than in the rich world," he says. "Around 80% of all childhood cancers are in developing countries, and 70% of cancer deaths are in low- and middle-income countries because access to care, for the most part, is extremely poor and expertise of all kinds is very limited."

"We in the rich world are actually losing out by paying so little attention to cancer in developing countries. Not only is there the humanitarian issue, but we're missing research opportunities to learn more about cancer that would benefit everyone."

It's a strength of conviction borne of a working lifetime spent challenging the assumption that cancer is the same whether it's in the USA or Africa; that cancer knowledge is easily transferable from country to country; that the best treatments devised for the developed world are also best for the developing world. But he's also proved it is possible to research and implement effective treatments and care structures that suit resource-poor environments – if only you work closely with doctors and care-givers there.

INCTR

The Burkitt lymphoma ward, St Mary's Hospital, Lacor. The low-cost, low-tech, less-toxic protocol used to treat these patients has proved its worth in other African centres, and was recently introduced at this highly respected hospital in northern Uganda after it joined the INCTR Burkitt's lymphoma programme

People assume that tackling cancer in a country like Africa is too complex, too expensive, and not a high priority compared to infectious disease, says Magrath, but they're wrong. With life expectancy increasing, cancer is overtaking infectious diseases, and, indeed, all other causes as the leading cause of global death, and there are more deaths from cancer in the developing world than from AIDS, tuberculosis and malaria combined, he argues. Only in the low-income countries do deaths from all infectious diseases combined outweigh those from cancer.

Furthermore, it is possible to achieve big cuts in cancer mortality in low- and middle-income countries. But this can't be done by sending over CT scanners, linear accelerators or expensive targeted therapies, as the main problem is that most patients are diagnosed too late. What is needed are simple and unglamourous interventions: introducing tobacco control, improving healthcare structures, ensuring prompt diagnosis, using locally appropriate protocols that best utilise surgery, radiation therapy and cheap and well-established chemotherapy drugs.

A spectacular success

The most spectacular example of how successful this approach can be is a protocol devised by Magrath many years ago for the treatment of Burkitt's lymphoma – a fast-growing cancer that has been the focal point of Magrath's career. Rare in the western world, Burkitt's lymphoma is the commonest of childhood cancers in equatorial Africa, causing 3000 deaths every year. Low-tech treatment protocols pioneered by Magrath and colleagues in the 1970s and adapted since then have resulted in survival rates in countries like Egypt and India rising from 45% to 70%–80%. They form the basis of ongoing attempts to improve survival rates in equatorial Africa.

His work has won him acclaim – he's received numerous awards, including the Princess Adela Bint Abdullah Recognition Award in Childhood Cancer, earlier this year. But Magrath is not the type to sell his achievements. Talking at the INCTR offices, housed

in the concrete block of the former Institut Pasteur, in Brussels, he recounts a career where he has written more than 340 articles centred on the pathogenesis and treatment of malignant lymphomas and leukaemias, as well as cancer in developing countries. He has also headed research on paediatric lymphoma at the US National Cancer Institute (NCI).

But as he chats, he consistently focuses on what he feels is important or interesting rather than dwelling on what has been achieved. Sometimes this involves a detour into evolutionary theory, philosophy or Chinese wisdom, but Magrath always remembers where he left off and returns to a starting point. He calls it his 'grasshopper' mind – "I go through phases where I'm interested in languages, then music, then quantum physics or mathematics."

He's always been a bit of an independent thinker, he reflects. Perhaps it had something to do with coming from what he describes as a "relatively humble background". He was brought up in a post-war London he can only remember as black, the buildings smothered in soot, food still rationed. "I suppose part of what drove me was a desire to get beyond the world in which I found myself and so I pushed hard to go to medical school. To be a doctor was something that as a child I couldn't conceive of being within the realms of reality."

After his basic medical training at the University of London, he developed an interest in cancer while a senior house officer at Charing Cross Hospital under Ken Bagshawe, a world expert in the treatment of choriocarcinoma – a cancer found to be curable by chemotherapy alone by pioneering chemotherapists. This led to an early interest in the lymphoma discovered in the 1950s by British surgeon Dennis Burkitt – another cancer highly responsive to chemotherapy.

INCTR

Building capacity. This group of data managers from centres across India are on an INCTR training course on monitoring outcomes in acute lymphoblastic leukaemia. The ALL protocol used in India was developed more than 30 years ago by Magrath (pictured standing in the doorway), in conjunction with staff at cancer centres in India

A taste of Africa

Magrath wasn't convinced he wanted to follow the conventional medical career course. He yearned for colour beyond monochrome London and was intrigued about how a condition such as Burkitt's lymphoma should be so rare in the UK whilst apparently so devastating in equatorial Africa. So in 1971 he started work at the Lymphoma Treatment Centre in Kampala, Uganda, run jointly by the American NCI and Makerere University.

His tenure there was to have a lasting effect. "It obviously made me want to continue in the field of oncology, because one could see some patients with massively disfiguring Burkitt's lymphoma of the jaw being cured by even one or two doses of chemotherapy alone," says Magrath. "It was also clear to me that patterns of cancer were very different in Uganda from in the UK." Along with Burkitt's lymphoma, hepatocellular carcinoma and Kaposi's sarcoma were very common (even prior to the AIDS epidemic). Here were some interesting research opportunities, thought Magrath.

Low-tech treatment protocols have resulted in survival rates rising from 45% to 70%–80%

"The knowledge is metastasising across India as young trainees at the cancer centres go off and use it elsewhere"

The potential to follow them up in a fully equipped laboratory increased when the American NCI contingent left the centre – mainly, says Magrath, because of the difficult situation being created by Uganda's notorious President, Idi Amin. It was not unusual at that time to hear gunshots coming from the nearby university campus. But in 1974, he was invited by the NCI to become a senior investigator at the new paediatric cancer branch being established at their headquarters in Maryland, USA. He was asked if he'd like to work there for a couple of years. It turned into a stay of 26 years, with Magrath eventually becoming chief of the lymphoma biology section.

His research over those years followed up the leads he found in Uganda, examining the treatment and molecular pathogenesis of B-cell lymphomas, particularly Burkitt's lymphoma, and the causative role of Epstein-Barr virus. This was no research sideroad, emphasises Magrath.

"Burkitt's lymphoma is so interesting not just because it is curable by chemotherapy, but because it led to the discovery of Epstein Barr virus," he says. The virus infects 95% of people – up to 100% of people in parts of the developing world – causes infectious mononucleosis and is associated with cancers such as nasopharyngeal cancer, types of T-cell lymphoma and Hodgkin disease. It was discovered from a cultured cell line derived from Burkitt's lymphoma cells in 1964. "It's also important because there's a specific chromosomal translocation associated with Burkitt's lymphoma which provided a model for understanding related cancers."

The potential practical applications for his research became clear when hospitals around the world began to ask him for help. In 1976, the director of a cancer institute in Chennai, India (then internationally known as Madras), visited the NCI seeking help because all the children she was treating for acute lymphoblastic leukaemia were dying. "All my colleagues were off doing examinations for their boards, so she spoke to me. I became interested in the problem, and asked her to send me some slides of blood and bone marrow, as well as information about the treatment they were using." Later, he visited the Indian centre himself and convinced the doctors that, though they wanted to set up a bone marrow transplant unit, a better option was to first make sure they were treating patients properly with standard therapy, adapted to the local circumstances. "We worked with them, and other hospitals that became interested in Bombay [Mumbai] and Delhi,

A fighting chance. This mother got her child to Tanzania's Ocean Road Cancer Institute, which has been using the INCTR protocol for Burkitt's lymphoma with great success for more than five years – most mothers in Africa will have no such facility to turn to

TRISH SCALAN

"I became interested in countries where often there wasn't just bad treatment but no treatment at all"

and developed a treatment protocol specifying the use of particular drugs at particular stages of treatment, which led quite rapidly to a doubling of the survival rate. This, or closely related protocols, are still in use in India, and the survival rate has continued to improve over the years. The knowledge is now metastasising across the whole of India as young trainees at the cancer centres go off and use it elsewhere."

The survival rates are now around 60%–70% – lower than in the US and Europe, because of lower levels of supportive care, more high-risk patients and later diagnosis, but it is a similar rate to high-income countries 10 years ago and to high-risk patients today. "It may be that they're getting as good results as they realistically can, given the patient population and available resources," says Magrath.

Later on, the same protocols were successfully used in another project, in Egypt, funded by the United States Agency for International Development. Magrath started to travel the world researching leukaemias and lymphomas and their treatment, discovering, with his colleagues, differences in the molecular abnormalities behind these cancers in different parts of the world.

Serving the greatest need

"In the 1990s, I became more and more interested in the tremendous need of these countries, where often there wasn't just bad treatment but no treatment at all. In countries like India and Brazil there were some centres able to provide high levels of treatment, but in the rural regions of many low- and middle-income countries it was like going back to the Stone Ages. I wanted to dedicate all my time to cancer in developing countries, and I started to look for ways to accomplish that."

The opportunity came in 1999, when he was appointed president and medical director of the INCTR. It had been founded a year earlier by the Belgian Institut Pasteur and the International Union Against Cancer (UICC), to help build capacity for cancer treatment and research in less economically developed countries. The executive committee of the NCI agreed to provide support.

Magrath, who still holds an NCI position and is adjunct professor of pediatrics at the University of the Uniformed Services in the Health Sciences, has concentrated INCTR efforts on children's and women's cancers – in part because paediatric cancers

INCTR

A strategy for the coming decade. To mark its 10th anniversary this year, INCTR invited representatives from the WHO, the IAEA, the UICC and the American NCI to a gathering in Brussels to review the successes and failures of past initiatives and discuss strategies for taking cancer control forward in developing countries

are his own field of interest, but also because of the vast numbers of children and young people in developing countries. Women are also more vulnerable in these countries, which generally remain patriarchal, yet much can be done for patients with, for example, early breast or cervical cancer. At the core of the organisation has been a mission to help health services find what works best in the here and now.

Before the establishment of the INCTR, which is still funded largely – though not exclusively – by the NCI, this wasn't happening to any significant extent, says Magrath. "You need to understand the local resource limitations and do research that's regionally appropriate. You have to be prepared to train and educate the professional staff – select a disease or discipline, and one or more centres, and try to develop those into centres of excellence or reference centres, with whom we can work on a long-term basis so that you develop a standardised, evidence-based approach to treatment, agreed with colleagues." Such centres also become resources in their own countries, where they serve as training centres and help improve access in other regions to better diagnosis, treatment and palliative care, which is sadly lacking in low- and middle-income countries in spite of enormous need."

These standardised approaches are then assessed in clinical studies – which examine the effectiveness of the treatment, and how it may be affected by the context in which it is given. "At the same time, because people have to collect data, they learn about evidence-based medicine – it's a concept that doesn't exist in much of the developing world, and it's important that we help train them in this." Currently, treatment protocols developed in the UK or USA are often modified in developing countries to cut costs, without follow-up to determine outcomes.

Tailored solutions

The obstacles to good cancer care in poorer countries are completely different to those in richer ones, says Magrath. There's the lack of human resources: in Tanzania, 16 histopathologists serve a population of 40 million while in Switzerland there are 400 histopathologists for 7 million people. There's the lack of physical resources – blood supplies are often very limited, for example. There are organisational problems that mean that chemotherapy drugs often don't arrive where they're needed. And there's a crucial lack of supportive care, which changes the whole nature of cancer management.

"If we took the treatments presently used for Burkitt's lymphoma in Europe and the United States, and applied them, unmodified, in equatorial Africa, we would probably kill more people than we cured," says Magrath. "Such treatments are very intensive, and many of the patients would die of toxicity, given the limitations in supportive care, poor hygiene and the higher incidence of underlying infections and infestations."

Which raises questions, says Magrath, about what international organisations mean when they call for the 'best' cancer treatments to be made available in every research setting. The World Medical Association's Declaration of Helsinki says that, in medical research, a new intervention must be tested against the 'best current proven intervention'. But 'best' where? "If you say 'best available in the world', then research in most developing countries would not be possible, because such treatment may either be unavailable, unaffordable and/or inappropriate given the local circumstances. We need to develop research designs that are appropriate for disease profiles, affected populations, and existing healthcare and support systems for cancer patients in developing countries."

That is not to say that Declarations of this kind do not play an important role, he is quick to add. "They focus attention on a specific problem and can often bring people to the realisation that one size does not necessarily fit all." Initiatives such as the UICC's World Cancer Declaration can also be important in helping bring problems to the attention of governments and civil society, and mobilising political will. "But expectations must be tempered in terms of their short-term benefits. For example,

"Many patients would die of toxicity, given the limited supportive care and higher rates of underlying infections"

INCTR
International Network
for Cancer Treatment and Research

Founded in 1998 by the International Union Against Cancer (UICC) and the Brussels-based Institute Pasteur, and largely funded by the American NCI, the International Network for Cancer Treatment and Research:

- is dedicated to reducing the suffering and the number of lives lost to cancer in developing countries;
- aims to promote evidence-based practice through long-term research projects investigating the most effective approaches to cancer care in specific settings, and supporting the growth of centres of excellence and training networks;
- has programmes in clinical research, pathology, palliative care and paediatric oncology, as well as programmes building capacity in clinical research, primary healthcare (for early detection), and gathering data to support evidence-based cancer control;
- has branches in Brazil, Cameroon, Canada, Egypt, France, Nepal, Tanzania, UK and USA;
- is creating, with other organisations, an open access resource of cancer educational materials, to aid the education of health staff and students in developing countries.

For further information see: www.inctr.org

they cannot be expected to have a rapid beneficial effect on incidence or survival rates in developing countries – only appropriate and sufficiently extensive actions in such countries can accomplish that, and signing declarations doesn't necessarily lead to action, especially when resources are so sadly lacking." Sensitising people to cancer, he emphasises is only half the battle. "You've got to have adequately trained healthcare professionals to diagnose and treat the people who have been sensitised and have symptoms that could be caused by cancer."

Magrath continually returns to the importance of the nuts and bolts of how you actually make people better. He avoids the exciting but often impractical aspirations for change that most of us get swept up by. So although the use of new technology – mobile phones, videoconferencing, e-learning, and web-based clinical information sharing – is very much on the INCTR agenda, he is wary of seeing it as a panacea (as some seem to) for the developing world's problems.

Such is his realism, that each time I ask Magrath what achievements he is proudest of, the conversation somehow strays into issues to be dealt with, or scientific discoveries awaiting a clinical response. One or two areas of satisfaction seep through: that this year the INCTR became one of only two cancer non-governmental organisations to enter into official relations with the World Health Organization; that by creating INCTR branches around the world he has helped create an international community of cancer professionals; that more people have access to palliative care in, for example, Hyderabad in India, or a poor region in São Paolo, Brazil or Katmandu, Nepal; that INCTR's project on Burkitt's lymphoma has now treated more than 360 children in four African countries. "Since that's the area where my international interest began, it represents a full circle in my journey," he says.

But then the hard demographics kick in again, and leave only a sense of the daunting task ahead. "Cancer is increasing, and if governments don't start doing something now, it's going to be more and more of a problem in the developing world as population structures change. If we miss the boat now, millions of people are going to die as a consequence."

"If we miss the boat now, millions of people are going to die as a consequence"

Chemoradiation in head-and-neck cancer — are we any closer?

Jacques Bernier and Lisa Licitra

A recent study analysed the timing of non-platinum chemotherapy in combination with radiotherapy in patients with head-and-neck cancer and showed that only those who had not undergone surgery benefited from the chemoradiation therapy. However, inconsistencies between some results of this study and those of previous studies, along with the advent of novel, less toxic combinations of radiotherapy, are likely to limit the development of the chemotherapy regimens used in their study.

In a recent study by Tobias and colleagues,[1] the authors report on the 10-year results of a UK head-and-neck trial (UKHAN1). This trial examined the effect of differential timing strategies of non-platinum chemotherapy administration, when combined with radiotherapy in patients with local advanced disease. In this study, 966 patients who had not undergone primary surgery were randomly assigned to receive either radical radiotherapy alone (group A, *n*=233) or radiotherapy with two courses of chemotherapy (chemoradiation). Individuals receiving chemoradiation were given the chemotherapy on either days 1 and 14 of radiotherapy (group B, *n*=166), days 14 and 28 after completing radiotherapy (group C, *n*=160), or both (group D, *n*=154). Patients who had previously undergone surgery were randomised to either radiotherapy alone (*n*=135) or concomitant chemoradiation alone (*n*=118). In all cases, chemotherapy consisted of either methotrexate alone, or vincristine, bleomycin, methotrexate and 5-fluorouracil. The primary endpoints were overall survival and event-free survival.

Among patients who had not undergone surgery, only those assigned to group B benefited from the addition of cytotoxic agents to radiation therapy, regardless of the endpoint (median overall survival or event-free survival). However, in patients who had undergone surgery, chemoradiation did not yield any significant benefit compared with radiation alone. The authors also reported an increase in acute toxicity (and a subsequent reduction in patient compliance) with chemoradiation, especially for those in groups C and D, and in patients who had previously undergone surgery.

When interpreting the results of this trial, the first consideration relates to the choice of drugs made by the investigators; a choice guided by the intention to use drugs less toxic and less expensive than platinum-derivatives. Did they achieve their objectives in terms of efficacy and drug safety profile? Upon reading these long-term results, one would be tempted to say these objectives were met "only partially". Indeed, while the results of this study are consistent with those comparing chemoradiation to radiation alone in patients who do not undergo surgery,[2] they are in sharp contrast with data accumulated to date in a postoperative setting.[3,4]

The results of the study by Tobias et al.[1] are in contrast with those of the European Organisation for Research and Treatment of Cancer (EORTC)[3] and Radiation Therapy Oncology Group (RTOG)[4] trials, as they indicate that patients who have undergone surgery for head-and-neck cancer do not benefit from the addition of

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This article was first published in ***Nature Reviews Clinical Oncology*** 2010 vol.7 no.5, and is published with permission. doi:10.1038/nrclinonc.2010.50, www.nature.com/nrclinonc

cytotoxic agents to radiotherapy. There are several possible reasons for this discrepancy. First, EORTC and RTOG investigators used a platinum-derivative, identified by the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) meta-analyses[2,5] as the compound of choice for patients treated with chemoradiation. Second, non-compliance to chemoradiation in the UKHAN1 trial was significantly greater in patients treated postoperatively, compared with patients who did not undergo surgery (27% vs 8%).[1] Notwithstanding the intention of the authors to deliver drugs less toxic than platinum-derivatives, the result of this non-compliance is that treatment intensity was reduced in a significant number of patients who had previously undergone surgical intervention. Furthermore, the toxic effects reported were not fully unexpected if one considers the usual toxicity profile of drugs like bleomycin (pulmonary and gastro-intestinal toxicity, skin reactions) or methotrexate (gastro-intestinal toxicity, myelosuppression, skin reactions, liver function impairment). The poor patient compliance, together with the fact that the chemotherapeutic agents used are known to be less efficacious than platinum-derivatives, casts doubt on any additive or supra-additive effect of the regimens delivered in this study.

In the group of patients who had previously undergone surgery, the intention was to completely clear the tumour. This objective was not achieved in a significant number of patients because in both arms surgical margins were cleared in only 47% of cases. Moreover, the authors provide no information regarding the time intervals between surgical procedures and onset of radiation or chemoradiation, a parameter known to impact negatively on local control when it exceeds six to seven weeks.

Furthermore, the fact that the chemotherapy in this study, in some cases, consisted of methotrexate as the sole cytotoxic agent raises some concern. Indeed, in 1986 the South-East Cooperative Oncology Group (SECOG)[6] demonstrated that addition of 5-fluorouracil to the vincristine, bleomycin and methotrexate (VBM) regimen yielded better results than VBM alone. In addition, the methotrexate dose used by Tobias et al.[1] was 100 mg/m^2, which is lower than the 200 mg/m^2 dose delivered in the SECOG study. In light of this, the chemotherapy schedule used by the authors might have been suboptimal.

The second consideration relates to patient compliance to treatment protocols. In patients who had not previously undergone surgery, only those in group B benefitted from the addition of chemotherapy to radiation. This finding actually mirrors the pattern of compliance to treatment protocols across the various treatment arms. There was considerable variation in compliance across the treatment arms, a factor that is likely to have significantly affected the reported efficacy because treatment intensity was significantly reduced, especially with respect to chemotherapy. This affect was particularly obvious in the arm that combined concomitant and maintenance chemotherapy in patients who had not undergone surgery, and in the treatment groups that combined radiotherapy and chemotherapy in a postoperative setting.

Interestingly, the direct relationship between poor compliance to chemoradiation and a less-favourable outcome is a systematic finding in this study. While a low level of non-compliance (8%) was associated with a significant benefit in patients treated by chemoradiation who had not undergone surgery, a high proportion of non-compliant patients in this study inevitably translated into an absence of therapeutic gain, regardless of the sequence of treatment modalities. Specifically, non-compliance in patients who had not undergone surgery was 44% and 31% with regards to chemoradiation plus maintenance chemotherapy and maintenance (adjuvant) chemotherapy, respectively. The non-compliance rate was 27% for patients treated by chemoradiation who had undergone surgery.

In summary, the UKHAN1 trial attempted to identify a pragmatic alternative to platinum-based protocols for the treatment of head-and-neck cancer, with respect to treatment cost and toxicity. However, the volume of data generated throughout the past decade in favour of these latter protocols, as well as the advent of regimens based on the combination of less toxic, targeted therapies with radiation,[7] is likely to limit the impact of this study on the current use and future development of chemoradiation in head-and-neck cancer.

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

Practice point

In contrast with recent data from randomised trials, which demonstrated a significant benefit in favour of the concomitant delivery of chemotherapy and radiotherapy for patients who undergo surgery, the present study did not elicit any benefit for non-platinum-based chemoradiation regimens in a postoperative setting. Beyond the fact that regimens using agents other than platinum-derivatives are known to be less efficient, this inconsistency might derive from the high rate of non-compliance to the treatment protocol observed in this trial, with a subsequent, significant reduction in dose intensities.

Competing interests: Jacques Bernier is a consultant for Imclone, Merck-Serono and Sanofi-Aventis. *Author affiliations:* Centre de Radio-Oncologie de Genève, Geneva, Switzerland (Jacques Bernier); Head and Neck Cancer Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy (Lisa Licitra)

Preoperative biliary drainage – better stents in specialised centres are needed

John Neoptolemos and Christopher Halloran

A recent trial concluded that preoperative biliary drainage (PBD) in patients with pancreatic head cancer increases complications but is unlikely to change clinical practice. The difference in the outcomes reported was because of excessive complications in the PBD group using plastic stents. We argue that these patients need treatment in regional pancreatic cancer centres using low-occlusion metal stents.

It is common practice that patients with obstructive jaundice caused by a tumour in the head of the pancreas undergo preoperative drainage of the biliary tree. This enables partial resolution of the physiological impairment of the liver parenchyma secondary to biliary obstruction, and allows easier logistical planning for both preoperative staging and surgery. Until now, the collective evidence could neither support nor refute preoperative biliary drainage (PBD) for patients with obstructive jaundice needing surgery.[1]

The recent Dutch multicentre trial reported by van der Gaag et al.[2] concluded that routine PBD in patients undergoing surgery "for cancer of the pancreatic head" increases the rate of complications. Patients with serum bilirubin >250 μmol/l were excluded as presumably all of these individuals had preoperative endoscopic stenting. The study was not blinded; 202 patients deemed to be resectable by preoperative staging using CT were randomised to surgery within one week of diagnosis (n=94) or PBD for up to six weeks before surgery (n=102). The trial opened in November 2003 and closed in June 2008. The primary endpoint was the rate of serious complications within 120 days of randomisation. In the final analysis, the mean time to surgery was 1.2 weeks for the early surgery group and 5.2 weeks for the PBD group. 74% of patients in the PBD group had serious complications versus 39% of patients in the early surgery group. However, the outcomes following surgery in both groups including major complications, hospital stay, readmission rates and mortality were similar. Thus the difference lay in the complication rates associated with the biliary stenting.

While the quality of the trial itself was satisfactory, we contend that the setting almost certainly predicted the outcome. The stenting was probably performed mostly in district general hospitals, although this is not specifically reported by the authors. Remarkably, antibiotic prophylaxis was left to local policy, while all patients undergoing laparotomy received perioperative antibiotics. Moreover, the use of plastic stents undoubtedly contributed

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This article was first published in ***Nature Reviews Clinical Oncology*** 2010 vol.7 no.5, and is published with permission. © 2010 Nature Publishing Group. doi:10.1038/nrclinonc.2010.45, www.nature.com/nrclinonc

to the outcome. The 46% complication rate following biliary stenting (perforation, bleeding and cholangitis) was far in excess of that which could be reasonably expected. The initial procedural failure rate was 25%, and in these cases percutaneous transhepatic stenting was employed, which is known to have a high complication rate (the number of percutaneous stents actually used was not reported). Most studies report an initial stent failure rate of around 5%–10% and a similar range for serious complications.[3,4]

Overall, stent occlusion accounted for more than half of the episodes of cholangitis, which occurred in 26% of patients who underwent endoscopic stenting, and necessitated a second endoscopic procedure in one third of these patients. This is almost certainly related, in part, to the routine use of plastic stents rather than short, non-foreshortening, self-expanding metal stents that are associated with a very low rate of occlusion and hence a minimal rate of acute cholangitis.[5] Indeed, the authors of the Dutch study themselves recognise this point, although only within the context of neoadjuvant treatment.

The authors also decided to include eight regional hospitals in addition to the five academic centres in order "to provide operating-room capacity to ensure that early surgery could be performed as required by the protocol".[2] Although each of the participating hospitals performed at least 10 resections of cancer of the pancreatic head per year, these would still be regarded as relatively low-volume hospitals and may account for the rather poor surgical results.

Resection was performed in only 67% of patients in the early surgery group and 56% in the PBD group, although it is noted that the authors relied entirely on CT for staging and apparently did not use laparoscopy or serum CA 19–9 levels.[6]

Surgery-related complications occurred in 37% of patients in the early surgery group and in 47% of patients in the PBD group. Furthermore, repeat laparotomy was required in 14% and 12% of patients in the early surgery group and PBD group, respectively. Death from any cause occurred in 13% of patients in the early surgery group and in 15% of patients in the PBD group. These mortality figures are excessive by any consideration and again emphasise the need to focus pancreatic cancer oncological management including surgery in regional high-volume cancer centres.[7-10] In addition, there is recent evidence that dramatically reducing the level of bilirubin preoperatively may actually improve survival in the medium-term follow up period.[10]

There are further criticisms of this study. The body-mass index, which is an adverse risk factor, was significantly higher in the PBD group compared with the early surgery group (25.2±3.9 vs 24.0±3.1, P=0.03); however, this imbalance might be due to the relatively small patient numbers in the trial.

The title of the article, "Preoperative biliary drainage for cancer of the head of the pancreas",[2] is itself probably a misnomer. It is not at all clear from the text whether the 95% of patients in the early surgery group and the 90% of patients in the PBD group who had "adenocarcinoma" actually all had pancreatic ductal adenocarcinoma. In fact, it seems that the study population probably comprised patients with periampullary cancer, and therefore also included patients with ampullary and bile duct cancers (both of these groups normally have significantly better interventional outcomes than individuals with pancreatic ductal adenocarcinoma). If this were so, the results are even harder to interpret.

We conclude that this study is unlikely to change the routine use of PBD as there might be specific needs for preoperative staging beyond CT[6] as well as neoadjuvant therapy. The focus needs to turn to patients undergoing endoscopic stent insertion in regional pancreatic cancer centres, and the need to use more modern, short, non-foreshortening, self-expanding metal stents with a low occlusion rate.[3–5]

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

Practice point

Preoperative biliary drainage before surgery in patients with tumours in the head of the pancreas using plastic stents is associated with a high incidence of complications due to stent occlusion.

Surgical outcome was unaffected by preoperative relief of jaundice in the context of unselected centres with a high postoperative morbidity and mortality.

Consideration should now be given to using low-occlusion, modern, short, non-foreshortening, self-expanding metal stents with a low complication rate.

This will provide a logistical advantage enabling more considered preoperative staging, the potential to use neoadjuvant therapy, and planning of surgery.

The study indicated rather poor results from both stenting and surgery, reinforcing the benefit of undertaking these procedures in high-volume regional pancreatic cancer centres.

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NEWSROUND

Selected reports edited by Janet Fricker

Widespread paediatric use of CAM

→ Pediatrics

Many paediatric patients with cancer use complementary and alternative medicine (CAM), according to a systematic review. It is important, conclude the authors of the UK study, that paediatricians be made aware of the extent of CAM use and furthermore encourage open communication with patients and their parents.

The researchers, led by Felicity Bishop from the University of Southampton, in England, set out to investigate the prevalence of CAM use among paediatric cancer patients and the quality of studies undertaken. The study, they said, represents the first comprehensive systematic review to summarise all the available evidence. The team developed a quality assessment tool (QAT) for surveys on CAM use composed of 17 items that assessed the quality of study design, data collection and data analysis on the reported information.

In total the team reviewed 28 studies, 14 of which were conducted in North America, with the remainder coming from the UK, Turkey, Israel, Singapore, Mexico, Taiwan, Denmark, Finland, the Netherlands, Germany, Hungary and Australia. Altogether, the studies surveyed a total of 3526 children from 14 countries, between 1975 and 2005.

Prevalence rates of CAM use found in the studies ranged from 6% to 91%, with 14 of the articles reporting prevalence rates between 20% and 60%. Herbal remedies were the most popular CAM modality (with use ranging from 2% to 48%), followed by diets/nutrition (3%–47%) and faith healing (3%–30%). Other CAMs commonly used included homeopathy (1%–17%), megavitamins (2%–19%), mind body therapies (9%–27%) and massage therapies (2%–17%).

Results showed that quality of the studies was mixed, with QAT scores ranging from 19% to 79%. Half the studies attained less than 50% of the maximum QAT score.

Altogether, 14 of the articles reported reasons for the children's CAM use, including to help cure or fight the child's cancer and to provide symptom relief from the cancer itself and from the side-effects of standard treatment. CAM use did not appear to be associated with the gender, age, ethnicity or family income of the paediatric patients, indicating wide use across all demographic groups. It did, however, appear to be more common in families with higher parental education.

"Additional research is warranted to better understand this behaviour [CAM use] and to determine and address any needs for patient support and education on CAM use," write the authors, adding that research should prioritise the cost-effectiveness and safety of the modalities.

"Pediatric oncologists need to be aware that their patients (and patients' parents) will be seeking and integrating other therapeutic approaches while undergoing conventional treatments," write the authors.

Limitations of the studies included lack of standardisation of sociodemographic details and definitions of CAM use. Osteopathy, for instance, is considered to be a CAM in the UK, but not in the US. The authors suggest that the use of a generally agreed-on definition of CAM, such as that provided by the NCCAM, alongside a standardised questionnaire would help

achieve the collection of consistent data across different settings.

■ F Bishop, P Prescott, Y Chan et al. Prevalence of complementary medicine use in pediatric cancer: a systematic review. *Pediatrics* 21 April 2010, 125:768–776

Deaths relating to gastric cancer reduced with more extensive lymph node removal

➜ Lancet Oncology

D2 extended lymphadenectomy delivers better locoregional control and cancer-specific survival than limited D1 surgery in patients with advanced gastric adenocarcinoma, concludes the 15-year follow-up results of the Dutch Gastric Cancer Trial (DGCT). The D2 procedure was, however, found to be associated with significantly higher postoperative mortality, morbidity and reoperation rates.

The extent of lymphadenectomy for curative resections in patients with gastric cancer has been under debate for several decades. For the DGCT trial, Ilfet Songun and colleagues from Leiden University Medical Centre, in the Netherlands, set out to assess the effect of D2 compared with D1 surgery on disease recurrence and survival in patients with resectable primary adenocarcinoma of the stomach. In all, 711 patients from 80 participating hospitals were randomly assigned (by means of a telephone call to the central data centre of the trial) between August 1989 and July 1993 to D1 dissection (n=380) or D2 dissection (n=331). D1 dissection entailed removal of the involved part of the stomach or the entire stomach including the perigastric lymph nodes (N1 level, station numbers 1–6) and the greater and lesser omenta. In D2 dissections, both the N1 and N2 lymph nodes (station numbers 7–11) were removed along with the omental bursa and the front leaf of the transverse mesocolon.

Of note is the fact that, at the time of trial, resection of the spleen and pancreatic tail were regarded as necessary for adequate removal of D2 lymph-node stations 10 and 11 in proximal tumours. Today, however, surgery for gastric cancer can be done with a spleen-preserving and pancreas-preserving D2 resection technique, unless removal is indicated because of tumour invasion into these organs.

The five-year results of the study, published in 1999 in the *New England Journal of Medicine*, showed no significant survival benefit in the D2 group, and a higher postoperative morbidity and mortality. However, the 11-year follow-up data, published in 2004 in the *Journal of Clinical Oncology*, showed better survival results in exploratory analyses in patients with stage II and IIIa disease who underwent D2 in comparison with D1 resections.

The results of the current study show that the overall 15-year survival was 21% (82 patients) for the D1 group, versus 29% (92 patients) for the D2 group (P=0.34). The gastric cancer related death rate was significantly higher for the D1 group (48%) compared to the D2 group (37%) (HR 0.74, P=0.01), whereas death due to other diseases was similar for both groups. Local recurrence was 22% in the D1 group versus 12% in D2, while regional recurrence was 19% in D1 versus 13% in D2.

Patients who had the D2 procedure had significantly higher operative mortality rates than those who had the D1 procedure (P=0.004), higher complication rates (P<0.0001) and higher re-operation rates (P=0.00016). Further results showed that patients older than 70 had significantly lower overall survival in both the D1 and D2 treatment groups, male patients had lower survival than female patients in the D2 group (P<0.001) and patients undergoing splenectomy and pancreatectomy had significantly lower overall survival in both D1 and D2.

"Considering that a safer, spleen-preserving D2 resection is currently available in high-volume centres, and our findings of better recurrence and gastric-cancer-related survival rates, D2 resection now seems likely to be the recommended approach for patients with resectable (curable) gastric cancer," conclude the authors.

Commenting on the subgroup analyses, they add, "In selecting patients with gastric cancer for surgery, we do not think that elderly patients should be denied surgery. However, we cannot advocate extensive surgery, especially in elderly male compared with female patients."

In an accompanying commentary, Kevin Roggin, Josh Hemmerich and Mitchell Posner, from the University of Chicago Medical Center, write, "Further debate on the absolute value of extended lymphadenectomy will likely detract from a needed emphasis on defining the optimum timing, choice of drugs and ordering of chemotherapies in patients with gastric cancer."

The authors go on to highlight inconsistencies in the studies, and question why the study did not show differences in gastric cancer deaths until several years after the procedures. "If we assumed that most of these recurrences were secondary to metastatic nodal disease that was not resected with D1 lymphadenectomy, why would the disease remain clinically quiescent for several years in the absence of adjuvant chemotherapy?"

■ I Songun, H Putter, E Meershoek-Klein Kranenbarg et al. Surgical treatment of gastric cancer: 15 year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncology* 20 April 2010, 11:439–449

■ KK Roggin, J Hemmerich, MC Posner. Extended follow-up after extended lymphadenectomy for gastric cancer: was it worth the wait? *ibid* pp 404–405

UK GPs overlook older women with suspected ovarian cancer

➜ British Journal of Cancer

Family doctors appear to be less likely to recognise and refer older women with suspected ovarian cancer for investigations as quickly as younger patients, concludes a UK study. The findings, suggest the authors, may partly explain the UK's poor cancer mortality rates for older people.

Recent studies have suggested that older patients in the UK are not benefiting as much from improvements in cancer treatments as younger counterparts. Rosemary Tate and

colleagues, from Brighton and Sussex Medical School, decided to investigate whether this might partly be due to differential rates of referral, using ovarian cancer as an example.

Studying the General Practice Research Database (GPRD), the investigators identified all women aged between 40 and 80 years on 1 June 2002 with a "Read code" for ovarian cancer recorded between June 2002 and May 2007. Using these records, the investigators compared the GPRD incidence of ovarian cancer with rates compiled from UK cancer registries and investigated the relationship between age and coded investigations for suspected ovarian cancer.

Of the 1107 cases registered on the GPRD over this period, 73% had been coded as having at least one relevant investigation or referral to a gynaecologist in the year before diagnosis. The proportion decreased with age – results showed that 82% of under-55s had undergone at least one investigation in the 12 months prior to diagnosis, in comparison to 75% of 55-to 69-year-olds and 66% of people aged over 70 years.

The researchers also found that GPs were slower to refer elderly women. Women aged 45–69 were typically referred within 10 weeks of visiting their GP, while those aged between 75 and 79 years usually waited for 20 weeks before seeing a specialist.

The rates of recorded diagnoses of ovarian cancer in the GPRD, the researchers found, were lower than those recorded in UK cancer registries for all age groups. However, these differences were much larger for patients aged over 60. For example, for women aged 45–50 the difference was only 5% as compared with 22% for those aged between 75 and 80.

"This study, based on recent information from GP surgeries, suggests that there is a decline in recorded investigation and referral in older women for ovarian cancer," conclude the authors. "Such delays could be an important cause of avoidable morbidity and mortality, and if our results are generalisable to other cancers, they could contribute to the lower survival rates and higher mortality rates experienced in the United Kingdom compared with other European countries."

While the investigators could not say whether the results could be generalised to other cancers, they added, "ovarian cancer would seem to be a good example to study as it is one of the most common cancers experienced by older women, and its prognosis is greatly improved if it is diagnosed at an early age."

The researchers stress that while the reasons for the discrepancy between the GP database and the UK cancer registry are not clear, they might be explained in part by how and when the data were recorded. It may be possible that GPs are less motivated to record cancer diagnoses in older people if they have other serious illness. Furthermore recording details of the disease may be deemed to be less important for older people.

The researchers now plan further studies investigating the different strategies used by GPs in different age groups, and exploring whether these findings can be generalised to other cancers.

■ A Tate, A Nicholson, J Cassell et al. Are GPs under-investigating older patients presenting with symptoms of ovarian cancer? Observational study using General Practice Research Database. *Br J Cancer* 2 March 2010, 102:947–951

Chemotherapy improves survival in NSCLC

➔ Lancet

Chemotherapy improves survival for patients with operable non-small-cell lung cancer (NSCLC), a meta analysis of 47 studies from the NSCLC Meta-analyses Collaborative Group has concluded.

The UK and French investigators, led by Sarah Burdett of the Medical Research Council Clinical Trials Unit, in London, set out to assess the effects of adjuvant chemotherapy, with or without postoperative radiotherapy, in patients with NSCLC who had begun treatment on or after 1 January 1965. The group has previously undertaken two meta-analyses. The first, published in 1995, suggested that chemotherapy with cisplatin-based regimens delivered a 5% improvement in five-year survival that was not statistically significant (HR 0.87, *P*=0.08); while the second meta-analysis, published in 2008, (which included only trials with modern cisplatin-based regimens) found a significant survival benefit of 5.4% (HR 0.89, *P*=0.005). Unlike the group's previous meta-analyses, the current analysis was restricted to patients with early-stage disease.

"In these meta-analyses, we have an opportunity to bring together most trials undertaken during the past few decades, and to assess the effectiveness of adjuvant chemotherapy in patients with non-small-cell lung cancer world wide," write the authors.

The investigators included trials (not confounded by additional therapeutic differences) comparing surgery plus adjuvant chemotherapy versus surgery alone, or surgery plus adjuvant radiotherapy and chemotherapy versus surgery plus adjuvant radiotherapy. The primary endpoint was overall survival, defined as time from randomisation until death from any cause.

The comparison of treatment with surgery alone to treatment with surgery and chemotherapy was made using information from 34 trial comparisons (8445 patients and 3323 deaths). Results showed the addition of chemotherapy provided a 4% absolute increase in survival at five years, from 60% to 64%.

The comparison of treatment with surgery and radiation to treatment with surgery, radiation and chemotherapy included information from 13 trial comparisons (2660 patients,1909 deaths). Results also showed a 4% absolute increase in survival at five years from the addition of chemotherapy, from 29% to 33%.

Subgroup analyses did not show any statistically significant effect of age, sex, histology, performance status, stage or type of chemotherapy on survival benefit. The authors, however, point out that the subgroup analyses contained only small numbers, delivering too low statistical power to detect clinically meaningful differences.

"Our results show a benefit of adjuvant chemotherapy after surgery, which has been already shown in some large trials but not in others," write the authors, adding that although

the absolute survival improvements of 4% at five years are fairly modest, they might result in 10,000 more patients being alive at five years.

In an accompanying editorial, Gregory Kalemkerian, from the University of Michigan, in Ann Arbor, writes, "Because adjuvant chemotherapy has already gained acceptance, the results of these meta analyses add little to clinical practice. Although the studies do offer insight into some unresolved questions, they lack power to provide definitive answers."

He added that adjuvant platinum-based chemotherapy can be recommended for patients who have complete resection of stage II-III NSCLC and have uncomplicated recovery with good performance status within three months of surgery. "Treatment can be considered for patients with larger tumours (T2b, T3) without lymph-node involvement. The scarcity of data means adjuvant treatment cannot be recommended for patients with stage IA." Future studies, he stressed, should focus on the role of adjuvant therapy in patients with IA disease and those aged older than 70 years, and the use of biomarkers to select those who would benefit from specific treatments.

■ NSCLC Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet* 24 March 2010, 375:1267–1277

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Dutasteride cuts prostate cancer risk but delivers questionable clinical benefit

➜ New England Journal of Medicine

Dutasteride reduces the risk of prostate cancer in men at high risk for the malignancy, results from the REDUCE trial have found. But in an accompanying editorial, Patrick Walsh from John Hopkins University, in Baltimore, Maryland, stressed that dutasteride only reduced the risk of low-grade tumours, considered unlikely to be of clinical significance, and appeared not to affect aggressive high-grade tumours, considered more likely to be lethal.

Testosterone, the major circulating androgen in men, is converted to the intracellular androgen, dihydrotestosterone, by steroid 5α-reductase isoenzymes, designated as type 1 and type 2. Dihydrotestosterone is known to drive benign prostate growth and the development of prostate cancer, leading to a move for treatments to target it. Finasteride inhibits the type 2 isoenzyme, while dutasteride inhibits both isoenzymes. Results of the Prostate Cancer Prevention Trial (published in the *New England Journal of Medicine* in 2003), which evaluated finasteride in men with no increased risk of the disease showed that, compared with placebo, finasteride reduced the risk of prostate cancer by 25%, but among the tumours that were detected, there was a 27% increase in the number with Gleason scores of 7–10.

In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, conducted at 250 sites in 42 countries, Gerald Andriole and colleagues, from Washington University (St Louis, Missouri), report on the effect of dutasteride in reducing the risk of prostate cancer. The trial included 8231 men, aged between 50 and 75, who had an increased risk of prostate cancer as reflected by an elevated PSA level, but no evidence of cancer on biopsies performed within six months of enrolling in the trial. They were randomised to receive a 0.5 mg daily dose of dutasteride or placebo, and underwent a 10-core transrectal ultrasound-guided biopsy at two and four years.

Results at four years show that 659 of the 3305 men (19.9%) taking dutasteride were diagnosed with prostate cancer compared to 858 of 3424 men (25.1%) taking placebo ($P<0.001$). Dutasteride, it was calculated, was associated with a relative risk reduction of 22.8% (95% CI 15.2–29.8, $P<0.001$). Among men with a family history of prostate cancer, the drug reduced the relative risk of a prostate cancer diagnosis by 31.4%. None of the men in the study died of prostate cancer.

Of particular note are results showing that during year 3 and 4 there were 12 tumours with a Gleason score of 8–10 in the dutasteride group, as compared with only 1 in the placebo group ($P=0.003$).

The drug was associated with an unexpected rise in the composite endpoint of cardiac failure, which included heart failure, ventricular failure, cardiopulmonary failure and congestive cardiomyopathy. However, no significant differences were found between the two groups in terms of the rates of cardiovascular events or cardiovascular mortality.

"Among men at increased risk for prostate cancer and for benign prostatic hyperplasia, dutasteride reduced the risk of prostate cancers and precursor lesions and improved many outcomes related to benign prostatic hyperplasia," concluded the authors, adding that dutasteride may be considered as a treatment option for men at increased risk for prostate cancer.

In the commentary, Walsh pointed out that the reduction in the rate of incident cancer was limited to the incidence of prostate tumours with Gleason scores of 5 to 6 (which are moderately well differentiated), and there was no significant reduction in the incidence of tumours that were less differentiated (Gleason scores of 7 to 10), which are considered more likely to be lethal.

"Dutasteride and finasteride do not prevent prostate cancer but merely temporarily shrink tumours that have a low potential for being lethal, and they do not reduce the risk of a positive biopsy in patients who have an elevated PSA level or an abnormal digital rectal examination," wrote Walsh.

Furthermore, he added, introducing these drugs for prevention may be risky. "Because PSA levels are suppressed, men may have a false sense of security, and if prostate cancer ever develops, the diagnosis may be delayed until they have high-grade disease that may be difficult to cure."

■ GL Andriole, DG Bostwick, OW Brawley et al. Effect of dutasteride on the risk of prostate cancer. *NEJM* 1 April 2010, 363:1192–1202

■ P Walsh. Chemoprevention of prostate cancer. *ibid* pp 1237–1238

When sex lives suffer

What some cancer patients go through, and how oncology teams can help

Peter McIntyre

Addressing issues of pain, fatigue and functional impairment such as incontinence is widely accepted as essential to helping cancer patients rebuild their lives. For many people, however, restoring a fulfilling sex life can be at least as important. Patients welcome good information, a listening ear and helpful advice. All too often, they don't get it.

When Dutch clinician Woet Gianotten talks to a group of young doctors or nurses he sometimes asks them to consider whether their parents still have sex. As they stumble backwards away from the question, he asks them something still more toxic. "What about your grandparents? Are they still at it?"

The best and brightest of the next generation of doctors and nurses seem suddenly to be distracted, staring at their shoes or studying something on the ceiling.

"OK," he reassures them. "We have established that your parents and grandparents never have sex. But let me tell you this – everybody else their age does!" He sees their faces begin to change. "They start to realise that as a professional they have to think about the sex life of people that age."

Quality of life issues are increasingly important in clinical training for oncologists and specialist cancer nurses, but it is still rare for anyone to talk to them about sexual health. Sex after cancer is considered as a side issue when measured against pain, incontinence and depression.

Yet there is real benefit in helping people to restore their sex lives after cancer – rebuilding self-esteem, confidence and a sense of purpose in life. There are even indications that a good sex life can increase tolerance to pain and prolong life, although there is woefully little hard evidence in this field.

One of the biggest barriers to finding out more about sexual dysfunction after treatment for cancer is the difficulty in opening up lines of communication between doctors and patients. Who is going to mention the sex word and when?

The effects of treatment

Cancer and cancer treatment disrupt and affect people's sex lives both physically and psychologically. The shock of diagnosis and the trauma of treatment naturally disrupt sexual activity, and it may not become obvious for six months or a year that things are not returning to normal.

Women treated for breast or gynaecological cancer may go into early menopause so that the vagina and vulva are no longer naturally lubricated. Radiotherapy to the pelvis can also induce a dry fibrotic vagina that is narrow (vaginal stenosis) and more susceptible to irritation, bleeding and tearing. Women who have a radical hysterectomy for cervical or endometrial cancer can lose a third of vaginal length. It is little wonder that many women end up suffering from dyspareunia (painful sexual intercourse). Apart from the mechanical effects on the body, treatment for breast cancer or gynaecological cancer brings fundamental hormonal changes that induce tiredness and loss of libido, while mastectomy or hysterectomy with loss of the uterus and ovaries often make a woman feel that she has lost her sexual identity.

For men too the effects are mechanical, hormonal and psychological. After surgery for prostate cancer, as many as 80% of men are left impotent, with about 40% of men treated with radiotherapy also losing the ability to have an erection. Those treated with hormone deprivation therapy lose their sex drive and, even where the mechanics of sex can be addressed through Viagra (sildenafil), Cialis (tadalafil) or Levitra (vardenafil), men may experience loss of libido or dry ejaculation and feel they have lost their manhood.

The benefits of good sex

Woet Gianotten has spent half a professional lifetime trying to help people restore their sex lives after stroke, cancer or spinal injury. "Sexuality is much more than only pleasure or fun," he says. "Sexuality also has positive physical effects. If you get sexually excited and you have an orgasm, your muscle tension goes down. That is why we sleep better after an orgasm. Sexual excitement also gives oxytocin, which is the hormone of pregnancy and delivery and breastfeeding and is also the hormone of trust between people. It is quite common for a man who has an orgasm to be able to talk afterwards. If I say this in a group I see a lot of women suddenly start to smile. They recognise their husband or boyfriend."

He says that women have a higher pain threshold after having an orgasm, and he sometimes encourages

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"Helping patients restore their sex lives after cancer can help rebuild self-esteem and a sense of purpose in life"

It is not the man with prostate cancer who does not want to talk – it is the physician who finds it difficult

cancer patients with bone metastasis to masturbate to help them with pain relief.

There are no randomised trials in patients treated for cancer to show the effect of sexual activity on survival, but in general Gianotten is convinced that there is a benefit. "We don't have trials, but we start to have a bit of indication that if you have a better sex life you live longer. In men, the frequency of sex determines how long they live, and in women the quality of the sex life determines how long they live."

Opening up the discussion

Luca Incrocci, a radiation oncologist at the Erasmus medical centre, Rotterdam, and a qualified sexologist, is pressing for better communication, better diagnosis and better treatment.

Incrocci is president of the International Society for Sexuality and Cancer, and with colleagues organised the 2nd Rotterdam Symposium on this topic in June 2010, bringing together about 100 clinicians and nurses from across Europe. He says that an inability for patients and doctors to talk about this issue has a hugely negative impact on quality of life.

"Oncological treatments are very complicated and we are getting very aggressive and seeing big differences compared to ten years ago. That is good because more people are cured and overall survival is getting longer and longer, but of course we also see many more side-effects and problems in general and specifically more sexual problems.

"What we are trying to do now is to teach ourselves to try make it easier to talk about this problem. It is not the man with prostate cancer who does not want to talk about this – it is the physician who finds it difficult. The younger doctors ask, 'How can I talk to a 75-year-old man about this?' But it is getting easier. All these patients really do appreciate it when we talk to them and they know we are open to it."

He points out that a lot more men are now treated for prostate cancer in their 50s and 60s while still sexually active. But a proportion of older men are also still sexually active.

"Sex is not only for the young, the beautiful and the healthy. I have an 82-year-old man who uses Cialis just once a month and he says, 'I am very happy. I am a male again.' His partner is 65 and they have a great life."

Incrocci says that the issue has to be raised soon after diagnosis, even if addressing the problem can wait. "If you don't tell them before treatment that they will get a dry ejaculation because the prostate is not working, they will be frustrated. That is something they need to know before the treatment.

"Patients might have problems due to treatment, urinary incontinence after prostatectomy; proctitis after radiotherapy. At this moment the most important thing is not sex. But after a year they come back and say, 'You told me there would be a possibility of treating erectile dysfunction. Now I have time to talk about that.'

"We are seeing that in some category of patients, quality of life and sexual functioning is so important that it can really make a difference in the choice of treatment."

Louis Denis, distinguished Belgian onco-urologist and himself a prostate cancer patient who is now secretary of Europa Uomo, the European patient organisation, goes further. Not only should men be given information about the effect on their sex life as soon as they are diagnosed, but they should be encouraged to keep up sexual activity before they are treated.

He points out that patients generally have a three-month delay before treatment begins, so they can consider how important sexual activity is in their relationship.

"Someone diagnosed with prostate cancer is probably not thinking of having intercourse. We want to reassure them that, up to the moment of treatment, they should maximise erectile potential. There should be some sexual activity, including masturbation, to prevent atrophy of the penis.

"We call that rehabilitation of the penis in advance, in the same way that we do with exercises for incontinence – nobody gets operated on without exercise for these muscles.

"HOW I REBUILT MY SEX LIFE"

Denton Wilson discovered he had prostate cancer at the age of 42, after watching his father die from the disease in Jamaica. When Denton, a champion body builder and fitness expert, returned home to Sheffield in the UK, he was determined not to die the same painful death.

Despite some scepticism from his GP, Denton was tested and found to have a cancer. The following year he had an operation at a Sheffield teaching hospital.

"I was told that I would not be able to have an erection and I would have peeing problems. I was advised to save sperm in case I wanted to have more kids. I saw my father die and saw the pain he went through, so I decided to go for the operation. I was just thinking of surviving really."

Afterwards he found himself incontinent and impotent. "I was wet all the time and I had to wear these nappies. That was uncomfortable. I never went out. I was basically housebound."

He had always been sexually active, but now he felt no sexual urges at all. "I could not feel anything. I felt useless and disheartened. I did not feel like I was a man any more."

Denton believes in exercise and positive thinking. "I kept doing the exercises and willing myself to get better. I had to get strong by doing pelvic floor exercises to strengthen my bladder."

His doctor offered him a pump to help him get an erection – but it was painful and undignified, and he rejected the idea of stents to make his penis rigid. Viagra, then a new drug, did help, but his girlfriend thought that sex-on-a-pill made him untrustworthy, and this contributed to them breaking up.

Eventually, Denton found his sexual function restored – he started waking up with an erection in the morning.

"Now I can have an orgasm and it feels much the same but I do not really ejaculate. I feel my sexual performance is better than it was before and I think this is due to my training. I cannot produce sperm but my life is more fulfilled."

Now at the age of 54, Denton talks to men in Sheffield about the need to watch out for prostate cancer.

"I don't think the black community in Britain are aware of this. That is why I am doing the work I am doing to show what can be done. If there is something that is going to knock their performances they would rather not do anything about it until it is too late. I tell them I have gone through that and I have got a good sex life, and I am all right."

"I feel my sexual performance is better than it was... I cannot produce sperm but my life is more fulfilled"

"My sex life is better – because I focus on it more"

At the age of 43, Gabriela was diagnosed with cancer in both breasts. She was the mother of a nine-year-old son, and divorced. Her life was thrown into turmoil. "I was very frightened because at first I thought I would die."

She had a double mastectomy followed by chemotherapy and the following year had her uterus and ovaries removed. Gabriela, a teacher in Lisbon, Portugal, feared this was the end of her life as a sexual being. "How would I reconstruct my life? Would I ever flirt again or be in love? I felt that this era of my life would be completely erased."

But she received strong support from friends and from a psychologist attached to her oncology team, and she felt her attitude changing.

"My point of view was, I have survived the worst, which was the threat to my life. I should adapt myself to the situation and try to do something fun."

> "I felt that this era of my life would be completely erased"

She had her breast reconstruction and found "I was in better shape than I was before and that was erotically interesting!" She went back to full time teaching and used social networking Internet sites to start dating.

At first this did not go well. "I felt I had an obligation to disclose my condition. I would do a lot of selection and try to have a lot of conversation and meetings. But when things were starting to get hot, I felt that I had to behave honestly and I was in a rush to tell. I was very anxious and stressed."

Mostly, after this conversation the man would disappear and she would never hear from him again. "I understood it was too much information, too soon. The next time my reaction was, let's go to the movies and concerts and take my time get to know the person. This new approach was OK!

"I am now in the stage that every woman has. Sometimes I have a relationship and sometimes I don't. I am a woman of my age."

Her view of men has changed. "Women have a prejudice and think men are neurotically emotionally limited. But men are not all narrow minded. They vary a lot. The best reaction from a man is for him to say 'I am not in love with your breasts; I am in love with you.'"

Gabriela is now more confident and assertive. "My sexual satisfaction is better because I focus better on looking for it. I do things I would never do before. I would say that now I am more secure in myself. I know what I want and I know what I don't want and I don't think I will ever be trapped in a relationship again. Naturally, I sometimes have fears for the future but I have a bit of empowerment. I am the master of myself. It gave me insight about life and love and affection."

As vice president of the patient association, Viva Mulher Via, Gabriela helps to ensure that other women undergoing treatment for cancer get access to psychological support. "In Portugal we have a culture of some repression in speaking about these issues. I had the opportunity for group therapy after my surgery, when I was really frightened about the future. These conversations with older and experienced women were very important. Many women live with this issue in a very solitary way. I think it should be included in the after care as part of breast cancer survival."

"Sexologists place more importance on communication between a couple than on pills and plastics"

"If there is a real interest from the patient, it is important that he still uses his penis. The penis is not just hanging there like your ear. It is an organ that goes up and down during sleep even if you don't have sex to keep vessels intact and the overall physiology active." Denis says that patients need advice on healthy living. He also encourages patients who want to have a sex life in the future to think about what turns them on.

"You have your body memories, fantasies or recall of actual events. They should not suppress them but can use them as a form of excitement. You need to be relaxed, nice music, pleasant company and massage and a bath and it goes a lot better. When you are tired and stressed and your wife is as well, then trying to have sex does not help too much."

However, research by Incrocci and colleagues at Erasmus University in Holland suggests that as soon as men have a diagnosis of cancer, their sex life takes a turn for the worse. "The moment the patients have the diagnosis of prostate cancer they already have a decrease in libido. They may have erections and an interest in sex, but they are more thinking about the consequences of prostate cancer. What I found in patients in that particular phase, where patients have not yet had treatment but have had a diagnosis, is that they are more interested in intimacy than in sexual activity."

The gender divide

Most experts agree that men and women respond differently to sexual difficulties – men being more concerned about the mechanics and women with the psychosocial and emotional impact. But this difference should not be overstressed. Often the cancer patient – man or woman – is more concerned for their partner than for themselves.

Isabel White, cancer nurse, researcher and a psychosexual therapist from King's College, University of London, did her PhD on the assessment of women's sexual difficulties after pelvic radiotherapy. She found that sexual problems started to become important 6–12 months after treatment.

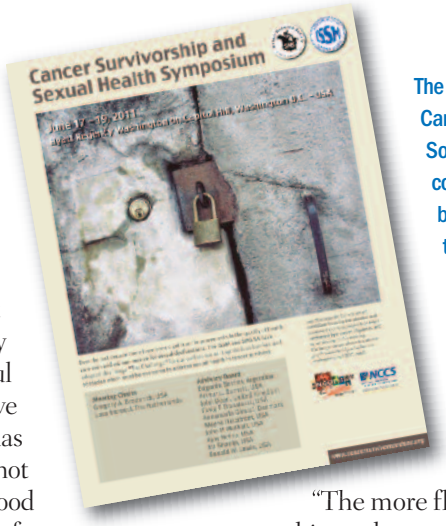
"Many of these women have had surgery to start with and then a combination of radiotherapy and chemotherapy, and for the first six months they are really still recovering from the onslaught of that, psychologically and physically. Many of them feel very fatigued. It is probably only from the six-month mark onwards that many feel well enough to broach the issue of sexual expression."

Women were better informed about the bladder and bowel side-effects of radiation than about possible side-effects on their vagina and the subsequent implications for sexual function. "It tends to be not as well discussed and not discussed in as much detail. Bowel and bladder are daily issues and sexual function is usually not."

Clinicians found it easier to speak to younger women in their 40s and 50s than women over the age of 70. "Some clinicians are superb at this but others find it more difficult to have a conversation about sexual consequences. If the person doing the explanation is embarrassed at discussing sexual issues with an older women the age of their grandparents or does not know as much about sexual consequences, it tends to be subsumed in all the other information they need to give."

Incrocci sees a big difference in reactions to sexual problems between a man and a woman. "A woman is not that interested any more in penetration after such a treatment, but they still want to be sexually active. They are interested in caressing, in intimacy, in masturbating and in stimulating. These things are still very, very possible after treatment for gynaecological cancer.

"You have to talk in a very different way to these women because they are shy about coming to the hospital to talk about that. But I have many patients who have accepted not having penetrative sex either because the man cannot get an erection or because the woman cannot be penetrated, and they are still having a great sexual life because they have found other ways."



The Challenge. This image, from the Lilly Oncology on Canvas℠ collection, was chosen by the International Society for Sexual Medicine to publicise their conference in June next year, as it symbolises barriers and obstacles which must be overcome to address sexual health in cancer survivors

Offering hope

Drugs such as Viagra have been very helpful for many men – but they do not work if there is no erectile function to build on, and while they stimulate blood flow to the genital area, they do not directly affect libido. This is one reason why they have not proved successful for women – a man gets positive feedback from the fact that he has an erection, but a woman does not become excited by increased blood flow to her clitoris and vulva. So far there has been no "pink Viagra" for women, although there are hopes that the selective serotonin uptake drug flibanserin may help women with loss of sexual desire – it had interesting side-effects on women taking it as an anti-depressant.

Women who no longer get wet naturally can use saliva, intimate lubricants or creams (although most doctors warn women treated for breast or endometrial cancer against using vaginal oestrogen creams). A woman whose vagina has narrowed can use vaginal dilators – like a small plastic 'trainer' penis – to gradually increase their capacity for penetration. There is anecdotal evidence that women are reluctant to do this once or twice a week. "They certainly don't find it an enjoyable experience and some find it reminds of them of their illness," says Isabel White. A Cochrane Review found poor-quality research evidence about whether dilators are helpful.

Therapists and sexologists tend to place more importance on communication between a couple and with the clinician or nurse than on pills and plastics.

Isabel White points out that even where Viagra helps a man it can be problematic for his partner. "How acceptable is it to see someone taking a tablet to become aroused? Unless you explain that he has to take a tablet because the treatment has altered his nerve and vascular function and in his head he is still aroused, you can find communication breakdown and the partner may be resentful."

Isabel White always tries to see couples together, since openness to discussing possible solutions and support of the partner are both crucial. "The more flexible and open the woman is to making changes with her partner the more amenable she is to being helped.

"If it is a relationship with good lines of communication, then the couple are more able to move forward. If one partner has always found sex a bit of a trial and has a rigid repertoire, and the couple cannot communicate with each other, then it is more of a challenge to initiate change."

Men sometimes find it less acceptable to substitute non-coital sexual expression for intercourse, but Isabel White helps the couple to explore solutions.

"We find out what helps them get aroused, whether that is fantasy, erotic language, erotic literature, visual images, either static or films." However, she does not recommend becoming over-reliant on porn since it can be a barrier to real sex. "You can almost reach saturation point, where the imagery has to be more explicit to turn you on. You have someone disassociated from the emotion of having sex with a partner and it can become a very lonely and isolating experience." In almost all cases, she says, couples can be helped to improve their sexual experiences even if they cannot go back to penetrative intercourse.

Where are the services?

The UK and the Netherlands are perhaps more advanced than most European countries in offering sexual support to cancer patients, but even here services are patchy. Even where sexual therapy

"He was shocked and angry with his surgeon for not keeping him informed"

"90% of couples could be helped by existing staff in oncology departments if they knew how to do it"

services exist, oncologists and patients may be unaware that they are there.

Throughout Europe, there are pockets of excellence. In Rotterdam, clinicians run outpatient clinics at nil extra cost to the hospital. At the Hospital de São José in Lisbon, the multidisciplinary care team for breast cancer has a clinical psychologist present whenever a woman is given her diagnosis. The head-and-neck cancer service is developing a similar system. Clinical psychologist Luzia Travado says that team work and training are essential to help professionals identify who may be having problems.

"Only when you open the dialogue and ask about their problems and allow space for them to say what is going on and use your listening skills will they open up. You make an environment where the patient feels safe to tell you about their most private issues – and of course sexuality is the most private issue of all."

Travado recalls having a 65-year-old married man referred to her private practice in a depressed and suicidal state because of erectile dysfunction following prostate surgery. "He was shocked and angry with his surgeon for not keeping him informed. He told me, 'If I had known this I would have preferred to live less and have my sex life back.'"

Incrocci is campaigning to have sexual issues better recognised in the training of oncologists and in budgets. He points out that no European countries routinely pay for Viagra or for vaginal dilators, even though they may pay for a woman to visit a psychiatrist.

"There is something very contradictory here, because a psychiatrist is much more expensive than getting a set of vaginal trainers and getting help to start using them from a sexologist or their medical oncologist.

"Governments, ministries and European organisations don't really see sexual function as a very important side-effect of cancer treatment. They will deal with bowel problems or urinary incontinence, but sexual function is not seen as important."

Isabel White points out that the evidence base for knowing how to help men and women is very weak – and budgets for psychosocial research are declining. "People like me are competing for smaller and smaller amounts of money. If you have to choose between funding a study on depression and anxiety, or on sexual recovery, you will choose the problem that is perceived as most prevalent."

Even so, she says that 90% of couples could be helped by existing staff in oncology departments if they knew how to do it. "The problem we have is that the majority of health professionals do not feel they have the expertise to have that conversation. The first thing we need to do is to improve education and development of existing oncology staff for nurses and doctors so they can manage the short-term minor difficulties that people experience – the things that do not really require a sex therapist or long-term work."

Incrocci says that this year's Symposium in Rotterdam is a step on the way to raising the profile of sexual issues and cancer in Europe. "I cannot ask every oncologist to become a sexologist as well, but you must remain open. If the radiation oncologist, medical oncologist, urologist or gynaecologist never once asks about sexual function, it is such a frustration and disappointment for the patient. People today expect more from their physician."

The International Society for Sexuality and Cancer (ISSC) was founded in 2002 to heighten awareness about sexuality in cancer by fostering research, encouraging training and increased service provision, and providing a forum for discussion. Membership is open to cancer clinicians, experts in sexual medicine, social workers, nurses and psychologists. Patient groups are eligible for affiliated membership. The society website is www.issc.nu and Luca Incrocci, president of the ISSC, can be contacted on l.incrocci@erasmusmc.nl

International Society for Sexuality and Cancer