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Luzia Travado

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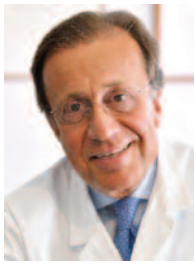

To cut or not to cut?

Why surgeons don't have all the answers

Alberto Costa ■ GUEST EDITOR

For more than one hundred years cancer was considered an external entity growing into the body and acting against it. The approach to treatment was: seek and destroy. Aggressive surgery, heavy radiotherapy, intensive chemotherapy were the norm. We now know that cancer cells result from genetic changes to normal cells, and we now try to 'cure' them without causing too much damage to healthy cells. Consequently, surgery has become more and more conservative.

When surgery was the principal way of treating most cancers, any cancer that was inoperable – for instance because it was so locally advanced that excision would inflict unacceptable functional damage – was, by definition, incurable. Nowadays, the use of combination treatments, radiotherapy and/or medical treatment can dramatically reduce the level of local invasion, making it possible to operate on previously inoperable tumours.

There are other ways in which the concept of operability is changing. For instance, poor cardiovascular health was always seen as a barrier to conducting cancer surgery. However, good pre-operative medical treatment can now address this problem and allow surgery to take place. Meanwhile, many surgical procedures that were once considered highly risky are now undertaken far more frequently, as cancer surgeons improve their results by specialising in particular types of surgery. Even the old rule of surgery – that you don't operate on a patient whose cancer has clearly spread to key organs – no longer applies. A greater focus on supportive care now means many more interventions are carried out to improve quality of life, for instance by treating intestinal occlusions or painful compressions.

With the greater weight given to the voice of the patient, their views are also influencing the concept of operability. Difficult as it is for health professionals to accept, patients sometimes refuse surgery because they dread the consequences of surgery more than the cancer itself, and they may not fully grasp the implications of their decision. The final word must be theirs, but effective communication and good psychological support can help them make a more informed analysis of the potential risks and benefits to reach the best decision for them. Some tumours will, of course, remain inoperable, and patients and health professionals will still sometimes have to accept this very frustrating reality, and leave the cancer to grow.

With multiple factors now influencing the concept of operability, the decision on whether or not to operate can no longer be left up to surgeons. The right decision can only be made through evaluation by specialists from multiple disciplines, communicated effectively to the patient, who will have the final say.

Alberto Costa is the scientific director of ESO, coordinator of the Breast Unit at the Maugeri Foundation, Pavia, Italy, and executive director of the Breast Unit of the Italian-speaking region of Switzerland (Canton Ticino), Bellinzona and Lugano, Switzerland

Luzia Travado:

improving outcomes for patients by attending to their distress

Marc Beishon

At a busy hospital in the centre of Lisbon, Luzia Travado managed to transform the role of health psychology from an intervention of last resort to a place in the frontline of cancer care, by showing time and again what can be achieved when you listen to patients and help them use their own coping skills. Her determination to improve the psychosocial care offered to cancer patients has made her a familiar face at seminars and conferences across Europe and beyond.

Given that a diagnosis of cancer often has a devastating emotional impact on people it is surprising that it is only relatively recently that 'distress' has started to be seen as the sixth vital sign to check for with patients. That is no fault of the advocates of psychosocial care in oncology, who have been patiently building up an impressive armoury of evidence for the role of health psychology in cancer. But the medical model in oncology – which is still catching up with the fifth vital sign, namely pain – is a tough mindset to change (the other four signs being, of course, temperature, blood pressure, pulse and respiratory rate).

"If you assess pain properly you might also be on your way to managing distress, as pain also has a psychological component," says Luzia Travado, head of clinical psychology at Hospital de São José in Lisbon, Portugal. "But if you don't ask the right questions at the right times you won't know what the patient is also enduring from a range of sources of emotional distress, not just pain, and so you could be neglecting a very important area of intervention.

"If you don't deal with distress – which can develop into depression, anxiety and maladjustment – patients will not have the best quality of life and clinical outcomes they might have had otherwise. They could stay in hospital longer, derive less benefit from chemotherapy, be a greater burden on their families and have a shorter overall survival."

About 50% of cancer patients will suffer from distress that may develop into psychological conditions such as depression, she says, which indicates the scale of potential need for support.

The evidence base for the impact of psycho-oncology interventions throughout the patient cancer journey is already strong and growing fast, adds Travado. "But there is still a lot of denial about the need to cope

JORGE NOGUEIRA

"We are part of the frontline team and not a separate department dealing with a different part of a patient"

with distress from both health professionals and patients, and the provision of psycho-oncologists in hospitals in countries such as Portugal is very mixed. At my hospital we have a team of seven clinical psychologists working in multidisciplinary teams in breast cancer, other cancer types and major health events such as burns and trauma. In other hospitals there may be only one part-time psychologist or psychiatrist and there is only so much they can do."

Across Europe too, the availability of psychosocial services varies greatly, although detailed figures are hard to come by at present. "If you look at whether psycho-oncology services are included in national cancer plans, a report from 2009 showed that of the 19 countries that had plans in Europe all specified palliative care and rehabilitation, and 16 specified psychological support," she says. "But the focus was on palliative and end-of-life care, and few plans today have information about evaluating any type of cancer service, let alone psycho-oncology."

She points also to a global survey of professionals working in psychosocial care that reports on where services are being offered, noting that it is by no means certain that the most cancer-oriented institutions – cancer centres and university hospitals – have regular psycho-oncology services for patients, and in other settings such as out-patient clinics and private practice they are rarely offered.

The baseline data about existing services should be boosted by a psychosocial oncology action project, part of the healthcare work package in the European Partnership for Action Against Cancer (EPAAC), which is proposing first to map the coverage of services and then develop and pilot education tools for com-

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munication skills and psychosocial care, initially in countries with low provision. Travado is leading this project, on behalf of the National Coordinating Body for Oncological Disease in Portugal, with a range of partner organisations. These include the International Psycho-Oncology Society (IPOS, for which she is currently treasurer) – a global organisation that is now promoting psychosocial services as part of standard care, which she says is being endorsed by an increasing number of cancer societies and patient groups.

The most high-profile support recently has come from the World Health Organization, which is currently involved in discussing the possibility of IPOS becoming a non-governmental organisation (NGO) partner to establish psychosocial care in cancer control programmes. In developing countries carrying out cervical cancer screening and treatment, for instance, it is hard to overestimate the importance of integrating counselling into care, as well as training professionals in communications skills – both cornerstones of psycho-oncology.

In Travado, the psycho-oncology movement has a tremendously energetic and passionate expert to help promote such support – and it must not be an optional extra for healthcare systems, she says. "All patients who need psychosocial care are entitled to it – it should be considered a human right in the same way as treatment for physical illness." Indeed, according to a recent report she mentions from the US Institute of Medicine, 'Cancer care for the whole patient: meeting psychosocial needs', it is just not possible now to deliver high-quality care without integrating the approaches and tools that are already available for taking care of psychological health. Every cancer centre under the US National Cancer Institute is now required to have a psycho-oncology programme.

"Psychosocial burdens can be more threatening in many cases than the disease itself," says Travado. "Even when a cancer is treatable someone may feel in despair and not cope. What we need to impress on policy makers and the medical community is that we are part of the frontline team and not a separate department dealing with a different part of a patient."

Travado's interest in therapy was sparked by a year-long stay in the US when she was just 17, as she was fortunate to gain a place on an intercultural exchange programme that had been established after World War II. "I finished my high school in America and learnt about the importance of contributing to society – in Portugal we had been used to the state providing for us. I spent time visiting people in a war veterans' hospital and learnt how to listen to their life stories – often they had no other visitors."

Back in Portugal, Travado decided not to do biology ("too much lab work"), and considered geology before landing in clinical psychology at Lisbon University, and was fortunate to learn from a professor who had worked with the famous psychologist Jean Piaget, and had imported cognitive behavioural therapy (CBT) from California. "I did my post-grad work on psychotherapy, focusing on what we call a constructivist approach, which we are now linking with psycho-oncology. Broadly, it's about patient-centred care and means attending to a patient's own preferences and decisions, and understanding what their resources are, and then helping them to explore alternatives based on what they already know, and so helping them to function.

"It's about respecting their own equilibrium and is the opposite of a paternalistic model, in which doctors and specialists pretend they know everything and patients should learn from them. I tell my students that they must learn from their patients – about how they function and what they use to deal with difficulties, and so build their self-esteem and confidence."

She adds that the cognitive behavioural model "arms you with brief, effective techniques and interventions for reducing patients' symptoms of distress, anxiety, depression and pain" – and has proved to be a great foundation for clinical health psychology, as has been extensively demonstrated by international colleagues such as Maggie Watson at the Royal Marsden in the UK. But Travado was very much on her own to start with.

She was trained first in clinical psychology with people who didn't have physical problems – that was

"They must learn from their patients – about how they function and what they use to deal with difficulties"

"There were even some people who had just pulled a sheet over their head such was their feeling of isolation"

to come soon – but says she "developed a passion for psychology and patient narratives". However, there were no jobs for a health psychologist in Lisbon, and she left to try to establish a private practice in a nearby town, which was to suffer an awful event. "There was a gas explosion in a high school – two children died and thirteen had severe burns. I was asked to help those affected and their parents with the ordeal."

Travado then met the director of Hospital São José at a community event in the town and, having heard about her work, he invited her to join the hospital as a health psychologist working with burn patients and others referred by the plastic surgery teams. "I was told, 'Put this white coat on, write your name on it and add "psychologist" and you'll be OK,' but some doctors said to me that I shouldn't be there, but at a psychiatric hospital."

Working on short-term contracts, it wasn't long before she was also asked to talk to head and neck cancer patients, who like trauma and burn patients had often suffered drastic physical change. "I was told that as long as I could prove myself with the number of referrals, I could have a full-time position. It was hard at first – but I was very assertive. I said, 'The psychological impact of a physical illness or trauma can lead to a patient becoming silent or angry: if you have one of these, come to me and I can help them cope better.'"

When asked why she was a lone psychologist in a hospital that did not even have a full-time psychiatrist, Travado would reply that clinical psychology has its own status as a science, "and I didn't recognise anyone as superior – except a professor of psychology or the hospital director."

The story will be familiar to others who carved out paths in psycho-oncology in the early days. "Many doctors would only call for me when they didn't know what to do with a patient anymore. But I would see something extraordinary – I would sit with the patients, saying that the care team was concerned about them and their treatment, and I would ask what was troubling them and empathise, saying how tough it must be for them. They would then say everything about their concerns and feel debriefed. No one had spoken to them like this before – not the doctors, nor the nurses – by sitting by their bedside to ask what was troubling them. There were even some people who had just pulled a sheet over their head such was their feeling of isolation."

Amid all the psychotherapy theory, Travado has adopted a straightforward approach to helping patients the best, and that is simply visiting them at the bedside, or what she terms 'proximity' work. In the hospital, she and her team wear white coats, which at first sight seems as though that could distance themselves from people. "But we wear white coats as part of hospital regulations, as it shows we are professionals and that there is no question we are staff. And very importantly, patients know we are part of their healthcare team, which helps to lessen the stigma of what we do – they shouldn't feel the other team members think they are a problem."

While patients are in hospital, she says, it is important not to make more difficulties for them by requesting they visit a psychologist in an office. "If they are on a ward it's because they need to be there, and we can usually talk to them privately using curtains or in the meal rooms in the wards."

Travado did indeed prove her worth, in doing much more than stepping in with 'problem' patients – albeit after five years or so of 'firefighting', working alone and running from one patient to another. She continued with severe burns patients – a speciality she maintains today – and became increasingly involved with cancer and other conditions such as spinal-cord injury, stroke, parasuicide, morbid obesity and chronic pain. She was then able to integrate psycho-oncology much more into the multidisciplinary cancer teams that were starting to develop, especially with a breast cancer surgeon who wanted all the right people in his team, including Travado, social workers, physiotherapists, plastic surgeons and others, which was particularly crucial when mastectomy was the main option.

"But he still wanted a referral system so that patients would have to make different appointments

to see team members such as myself, and I would be at the end of the list," she says. "I said that would just add more burden to people and instead I developed a protocol for a psychologist to be in the room when the surgeon actually gives the diagnosis. This is the time when people really feel a great impact as they receive bad news – and in many places it is often poorly managed by doctors." This initial part of the protocol is in two steps. The first is with the surgeon or oncologist, so you can hear what is being said and see the patient's reactions. Then afterwards the patient goes with the psychologist to a separate room for discussion about their concerns.

She explains that this model – of providing psychosocial care alongside other clinicians when and where it is needed – also applies throughout the cancer journey, including decisions about treatment, difficult treatments such as chemotherapy, when there are recurrences later on, and palliative care, and is one that has been most applied to breast cancer patients at the Lisbon hospital.

"In particular we look after patients who have recurrences here – they do not tend to get much support in many other places. When I was at an international patient group conference in Munich I heard from women with metastatic breast cancer about their needs – while they had medical care their biggest need was for psychosocial support, as a recurrence is the thing you fear the most after initial treatment. A lack of referral to psycho-oncologists for recurrences is a big gap in treatment – it is vital that we do not lose them from our services at such a dramatic time in their lives."

As Travado adds, psychosocial care does come on-stream well in most places when people enter palliative care, but this stage she feels can happen too late in the cancer journey and she would like to see oncologists calling in such support earlier. "I have also argued in an editorial that oncologists should have quality-of-life assessment as part of their standard agenda at all stages," she says.

By the 1990s, Travado was able to build up a team of health psychologists, and in 2000 she started to participate in international networking at the IPOS World Congress, and was pleased to find that colleagues abroad were working on similar cognitive behaviour interventions, and that protocols such as SPIKES, for breaking bad news, were being introduced, based on research with patients. SPIKES was developed by Robert Buckman and Walter Baile (the latter heads the Interpersonal Communication and Relationship Enhancement (I*CARE) programme at MD Anderson in the US, a unit with which Travado collaborates closely).

In the last 10 years, Travado has engaged in a whirlwind of national and international activities, having been asked to advise Portugal's National Coordinator for Oncological Diseases – the country's cancer 'czar' – on national psycho-oncology coordination, and helping to organise a Europe-wide 'round-table' on cancer when Portugal had the European Union presidency in 2007. "The Slovenian follow-up in the following year led to the EPAAC European partnership action plan," she adds.

With colleague Luigi Grassi, a psycho-oncologist in Italy, she secured a chapter on psychosocial care in 'Responding to the challenge of cancer in Europe', the book produced under the Slovenian presidency. This is an in-depth piece on how cancer affects people at various levels – socially and spiritually, as well as psychologically – and tells the story so far on the main tools for measuring distress, the psychosocial interventions, and the training and standards now on offer for clinical settings

The chapter presented some simple tools such as the 'distress thermometer', developed by a panel of the US National Comprehensive Cancer Network, which helps all healthcare professionals to screen for distress, and which could help establish the 'sixth vital sign' in practice.

That relates to her involvement in one of her most important international research projects to date, the Southern European Psycho-Oncology Study (SEPOS), which is a collaboration between professionals in Portugal, Spain and Italy (and led by Luigi Grassi). "Southern Europe has been underserved by

Travado did indeed prove her worth, albeit after 5 years of working alone, running from one patient to another

"A small difference in a doctor's communication approach can make a big difference in outcomes"

services compared with the north, and a key part of the project has been developing communication skills for healthcare professionals and also carrying out research that we could apply across the region and not reinvent the wheel in each country," she says.

Given that many hospitals do not have a full psycho-oncology service, it is often up to oncologists and nurses to provide the main support roles, and SEPOS has found that the vast majority of cancer doctors in the three countries had received no or very little communication skills training during their medical education. Although they felt proficient in talking with patients, says Travado, "learning how to communicate with empathy is a difficult technique for many – but once they practice asking about a patient's concerns and feelings in role-play training sessions, the outcomes can be different, such as helping patients to come to terms with difficult treatments they may have first refused. You have to understand concerns, letting patients talk without interruption and allowing them to bring their own agenda to the discussion. A small difference in a doctor's communication approach can make a big difference in outcomes."

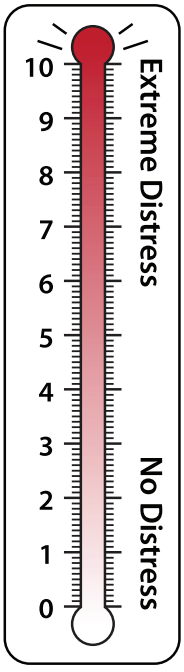
The SEPOS group, she adds, has developed training modules for cancer doctors, and in Portugal Travado has been instrumental in launching a national communication skills training programme in 2009, although she has been running local training for much longer. A hundred cancer professionals – more than expected – turned up at the national launch event in Lisbon to hear invited speakers such as SPIKES protocol developer Walter Baile, and Lesley Fallowfield from the UK – the latter has carried out considerable research into communications skills in cancer.

"We then ran workshops in main cities, targeting cancer physicians, oncologists and others, but surgeons were the ones who needed the most support for this skill, and I worked with my husband, Joaquim Reis – also a health psychologist – to produce a two-set DVD that includes communication techniques and an introduction to the SPIKES breaking bad news protocol, as an educational tool to support this training.

"But as in many other countries, communication skills training is not mandatory and is still scarce in medical education. I of course would like it to be much more widespread." Travado adds that when other healthcare professionals are properly trained, they can pick up distress in a 'tiered' system, as patients move around clinics. "For example, we are working with oncology nurses at the hospital's chemotherapy outpatient day clinic in Lisbon to assess distress levels before chemotherapy treatment, where they can refer those who are suffering more to my team." Communication skills can also help prevent physician 'burnout', she adds.

Although she is critical of the 'medical model' and prescribing drugs as a first choice for dealing with the symptoms of distress, she is keen to point out that there

MEASURING THE SIXTH VITAL SIGN



The concept of a distress thermometer emphasises that distress level is a vital sign, just like temperature and blood pressure, that can and should be measured on a regular basis.

Patients are asked to circle their distress level over the past week on a scale of 0 to 10, and to check 'yes' or 'no' to a list of specific stressors that are listed under five main headings:

Practical problems (e.g. childcare, housing, treatment decisions)

Family problems (e.g. dealing with children or partner, ability to have children)

Emotional problems (e.g. depression, fear, sadness, loss of interest in usual activities)

Spritual/religious concerns

Physical problems (e.g. appearance, diarrhoea, fatigue, memory/concentration, mouth sores, sexual)

The distress thermometer screening tool was developed by the US National Cancer Center Network, and can be accessed under their guidelines for supportive care at www.nccn.org

JORGE NOGUEIRA

A roomful of experience. Insight, support and advice from fellow patients and survivors can be immensely important, so at the São José Hospital, Viva Mulher Viva is considered part of the care team

is no great dividing line between the professions of psychology and psychiatry in the field, at least among those who support the aims of IPOS. Close international colleagues such as Grassi and Baile, and also William Breitbart in the US and Sylvie Dolbeault in France, are psychiatrists. It is still common, though, for antidepressants and tranquillisers to be prescribed, including by medical oncologists.

People in southern Europe can have different psychosocial needs to other populations, she adds. Many cancer patients in Portugal are older people with little formal education, and they often adopt a more fatalistic and spiritual approach to their condition, in line with the 'fado' mournful music tradition in the country. "That does not mean people necessarily feel hopeless – in other countries fatalism can be seen as negative, but not here," says Travado, who has also explored the role of spirituality in a SEPOS study, finding it is a protective factor against depression, which is important in countries with a strong religious background.

But in Portugal, as in other parts of southern Europe especially, it has taken time for doctors to fully disclose a cancer diagnosis with the majority of patients. "You can't adjust to something you don't understand, and a psychologist then cannot help them. I used to find patients who were angry because they thought they were being given inferior treatment, but they hadn't been told the truth." Following a survey in Portugal that showed that 85% of people wanted to know about a cancer diagnosis, the situation has begun to improve, she says.

At Lisbon, Travado's team has several of the major cancers – especially breast cancer and head and neck – firmly integrated into psycho-oncology, but by no means all. A few surgical teams have been less receptive. Personally, she focuses primarily on breast cancer and palliative care, and has established teamworking protocols and hospital education programmes in both, as well as also supervising health psychology students. Ongoing research includes women's subjective meanings about breast cancer and how they affect the type and intensity of their emotional reactions and coping.

An initiative that she is especially proud of is helping to set up a Portuguese patient group for breast can-

"I'll be happy when ... distress is routinely assessed and managed throughout the cancer journey"

cer patients within her hospital. Viva Mulher Viva started in 2003 "to bring professionals and patients together," and is not a typical advocacy group. "Though we were providing the best care as professionals, patients were not seeing how others were going through the experience of having cancer – if they could see that, we could show them that a good quality of life is possible. And we wanted patients to feel welcome in the hospital, and that it is their institution – it doesn't belong to healthcare professionals – and that we could collaborate together in making patients' experiences less traumatic and more hopeful.

"It was my vision that women survivors of breast cancer should be part of the team, bringing their expertise in to help others going through the treatment process and complement the professionals' role, and we have taken to heart the tagline of the European Cancer Patient Coalition [ECPC], 'Nothing about us without us', and we have joined ECPC as a member."

The emphasis is on the patient's experience and quality of life, with awareness events, calendars, DVDs (addressing topics such as intimate relations and sexual matters), and communication training for volunteers, who wear pink T-shirts in the hospital and visit breast cancer patients in treatment, in close collaboration with the psycho-oncology team. "We encourage women to be more assertive about their healthcare and to make informed decisions – there is a tendency here for people to be passive in front of authority figures and to 'victimise' themselves after traumatic events. We want to help them participate in their healthcare and wellbeing, and gain more control for making better choices to maximise treatment and improve their quality of life."

The partnership between psycho-oncologists and patient advocacy groups such as ECPC is critical to improving multidisciplinary care, she adds, and both are prime movers in EPAAC's psychosocial oncology action initiative.

As treasurer of IPOS, Travado is earmarked for possible promotion to the presidency, but this is not in her sights at present. The society has annual conferences, which are well attended, and which are now receiving hundreds of abstracts, and has recently developed a federation of psycho-oncology societies for national and regional groups, but there is no pressing need yet to establish a European branch.

"What we are doing at a high level is pressing for the IPOS statement on psychosocial care to be taken up as widely as possible." One great quality of the statement, as she points out, is its simplicity:

1. Quality cancer care must integrate the psychosocial domain into routine care.

2. Distress should be measured as the sixth vital sign after temperature, blood pressure, pulse, respiratory rate and pain.

"We did want a third point, for psycho-oncology to be included in national cancer plans, but we left it out because too many countries still don't have plans," she says. The IPOS core curriculum, developed recently with ESO, is also an important step forward, she adds (see also *Cancer World* March–April 2007).

Travado's husband, Joaquim, is now working in social health marketing, a field that interests her as it's about the use of marketing principles to influence human behaviour, such as smoking, to improve health or benefit society. She has two children and is a fitness and dance activist, which no doubt helps fuel her energy levels at work.

International colleagues could hardly speak more highly of Travado, describing her as the leading Portuguese authority on psycho-oncology and an important organiser and voice now in cancer control policy in Europe, as well as a pioneer of integrated psychosocial care in breast cancer and palliative care.

"I'll be happy when psycho-oncology is recognised in all national cancer plans and distress is routinely assessed and managed throughout the cancer journey," she says. As one policy maker said, after he had heard Travado speak at the European Cancer Conference in Ljubljana in 2008, "Now I finally understand what this is all about," so there is a good chance these aims will be realised sooner rather than later.

Prognostic and predictive markers in colorectal cancer:

implications for clinical management

Only two biomarkers for colorectal cancer are currently used in the clinic. However, efforts to find genetic patterns that distinguish between tumours with good or poor prognosis, or between patients who do or don't respond to various therapies, may offer the basis for identifying subgroups of colorectal cancer similar to those now used in breast cancer.

Colorectal cancer is a very heterogeneous disease, possibly even different diseases hitting the same organ. This has huge implications for clinical practice. For example, in the adjuvant setting, our ability to accurately predict the prognosis for a patient is around 50% in stage II/III resected disease. This is the clinical reality we face every day, so we are unable to inform our patients of their prognosis with more than about 50% accuracy.

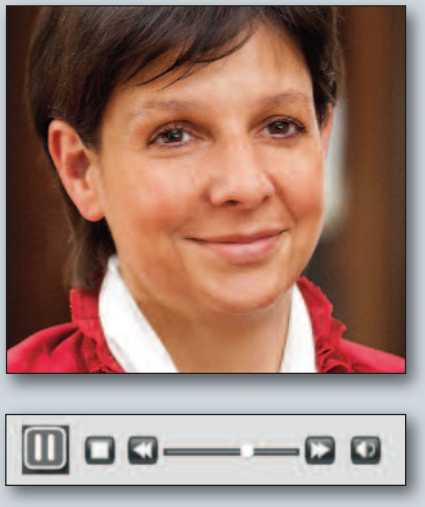
Even our best-guess models, based on traditional histopathological markers such as that lymph node metastases would be associated with a worse outcome than no lymph node metastases, are not straightforward. For example, some patients who have no lymph node metastases but have T4b tumours fare worse than patients with lymph node metastases (see table overleaf). This indicates that our current understanding of how colorectal cancer behaves in the body and metastasises is probably flawed.

Colorectal cancer is also heterogeneous in the metastatic setting. This is where drug efficacy needs to be pre-

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, Sabine Tejpar, from the University Hospital Gasthuisberg, Leuven, Belgium, provides an update on the implications for clinical management of developments in prognostic and predictive markers for colorectal cancer (CRC). Daniel Helbling, Onkozentrum Zurich, Switzerland, poses questions arising during the e-grandround live presentation. It was summarised by Susan Mayor.



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

RELATION BETWEEN TUMOUR SUBSTAGE AND SURVIVAL

Category	SEER				SEER	
TN	Relative survival, 5-year (%)	SE	TNM stage, 6th ed	TNM stage, 7th ed	Observed survival, 5-year (%)	SE
T1N0	97.4	0.6	I	I	78.7	0.5
T2N0	96.8	0.6	I	I	74.3	0.4
T3N0	87.5	0.4	IIA	IIA	66.7	0.6
T4aN0	79.6	1.0	IIB	IIB	60.6	0.8
T4bN0	58.4	1.3	IIB	IIC	45.7	1.0
T1-2N1a	90.7	1.5	IIIA	IIIA	73.7	1.2
T1-2N1b	83.0	2.0	IIIA	IIIA	67.2	1.6
T1-2N2a	79.0	3.6	IIIC	IIIA/IIIB	64.7	3.0
T3N1a	74.2	0.8	IIIB	IIIB	58.2	0.6
T4aN1a	67.6	2.0	IIIB	IIIB	52.2	1.5

These relative survival figures, based on expanded SEER data and presented according to AJCC substaging for stage II and III colon cancers, indicate flaws in our current understanding of how colorectal cancer behaves

SEER – Surveillance, Epidemiology and End Results. *Source:* SB Edge, DR Byrd, CC Compton et al. (eds) (2010) AJCC Cancer Staging Manual, 7th edn. Springer, reprinted with permission © Springer 2010

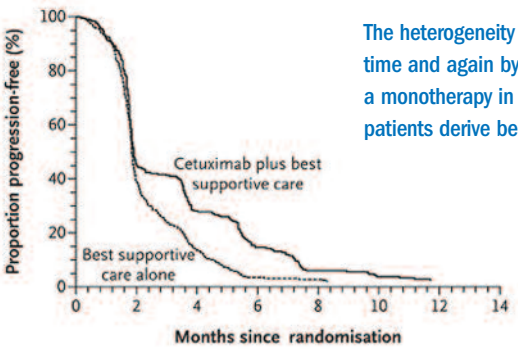
dicted to obtain the best possible outcome for the patient. With the recent drugs, not just targeted agents but also chemotherapy, we have accepted survival curves showing that drug A or B works in a subset of the population, for example cetuximab in unselected patients (see figure, below right). However, these curves also indicate a whole set of patients that do not benefit from these drugs, and we are unable to separate the patient groups, even though we use the drugs in our daily practice. We see these types of curves repeatedly for many types of drugs, both standard therapies and targeted agents, with a group of patients that benefits and a group that does not. This is because of the inherent heterogeneity of colorectal cancer, which we need to understand in order to better target therapy.

Continuing with the example of EGFR monoclonal antibodies, there are two key messages. Firstly, these drugs are remarkably effective as monotherapy. This is crucial because if a drug works as a monotherapy, it means that it addresses the biology underlying the disease. The second point is the limited groups of patients in which they work: 10% in monotherapy if patients are unselected; 25% in monotherapy if patients are *KRAS* wild type. To do a good job we must identify the subgroup upfront, and we are not yet at that stage.

Many pathways are involved in colorectal cancer, and any one of these could be affected in a particular colorectal cancer patient. This means there are many different versions of the one disease that we call colorectal cancer, but we currently have only two markers that have been more or less validated: *KRAS* and microsatellite instability (MSI). The first of these is used to predict response to EGFR targeted therapies and the second for prognosis in stage II disease.

We tend to simplify the way we look at the biology of tumours. For example, having found the role of EGFR signalling in non-small-cell lung cancer, or the role of HER2 signalling in breast cancer, we assume that these pathways act in the same ways in other diseases. However, we know that EGFR in non-small-cell lung cancer does not act in the same way as the EGFR pathway in colon cancer. Having identified a pathway, we have to look at which disease it is working in, and remember the effect of the pathway can be completely different according to the tumour type. *KRAS* mutations have different roles in pancreatic cancer, melanoma and colon cancer. This means that we have to look at tumour environment specificity for each marker.

PROGRESSION-FREE SURVIVAL FOR CETUXIMAB IN UNSELECTED PATIENTS



The heterogeneity of colorectal cancer is demonstrated time and again by graphs like this one for cetuximab as a monotherapy in unselected patients, showing some patients derive benefit while others don't

Source: DJ Jonker et al (2007) Cetuximab for the treatment of colorectal cancer. *NEJM* 357: 2040–48, reprinted with permission © Massachusetts Medical Society 2007

Tumour origin

Colorectal cancer originates from the very undifferentiated stem cell compartment in the colon. This is important for everyday functioning of the bowel, but the negative impact is that colon tumours have properties of self-renewal, de-differentiation and plasticity. This means we are faced with a very difficult disease. We are not sure which cells in the bowel give rise to the majority of tumours, and it is not something we currently take into account. There is probably a lot of refinement needed in terms of cell subtype and cell origin.

A distinction that we often forget to make, and which is very relevant, relates to the primary tumour site – between tumours originating from the right side of the colon, which is the mid-gut in embryonic origin, and those from the left side of the colon, which is the hind-gut. The mid-gut and hind-gut have different origins, driven by different genes. Tumours arising on the right side, which goes almost to the hepatic flexure, probably have inherently different biology compared to left-sided tumours.

Data reported by Arnaud Roth at ASCO two years ago showed Kaplan-Meier survival curves for patients based on the origin of their tumour (see figure, right). Patients whose tumours had a left-sided origin had better prognosis than those with tumours originating on the right. This is because the driving biology is different, with different genes in tumours originating on the left versus right.

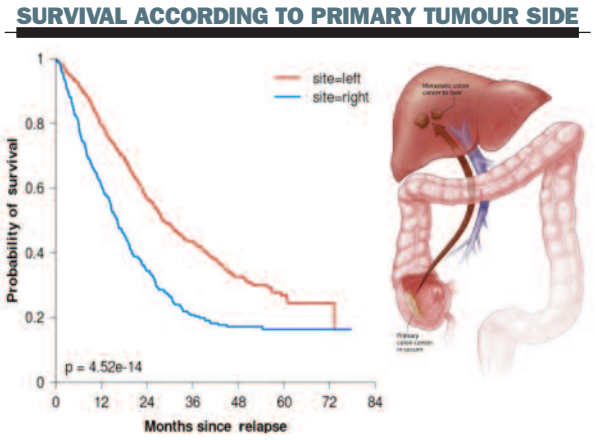
Current descriptors of CRC heterogeneity

At the moment, only the *KRAS* and MSI markers have made it into clinical practice. We are all accustomed to the Vogelgram, which suggests *APC*, *KRAS* and *TP53* are needed to drive colon cancers. However, although a very useful model, it is not clear if this is the way all colon tumours progress. Most of our mouse models develop small bowel instead of large bowel cancer, and further refinement is needed with modelling of the effect of multiple genes in dedicated models.

Furthermore, while tumour initiation is something that we should be able to understand in appropriate mouse models that assess whether particular mutations lead to tumour development, in clinical practice this is not what you are treating. In clinical practice, patients present with metastatic disease that has evolved in ways we do not yet understand and cannot yet model. Molecularly, this is probably quite far from the simple situation of tumour initiation.

Metastatic disease is several years removed and can have a lot of new alterations that would be very difficult for researchers to map. It would be very difficult to make a mouse model of the whole metastatic cascade. In addition, every time you give drugs to a patient you are probably changing the identity of the tumour, particularly with very targeted agents such as an *EGFR* inhibitor or an HGF (hepatocyte growth factor) inhibitor. This will probably remove certain cell populations and enable others to take over as part of a resistant mechanism. A static image of a patient's tumour is probably not correct and it might be that we should biopsy multiple times during treatment to check the molecular identity over time. This may explain why current biomarkers do not correlate well with outcome, because they do not reflect the actual disease in a patient.

Recent studies have demonstrated tumour plasticity. For example, a study giving a MAP kinase inhibitor to a *BRAF* mutant cell line or to a *KRAS* mutant cell line showed that the cell lines were able to escape the drug in a few months. In the *BRAF* mutation, this was achieved simply by amplifying the BRAF chromosome, and in the case of *KRAS* mutation, the KRAS chromosome (*Sci Signal* 2010; doi: 10.1126/scisignal.2001148; *Sci Signal* 2011; doi: 10.1126/scisignal2001752). So, there is a very targeted and selective way of acquiring resistance to whatever drug treatment we are giving, which I think happens frequently in patients as we treat them.



Differences in survival according to the side the tumour originates reflect a difference in tumour biology

Source: Arnaud Roth, presented at ASCO 2009

Question: *If they amplify these cells, the genes, can it not be circumvented by giving more of the drug, and increasing the dose?*
Answer: *Yes, that could be a solution if you know that it is going on, but there might be some dose-limiting toxicity. However, what really struck me in these reports was the very targeted way that the cancer uses the genetic instability that underlies all cancers to simply select cells that are resistant to the drug being used, so those cloned cells survive.*

Question: *What do you think about sequencing the whole genome for a patient?*
Answer: *There are fantastic technologies at hand and sequencing a patient's tumour at repeated time points will be feasible and cost-effective in the future. The problem is how to interpret that information: which of the markers is the important one and which therapeutic drug do you link to this?*

Our current efforts are focused on taking a step back: taking a very unbiased approach, not dividing the disease into MSI+ or MSI– or to *KRAS*+ or *KRAS*–. We should adopt a very comprehensive approach, including analysing DNA, RNA, and protein, and measuring everything without a hypothesis, and biology may become apparent in that information. Very useful information is emerging in the *Cancer Genome Atlas* on colon cancer in 2011.

We are trying to generate subgroups similar to those now used in breast cancer, which are based on gene expression and show both prognostic and predictive relevance. To gain the necessary critical mass of information, large consortia will be needed, and everyone will have to share information, including doctors, patients, and the pharmaceutical companies who often have very large series of well annotated samples from clinical trials.

There is another factor underlining why collaboration is necessary. Even if you have full sequencing for a patient and have identified all the mutations – there are 71 mutations on average for colorectal cancer (B Vogelstein, *Science* 2007, 318:1108–13) – you still do not know what these mutations mean for the patient, nor the drugs he or she will respond to, because a map of the mutations does not mean that we understand what they are doing.

The big challenge now is to get functional annotations of the mutations we see. We have identified some of the mutations, including *KRAS* and *BRAF*, and we know that there is *HER* amplification but we have no idea what they are doing. One way to do functional annotation is to use cell lines and mouse models, and this is ongoing but it is time-consuming and difficult and sometimes unproductive. Another way is to explore what these genes are doing in patients. If you have a very specific mutation in a patient, for example a deletion of *PTEN*, and look at how patients with this amplification respond to different drug treatments, you will probably be able to learn about the function of the mutation, because it will show high sensitivity or resistance. This is using the patient as the ultimate test tube, which is necessary because *in vitro* methods are not always successful.

Question: *Are these small trials, where you just test out hypotheses in certain mutations and certain drugs with a low number of patients?*
Answer: *A ballpark figure from our experience is around 60–80 patients, often in phase II trials. As long as you have a clear map of the molecular alterations you are looking at, so the biomarker is clear, and you track it throughout a trial, for example with an IGF inhibitor versus a C-MET inhibitor, and you see that the biomarker predicts something completely different in these two trials, then you have learnt something about the pathway of your biomarker.*
Question: *You just mentioned that patients have mutations in 71 genes, on average. How many pathways are relevant in colorectal cancer, if 71 genes are affected?*
Answer: *Bert Vogelstein presented a schema of all the relevant pathways at ASCO last year and ended up with about 15, including Wnt and Hedgehog (JCO 2009, 27 Suppl 15). But we can't yet put a number to this. We now have enough samples for colorectal cancer analysed worldwide to get a first grip on the subgroups; however, the static versus dynamic element probably makes this more complex.*

Clinical trials with targeted agents have been very helpful. We never really knew where to position *KRAS* in colon cancer signalling until EGFR inhibitors came along. We now know much more about *KRAS* thanks to the cetuximab and panitumumab trials. This is just one example, but many more trials with other drugs are coming through. It will be interesting to see whether other receptor tyrosine kinase inhibitors will show the same influence of *KRAS* mutations.

Biomarker development

The necessary factors for biomarker development include:

- A good understanding of what is going on in metastatic colorectal cancer
- Therapies with known targets
- Knowledge of the effect of target inhibition
- Tractable risk/benefit profile
- Biomarkers that have a large impact
- Validation

The first step is a good understanding of what is happening in the disease. We do not really yet have that. We do have some therapies with known targets, although a lot have no clear cellular anticancer mechanisms, which makes it difficult to make biomarker/therapy relationships. Validation is essential, requiring large datasets for which we have to learn to collaborate much more.

KRAS and MSI

KRAS and MSI are the first biomarkers in colorectal cancer. However, we sometimes oversimplify things. We know MSI is a marker for good prognosis and we would like to be able to use it in clinical practice, but there are some pitfalls. There is a different incidence of MSI in stage II and III tumours, as for many markers. However, many publications report stage II and III series together, or analyse the effect in a compound way. We must be very cautious and try to be as precise as

possible in studying the effect of a biomarker in a homogeneous population.

Not only does the incidence of MSI, and maybe also its prognostic value, differ between stages II and III, but the prognostic value also differs according to the presence or absence of other markers and features. The table below shows that MSI and 18qLOH behave differently as markers in stage II and III disease.

The take home message is to be very precise about the disease group you are looking at and never forget that a marker, as simple as it may seem, may have hidden complexity, such as interaction with stage or other markers.

MSI instability is a good prognostic marker in univariate analysis. The same is true for 18qLOH as a marker of poor prognosis. However, would the 18q information still matter if you knew the MSI status of your patient? In the microsatellite stable (MSS) population, which is the largest population, 18q is no longer prognostic (see figure, above right). This means 18q only gives useful information if you do not know the microsatellite status. This is just one of many examples where you might see strong effects of a marker in univariate analysis, yet it is no longer present in multivariate analysis with relevant interacting markers.

E5202 is the first trial to use risk assessment based on 18q/MSI to determine treatment in stage II colon cancer (www.clinicaltrials.gov). High-risk patients, defined as MSS and 18qLOH, are treated with chemotherapy. Low-risk patients, defined as MSI-high and MSS with no 18q, undergo only observation and no treatment. The design is flawed, however, as 18q does not matter in MSS disease, and these patients are still at high risk. This design was based on a combination of two univariate analyses that were not put into a multivariate analysis.

Another interesting study was presented by Dan Sargent at ASCO 2008. He conducted a pooled analysis of multiple trials in patients with stage II and III tumours, comparing patients treated in the adjuvant setting with those who were untreated (see figures, p 20, left, centre). Patients with high MSI who were untreated did much better than MSS patients. However, this effect completely disappeared in the treated patients, and it might be that giving 5FU to patients with high MSI is harmful because the benefit of being MSI disappears.

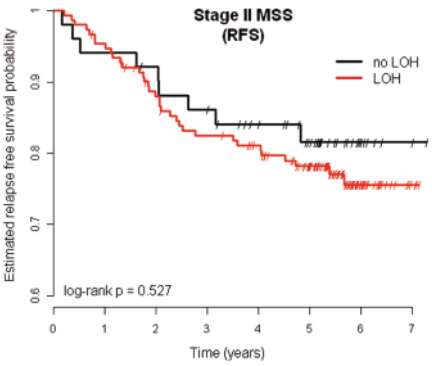
PROGNOSTIC VALUE OF MARKERS IN STAGE II AND III TUMOURS

The prognostic value of these markers (looked at in isolation – univariate analysis) varies according to the stage of disease, which has implications for how studies of biomarkers are designed and reported

Marker	Stage II (n=420)		Stage III (n=984)		Interaction
	HR	p val	HR	p val	
MSI (Hi vs Stable)	0.3	0.004	0.7	0.06	0.04
18qLOH	2.1	0.03	1	0.91	0.05
SMAD4 (any loss)	1.4	0.21	1.6	<0.0001	0.23
hTERT (High)	1.4	0.32	1.5	0.01	0.92
p53 (High)	1.0	0.98	1.3	0.03	0.37
TS (High)	0.5	0.03	0.7	0.02	0.30
KRAS (Mutated)	1.1	0.84	1.0	0.72	0.32
BRAF (Mutated)	0.9	0.90	1.2	0.28	0.38

Source: Arnaud Roth, presented at ASCO 2009

PROGNOSTIC VALUE OF 18QLOH ON MSS STAGE II DISEASE



18qLOH and microsatellite instability (MSI) status are both good prognostic markers when used alone, but for patients known to be microsatellite stable (MSS), 18qLOH loses its prognostic value

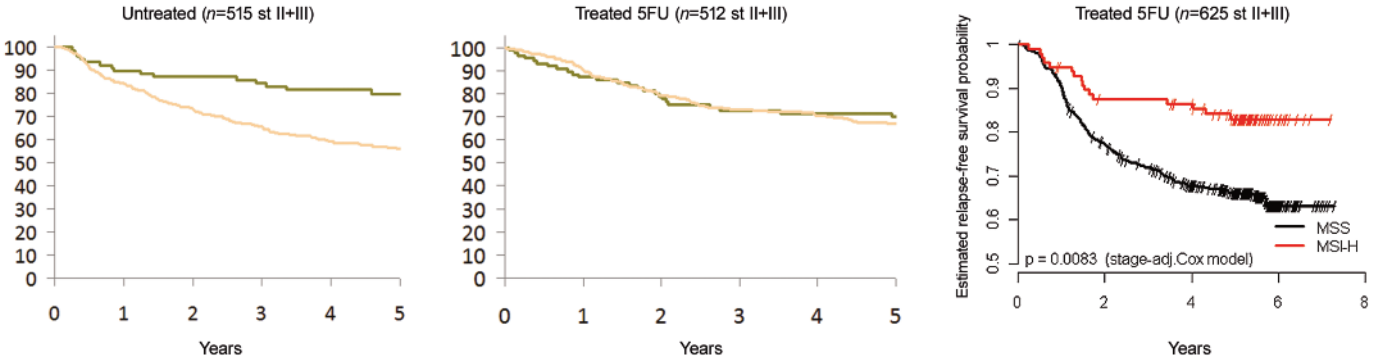
Source: Arnaud Roth, presented at ASCO 2009

In contrast, a clinical trial from our group (see figure, p 20, right) showed a very strong prognostic effect of high MSI versus MSS, unlike the Sargent data. The difference in results between similarly powered studies suggests there is still something that we are not capturing, and more and larger studies are needed.

The take home message on MSI status is that, although we would love to say that MSI is a simple marker of prognosis and response to adjuvant treatment, there are several unresolved issues, including sporadic versus hereditary MSI, the role of CIMP, the role of *BRAF* and the impact of novel therapies. We should not embrace biomarkers if they do not have clear validation for clinical practice.

Question: *In clinical practice, do you measure MSI and do you consider it in treatment decisions for stage II patients?*
Answer: *At the moment, I do not make decisions based on MSI status, although I acknowledge it is a very strong marker*

THE EFFECT OF TREATMENT BY MSI STATUS – CONFLICTING TRIAL RESULTS



A study by Dan Sargent and co-workers showed that patients with high MSI lost their survival advantage when treated with 5FU (left and centre graphs); however, in a study conducted by Sabine Tejpar and colleagues, patients with high MSI (MSI-H) responded much better to 5FU treatment than MSS patients

patients with high MSI; microsatellite stable (MSS) patients.

Sources: Dan Sargent, presented at ASCO 2008 and Sabine Tejpar, presented at ASCO 2009

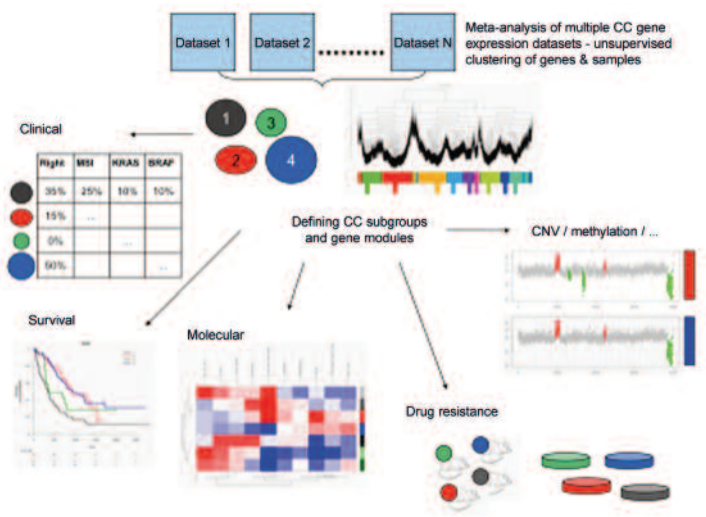
and a good basis for patient risk stratification. However, I presented data at ASCO 2010 on the uncertainty that still exists if you use MSI for treatment decisions in stage II patients. In stage II patients, we also use ASCO clinical high-risk criteria, such as fewer than 12 lymph nodes examined, T4, poor differentiation, and obstruction. MSI patients are often poorly differentiated, which is high risk, and T4, which is also high risk. So, on the one hand you have MSI telling you that this is a good prognosis patient, and on the other hand there are high-risk features telling you that this is not a good prognosis. If you combine all these factors in a multivariate risk model, you would still be wrong in a small number of cases if you used MSI as a standalone marker. A paper was recently published by Frank Sinicrope and Dan Sargent's group looking at the difference between sporadic and hereditary MSI, which reports intriguing findings that again warrant further detailed investigation into MSI as a standalone marker (JNCI 2011, 103:863–875).

Question: *Do you use clinical markers, or do you not consider any markers?*

Answer: *We use clinical markers from ASCO guidelines, as these have quite a lot of data behind them. I am not discouraging people from using MSI, but you have to be aware of the margin of error, and the need for further studies.*

PETACC3 provided a very large series of 1400 patients to look at multiple markers (*Clin Cancer Res* 2009, 15:5528–33). It showed how the integration of molecular markers often changes the view that you have based on a single marker, and the impact of integrating variables such as T stage and

SUBGROUPING BASED ON GENE EXPRESSION



This analysis of unprespecified gene expression identified four main subgroups that seem to be in agreement with other studies, but not with currently used descriptors of the disease

CC – colon cancer.

Source: Swiss Group of Bioinformatics in Lausanne, presented at AACR 2011

N stage. These are very large effects that have not been modelled sufficiently, and offer important work for the colorectal cancer community that can easily be performed over the next few years.

Eva Budinska and Mauro Delorenzi, of the group at the Swiss Institute of Bioinformatics in Lausanne, took multiple data sets and looked at gene expression in an unprespecified way, trying to identify spontaneous subgroups in the disease (see figure, p 20, lower). Results showed subgroups, in agreement with other studies. I think we are at the point of identifying the subgroups in colon cancer just as in breast cancer. This figure simplifies the subgroups into four colours, numbered 1, 2, 3, and 4 (although there were a few more).

These subgroups, which are spontaneously present in the disease, correlate poorly with current descriptors of the disease, including clinical descriptors such as stage, T or N status, and even *KRAS*, *BRAF* or MSI. This means the subgroups better describe the ongoing disease process than current markers. The existing cell lines can be compared to see whether they match the patient subgroups, as well as mouse models. This means we can now refine the tools that we use in the lab, such as cell lines, to ensure they better match the true subgroups present in tumours. Another similar study used unsupervised subgrouping analysis of colorectal cancer (*BMC Med Genomics* 2011, 4:9), and I think these studies are going to be very important over the next few years.

The same message is emerging from recent work on *KRAS*, questioning whether all *KRAS* mutations have the same effect. The table above summarises the incidence of different *KRAS* mutations. There may be differences between mutations, and maybe even between different patients with the same mutations.

NOT ALL *KRAS* MUTATIONS ARE ALIKE

KRAS mutation		Incidence (%)
Amino acid substitution	Nucleotide substitution	
Codon 12 mutations		
Aspartate (G12D)	G35A	32.5
Valine (G12V)	G35T	22.5
Cysteine (G12C)	G34T	8.8
Serine (G12S)	G3A	7.8
Alanine (G12A)	G35C	6.4
Arginine (G12R)	G34C	0.9
Codon 13 mutations		
Aspartate (G13D)	G38A	19.5
Other Mutations		1.8

Different mutations in the *KRAS* gene affect tumour behaviour in different ways

Source: N Normanno et al. (2009) *Nat Rev Clin Oncol* 6: 519–527, published with permission, © Nature 2009

In some patients a *RAS* mutation may activate the RAF MAP kinase pathway, but in other patients the same mutation may activate another pathway, such as PI3 kinase or RAL (see figure below). Just because we have *KRAS* mutants or wild types does not mean the two types have homogeneous biology.

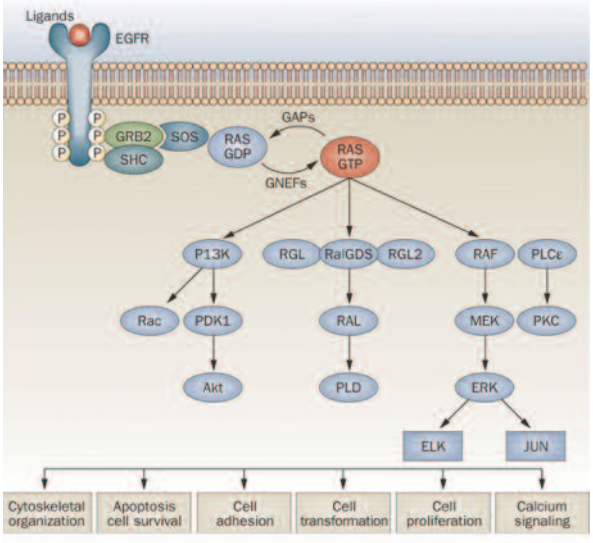
To find proof of this we looked at gene expression data in patients with *BRAF* mutations, patients with *KRAS* mutations and those with neither of these mutations (double wild type). Results showed that *BRAF*-mutant patients have some genes always on and some genes always off, while these are reversed in wild type patients (Popovici et al, manuscript in preparation). The conclusion is of very homogeneous disease in *BRAF* mutants, so this marker is indicating something useful.

However, this division of gene expression is not nearly as clear in *KRAS* mutants versus wild types. There still seem to be different groups of *KRAS* mutants, which are quite different in terms of gene expression. This indicates *KRAS* is not a marker of homogeneous disease.

The take home message is that the underlying biology is much more heterogeneous than current markers might indicate, and an unsupervised approach is necessary that does not separate patients into prespecified groups. This has important therapeutic implications. For example, treating all *KRAS* mutant patients with MAP kinase inhibitors is not going to be successful, because of heterogeneity between them.

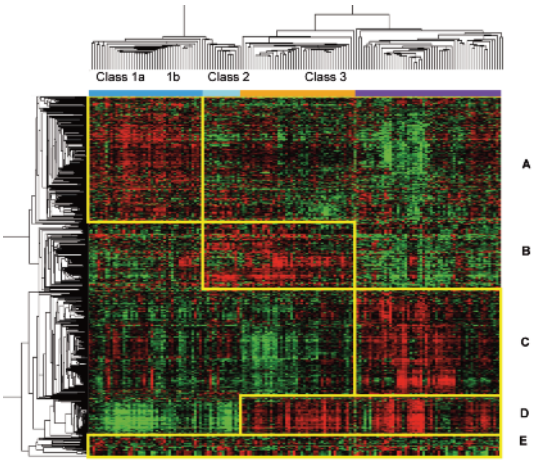
A solution to this problem is illustrated by a study performed by Shirin Khambata-Ford at Bristol Myers Squibb (the company that markets cetuximab in the US) in 2007 (*JCO* 25:3230–37). This study was very open, and was not just looking at *EGFR*

RAS MUTATION PATHWAYS



Source: N Normanno et al. (2009) *Nat Rev Clin Oncol* 6: 519-527, published with permission © Nature 2009

BIOMARKER DISCOVERY STUDY IN PATIENTS TREATED WITH CETUXIMAB



Studies like this one, which analysed how gene expression profiles differ between patients who did well on cetuximab and those who did not, will help identify markers of response

Source: S Khambata-Ford et al. (2007) *JCO* 25:3230–37, published with permission © ASCO 2007

copy number or *KRAS*. The trial biopsied liver metastases in 80 patients just before treatment with cetuximab. Full Affymetrix profiling compared gene expression in patients who did well against those who did badly, revealing the biomarkers for sensitivity to the drug (see figure above).

If we collect material in the many ongoing trials with targeted agents and analyse it in an unprespecified way, we can make a lot of progress in understanding the biology of colorectal cancer over the next few years (see figure below).

SUMMING UP

In terms of biomarker development in colorectal cancer, we have a good grasp of what is going on in metastatic disease. Therapies have been developed that have known targets and the effect of target inhibition is known. It is essential that we keep an open mind on biomarkers and critically evaluate the available information, ensuring all findings are thoroughly validated.

Question: *Looking at gene expression profiles – do you think there are three or four groups, or more?*

Answer: *The published data mentioned previously show two big groups. I believe the number is likely to be fewer than 10, but more than two. We are pleased with this number, because it comes close to something that people can use in the future. It is important to note this grouping was based only on gene expression. If you add in copy number, mutation data and microRNA, you can probably refine subgroups further.*

This is not the end of the story, but, in a similar way to breast, it is a very good start. It puts us on track for planning a clinical trial, giving an idea of benchmarks, what to power for, and how much heterogeneity to expect within the population or within the drug effect.

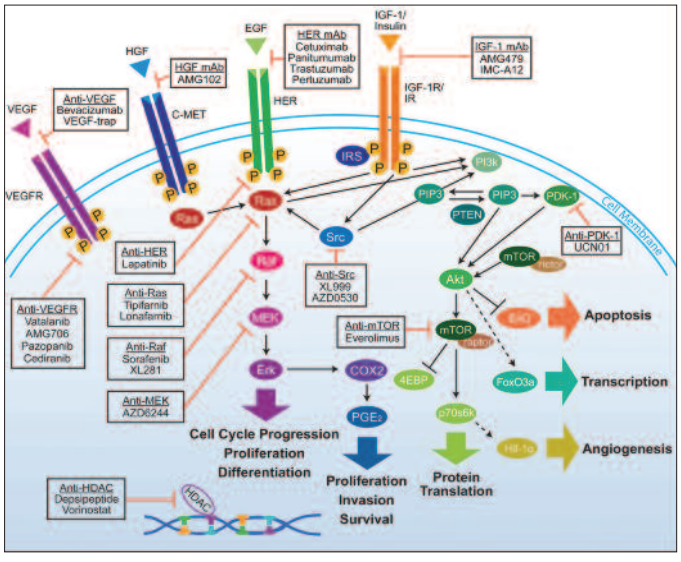
Question: *Do you think the future will be based on these different groups distinguished by gene expression, and then digging deeper by knowing more about it?*

Answer: *Yes, I hope that nature has not made every colon tumour completely different, but that there are recurring themes. The assumption is that every tumour would fit into some category and we are working hard towards getting that classification.*

Question: *What is the general methodology to adopt in biomarker studies?*

Answer: *It is important to be aware of the shortcomings of whatever assay you are using. You need large sample sizes, and you need to be sure that effects are stable and that there are no other variables that change the effect of the marker. Setting up both a discovery and one or two validation sets is very important.*

SUBGROUPING BASED ON GENE EXPRESSION



This analysis of unprespecified gene expression identified four main subgroups that seem to be in agreement with other studies, but not with currently used descriptors of the disease

S Siena et al (2009) *JNCI* 101:1308–24, published with permission © Oxford University Press 2009

Hope for me, and for others who come after

Award-winning article explores the impact of a new network of early trial centres

Delays in getting promising new treatments into trials are slowing progress in cancer care and failing patients who have run out of options and are running out of time. This article, which earned freelance journalist **Victoria Lambert** a Best Cancer Reporter Award, looks at what UK efforts to cut these delays has meant for three patients with advanced cancer.

"Death is a huge, vicious dog. We are trapped together in an alleyway, and every day I must stare him in the face, and challenge him. I must attack him first, with all my strength, and every weapon at my disposal. I have to – if I turned for one moment, if I lost my courage, if I tried to run away instead, he would chase me and he would leap on me, he would savage me and he would kill me."

Julie-Ann Gallagher is 45 years old; she has spent the past 14 years in a near daily battle with cancer. Her fragile beauty masks an internal conflict between her body – where tumours ravage her lungs, breast, throat (one wraps around her windpipe), and clog her bones – and her mind, which is still sharp, decisive and brave.

She has fought on many fronts: not only has she been determined to stay alive, but she has also found the strength to survive the loss of her husband, Alan, an infantry soldier, who committed suicide six weeks before her first cancer appeared, and to bring up two children. Somewhere along the way she found a deep faith in God; she also found an equally profound trust in medicine. So much so that she has now been given a desperate last chance, taking part in a clinical trial of an experimental treatment that may grant her more time – but equally might not help her and might have side-effects. The trial results, however, will contribute to the development of better treatments for the cancer patients who will come after her.

ELLEN NOLAN

Victoria Lambert

Gallagher is a vital human element

A programme of clinical trials is bringing experimental treatments to seriously ill cancer patients years ahead of schedule and giving them a second chance for life.

Victoria Lambert talks to three people who have taken part in the trials, set up by Cancer Research UK, one of the charities supported by this year's Telegraph Christmas Appeal.

Photographs by Ellen Nolan

Telegraph magazine

The patient's voice. Given that fears about safety and exploitation form the framework for many drug development stories, this article was important in providing an alternative perspective: that of patients with advanced cancer, for whom access to drug trials offers their only hope

in a clinical trial programme, the Experimental Cancer Medicine Centres (ECMCs), created in April 2007 by Cancer Research UK. Together with the departments of health of England, Scotland, Wales and Northern Ireland, the charity is jointly funding a network of 19 centres of excellence across Britain, at a cost of £35 million over five years until 2011.

The centres run clinical trials to bridge the gap between treatments that look promising in the lab and therapy that can be given to patients. They speed up what can often be a slow and expensive process. Before human trials, drugs are tested in the lab to obtain preliminary information on efficacy, toxicity and pharmacokinetics (what happens to a drug when it is applied to a living organism). Then they pass through three stages of trials in patients: phase I, assessment for safety and side-effects; phase II, testing for efficacy and safety on a larger scale; and phase III – a definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment in a large population group. No wonder that with new cancer treatments the average development time is about 10 years from bench to bedside.

The work of the ECMCs covers all types of cancer, from breast, colon and prostate to the 10,000 Britons whose primary tumour location is impossible to find; and all manner of therapies from those home-grown in the Cancer Research UK labs, such as Parp (Poly ADP ribose polymerase) inhibitors, which cleverly target natural faults in certain cancer cells and exploit them, increasing the chance of cell suicide, to those created by the huge pharmaceutical companies such as GlaxoSmithKline.

Cancer patients taking part in phase I trials have already received all standard treatments, such as conventional radiotherapy and chemotherapy, available to them. As a result they have limited treatment options, and only months or weeks to live. Other trials are carried out to test medicines already licensed by the National Institute for Clinical Excellence (NICE) for a specific purpose – but combining them with other drugs or radiotherapy, or simply to assess them in other cancers.

For example, Avastin is licensed by the NHS [National Health Service] for advanced bowel cancer that has spread; scientists have been looking at ways it could help treat bowel cancer at an earlier stage or even different types of cancer. Until those treatments have also been approved by NICE, however, the drug remains available only in trials or at an oncologist's discretion

(the practice of giving a patient a licensed medicine for a condition other than that approved by NICE is known as prescribing off-licence).

In either case the common thread of ethics remains – if there is an established treatment for their condition already in existence, patients must try that first. Experimental treatments still come second.

Dr Sally Burtles, the director of cancer centres at Cancer Research UK and who oversees the ECMC programme, explains that the impetus to set up the scheme came from a recognition that while superb cancer centres already existed in Britain, a network was needed to draw them together and to encourage collaboration: "We wanted to speed up the development of new drugs, and we knew that by providing specialist resources we could improve the system we had." The programme is also an excellent way to ensure that each centre can concentrate on its own oncological specialty, while ensuring that patients get the most appropriate new therapy for them. Patients can be referred between centres depending on their ability to travel, or receive their treatment close to home.

Cancer Research UK facilitates the ECMC programme, and in 2011 its results will be peer-reviewed, the official test of whether it has been a success. Prof Ruth Plummer, the clinical professor of experimental cancer medicine based at Newcastle University, believes that the network has been enormously positive – in the first year, 400 trials took place, by year three (2008) that number had doubled, and by the end of this year it will no doubt have expanded exponentially again. "It has really made the UK research situation attractive to the global pharmaceutical companies; one recently contacted me to ask if we had the facilities to take on a major trial. If not, they would take it to Europe. A few emails later, I was able to inform the company that we were more than set up to take on the work." Plummer also points out that Britain is the only country to have such a network, although other countries are watching closely – and a similar EU-wide scheme is in the process of being set up.

Agreeing to go on to a trial was a surprisingly easy choice for 21-year-old Calum Elliot, because it seemed a bonus – both for him and others. "I was more than happy," he says, "whatever the side-effects or results. It was good to think that my experience might make it easier for other young people who are diagnosed like me." Two years ago, Elliot, a plasterer, started having episodes when he would become mentally 'absent' for a few moments; his family – mother, Jane, 40; stepfather, Craig Watson, a 43-year-old driver; and his 17-year-old sister, Danielle, with whom he still lives in a flat close to Glasgow airport – and his friends spotted that he simply didn't respond to anything – conversation or action – for two to three minutes at a time. These moments might occur in the pub or playing football, or even when watching his team, Glasgow Rangers. Concerned, in 2008 his mother took him to the GP, who referred him to a specialist. An MRI scan revealed a tiny abnormality on the left side of his brain and epilepsy was diagnosed. For the next year and a half, Elliot took anti-epileptic drugs but the drugs did not stop the seizures, which had become weekly.

For Elliot the toughest news was being told that his driving licence would be suspended (as it is with all epilepsy sufferers on safety grounds). Not long after, he suffered an episode at work and was 'let go' four weeks later. Yet he still didn't feel ill and played football with an understanding team and league mates (who took him to the side when a seizure struck and allowed him back on to the pitch when he 'came round'). Then, in September this year, Elliot's doctors sent him for a routine MRI scan; he was called in for an appointment to discuss it the next day. The night before, he suffered a terrible headache and began vomiting. His mother drove him straight to the hospital. "I was given a CT scan that showed there was bleeding on the brain,' he says. 'The doctor who I had been due to see the next day showed up to see me. He explained he was a surgeon; I guess he must have known already he would need to operate on me."

Elliot underwent a five-hour operation: the small spot on the original MRI scan from 2008 had grown into a 2 cm tumour, and after 90% was removed, leaving a small horseshoe-shaped scar on the left side of his head, it was proved malignant. Of the diagnosis itself, Elliot says now, "That's something you don't want to hear. But you have to deal with it and be strong." His stepfather says, "We told everyone that first day – friends and family and especially Calum's granny; they're very close and that was the hardest bit, I think."

Elliot was warned that his was one of the worst cases the surgeon had seen – a grade 4 glioblastoma (one of the most aggressive brain tumours at its most advanced state – cancers are graded 1 to 4 in severity). But Elliot was immediately offered the chance to go on a trial organised by an ECMC locally as – incredibly – a blood sample showed that his DNA matched the exact requirements of a new drug. He would be the first person in the world to try a vaccine created in a Glasgow lab that aims to boost the body's own defences.

Prof Jim Cassidy, who runs the ECMC at the University of Glasgow with his fellow oncologist Prof Jeff Evans, believes that there are tremendous benefits to the scheme. "We have always been good at research and at clinical care here; establishing the ECMC helps us bring the two together, so not only does bench get close to bedside, but we can also work the other way round. We can take samples from patients who are undergoing experimental medicine and see what the drug is doing to the tissue or tumour, to see how it succeeds or fails. It's not trial and error, it is trial and understanding."

Calum Elliot needs to have 13 injections in the course of the trial and has already had nine. He is undergoing a course of radiotherapy that will be over before Christmas, and chemotherapy, which will last until April.

"I was warned to expect side-effects but I'm fine," he says. "The injections which go into my upper thigh sting for 10 minutes but that's it. I haven't even lost much hair from the other treatments." Overall he feels fit, eats well, and has had no 'episodes' since the operation. He goes clubbing with his friends, drinks 'in moderation' and is planning a four-day weekend in Butlins Skegness to celebrate the end of the radiotherapy. It will be a few months before Elliot knows whether the experimental treatment has worked – when he is scanned a few weeks after the end of radiotherapy. It will not be until a second MRI another six weeks later that an accurate result will emerge – but he seems to be focused less on getting through the course and more on counting down the days until he regains his driving licence.

ELLEN NOLAN

Calum Elliot, 21, has been taking part in a trial that aims to limit the aggressive tumour in his brain by boosting his body's natural defences

In the South Yorkshire town of Penistone, 72-year-old Terry Windle is also waiting to see if his experimental cancer treatment has worked. Slim and healthy-looking, he could easily pass for a decade younger. The home he shares with his wife, Kathy, 58, a retired pharmacist, is decorated with paintings and photographs of motorsport – he has spent his life designing, building and racing motorbikes. Next year Windle plans to cross the US on a Harley-Davidson ("It'll be me and a couple of other fellows: one's 70-odd and the other's 84. We can't wait"). But before he can buy the plane ticket, he has to have a check-up with his oncologist at St James's Hospital in Leeds, an ECMC where he received treatment for his ocular melanoma – an incredibly rare cancer that first appeared in his eye 29 years ago.

"I should have died then," Windle says, enormously cheerful. "But I didn't even know it was cancer. I'd had problems with my sight playing squash, and I was sent to hospital, where they found a tumour on the back of the right eyeball, which they removed. No one said the tumour might be malignant."

"It was good to think that my experience might make it easier for other young people"

"My condition can be managed. It's extraordinary. I'm not even considered terminally ill any more"

ELLEN NOLAN

Terry Windle, 72, with his wife, Kathy, at their home in Penistone, South Yorkshire. Terry has had a successful outcome to his clinical trial treatment at St James's Hospital in Leeds, which 'teaches' immune cells to kill melanoma cells

Then 23 years later, in 2004, Windle started experiencing unusual stomach pains; that August he was sent for an MRI. A specialist told him they had found a tumour on his liver, which they intended to remove within a fortnight. "I wasn't that surprised. A few years before, a friend had undergone the same eye experience – an extraordinary coincidence. He had been warned it was cancer and that it might spread to his liver, which it duly did, and he died. So I had begun asking questions and learnt that ocular melanoma usually kills you within five years. By my own reckoning I should have been dead by 1986." However, a series of regular monthly, three-monthly, and six-monthly CT scans showed no recurrence. "I just got on with life," he says. But the cancer did recur in 2006, first in his navel in the form of an inoperable tumour, and then a lump on the back of his neck. "They sat me down in 2007, and said, it's months, not years now. You're 69, pack in your work and enjoy what time you have left – we can do nothing."

But they did suggest that Windle could join the ECMC at St James's Hospital, and in the summer of 2008 he was invited to join a phase I trial for gene therapy for ocular melanoma which had spread to the liver. The trial was of a new treatment called a PolyMEL DNA vaccine. It works by teaching immune cells to recognise certain proteins (antigens) made by melanoma cells. Theoretically, the immune cells will then kill the melanoma cells.

"I had three jabs over a few weeks – that's all – just like any other vaccine in my arm." While he waited to see if it would work, Windle spent the next year building a shining Lotus racing car from a kit.

The results appear to be good – his oncologist has told him the cancer has "stalled". And despite his tumours, which all appeared in the two years preceding the trial (one in the muscle of his shoulder, one in his breast, one on his side, two in the lungs and one by the navel), he looks fit and well, and is planning another skiing trip. "From what I can gather this has completely stalled them; I can't be cured, but my condition can be managed. That will do for me. It is extraordinary. I'm not even considered terminally ill any more."

Julie-Ann Gallagher, who lives in Bishops Waltham, Hampshire, cannot make the same bold statement. Like Windle, her experience has been extraordinary, her endurance inexplicable. But unlike Windle and Elliot, she has also undergone lengthy bouts of pain and discomfort – and she looks as ill as she is. We talk in her sitting-room – family photographs of her daughter, Sarah, now 20, a fitness instructor, and son, Carl, 15, who intends to take up an apprenticeship in plumbing after school, are proudly displayed on a table.

Gallagher is wrapped in myriad layers, furry boots and a fleecy blanket. The temperature is nearly as cold inside her small council house as it is out. Gallagher has spent most of her adult life fighting cancer and raising her children alone; she hasn't been able to develop a career or save for infirmity. "I can't afford to put the heating on yet," she says. "I told Carl, we must wait until it is really necessary. We simply can't afford it." She looks blue-grey with cold. Advanced cancer patients are not allocated winter heating support as pensioners are – an issue that the cancer support charity Macmillan is campaigning on strongly. It is the only occasion that Gallagher shows her frustration at her lot. "I'm never warm – the

tumours in my lungs feel like icicles, and the only time I know the sensation of heat is when I'm in hospital undergoing an iodine transfusion."

Gallagher first developed cancer at the age of 31, in August 1996, when six weeks after her husband's death (he suffered, she believes, from manic depression) she found a lump in her left breast "the size of a piece of coal; one day there was nothing, the next this thing. It felt like it had smaller tumours, like grapes, hanging off it. I have no doubt it was due to the extreme shock and stress of my situation. I was the widowed mother of six-year-old Sarah and Carl, then aged 18 months." Her GP took one look and sent her the same day to a specialist. "The breast sister appeared with dread in her eyes – I thought, I am going to follow my husband." That was the first and last moment of self-pity she allowed herself. "I thought, I must fight this for my children – they don't deserve this."

Moreover, she wanted them to understand that, despite their father's suicide, life is worth choosing. She underwent a mastectomy and reconstructive breast surgery, but the tumour, which was a grade 2/3, had already spread to her lymph glands. She underwent six months of chemotherapy, and began taking tamoxifen to prevent it recurring. "I lost my hair but I didn't care; I even stopped wearing the wig I was given, when Carl pulled it off in the supermarket. Nothing mattered but surviving." Her breast sister warned her, "It will come back, you may get 10 years if you're lucky."

Gallagher shakes her head. "That wasn't enough time for me, but it made me start planning. I promised my daughter I would be at her wedding, which, last year, I was."

She began to feel well, fit and strong, and launched a business, selling decorative gold and silver nipple 'jewellery' for mastectomy sufferers. Life was briefly good. "And then, in 2004, I came last in the parents' race on sports day – I had no puff. A few days later, I raced a parking warden back to my car, and lost, feeling breathless." Her doctor ordered an X-ray, and Gallagher admitted that she had felt a lump on her neck, too.

A tumour had appeared, wrapping itself around her jugular vein and the windpipe next to it. A tiny patch of cancer cells had somehow survived, undetectably hidden behind the reconstructed breast, and had spread – not only to her windpipe, but also pitting both lungs.

The tumour on her side was cut out, but although she was offered chemotherapy, Gallagher was told that there was no hope of recovery. "When I said, 'Don't you bet on it,' they told me, 'That's what all the patients say.'"

Gallagher refused to give in. She underwent a year of very gruelling chemo. Then, in 2006, her oncologist announced there was no more she could do for Gallagher and told her firmly that she should not expect to collect her pension. "I think if you get secondary cancer you become a nuisance; they know what to do with primary and they know how to support you, but once you get to my stage, it's so different."

Gallagher was not prepared to give up – she moved to Southampton University Hospital, and after demanding to try something, was given hormone therapy, which had to be injected painfully into her stomach to slow down her ovaries, which seemed to be fuelling the growth of the cancer. By 2008 she was becoming more breathless. "I could smell death on myself – my lungs were filling up with fluid and I was drowning." An operation to drain her lungs worked but left her ill; she lost a stone in weight.

A scan revealed the cancer was now in her spine and hips, and her body was clearly too weak for chemo to be considered. It was time to stop the agonising injections too – Gallagher simply couldn't stand them. "I was so close to death last Christmas, I know that,' she says. But then a small miracle happened. 'I was asked to join the ECMC trial at Southampton University Hospital for a drug called zoledronate, which is given intravenously once a month."

Her consultant oncologist, Jennifer Marshall of Southampton University Hospital Trust, explains this is a trial of a bisphosphonate therapy, principally used in osteoporosis patients as it strengthens bones and helps to reduce bone pain. "We have learnt that it possibly also has an anticancer effect, too," she explains, "hence the idea for a randomised trial."

"And in Julie-Ann's case, while we couldn't 'cure' the bone cancer," Marshall says, "we could at least put her on the trial and do something about the pain she was suffering while hopefully protecting her from fractures."

Gallagher recalls, "After the first infusion I felt relief. I just felt better, somehow." But after six months, her veins collapsed to the extent that injections were no longer an option. She was taken off the trial as she could not carry on, but prescribed off-licence another form of bisphosphonate therapy called ibandronate, which she takes in tablet form once a day.

"Although Julie-Ann was not on the trial for the full period of two years, it did reduce her pain and continues to – nor has she suffered any breaks, so I think for her you could say it has been successful," Marshall says.

Gallagher is now busy planning Christmas and looking forward to her

"Without these new drugs, cancer would have taken me. But I'm not ready to go yet. I love life"

son's 16th birthday, and then her daughter's 21st. Jennifer Marshall is happy to keep looking out for new trials because, she explains, "Julie-Ann's defied the odds; we just want to give her as good a quality of life as possible and keep her well."

Part of the problem with any cancer is its mutability. "Tumours change and become resistant," Dr Sally Burtles explains, "which is why single drugs, however good they may be when they get passed by NICE, are often more effective when we start trying them in combinations with other drugs or radiotherapy. Plus much of the work done in ECMCs is the search for biomarkers: these are the factors in our DNA that mean once we understand them we can start to anticipate who will do best from which drug before treatment even begins."

Highly personalised treatment is the future, she confirms. "We call it stratification: ultimately the aim is that every individual will be treated according to the exact genetic code of their cancer. Obviously there is still much work to be done, but I have no doubt this will come." As for the ECMCs, she admits that it is too early to talk of general success rates; that will be decided after peer review in 2011, but she anticipates that the project will be deemed a success.

ELLEN NOLAN

Julie-Ann Gallagher, 45, mother to 15-year-old Carl and 20-year-old Sarah, has lived with cancer for the past 14 years. Gallagher has been involved in a clinical trial during the past year

Prof Ruth Plummer admits she is sometimes in awe of the patients who join the ECMC's nationwide trials. "It is very humbling to meet these people who want to join our studies; they know they are often incurable and many are running out of options. We have to be really honest about what they are doing but they accept that this is unknown territory. They say – I know this may not help me but maybe it will help someone in the future. It makes our centres very positive places to be. And there is a very low refusal or dropout rate on the trials. It is unusual for anyone to decide not to join in if they physically can."

None of the three people interviewed knows for certain if their treatment has been a "magic bullet" either, yet all would take up the offer to do another trial. Even Gallagher, for whom the future does not look so hopeful, feels blessed. "I am grateful for the 14 years I have had. I am grateful I have seen my daughter's wedding. But you have to help yourself and make your own luck. Last Christmas I felt I didn't have long – but I am still here and I have no doubt that getting the bisphosphonate therapy has helped.

"Without these new drugs, cancer would have taken me, but I am not ready to go yet. I love life. And I still hold out hope for a miracle cure."

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Redefining the role of pathology

How Giuseppe Viale embraced the new responsibilities of the molecular era

➜ Simon Crompton

In the era of personalised therapies, complete and accurate pathology reports are vital. Helping pathologists rise to their new responsibilities, and ensuring they are given the opportunity to play a full role, has been a mission for Giuseppe Viale, a leading Italian pathologist whose career has spanned the transition from microscope to molecular imaging.

Pathologists are meant to be retiring types, locked away in white rooms poised above their microscopes, feeding their findings through to physicians but rarely involved with patients. Not Giuseppe Viale.

He's confident, gregarious and influential, and when he shows me the certificates on the wall of his office in the European Institute of Oncology buildings in Milan, he emphasises he's not doing it to show off. "This is what matters," he says, pointing to the citations that are for his contribution to "cancer treatment" and "cancer therapy" – not simply pathology. Giuseppe Viale, known as 'Beppe' to his friends, has brought pathology out of the white rooms and onto an equal footing with oncology.

A Fellow of the Royal College of Pathologists and a leading light in the Breast International Group since 2002, he was among the first pathologists to introduce immunohistochemistry (detecting antigens in cells through the use of antibodies) into oncological pathology at the end of the 1970s. In 1994 he was instrumental in setting up the Division of Pathology at the European Institute of Oncology, where he is director.

When I first spy him in the pathology department, it's clear straight away that force of personality as well as professional skill has played its part in his achievements. He's talking intently to a student in a corridor, hands on her shoulders, imparting some light-hearted words of wisdom. Everywhere he moves in the institute people know him and greet him. Viale has an easy charm, mixing strong opinions with self-deprecating humour, and it is easy to see how he wins over students, oncologists and decision makers alike.

As he tells me the story of his career, he admits

that some of what he tells me is also regaled to his students – as the University of Milan's professor of pathological anatomy and histology, he supervises the budding pathologists of the future. The sum of his tales are an essay in good pathology.

Two revolutions

He has been in Milan since beginning his medical training there in 1969. During that time he has witnessed two revolutions in cancer pathology. The first came at the end of the 1970s. Until then, cancer pathology had been based almost entirely on observing the morphology of cancer tissue under a microscope. But then immunohistochemistry became widely introduced, allowing individual cell components to be identified. This opened up the way to biological tissue characterisation and the identification of important markers.

"We were among the first in this country to break into immunohistochemistry in oncology," says Viale. "At the beginning it was used diagnostically to differentiate different tumour types, but then we used it to identify markers that were not only diagnostic but enabled us to look into prognosis and predict the response to therapy." This revolution, he says, was largely a technical one, resulting from the discovery of new techniques to extract biochemical information from formalin-fixed tissue samples. But it still led to enormous improvements in treatment and life expectancy.

The second revolution was an oncological one. Until the late 1990s, says Viale, prescriptions of systemic treatments were mainly informed by tumour size and number of metastases. Then the oncological community began to distrust this approach – clearly something was wrong with it when small tumours with no metastases were killing people within three months, and people were also surviving large tumours with many metastases. So the quality of the cancer cells, not the quantity, and the biological features that would predict responsiveness to therapy became the focus of attention.

"This, to me, was the most important revolution in oncology," says Viale. "There was this important change where systemic treatment became based on expected responsiveness of the tumour."

At the same time, through immunohistochemistry, pathologists were now able to measure

oestrogen receptors and *HER2* status. Then, around 2004, targeted therapies such as Herceptin (trastuzumab) started to become available, so that markers like *HER2*, which had previously been used for diagnosis and prognosis, became specific targets for interventions.

All this made the information provided by the pathologist more directly important to patient welfare than ever before. "There are three pillars to build a systemic treatment: the pathologist's report, the patient's preferences and the oncologist's opinion of what is best for the patient. But the pathologist's report is absolutely essential to support the other two."

There is a problem, however. Nationally and internationally, the potential impact of modern pathology in oncology is not always fulfilled. Viale says there are worrying variations in practice and standards, often because pathologists are too isolated.

Dangers of isolation

"Let us divide pathologists into two groups," he suggests. "There are those active in multidisciplinary teams, say in cancer institutions, and those who are not. The second group don't see the full picture of a tumour that has to be treated according to biological features, the presence of specific targets, within the context of the tumour burden, within a given person in a given time and given resources. So for them, the diagnosis of cancer, 'yes' or 'no', is the peak of their activity. Some don't actually care about staining for oestrogen receptors or *HER2*."

This is one reason for disturbingly high rates of erroneous pathology reports. Viale says that looking at *HER2* status assays across the world, around 15–20% can be expected to be false. "Unfortunately this discordance rate implies that quite a large number of patients, today, in 2011" (he bangs the table with his finger pointedly) "are mistreated because of an inaccurate assessment of the predicted parameters of breast cancer."

The reasons for variability can sometimes be traced to technical faults in the ways assays are run. This can be minimised with modern automated immunohistochemistry stainers and approved reagents. But more significantly, variation comes because of the very nature of pathology: it is observational and subjective, and two pathologists looking at the same slide may interpret it differently.

"To minimise this is much more difficult," says Viale, "because it depends on experience, expertise, the number of cases you have seen, the clinical feedback you get, whether you participate in quality control." The problem is widespread even among western countries – so much so that when patients are referred to the European Institute of Oncology for a second opinion (there are around 2500 such referrals every year), the oncologists there do not trust the original pathology reports and ask Viale's department to carry out their own. "If you are not confident in data how can you be confident in your prescription?" he asks.

Equally, he points out, how can you have a clinical trial looking at tailored treatments for specific breast cancers if you are not confident that the right patients, with the right pathology, are being selected

The next generation. Viale allows students to share his office because learning about roles, responsibilities and interactions is as important as the purely medical side of the job

Viale is confident that this kind of double-checking will lead to pathology standards being driven up worldwide

for the trial? In large multicentre, international breast cancer studies it is now becoming mandatory that local pathology samples and reports are sent to a central facility for checking, and Viale is confident that – in breast cancer now, and other cancers to follow – this kind of double-checking will increasingly lead not just to benefits for the patient, and not just to more significant trial results, but also to pathology standards being driven up worldwide. Viale's own laboratories at the Institute have had this central checking role in many major international trials. "We can force improvement," he says.

He explains what he means with a story. In a recent breast cancer trial involving more than 10,000 women across the world, Viale's laboratory discovered a very high discordance rate of more than 14% in one European country where more than 100 centres participated. "This was most unexpected by the oncologists there. So we worked together with the pathologists in that country, looking into results from all their centres, and discovered that in a handful of centres the discordance rate was more than 50%, bringing the whole national rate out of scale.

"So they went back to them internally, and they are now acting on it. We are happy to talk to any of the centres involved in trials about the way they are working, because this is a good way of having international quality control, which may lead to improvements in leading centres."

Learning lessons

Viale's belief in the importance of pathologists working as part of a team have been forged by influential figures through his career. He was born in Turin in 1952, an only child. His father died of melanoma when he was just 10, leaving his mother – a figure Viale clearly admires for her enterprise – to pick up and run the car-painting business he had just set up. Driven by ideas of helping people, Viale started medical school at the University of Milan and knew straight away he wanted to be a pathologist.

"I wasn't interested in collecting symptoms, like many of my colleagues. I wanted to know, 'Why? Why fever? What is the mechanism?'" In his second year of study, he started performing autopsies at a general hospital in Milan on Saturday mornings, wanting to know about the feeling and consistency of organs, not just what he read in books. "It said in the books that liver had a 'parenchymatous' consistency, but what did that feel like?"

His professor of pathology during university training was Guido Coggi, whose inquiring lectures further inspired Viale. He joined Coggi as an intern at the university's pathology institute at Ospedale San Raffaele, Milan, and remained with him after qualification for 20 years. In 1994 Viale became professor of pathological anatomy and histology at the University of Milan – and then came an additional role: director of the Division of Pathology and Laboratory Medicine at the European Institute of Oncology. His move into cancer was down to the influence of another giant in his career, Umberto Veronesi.

Veronesi had just set up the European Institute, and phoned the university to see if there were any bright young pathologists available. Viale remembers how Coggi, despite being highly dependent on Viale to run his own department, instantaneously told him he should take the job. "This was so instructive. The greatness of the man was to be able, in 10 seconds, to figure out that, for the sake of my career, I had to move." It's a valuable lesson that Viale often tells others. There are two more pieces of instruction from mentors that Viale mentions as key to his career.

One came during his interview for the job with Veronesi. Viale expressed surprise that Veronesi should want a pathologist like himself to head the new Department of Pathology and Laboratory Medicine – normally such roles went to the laboratory medicine side. "He said, 'Listen, this is a cancer centre, and what I know is that a cancer centre is only as good as its pathology department.' It is absolutely true."

He immediately warmed to Veronesi's understanding of the treatment issues that needed to be tackled for the good of patient welfare, and the need for extra resources to research those issues.

But the third lesson initially came as a jolt to his confidence. It was from oncologist Aron Goldhirsch, director of the Department of Medicine at the European Institute – "another giant in my career". A few months after Viale arrived at the Institute, "most likely a reasonably good general pathologist," Goldhirsch came into his office. "He said, 'Listen, I have a problem. This is your pathology report. But it does not tell me how to treat this lady. So I told her, she should come to you and you should treat her.' I thought, 'Are you crazy?' But that was his message – that the oncologist was always searching the pathology report for data that would inform the systemic treatment, and there was something inconsistent in this report that made interpretation impossible. This was fantastic because it taught me what it is to be a breast cancer pathologist."

Goldhirsch involved Viale in the International Breast Cancer Study Group, and he became co-chairman of its Central Pathology Office in 2002. This work drew him into the Breast International Group – he became a member of its executive in 2004. During the past decade he has had a central role in some of the most important recent breast cancer trials. These include the HERA trial into the use of trastuzumab in the adjuvant treatment of *HER2*-postive breast cancer.

He is on the steering committee of the ALTTO trial, a worldwide study involving more than 8000 patients to evaluate the effectiveness of a new therapy, Tyverb (lapatinib), in treating early breast cancer following surgery. He is also on the steering committee and lead pathologist of the MINDACT trial, which is run by the EORTC and aims to demonstrate how molecular profiling can be used to assign risk and determine whether breast cancer patients without lymph node involvement, or with between one and three nodes positive, need to receive adjuvant chemotherapy or not. He has authored 328 articles in international journals and written 36 chapters in books.

Through all this, and with his responsibilities for supervising young researchers and fellows, Viale admits that he has little time for relaxation – apart from spending as much time as he can tending to his vegetable patch.

His family is fortunately understanding. His wife is a biologist who works alongside him at the European Institute – they met whilst working together under Coggi to develop immunohistochemistry staining techniques, and Coggi was insistent that she should go with him when he moved to the Institute. They have two grown-up daughters, aged 22 and 21, the eldest in her fifth year at medical school, the other working to be a script writer. And he still regularly sees his mother, now 91 and still living in Milan, having retired after 30 years of running her business.

Passing on the lessons

It is the power of people – as a motivating force and as interpreters of scientific data – that Viale continually re-emphasises. Science is nothing without them. He shows me his office, which contains three desks with three microscopes, and which he always shares with the two youngest students he is supervising. "I spend around 12 hours here every day, but when I leave, although I'm happy to see my family, I'm sorry to leave my students. Their enthusiasm is so fantastic."

As students discuss with him what they are examining, and as they listen to Viale's phone conversations with oncologists and surgeons, he can give them some insight into what pathology in cancer really means, passing on the sorts of advice that he received from his own mentors.

"Hopefully, what they're exposed to daily is that behind the microscope is a patient. They should always keep in mind that making the pathology diagnosis is not something unrelated to a patient, a family, a history, to a problem with systemic therapy, indication from a surgeon, whatever. If you want to do something useful for the patient, you need to insert the pathology diagnosis into a wider context.

"He said, 'I have a problem. This is your pathology report. But it does not tell me how to treat this lady'"

"It is dangerous to think, 'This tiny piece of the problem is my responsibility and the rest is not my business'"

What I'm trying to teach them is that it is very dangerous to have the attitude: 'This tiny piece of the problem is my responsibility and all the rest is not my business.' So if the diagnosis is difficult, open the medical charts, talk to the treating physician, ask the relatives – be proactive."

Viale wears the pathologist's white coat proudly, because he believes it sends an important message to patients and others he is working with. "They see someone who is looking and acting like a doctor. That is important, and reassuring," he says.

So as we talk about where pathology is heading, and the increasing potential of new techniques to take objective readings that could rule out the human error that he knows can prove so devastating to patients, he is also adamant that pathologists should never be mere "machines of the clinical laboratory".

Yes, efforts to improve accuracy in pathology have already brought down international variance rates in the assessment of oestrogen receptors and *HER2* status from around 21% to 15% in a decade, and new genomic and proteomic techniques, which rely on objective testing rather than subjective observation, could bring this rate close towards zero. In 20 years time, says Viale, blood tests may provide as much information as a tumour sample. In theory, pathology itself could become redundant.

"But honestly, I believe that in the next few years, pathologists will not be replaced by these tests. We need these techniques to add to what we have, not replace them. We need as comprehensive a picture as possible of the tumour."

It may be always necessary to accept some variance rate, he says. What is important is to offer minimum standards and constantly encourage improvement. The best way to do this is to adopt a multidisciplinary approach in all cancer centres and involve as many patients as possible in clinical trials. But he realises that this can be politically difficult in many countries where professional hierarchies are deeply embedded.

As he shows me out of his office at the end of the interview, past all those certificates on the wall, he comments in passing that he can't remember a pathologist being on the cover of *Cancer World*. I realise that despite all his self-mocking humour, Viale is extremely proud of what he has done to raise the profile of his profession. He enjoys the status and influence he has attained through hard work, and greets and chats with friends and colleagues as we pass down to the Institute's reception, finding me a taxi driver he knows well to take me back to my hotel.

As I head off out of the doors, I hear him jokingly call after me, "Remember, I want the cover!" Beppe Viale has established himself as on equal terms with oncologists, and wants the world to know it.

Family time. Patrizia, Viale's wife, works as a biologist at the European Institute of Oncology, daughter Giulia (left) is at medical school, while Elena is working to be a script writer

An important piece of the localised prostate cancer puzzle?

James Denham

A recent trial randomly allocated 1979 men with localised prostate cancer to radiation therapy with or without neoadjuvant androgen deprivation. Despite the combination reducing prostate cancer-specific mortality by approximately 60% and producing a modest overall survival benefit in men with intermediate-risk cancers, the authors did not recommend changing the standard of care – why?

It is very common for men with apparently localised prostate cancer to be unsuitable for radical prostatectomy because of advanced age (at least 70 years of age), comorbidities (for example cardiorespiratory disorders and obesity) or inoperable cancers (such as those with local extension to other structures and high Gleason grade). It is common practice for these men to receive radiation therapy instead. Until the turn of the century, radiation therapy techniques had serious limitations and adverse outcomes occurred often, including primary tumour progression, and radiation-induced morbidity.[1] To make matters worse, men with high-stage and high-grade cancers frequently developed metastases and died of their disease.

The advent of luteinising-releasing hormone analogues and antiandrogens in the 1980s provided a means of delivering temporary androgen suppression to patients with prostate cancer. Owing to the success of androgen suppression in the palliation of metastatic prostate cancer, a multicentre US trials group – the Radiation Therapy Oncology Group (RTOG) – initiated trials to determine whether temporary androgen suppression could improve outcomes for men with localised cancer selected for radiation therapy.[2,3] Over the next 20 years, RTOG, EORTC (European Organisation for Research and Treatment of Cancer) and other trial groups demonstrated that various durations of androgen deprivation therapy (ADT) could reduce prostate-cancer-specific mortality (PCSM) by more than half, and produce clinically relevant improvements in overall survival in men with 'high-risk' localised cancers. The trials collected patterns of progression data and it was the reduction in metastases that was thought to be the major contributor to survival improvements.

Three of the trials included men with 'intermediate-risk' cancers, which have a lower propensity to recur within the prostate and/or metastasise than high-risk cancers. The largest of these was the RTOG 94.08 trial whose outcomes were published in the *New England Journal of Medicine* in July 2011.[4] This trial involved 212 centres in the USA and Canada and reached its enrolment target of 1980 men in 6.5 years, a remarkable achievement. The investigators found that patients receiving four months of ADT starting two months before radiation therapy (≤66.6 Gy) had a significant relative improvement of 17% (P=0.03) in 10-year overall survival when compared with patients who received radiation therapy alone (62% vs 57%). Over the same time period, PCSM was reduced from 8% in the radiation therapy arm to 4% in the combined treatment arm (HR=1.87, P=0.001). An unplanned subgroup analysis that assessed patients according to risk category (see table) revealed that men in the largest subgroup – intermediate risk (1068 men) – were the ones to achieve the most benefit from four months of ADT, with an

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approximate reduction of 60% in PCSM – from 10% at 10 years in the radiation therapy arm, to 3% in the ADT combination arm (P=0.004). This translated into a significant overall survival improvement.

These results supported those from two smaller trials that included fewer men with intermediate-risk cancers but used similar radiation doses.[5,6] The Dana-Farber trial compared radiation therapy alone with six months of ADT before and during radiation therapy; the total accrual was 206 men, including 135 with intermediate-risk prostate cancer.[5] This trial reported a significant improvement in overall survival at eight years that was associated with the use of ADT (HR=1.8, P=0.01).[5] The Trans Tasman Radiation Oncology Group (TROG) 96.01 trial, which randomised 802 men to radiation therapy alone or preceded by three months or six months of ADT, included 130 men with intermediate-risk cancer.[6] The 10-year data from TROG 96.01 indicated PCSM benefits for both three months and six months of ADT for these men; however, the benefits were not statistically significant, possibly because the study was underpowered. This underpowering could also have been a problem in two other relatively small trials conducted in Canada[7] and Ireland[8] that randomised men to their own 'standard' duration of ADT (three months and four months, respectively) or to eight months ADT, each followed by radiation therapy. In the 308 men with intermediate-risk cancer, a benefit for the longer ADT treatment could not be found. Therefore, largely due to the contribution of RTOG,[4] the available evidence points to a modest but real survival benefit for the use of four to six months of ADT and radiation therapy in men with intermediate-risk cancers considered unsuitable for prostatectomy.

The RTOG 94.08 investigators, however, did not conclude that four months ADT plus radiation therapy should be the new standard of care for men with intermediate-risk cancer. Instead, they pointed out that the higher radiation doses that modern radiotherapy equipment can now deliver safely might achieve the same benefits without using ADT.[4] The reader might ask: how can this be true? Increased radiation dose might prevent fatal obstruction of the urinary tract by preventing progression of the primary tumour, but how could it eradicate micrometastases outside the pelvis that have formed before treatment? Increased dose could, however, prevent metastases that arise from a primary tumour that has regrown after the modest radiation doses used in the trials mentioned. Biopsy data from the substudy of RTOG 94.08 that evaluated signs of persisting cancer two years after irradiation lent support to the hypothesis that persisting localised cancer was common enough after 66.6 Gy to be a source of many new metastases. In men with intermediate-risk cancers, 41% had persisting cancer at two years following radiation therapy alone; this figure was reduced to 24% in men also receiving ADT.[4] Metastases arising from a persisting or recurring tumour in the prostate are expected to be diagnosed later than metastases originating before primary therapy. In fact, a distinct 'second wave' of metastases commencing 7.5 years after radiation therapy was observed in the TROG 96.01 trial (JW Denham et al., unpublished data). The magnitude of this second wave was reduced in men who received three months ADT, and it was almost completely prevented in men receiving six months of ADT (JW Denham et al., unpublished data). Unfortunately, the report from RTOG did not present the time course of distant progression in either trial arm, nor how frequently a diagnosis of metastases could have been prevented by the initiation of secondary therapy.[4] Nevertheless, RTOG have sounded a very reasonable cautionary note and, to their great credit, have initiated a second trial to determine whether four months ADT remains necessary when higher radiation doses are delivered. In the meantime, TROG is addressing the same question on the other side of the Pacific in its 03.04 RADAR trial for men with high-risk tumours.[9] It is probable that it will be shown that both ADT and higher radiation doses are necessary to achieve the best outcomes, particularly in men with high-risk cancers.

D'AMICO RISK STRATIFICATION FOR PROSTATE CANCER[10]

Risk level	Markers
Intermediate risk	PSA >10 and PSA ≤20, Gleason score 7, or T2b*
High risk	PSA >20 or Gleason score 8–10 or ≥T2c*

*2002 American Joint Committee on Cancer category. Abbreviation: PSA, prostate-specific antigen

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

Practice point

The RTOG 94.08 investigators did not conclude that four months of androgen deprivation therapy (ADT) plus radiation therapy should be the new standard of care for men with intermediate-risk prostate cancer considered unsuitable for prostatectomy. Instead, they pointed out that higher radiation doses might achieve the same benefits without using ADT.

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Front-line therapy in lung cancer with mutations in *EGFR*

Lorenza Landi and Federico Cappuzzo

Large randomised phase III trials conducted in patients with non-small-cell lung cancer (NSCLC) harbouring activating mutations in *EGFR* have demonstrated that erlotinib or gefitinib are superior to platinum-based chemotherapy. Zhou and colleagues have now confirmed that these agents represent the best treatment we can offer today as front-line therapy for *EGFR*-mutant NSCLC.

During the past few years, treatment of metastatic non-small-cell lung cancer (NSCLC) – the leading cause of cancer-related deaths worldwide – has changed dramatically. For decades we have treated all patients with NSCLC with chemotherapy, without any clinical or biological selection and, inevitably, with disappointing survival results. Today, we know that patient selection is crucial for providing appropriate treatment and that stratification based on histology and *EGFR* status is mandatory before starting a front-line therapy. Results from large phase III trials have demonstrated that the best treatment option for patients harbouring activating *EGFR* mutations – mainly represented by deletion in exon 19 or the L858R substitution in exon 21 – is tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib that are directed towards the tyrosine kinase domain of EGFR. By contrast, for patients with wild-type *EGFR* tumours, platinum-based chemotherapy – including pemetrexed and bevacizumab or a combination of platinum with gemcitabine, vinorelbine or taxanes – remains the gold standard in non-squamous histology and squamous histology, respectively. The efficacy of EGFR TKI therapy in patients harbouring *EGFR* mutations has been confirmed in a recently published trial conducted in China, which compared erlotinib with the combination of carboplatin and gemcitabine.[1]

Only a few years ago, some investigators were convinced that an EGFR TKI could be given as front-line therapy without an *EGFR* mutation assessment.[2] Prospective phase II trials with gefitinib or erlotinib showed that these agents had a response rate in unselected patients of approximately 10%, with a median progression-free survival (PFS) of two to three months and median overall survival of 10–12 months.[3] Although response rate and PFS results were clearly inferior when compared with historical data of platinum-based chemotherapy, median survival seemed comparable to standard chemotherapy. These data supported the hypothesis that an EGFR TKI could be given as front-line therapy in an unselected population because even if the patient was

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not sensitive to the targeted therapy, platinum-based chemotherapy could be given as salvage therapy. Two phase III randomised trials have compared erlotinib with chemotherapy in chemotherapy-naive and unselected patients with NSCLC.[2,4] In the TORCH trial,[2] unselected patients with NSCLC were randomly assigned to receive erlotinib or platinum-based chemotherapy. The trial was designed to demonstrate non-inferiority of survival in patients receiving erlotinib versus chemotherapy as front-line therapy. However, as expected, chemotherapy had a superior response rate and PFS. Most importantly, the study clearly demonstrated that giving an EGFR TKI without any assessment of mutations in *EGFR*, translates into a detrimental effect on patient survival. More recently, Thomas et al.[4] compared erlotinib plus bevacizumab as front-line treatment versus the combination of cisplatin–gemcitabine–bevacizumab in patients with NSCLC unselected for mutations in *EGFR*. Similarly to the TORCH trial, the study demonstrated a detrimental effect on survival for patients randomly assigned to the erlotinib–bevacizumab arm.[4]

Initial studies with gefitinib and erlotinib had already shown that these agents are more effective in patients with certain clinical characteristics, such as female sex, never-smoker, adenocarcinoma histology and Asian race, likely because these characteristics are associated with the presence of mutations in *EGFR*.[5] Unfortunately, *EGFR* testing is not possible in all patients with NSCLC, mainly because of the lack of tumour tissue suitable for biomarker analyses. Therefore, a relevant clinical question is whether clinical selection based on the characteristics of the patient could replace selection based on genetically established *EGFR*-mutation status. To assess this, two phase III studies compared gefitinib with platinum-based doublets in patients with NSCLC and the previously mentioned clinical characteristics predictive for sensitivity to EGFR TKIs.[6,7] In these studies (FIRST-SIGNAL and IPASS) – which included East-Asian patients with adenocarcinoma histology, who were only (FIRST-SIGNAL[6]) or mainly (IPASS[7]) never smokers – PFS improvement with gefitinib was confined to patients with activating *EGFR* mutations. At the same time, patients with wild-type *EGFR* who received chemotherapy had a significantly lower risk of progression than those who received an EGFR TKI. From the clinical point of view, that means that an EGFR TKI cannot be used as front-line therapy when *EGFR* status is unknown, even in patients who present with all the clinical predictors of EGFR TKI sensitivity.

Four studies, two with gefitinib and two with erlotinib, investigated the efficacy of front-line treatment with an EGFR TKI compared with standard chemotherapy in patients with NSCLC with proven *EGFR* mutations. The WJTOG3405 and NEJ002 trials randomly assigned chemotherapy-naive patients with NSCLC harbouring activating *EGFR* mutations to gefitinib or platinum-based chemotherapy.[8,9] In both trials, gefitinib was superior to chemotherapy according to response rate and PFS, with a more-favourable toxicity profile. More recently, Rosell and colleagues[10] presented the results of the EURTAC trial, the only available study conducted in white patients harbouring activating *EGFR* mutations. This trial assigned 174 patients with advanced-stage NSCLC from Spain, Italy and France to randomly receive erlotinib or platinum-based chemotherapy. In this study, patients treated with erlotinib had a significantly higher response rate and significantly longer PFS than the chemotherapy group.

In a recent issue of *Lancet Oncology*, Zhou et al.[1] published the results of the OPTIMAL trial, a phase III study comparing erlotinib with gemcitabine–carboplatin chemotherapy in Chinese patients with NSCLC harbouring *EGFR* mutations. The study, which included a total of 165 patients, met its primary endpoint of PFS. Patients assigned to the erlotinib arm had a significant reduction of risk of progression, with a hazard ratio of 0.16. Importantly, subset analyses showed a significant PFS benefit favouring erlotinib in all subgroups, including those classically considered to be less sensitive to EGFR TKIs (male sex, smokers, non-adenocarcinoma histology). This is a relevant finding confirming that tumour biology might be much more important than clinical factors in determining whether a patient should receive EGFR TKI therapy and that when tumour growth is sustained by a specific target, drugs effectively inhibiting such a target can be dramatically effective irrespective of any clinical characteristic. The PFS improvement observed in the OPTIMAL trial was impressive: median PFS 13.1 months for the erlotinib arm versus 4.6 months in the standard chemotherapy arm. It is possible that this huge difference is not 'real', since *EGFR*-mutant tumours are more sensitive to both EGFR TKIs and chemotherapy than *EGFR* wild-type tumours. In the IPASS trial[7] – where investigators ignored the *EGFR* status – median PFS in the chemotherapy arm was 6.3 months among patients with *EGFR* mutation, about 2 months longer than reported in the OPTIMAL trial[1] – where investigators knew the *EGFR* status of the tumours.

It is important to highlight that no phase III trial has demonstrated any improvement in overall survival for patients with NSCLC harbouring *EGFR* mutations and treated with EGFR TKIs versus chemotherapy. This result is probably because of the confounding effect of post-study therapies, because in such

trials the vast majority of patients assigned to the chemotherapy arm received an EGFR TKI as second-line or third-line therapy, with an inevitable mixed effect on survival results. This resulted in a hazard ratio for overall survival that was slightly in favour of EGFR TKIs, even though the difference was not statistically significant. This trend in the hazard ratio is of clinical relevance as it suggests that the order that patients receive the treatment could be of importance and that if a patient with mutations in *EGFR* does not receive an EGFR TKI as a front-line treatment, they might be unable to receive an EGFR TKI as second-line therapy (for example, because of rapid progression), with a potential detrimental effect on overall survival as a consequence. However, if all eligible patients receive an EGFR TKI as first-line treatment, then 100% of patients would be able to benefit from the overall survival improvements and they would still likely have the option of receiving salvage chemotherapy.

In conclusion, all available data demonstrate that in the presence of activating *EGFR* mutations, EGFR TKIs are the best option that we can offer today as front-line therapy. On the one hand, even in the absence of a proven overall survival benefit, offering an EGFR TKI as soon as possible is strongly recommended in patients with *EGFR*-mutant NSCLC. On the other hand, for patients with negative or unknown *EGFR* mutation status, platinum-based chemotherapy remains the standard of care, with cisplatin–pemetrexed being the most active regimen in patients with non-squamous histology.

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

Practice point

EGFR tyrosine kinase inhibitors are the standard first-line therapy for patients with metastatic non-small-cell lung cancer who harbour activating *EGFR* mutations.

Author affiliations: Istituto Toscano Tumori, Ospedale Civile, Livorno, Italy (Lorenza Landi and Federico Cappuzzo). *Competing interests statement:* Federico Cappuzzo receives honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Roche and he owns a patent on *EGFR* testing using fluorescence in situ hybridization. Lorenza Landi declares no competing interests.

NEWSROUND

Selected reports edited by Janet Fricker

Elderly pancreatic cancer patients benefit from chemotherapy

→ Journal of Geriatric Oncology

Chemotherapy is associated with improved overall survival in patients with metastatic pancreatic cancer aged over 80, a US retrospective analysis has found.

Metastatic pancreatic cancer is an incurable disease with a dismal prognosis. Survival ranges from three to six months for all patients, but drops to two to three months for untreated patients. Despite the incidence of pancreatic cancer peaking at between 70 and 79 years of age, patients aged 65 years or older have been under-represented in clinical trials, resulting in a lack of evidence-based data to make treatment decisions with regard to chemotherapy.

In the current study, Shanmuga Subbiah and colleagues, from Creighton University Medical Center (Omaha), identified patients aged 80 or older treated by the Veterans Health Administration between 1997 and 2007, whose data had been recorded in the VA Central Cancer Registry (VACCR). Altogether, 440 patients were identified who had information available with respect to age at diagnosis, race, sex, tobacco history, tumour location, tumour histology, grade and type of therapy received.

Of the patients identified, 83% (n=367) received no therapy, 12% (n=52) received chemotherapy alone, 2% (n=9) received radiotherapy alone, 1% (n=5) received chemoradiation therapy and 2% (n=7) underwent surgery.

Multivariate analysis demonstrated that median overall survival was 4.9 months for patients receiving chemotherapy versus 1.7 months for patients receiving no therapy (HR 0.41, P<0.0001). Survival at one year was 13% for patients receiving chemotherapy versus 3% for patients receiving no therapy (P<0.0001). Furthermore, current smoking was associated with decreased median overall survival compared to past or never smoking status (1.18 vs 1.63 and 1.57 months respectively, P=0.0087).

"Our results regarding the effectiveness of treatment vs no treatment in pancreatic cancer are encouraging and consistent with similar data in other malignancies but are not definitive. However, we recommend that very elderly patients with good performance status should be offered chemotherapy based on our analysis, and age by itself should not preclude these patients from receiving chemotherapy," write the authors. Treatment decisions, they add, should be based on physiologic rather than chronological age, with the factors that need to be evaluated including functional status, comorbidity and cognition.

Limitations of the study included its retrospective nature, the predominance of men in the study population (only 10 women were included in the analysis), and the lack of information regarding performance status and patients' quality of life. "This is very important in elderly patients since increasing survival by a few weeks at the cost of decrease in quality of life is not acceptable in this patient population," the authors write. Further randomised studies, they add, will be needed to confirm whether chemotherapy offers benefit in very elderly patients with advanced pancreatic cancer.

■ IT Aldossa, T Tashia, W Gonsalvesa et al. Role of chemotherapy in the very elderly patients with metastatic pancreatic cancer. A Veterans Affairs Cancer Registry analysis. *J Geriatr Oncol* 2 July 2011, 2:209–214

Goserelin does not protect ovarian function

→ Journal of Clinical Oncology

Giving goserelin to young women undergoing standard anthracycline-based chemotherapy for hormone-insensitive breast cancer shows no effect on preserving ovarian function, the ZORO study has found.

Currently 1.9% of breast cancers are diagnosed in women aged between 20 and 34 years, and 10.5% in women aged between 35

and 44 years. Although patients younger than 50 years achieve significant benefit from adjuvant systemic chemotherapy in terms of prolonged disease-free and overall survival, a significant number suffer from premature ovarian failure. Cytotoxic agents, especially anthracyclines and alkylating agents, are known to induce premature ovarian failure, most probably through causing apoptotic oocyte death in primordial follicles.

Observational studies and one recent single-institution randomised study have suggested that luteinising hormone-releasing hormone agonists (LHRHa) might offer protection against premature ovarian failure. No explanation has been offered for the benefit.

The German Breast Group ZOladex Rescue of Ovarian function (ZORO) study was designed to investigate the preventive effect of the LHRHa goserelin on chemotherapy-induced ovarian failure in young patients with hormone-insensitive breast cancer who are treated with neoadjuvant chemotherapy based on anthracycline/cyclophosphamide (with or without a taxane). Between March 2005 and December 2007, the study, led by Sibylle Loibl, recruited 60 patients from 16 centres, who were randomly assigned in a 1:1 ratio to receive chemotherapy with goserelin (n=30) or chemotherapy without goserelin (n=30). To be eligible, patients needed to be aged between 18 and 45 and to have requested preservation of ovarian function; they also needed to have had regular and spontaneous menstrual periods, and follicular stimulating hormone levels below 15 mIU/ml in the follicular phase of the menstrual cycle. Patients assigned to goserelin received their first injection of 3.6 mg at least two weeks before the start of chemotherapy and then every four weeks until the last chemotherapy cycle.

At six months, 70% of patients in the group taking goserelin had regular menses compared to 56.7% in the group without goserelin (P=0.284). After adjusting for age (patients in the goserelin group tended to be younger), 70.7% of patients in the goserelin group versus 65.9% in the group without goserelin menstruated (P=0.708). The median time to restoration of menstruation was 6.8 months in the goserelin group versus 6.1 months in the group without (P=0.304).

"The ZORO trial did not provide evidence that use of goserelin for ovarian suppression was associated with a large clinically and statistically significant protective effect on ovarian function in patients with hormone-insensitive breast cancer. The resumption rate of regular menstruation within 2 years after modern chemotherapy was highly independent of goserelin," write the authors, adding that other ongoing randomised trials may clarify the role of LHRHa in protecting ovarian function. "Until these results are available, the uncritical use of LHRHa for ovarian protection should be stopped, and patients should be enrolled onto clinical trials," the authors conclude. Other fertility preservation strategies such as oocyte or embryo freezing, they add, might be preferred.

■ B Gerber, G von Minckwitz, H Stehle et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: The GBG 37 ZORO study. *JCO* 10 June 2011, 29:2334–41

Low-dose CT screening reduces mortality in lung cancer

➜ NEJM

People at high risk from lung cancer randomly assigned to screening with low-dose computed tomography (CT) had fewer deaths from lung cancer than did those randomly assigned to screening with chest radiography, reports a study from the US National Cancer Institute. Researchers showed that three times as many clinically significant abnormalities were identified in the low-dose CT group compared with the radiography group, and furthermore mortality was decreased by one-fifth in the low-dose CT group.

Although effective mass screening of high-risk groups for lung cancer might potentially offer benefits, randomised screening trials with chest radiography with or without sputum cytological analysis have shown no reduction in lung cancer mortality. However, advances in multidetector CT have recently made high-resolution volumetric imaging possible in a single breath hold with acceptable levels of radiation exposure, thereby enabling lung-specific applications.

In the current study, the National Lung Screening Trial (NLST), funded by the American NCI, enrolled 53,454 people considered at high risk for lung cancer who were randomly assigned to undergo three annual screenings with either low-dose CT (n=26,722) or single-view posteroanterior chest radiography (n=26,732). To be eligible, participants needed to be aged between 55 and 74 years of age, and have a history of cigarette smoking of at least 30 years; former smokers were eligible providing they had quit less than 15 years prior to the study. Volunteers were invited to undergo three screening sessions at yearly intervals, with the first performed soon after randomisation.

Results show substantially higher rates of positive results for all three screening sessions in the low-dose CT group compared with the radiography group – 27.3% versus 9.2% for the first round; 27.9% versus 6.2% for the second round; and 16.8% versus 5.0 % for the third round. Altogether 247 deaths from lung cancer per 100,000 person-years occurred in the low-dose CT group compared with 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95%CI 6.8%–26.7%; P=0.004).

"The observation that low-dose CT screening can reduce the rate of death from lung cancer has generated many questions," write the authors. These include whether populations with risk profiles differing from those of the NLST participants would benefit; whether less frequent screening regimens would be equally effective; and for how long screening should be continued?"

The potentially harmful effects of low-dose CT, they add, include false-positives, detection of cancers that would never have

become symptomatic, and the association of low-dose CT with development of radiation-induced cancers.

In an accompanying commentary, Harold Sox, from Dartmouth Medical School (West Lebanon, New Hampshire, US), suggests that, with around seven million adults in the US meeting entry criteria for the study and an estimated 94 million current or former smokers, the introduction of a national screening programme for lung cancer would prove prohibitively expensive. "Policymakers should wait for cost-effectiveness analyses of the NLST data, further follow-up data to determine the amount of over diagnosis in the NLST, and, perhaps, identification of biologic markers of cancers that do not progress," he writes.

■ The National Lung Screening Trial research team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *NEJM*, 4 August 2011, 365:395–409

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Ipilimumab improves survival in melanoma

→ NEJM

Ipilimumab combined with dacarbazine improved survival in patients with previously untreated metastatic melanoma compared with dacarbazine alone, reports a phase III study, which was presented at ASCO and published simultaneously online in the *New England Journal of Medicine*.

Metastatic melanoma has a low survival rate, with only 10–20% of patients alive at two years. Ipilimumab, approved by the US regulatory body, the FDA, in March 2011, is a fully human IgG1 monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), known to be a negative regulator of T cells. An earlier phase III study, presented at ASCO in 2010, showed that ipilimumab improved survival in comparison with an experimental vaccine. The earlier study involved a different population of patients who had received prior therapies for metastatic melanoma.

In the current phase III study, Jedd Wolchok and colleagues, from the Memorial Sloan-Kettering Cancer Center, in New York, randomly assigned 502 patients with previously untreated metastatic melanoma in a 1:1 ratio to receive ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m^2 body-surface), or dacarbazine (850 mg/m^2) plus placebo, given at weeks 1, 4, 7, and 10, followed by dacarbazine alone every three weeks through week 22 (n=252). Although dacarbazine has never been shown to improve survival in randomised controlled studies, it is the drug that is most frequently compared with new agents in trials of patients with melanoma.

Results showed that the median overall survival was 11.2 months in the group receiving ipilimumab plus dacarbazine versus 9.1 months in the group receiving dacarbazine plus placebo (HR 0.72; P<0.00). At one year, the estimated overall survival rate was 47.3% in the ipilimumab plus dacarbazine group versus 36.3% in the dacarbazine plus placebo group, at year two the results were 28.5% versus 17.9%, and at year three 20.8% versus 12.2%. Grade 3 or 4 adverse events occurred in 56.3% of patients treated with ipilimumab plus dacarbazine, as compared with 27.5% treated with dacarbazine plus placebo (P<0.001). No drug-related deaths or gastrointestinal perforations occurred in the ipilimumab–dacarbazine group.

"This trial showed that there was a significant improvement in overall survival among patients with previously untreated metastatic melanoma who received ipilimumab plus dacarbazine as compared with dacarbazine plus placebo," conclude the authors, adding that the present study showed notably higher rates of high-grade hepatic adverse events than previous studies of ipilimumab.

"The apparent shift in the rates of adverse events associated with ipilimumab may be due to its combination with dacarbazine, which is known to cause hepatotoxic effects when it is used as monotherapy," write the authors.

Key side-effects of ipilimumab, such as entercolitis and endocrinopathy, could be managed effectively according to established guidelines, including the administration of systemic glucocorticoids or other immunosuppressive agents.

■ C Robert, L Thomas, I Bondarenko et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *NEJM* 30 June 2011, 364:2517–26

Vemurafenib improves overall survival in melanoma

→ NEJM

Vemurafenib (PLX4032) improved both overall and progression-free survival in previously untreated melanoma patients with *BRAF* mutations in comparison to dacarbazine, according to the findings of a phase III study presented at ASCO 2011 and published simultaneously online in the *New England Journal of Medicine*.

Approximately 40–60% of cutaneous melanomas carry mutations in *BRAF* leading to activation of downstream signalling through MAPK pathways. Vemurafenib is a potent inhibitor of mutated *BRAF* that has been shown to have marked antitumour effects against melanoma cell lines with *BRAF* mutations, but not against cells with wild-type *BRAF*. Phase I and II clinical trials of vemurafenib have demonstrated response rates of more than 50% among patients with metastatic melanoma and *BRAF* mutations.

In the current study, Paul Chapman and colleagues, from the Memorial Sloan-Kettering Cancer Center in New York, randomised 675 patients with previously untreated *BRAF* mutations in a 1:1 ratio to receive either vemurafenib (at a dose of 960 mg twice daily orally) or dacarbazine (at a dose of 1000 mg/m^2 body surface area by intravenous infusion every three weeks). Patients with the required mutation had been identified from a total of 2107 patients undergoing initial screening at 104 centres in 12 countries.

Results show that, at six months, overall survival was 84% in the vemurafenib group versus 64% in the dacarbazine group (HR 0.37, 95%CI 0.26–0.55; *P*<0.0001). The final analysis for progression-free survival (evaluated in 549 patients) showed that vemurafenib was associated with a relative reduction in the risk of either death or disease progression of 74% compared with dacarbazine (*P*<0.001).

Survival benefits for the vemurafenib group were observed in each prespecified subgroup according to age, sex, ECOG performance status, tumour stage, lactate dehydrogenase levels and geographic regions. Common adverse events associated with vemurafenib were arthralgia, rash, fatigue, alopecia, photosensitivity, nausea, and diarrhoea. Altogether, 18% of patients treated with vemurafenib developed at least one squamous cell carcinoma, but the lesions could easily be excised and none required dose modifications of vemurafenib. Overall, 38% of the patients receiving vemurafenib required dose modifications due to adverse events.

"Our results show that single-agent vemurafenib improved the rates of response and of both progression-free and overall survival, as compared with dacarbazine, in patients with metastatic melanoma with the *BRAF* ...mutation," write the authors, adding that their findings provide a solid foundation for the development of future combination therapies.

The mechanism for induction of cutaneous neoplasia (which are far easier to treat than melanoma) is currently under investigation, write the authors, who speculate that it involves the activating effect of vemurafenib on preneoplastic cells.

In an accompanying commentary, Marc Ernstoff, from Dartmouth Medical School (Lebanon, New Hampshire), writes, "Although little is known about the use of targeted adjuvant agents in patients undergoing surgery, it is now reasonable to consider testing of adjuvant vemurafenib in patients with high-risk stage II or III melanoma with the BRAF V600E mutation on the basis of the findings in the BRIM-3 study."

■ PB Chapman, A Hauschild, C Robert, et al. Improved survival with vemurafenib in melanoma with *BRAF* V600E mutation. *NEJM* 30 June 2011, 364:2507–16

■ MS Ernstoff. Been there, not done that – melanoma in the age of molecular therapy. *ibid* pp 2547–48

CT-based simulation improves survival in non-small-cell lung cancer

➜ Journal of Clinical Oncology

The introduction of CT-based simulation improved survival in patients with stage III non-small-cell lung cancer (NSCLC) undergoing thoracic radiation therapy, a retrospective analysis of the US SEER data has found.

Thoracic radiation therapy is commonly used in the management of patients with stage III NSCLC to improve local control and survival. Technical studies have shown that introducing CT-based simulation helps improve local control by allowing for better anatomic definition of the targeted lesion and more precise calculation of dose to both tumour and normal tissues. Despite a good theoretical rationale, prospective data supporting CT simulation has been lacking.

In the current study Aileen Chen and colleagues, from the Dana Farber Cancer Institute (Boston, Massachusetts), analysed data from Medicare's SEER database to identify patients with stage III NSCLC who had received thoracic radiation therapy within six months of diagnosis, between 2000 and 2005. Investigators analysed the effectiveness of CT-based simulation versus conventional simulation with respect to overall survival.

Results showed that the proportion of patients treated with thoracic radiation therapy who had CT simulation increased from 2.4% in 1994 to 34.0% in 2000 and 77.6% in 2005. Overall, of the 5540 patients treated between 2000 and 2005, 60.1% received CT simulation. After controlling for demographic and clinical characteristics, CT simulation was associated with a lower risk of death (HR 0.77; 95%CI 0.73–0.82; *P*<0.01) compared with conventional simulation.

The investigators found regional variation in use of CT simulation. Patients from the northeast and midwest were more likely to receive CT simulation than those in the west or south, and CT simulation was more common in urban areas and among patients with higher incomes.

Furthermore, patients treated with chemotherapy were more likely to have CT simulation (65.2% vs 51.2%; adjusted odds ratio 1.67; 95%CI 1.48–1.88; *P*<0.01), but no significant association was found between surgery and use of CT simulation.

"We cannot be certain whether patients who had CT simulation had better outcomes because of the technique itself, or because CT simulation is a marker for higher TRT [thoracic radiation therapy] doses, more aggressive treatment, greater institutional resources, or differences in the attitudes and mindset of providers likely to adopt new technologies," write the authors, adding that in the absence of randomised data, the results indicate that the new technology is not associated with any unanticipated harms.

In an accompanying commentary, Andrea Bezjak, from the University of Toronto (Ontario, Canada), writes that the regional differences observed suggest that it was not the medical situation or the appropriateness of high-dose radiation that influenced selection of CT-based simulation, but availability of the technology in the centres where patients were treated. "This suggests a potential alternative hypothesis for the survival outcomes: it may be that whether or not a patient underwent CT based simulation was a marker for overall quality of care in the center in which the patient was treated," she writes.

■ AB Chen, BA Neville, DJ Sher et al. Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation. *JCO* 10 June 2011, 29:2305–11

■ A Bezjak. Harnessing radiation technology to improve survival. *ibid* pp 2295–96

Taking the first step on the road to cancer control

How two proposed registry projects could help

Anna Wagstaff

The UN Summit on Non-Communicable Diseases opened a window of opportunity for decisive action to set poorer countries on the road towards sustainable cancer control. Two major international cancer registry initiatives now offer the chance to show governments what can be achieved even with limited resources, and help equip their countries with some vital skills.

September 20th 2011 was the day when the world's governments finally made a commitment to addressing suffering and death from cancer. They were attending the first ever UN Summit on Non-Communicable Diseases (NCDs), the convening of which was a significant achievement in itself: many countries currently have no policies at all for controlling cancer or other non-communicable diseases.

More than 30 heads of State and Government, and at least 100 other senior ministers and experts, participated in the high-level meeting, which ended in a vote for a political statement that committed these governments to: "Promote, establish or support and strengthen, by 2013, as appropriate, multisectoral national policies and plans for the prevention and control of NCDs." Other commitments, for which no deadline is given, include improving prevention, early detection and access to treatment and palliative care, as well as capacity building and strengthening information systems for health planning and management and the development of population-based national registries and surveys.

It's a good start, but as the UICC (Union for International Cancer Control) noted in a broadly welcoming statement, the declaration avoids specifying targets, indicators or timelines by which to monitor and evaluate how successful member states are at fulfilling these commitments.

The task of formulating such targets and indicators has been ceded to the WHO, which has been asked to "develop before the end of 2012, a comprehensive global monitoring framework, including a set of indicators, capable of application across regional and country settings, including through multisectoral approaches, to monitor trends and to assess progress made in the implementation of national strategies and plans on non-communicable diseases."

These would then be presented for agreement at the 2013 World Health Assembly. The UICC is rallying its forces for another two years of determined advocacy to make sure that these recommendations will enable effective global monitoring of trends in the overall cancer burden and the impact of cancer control interventions – look out for the launch of this campaign at the World Leaders Cancer Summit in Dublin this November.

Achieving effective global monitoring of cancer will take more than agree-

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Left: Tanzania's Ocean Road Cancer Institute is one of few such facilities in Africa. It cannot serve the needs of the country's 43 million inhabitants and most patients it does see present too late for effective treatment
Below: UN member states have now committed themselves to developing sustainable policies for controlling cancer

ment at the World Health Assembly, however. Most countries lack both the capacity to gather, process and analyse cancer data, and the understanding and political will to use that data to inform policy. Tackling this challenge is the goal of two major international cancer registry projects – the CONCORD-2 comparative cancer survival study, led by the London School of Hygiene and Tropical Medicine, and a Global Initiative for Cancer Registry Development, led by IARC (the International Agency for Research on Cancer). Securing the backing to get these projects up and running as quickly as possible could be vital to keep up the momentum created by the UN NCD Summit.

A GLOBAL SURVIVAL STUDY

CONCORD-2 is set to be the most comprehensive international comparative study of cancer survival to date. With backing from key parts of the cancer community including the UICC, IARC and the International Atomic Energy Agency's Programme of Action for Cancer Therapy (PACT), it seeks to provide comparable data on survival, cure and premature avoidable deaths, for 10 major cancers in adults plus leukaemia in children across fifty countries, developed and developing, broken down by age, sex, race/ethnicity, calendar period from 1995 to 2009, and (where separate registries exist within a country) geographic region.

The full project comes with a price-tag of £3 million (€3.5 million) – not a lot by the standards of international collaborative translational research projects, but on the ambitious side for epidemiological studies. CONCORD's sponsors are now hoping to convince enough funding sources that the project can provide value for money in terms of its contribution to the current concerted efforts to improve cancer control around the globe.

"Some of the most motivating results come from contrasting cancer survival between rich and poor"

Michel Coleman, who is leading this initiative on behalf of the London School of Hygiene and Tropical Medicine, points out that improving global cancer survival rates is one of the 11 targets the World Cancer Declaration (WCD) has set out to achieve by 2020, and CONCORD-2 can provide baseline measurements and hopefully also regular updates on progress towards this goal.

But Coleman believes that the project's biggest contribution will be in developing local expertise in gathering and analysing cancer data, thereby improving the measurement of the impact of cancer control interventions (WCD target no.2) – that and the political leverage generated by publishing comparative figures on survival.

"Some of the most important and motivating results come from contrasting cancer survival between rich and poor or advantaged and disadvantaged," says Coleman, who points to the importance of the EUROCARE studies first in drawing attention to the serious survival gaps between central/eastern European countries and the rest of Europe, and then charting the gradual narrowing of those gaps as a result of government measures.

He also cites an earlier international survival study, CONCORD-1. This was the first credible large-scale study to confirm that racial disparities in cancer survival are systematically replicated across the US for a wide range of cancers. CONCORD-1 led to renewed efforts to explain and address this disparity.

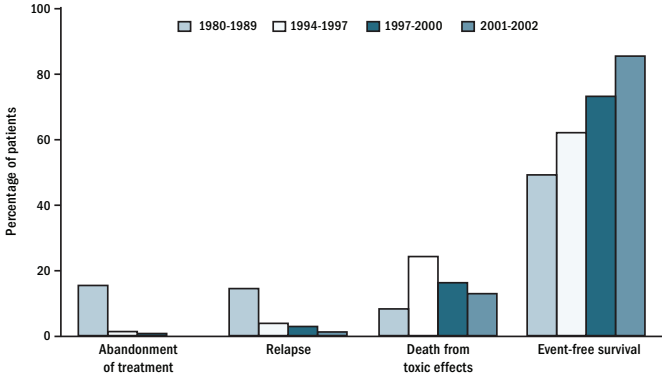
Whether statistics showing vast survival differences between countries at very different levels of development will carry the same shock value is, perhaps, a different question. Coleman is confident they will – if nothing else, he says, it should challenge the myth prevalent in developing countries that cancer is a uniformly fatal disease. "If health ministers in those countries conclude that in some cases it is possible to survive cancer pretty well – and in some cases very well – then that will help educate the public and politicians that something can be done to reduce the adverse outcomes of cancer once it is diagnosed," he says, pointing out that this will contribute to achieving WCD target no. 5 – the one about challenging damaging myths and misconceptions.

As a public health specialist at Colombia's National Cancer Institute in Bogota, Marion Piñeros spends a lot of time helping educate the public and decision makers that it is possible to treat some cancers effectively, and she agrees that comparative survival studies can indeed play a very useful role. She finds the example of childhood leukaemia to be particularly instructive, and the CONCORD-2 study – for which she serves on the steering committee – has included this cancer alongside 10 adult cancers at her express request.

"You can see that at relatively low cost in terms of treatment, high-income countries have reached very good survival very fast in children with acute lymphoblastic leukaemia. In fact childhood cancer survival has become one indicator of access to and quality of healthcare. I think that could be relatively easy to achieve in developing countries, if there is the commitment and strong social support." To illustrate the point, she cites the experience at a public hospital in Recife, Brazil, where outcomes of children with acute lymphoblastic leukaemia were completely transformed between 1980 and 2002 (see figure above).

"With the provision of social support, including help for mothers and families to remain economically active while the child is in treatment, it should be possible to achieve survival close to

THE POWER OF STATISTICS



These bar charts, charting progress in treating childhood ALL at a public hospital in Recife, show Brazilian decision makers they are doing something right – and show countries with similar socio-economic profiles what they too could achieve with the right policies

Source: R Ribeiro et al. (2005) *NEJM* 352:2158–60, reprinted with permission, © Massachusetts Medical Society 2005

"That will help educate the public and politicians that something can be done once cancer is diagnosed"

"80–90% of cancers registered have quality control that is not applied to mortality data at all"

that in many developed countries. So I think the comparison between rich and poor is very important. You can compare within your region, and also compare with other countries."

For poorer countries, however, the value of participating in international studies goes beyond the impact of the comparative statistics, says Piñeros. It is a way of giving 'visibility' to the data that their own registries gather and collate. "We can make a lot of effort, but the staff is scarce, and we have less time to prepare and write up scientific articles. Often you have very good people who don't speak English, and translating the articles is very costly. In Latin America, it is only really Brazil and Mexico that have relatively good visibility in terms of published scientific papers."

Data published in the context of major international studies also carry more weight with decision makers, adds Piñeros, "It is not only more visible, but it also puts on more pressure, and that makes a difference to what you can do afterwards."

The heavy focus on survival does have its critics, however. One criticism is that population-based mortality statistics, which show the number of deaths from different cancers per 100,000 population, provide a more useful picture of a country's overall cancer burden than survival statistics, which only capture information about people diagnosed with cancer. Other criticisms focus on the complexity of collating and interpreting survival data, which – so the critics argue – make them less reliable than mortality statistics, which are collected from official death certificates.

The mortality vs survival debate

This mortality versus survival debate tends to bubble up from time to time in heated exchanges in academic journals and epidemiological gatherings, often to the dismay of advocates who feel it offers an excuse for doing nothing.

Piñeros argues that to get a good picture both are needed. Trends in cancer mortality provide a good indicator of the impact of overall cancer control plans, because they reflect prevention as well as survival. However, survival statistics are better for monitoring access to early detection and treatment – aspects of cancer control that many feel are given insufficient attention by governments who find it easier to focus purely on promoting lifestyle changes.

The issue of relative credibility of mortality and survival statistics is, of course important – you don't change minds, or policies, when there are serious doubts about the accuracy of the data. But arguments held in the context of western health systems, where serious efforts have been made to ensure that all deaths are recorded accurately according to the latest WHO international classification of diseases, do not readily transfer to the developing world.

As David Forman, head of the section of cancer information at IARC explains, "You have to remember that in most African countries, for example, there are no reliable mortality data whatsoever – and even when they are available, they are often not helpful in monitoring cancer. The same is true in a number of Asian countries. I was talking recently to a colleague from India who said that, although there is a process for recording deaths, officials writing death certificates are under real pressure from families not to mention cancer as a cause.

"So you've got, particularly in the developing world, many populations where death certification is either inadequate, unreliable or non-existent. In that context, to pose mortality as an alternative to survival doesn't really get you anywhere."

Coleman is confident that he can convince backers of the quality of the data that will be used in CONCORD-2. "To the extent possible, those data are subject to quality control that beggars belief in comparison with mortality statistics. When a cancer is registered the clinical data are checked at the point of tumour registration, and if they fail local checks in the registry they are corrected from the original source records by the registry concerned.

"After that, they are subject to internal quality control in the registry, often using standardised checks such as those produced by IARC. And finally, when they are brought to collaborative international comparative analysis, they are subject to further quality control checks, and the same standards are applied internationally and registries are required to meet them.

"That level of quality control, based on hard pathological data in something like 80–90% of registered cancers is simply not applied to mortality data at all."

The Challenge of sustainability

While prospective funders may be reassured by all this, they will undoubtedly also be looking at sustainability – will this

"District officials have to take decisions, but they don't know how to follow a logical path to develop policies"

effort just give us a one-off survival snapshot (valuable in itself as a comparative exercise and a baseline assessment) or will it also give decision makers a better understanding of the value of measuring cancer indicators and develop an enhanced capacity to carry out the data gathering and analysis?

"This is a topic very close to my heart," says IARC's David Forman. "Report after report is identifying the absence of basic vital statistics as a significant black hole in our understanding of the worldwide patterns of cancer. One of IARC's primary objectives is to produce global statistics on cancer [e.g. the Globocan database http://globocan.iarc.fr/], and we more than anyone are aware of areas of the world where the statistics are, at best, very crude estimates because of the absence of cancer registration data – largely Africa, parts of Asia and parts of Latin America."

In response to a request from the director of IARC, Chris Wild, CONCORD-2 now includes a commitment to capacity building that may be a drop in the ocean in terms of global need, but nonetheless represents a substantial commitment in terms of the project as a whole, says Coleman.

"In terms of training development and technology transfer, capacity building represents roughly 10% of the overall budget. We're planning to offer training for cancer registrars in 30 developing countries, which is in line with what IARC asked for, costing roughly £300,000 [€350,000] – not at all trivial. We are also looking for fellowships from agencies such as the UICC and IAEA, which supported three fellowships a year ago on our cancer survival course, to enable registrars from developing countries to come and learn how to improve their skills in cancer survival analysis.

"We are also committed to support courses that IARC would lead, in Africa, Asia and possibly Latin America. We have a group of experienced scientists and teachers in cancer survival analysis, who have taught courses all over the world, so we are confident that if we get the budget for CONCORD-2, we will be able to make, over the three-year span of the programme, a substantial difference to the capacity of registries or institutions working with cancer data in developing countries to perform survival analysis to the highest standards locally."

However, a three-year survival analysis project is not designed to address the 'black hole' of global cancer data that Forman talks about. That task falls to IARC, which is gathering support for a Global Initiative for Cancer Registry Development, to be launched at the UICC's World Cancer Leaders' Summit in Dublin this November.

"We are trying to establish a system of regionally based support, rather than the entire world looking to IARC in Lyon for support, as happens at the moment," explains Forman. "We want cancer registry hubs in Asia, Africa, and Latin America, staffed by those with expertise in registration and registration methods, and the software that we use, who can then provide support to registries within their region.

"The idea is to build up a network of six or seven such regional hubs around the world as a step towards improving cancer registration capacity in those areas." Like CONCORD, this project will rely on support from an array of partners, says Forman, including the UICC, the International Network for Cancer Treatment and Reseach, the International Association of Cancer Registries, the American Cancer Society and Centers for Disease Control, the US National Cancer Institute and the IAEA Pact programme. "All of them, and others, have said in many recent statements that something needs to be done about improving cancer registration in low- and middle-income countries. This initiative is to try to put substance behind that particular demand."

Piñeros welcomes any efforts to develop cancer registration capacity in developing countries. She cautions, however, about the need for strategic thinking to avoid the investment in capacity building being wasted. In particular, she argues, it is preferable to keep the funding base of registries as independent as possible.

"We have seen that when registries depend heavily on local public health institutions or governmental agencies for their funding, they are very vulnerable to political changes. Some of the registries that started up were not given funds some years later, because the political figures changed. What has worked relatively well in the Colombian case has been to set them up in a university setting."

She talks too about the need for advocates or 'ambassadors' who can demonstrate the value of cancer statistics to decision-makers and explain how they can be used to shape effective health policies.

"At local level, districts and cities, there is a need to take decisions, but their capacity of analysis, particularly for chronic diseases like cancer, is usually very low. They may well have information from the vital statistics system, but they don't know how to group the cancers or follow a logical pathway to develop appropriate policies."

To help with this, Piñeros and her colleagues are set to publish a handbook on analysing the cancer situation, which gives "an easy and practical pathway to prioritising cancer control objectives, and taking evidence-based actions".

"It is a stepwise approach where you say, for instance, if cervical cancer is showing as a major burden you can orientate resources according to scientific evidence. If you set up cervical cancer screening, you then have to evaluate how effective it is. You have to plan using a long time frame and go through logical steps according to your distribution of cancer burden in your particular locality."

This approach has worked well, she says, in Cali, and some other major cities where she and her colleagues have been working with the health minister to put together a programme, hopefully a long-term one, based on a situational analysis, where registry data are of particular value. The data showed that, in Cali, breast cancer has overtaken cervical cancer in significance, and this has led to more resources being directed towards breast cancer control, particularly early detection.

This sort of stepwise logical progression, from data gathering and analysis to the formation of sustainable plans and policies, followed by monitoring and evaluation, is what the World Cancer Declaration roadmap is all about. With the NCD Summit still fresh in the minds of policy makers, projects like CONCORD and the Global Initiative for Cancer Registry Development offer the opportunity to take a leap forward in global cancer control that should not be squandered. Of course, the current economic turmoil may not be the ideal time to be searching for funds, but as the UN Summit on NCDs recognised in point 1 of the political declaration, "the global burden and threat of non-communicable diseases constitutes one of the major challenges for development in the twenty-first century, which undermines social and economic development throughout the world." Looked at in this way, helping countries get the information they need to tackle those diseases most effectively could be seen not as a drain on hard-pressed resources, but as part of the solution to the global economic crisis.

Strengthening cancer surveillance across the globe

The CONCORD-2 study will draw data from up to 160 registries in up to 50 countries in every continent (participants in Asia and Latin America are shown below). IARC wants to set up regional hubs to support cancer registration in the many countries where information is limited or non-existent

This sort of stepwise logical progression is what the World Cancer Declaration roadmap is all about