European School of Oncology
Learning to care

Cancerworld

Number 42, May-June 2011

Education & knowledge through people & facts

Jean-Yves Blay

➜ Jean-Yves Blay: integrating translational and clinical research ➜ Pioneering trials coordinator reveals the secrets of success ➜ Cervical cancer: closing the gap between the best and the worst ➜ Negotiating the principles and procedures for European biobanking

Contents

All enquiries about Cancer World should be made to:
ESO Editorial Office
Via del Bollo 4
20123 Milan, Italy
e-mail: magazine@eso.net
Tel: +39 02 8546 4522
Fax: +39 02 8546 4545
All correspondence should be sent to the Editor at editor@eso.net

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

Adapting services to the age of oral therapies

Kathy Redmond ■ EDITOR

The increasing use of oral cancer drugs is contributing to a change in the way cancer services are organised, leading to many more patients receiving care in an ambulatory setting.

Cancer patients are certainly benefiting from this change. Many oral targeted therapies hold the disease in check and, if taken continuously, can keep patients alive for years. Reductions in hospital stays make a big difference to their ability to get on with their lives. Unlike conventional chemotherapy, side-effects associated with oral targeted therapies are mostly mild, reversible and tend to get better over time. Avoiding needles and the need to keep accessing central veins is also a big plus, not to mention protecting their veins from the damage inflicted by vesicant chemotherapy agents.

Yet oral drugs come with their own challenges, many of which are under-recognised and poorly tackled. While the side-effects of oral targeted therapies are generally mild, they are nonetheless a burden, and all the harder to bear because of the long-term nature of the therapy. Some oral therapies also have complex administration schedules, which can be awkward for patients to incorporate into their everyday life. Consequently, patients' persistence with oral treatments tends to drop off over time, which can have a significant impact on their outcome.

As treatment is no longer delivered in hospital, there are fewer opportunities for health professionals to address all these issues and help educate patients about adherence to treatment, managing side-effects and avoiding dangerous interactions with other drugs or herbal therapies.

Cancer services need to adapt to make sure that patients on oral therapies do not receive inferior care because of a lack of interaction with health professionals. In many countries, it is becoming apparent that health services also need to remove unhelpful and unjustifiable obstacles to or biases against oral cancer therapies.

In some health systems, for instance, oral cancer drugs are reimbursed at a lower rate than IV chemotherapy, with the result that some patients have no choice but to take IV therapy, even if the overall cost of treatment is more expensive. The UK Parliament, meanwhile, is currently debating a proposal that will make it harder for cancer patients to access a new type of welfare benefit if they are on oral rather than IV therapy.

There appears to have been limited health service planning to address the many challenges posed by the introduction of oral therapies in cancer. Ambulatory cancer services need to be developed to ensure that patients' educational and support needs are met, treatment-related side-effects are managed effectively and patients are helped to stick with the treatment in the long term. Reimbursement and benefit difficulties also need to be addressed, so that services using oral therapies are not compromised by lack of funds, and patients are not denied beneficial oral treatments because of financial penalties.

Jean-Yves Blay

integrating translational and clinical research

Marc Beishon

Major clinical breakthroughs come from understanding molecular biology. So says EORTC president Jean-Yves Blay, who is leading efforts to reshape cancer research so that every trial has a translational element that can build knowledge about the mechanisms driving the disease.

If the fight against cancer is mainly an incremental process scientifically, building carefully on evidence, step by step, the same approach should apply to the people and agencies working on the problems. This means that, in the clinic and in research, we need to keep refreshing the centres and team leaders, and generate a continuous stream of young investigators, to ensure that the brightest and the best are in a position to help move things forward. Without this, momentum can slow down or even stop.

That is the firm view of Jean-Yves Blay, the current president of the European Organisation for the Research and Treatment of Cancer (EORTC), who can himself be seen as an injection of new thinking at the head of an organisation that is at the forefront of many critical issues in oncology. Heading the EORTC is one of the most challenging jobs in European cancer, as there are so many obstacles in the way of unifying research efforts around the continent – not least the differences in national healthcare systems and in the rules and regulations governing research, the lack of resources and, in recent years, the huge impact the Clinical Trials Directive is having on academic studies and groups. And the EORTC has faced criticism – notably that an 'old guard' has been in place for years.

"The challenges are certainly real and the criticism we've had is fair to some extent," says Blay, adding that the problem has been greater in some parts of the organisation than others. "We are made up of a number of research groups, and some are very active, although others have gone through a lifecycle where we need to bring in new blood. The EORTC board, with director Françoise Meunier and Denis Lacombe from the headquarters, has asked each group to identify young investigators and we are holding meetings to help them become involved, and we have closed some groups while others are starting again from scratch."

The EORTC is also looking much more towards collaborating with other networks and agencies in intergroup studies to avoid duplicating efforts and get the most out of limited resources. "What is

NIGEL DICKINSON

clear though is that the EORTC is probably the only body with the long-term expertise to organise clinical research in a range of cancers across countries in Europe," says Blay, "and we have other groups coming to us for this experience and not just to add patients to their studies."

Another part of the EORTC's strategy is to focus on a smaller number of expert centres to carry out complex and demanding clinical and translational trial work. The Network of Core Institutions (NOCI), under discussion for many years, has now been set up for this purpose. Last year agreements were signed with core centres – there are 26 now. They will implement complex molecular trials, but will, says Blay, also involve smaller centres, when needed, via EORTC's disease-specific groups. But smaller centres do lack the patient numbers and multidisciplinary groups needed to participate in increasingly complex translational research studies.

"The door is always open, but we must have centres capable of contributing a high level of accrual in studies, expertise in rare tumour subtypes, excellent molecular biology facilities and so on – and even the top centres do not have all the resources and people on their own. There are hundreds of new, targeted agents in development and hundreds of tumour subtypes, with more being uncovered each year. We simply do not have the resources to test

"We need to generate a continuous stream of young investigators to help move things forward"

combinations in an empirical way anymore and we must truly integrate translational research for rational treatment development that is both effective and less costly to carry out."

Blay's main job is professor of medical oncology at the University of Lyon and head of the medical oncology department at Lyon's Centre Léon Bérard, one of France's top dedicated cancer hospitals. As befits someone entrenched in the intricacies of translational research, he is a rare tumour specialist, having opted to focus on sarcoma from an early stage of his career.

That means he has been closely involved with the development of treatment with the standout targeted drug Glivec (imatinib) in the treatment of gastrointestinal stromal tumour (GIST). But as a medical oncologist who attends virtually every major cancer research conference, he is also familiar with most of the promising new drugs and their molecular targets, not least because some are in EORTC trials.

"We are now seeing several examples each year of new targeted agents, such as that targeting ALK, with effect in both a rare tumour and a subtype of common tumours such as lung cancer. Another example is an agent targeting RANKL that exerts Glivec-like tumour control in a rare cancer – giant cell bone tumour – it has about 95% control, but also potent antitumour effect in bone metastases of more common tumours. We are also seeing a success story with the RAF inhibitor for melanoma developed by Plexxikon and now Roche. Crizotinib, an ALK inhibitor, is being evaluated in lymphoma, sarcoma and other rare tumour subtypes in a NOCI trial in the EORTC. It is this kind of translational research – where we select subtypes of patients with different, non-standard diagnostic tests – that we are setting our sights on now, in what should be practice-changing trials."

Most medical oncologists with strong research interests have of course focused on biological target selection for some time, but as Blay adds, actually pulling together the resources to get speedy answers

NIGEL DICKINSON

"It is harder for a team to keep in touch with patients on oral therapies and address their concerns"

to the right translational research questions is still a huge challenge. Having the right sort of platform in NOCI, together with other partners in Europe and further afield, is at least an important step forward he feels. His own contribution to French translational cancer research – he has helped put the country on the international map – and his confidence and infectious enthusiasm no doubt played a role in the decision to elect him to the EORTC presidency in 2009.

Blay comes from a family of doctors – including both parents and various other relations – and he says he was 'predisposed' to go the same way. "I did my medical training in Lyon and had my first placement at Léon Bérard, and from then on I didn't want to do anything other than oncology – I wanted to work in a difficult area with great promise for development and I wanted to do research."

He then spent a year at France's top cancer centre, Gustave-Roussy in Paris, training in research, where he was fortunate to come under the wing of the renowned and late medical oncologist Michel Clavel, who encouraged him to look around for research topics – and also to become involved with the EORTC. "I did my PhD on immunotherapy in cancer, but also looked at tumours that were not already crowded with researchers – and some then were almost 'unknown lands', including sarcoma. We could see that what we were learning about molecular biology would one day translate into treatment, but it did take some time."

Blay was offered an assistant professor's position at Léon Bérard and proceeded to develop a research-based clinical career during the 1990s, working on a range of cancers, but primarily sarcoma, lymphoma and kidney, trialling high-dose chemotherapy, continuing his work on immunotherapy with agents such as interleukin, and heading a cytokine ('immuno-modulating') research lab that is now part of a major cancer research centre. Léon Bérard, he says, is now second in clinical research in France after Gustave-Roussy, and in and around the centre are an increasing number of labs and partner agencies.

Sarcoma did indeed become fertile ground for Blay, but the first major breakthrough from the medical oncology standpoint did not come until the identification of GIST as a distinct molecular entity, and soon afterwards the introduction of imatinib, which fundamentally changed treatment for this type of sarcoma. "Then in about 2002 we came to the understanding that other sarcoma subtypes needed different treatments based on molecular typing and surgical classification, and that is what is driving research into new agents now – understanding the molecular biology and designing rational treatments that target the tumour's causation event."

As Blay points out, molecular differentiation has now uncovered as many as one hundred sarcoma subtypes, and he expects at least another hundred more. "For example, we've found some very rare molecular subtypes such as a Ewing sarcoma where there may only be about 15 cases a year in Europe, while in the more common liposarcoma there are three completely different molecular subtypes that need different treatment."

Actually treating patients is also changing, as new agents, particularly those taken orally, are reaching clinics. "We used to do mainly in-patient clinics where people would come for two to three days of high-dose chemotherapy. Now we have mostly outpatient clinics, as 30% of people are taking only oral drugs and some IV chemotherapy can be done in an hour or so," says Blay. But this does bring other pressures. It is harder for a team to keep in touch with patients and address their concerns, and in France, as in some other countries, reimbursement for giving oral drugs is much lower than for administering IV-based therapy, which he says could raise funding problems in the future.

France had been lagging behind some other countries in the management of sarcoma patients, notably the UK and Scandinavian countries, says Blay, but he adds that the French sarcoma group, which he co-chairs, has started to follow by agreeing funding for

a concerted national referral programme to major centres. "This started in 2009 and is progressing well. It is also mandatory under our national cancer plan for all patients to have a multidisciplinary assessment, although we are still far from this target. One problem is manpower – if you aim to have a large team of specialists discussing all cases, it may be that some of their time is better spent somewhere else. But we have shown in a small local study in Lyon that patients who do reach a multidisciplinary board may have a better progression-free survival – about 20%." About 10% of French sarcoma patients are now in trials, he adds, although in the UK, one of the European leaders, it stands at about 18%.

Now, he adds, a much larger study is underway comparing the management of sarcomas in the Rhône-Alpes region with national recommendations and with other regions in both France and Italy, again to demonstrate the impact on survival. This work is led by a certain member of his group at Léon Bérard, namely Isabelle Ray-Coquard, a medical oncologist who also happens to be married to Blay, in what must be one of the closest personal/professional partnerships in European oncology.

SIMON BACONNIER

Partners. With a group of patient advocates at the first Conticanet Patient Advisory Group workshop, Paris, 2006

That study is work that was part of Conticanet, a 'network of excellence' for connective tissue tumours funded by the European Union's sixth framework programme (FP6), and which has now ended. Blay was the coordinator of the project, which aimed to improve the molecular characterisation, management and treatment of what many think is a rare disease group, but which does affect up to 10,000 people a year in Europe. As usual with these projects, which comprise a number of work packages, Blay says what was actually achieved was different to some initial proposed outcomes: "But I suspect something is not going well if it's not changing or evolving," he says. Two particular changes he mentions are including molecular subtypes in cataloguing the epidemiology of sarcomas in Europe, and integrating academic research on surgical and radiotherapy treatment, and also imaging. Blay helped set up a Europe-wide patient group as part of the project, the Sarcoma Patients EuroNet Association (SPAEN).

These framework programme projects have the aim of leaving a sustainable legacy, and one Blay is particularly pleased about is a virtual tumour bank, which so far has 10,000 paraffin and fresh-frozen sarcoma samples (see also Cutting Edge, p22). "This is accessible by anyone in the world, with agreement for research based on each contributor, and should be a good model for rare cancers – anyone can contribute provided they meet quality guidelines such as central pathology review, and we will see if it will be used to identify new treatment targets."

Even without Conticanet, Blay says that the world of sarcoma researchers has been particularly close and there is a good deal of cooperation on who does what work. Researchers from some countries, China, for example, have recently joined clinical trials for the first time, and he says multinational collaborations are increasing rapidly. And clearly, as the complexity of translational research increases, the issue of how centres cooperate to answer the right question in any cancer type will be crucial.

"I have done a lot of translational research, and much of it has been what we call descriptive, or

"This tumour bank is accessible by anyone in the world and should be a good model for rare cancers"

"We need much more to build what I call integrated translational research"

more harshly, cosmetic, where we may not understand the mechanisms, and of course we must carry on supporting this work. But now we need much more to build what I call integrated translational research, which is our aim at the EORTC and was set in train by my predecessors as president, Martine Piccart and Lex Eggermont."

Taking his own work to explain the progression in translational research, Blay says one of his most cited earlier papers found that patients responding to immunotherapy with IL-2 (interleukin-2) did less well if they were overexpressing a factor called IL-6 during treatment. "This is probably true and has been reproduced by others, but it did not go much further. But another study looked at a serum test to identify patients who would not benefit from treatment and we were quite successful in also correlating VEGF level with a lack of response. This was confirmed later by other studies, not just those on immunotherapy, and is an important phenomenon that may have contributed to the development of VEGF inhibitors in kidney cancer, in particular in combination with interferon.

NIGEL DICKINSON

"Then we had another example, the EORTC phase II trial of imatinib in GIST, where in one arm we showed there was 90% control in GIST and none in non-GIST sarcoma. That was proof that selecting patients on the basis of a molecular alteration made sense. And finally an example of truly integrated translational research was finding that GISTs with a certain uncommon mutation (PDGFRA) were not going to respond to imatinib, so we can now identify these patients and drive them to another protocol where there is response."

A recent example that has been a major translational research success for the EORTC is in glioblastoma (a high-grade brain tumour), where the drug temozolomide was found to benefit mainly patients with an inactivated repair gene called MGMT.

The most well-known translational study coordinated by the EORTC is, of course, MINDACT, large-scale research using gene expression captured on microarrays to improve the selection of breast cancer patients who can be spared chemotherapy. "I know there are strong opinions about it, and I accept that some see MINDACT as a complex academic exercise, but it is important not only because of the question but also for demonstrating that such research is feasible at this level," says Blay. "If it shows improvement in patient survival, that will be a real proof of the clinical value of the gene expression concept, and if not, then we will go in another direction."

He is still sceptical though of the applicability of gene expression in routine practice, although he does not doubt its value. "It offers an integrated view of genes being expressed in the cancer cell, but it may be hard to apply ultimately in clinics outside of major centres. What may be reproducible are the

"Blay talks of seeing encouraging signs that industry is investing in European centres"

structural alterations of DNA – there are easier tools to test things like amplifications from paraffin embedded tissue."

So one direction for research is the smaller trial on more focused populations of defined molecular subtypes, where the value of large-scale randomised trials can be less useful, says Blay, pointing to the ten or so key targets now in play, such as RAF and ALK. "If the population is not homogeneous enough, of course we will be doing large randomised controlled trials, but we may not need them for certain agents with a targeted population when an outstanding clinical benefit is observed, imatinib being a prime example."

A thread common to both types of trial is increasing organisational complexity, given the need to link a wide pool of researchers working in different countries and continents, often across different cooperative networks, to accrue both expertise and patients, especially for rare subtypes. As Blay points out, there are two main types of clinical trial – drug development, where there is usually industry input, and therapeutic strategies, which really need multidisciplinary approaches, and for which funding is hard to find for independent academic research.

Although much early-phase drug development is done in the US, Blay talks of seeing encouraging signs that industry is investing in European centres, thanks to the quality of the researchers, "and possibly we are better placed for the focus on accruing patients for subtypes – a well understood molecular pathway is a good way to get to market now." And while major obstacles still stand in the way of academic research, the EORTC has found ways to mitigate the worst effects of the Clinical Trials Directive, which reduced the number of EORTC trials to a mere handful when it first came into force. The Directive is now up for revision.

Blay is keen to stress that the EORTC will be networking more widely on research, and will be happy for agencies such as the UK's Medical Research Council to take a lead on projects, for example, while the NOCI grouping, he says, will be a "truly efficient network instigating new trials that have molecular alteration as an inclusion criterion." NOCI is, though, currently dominated by centres in northern Europe and especially France, the UK and the Netherlands, and Blay acknowledges that there is still too much fragmentation in research networks around Europe. The EORTC itself has a budget of less than €20 million – a far cry from its main international partner, the National Cancer Institute in the US.

Nevertheless, the EORTC, which is funded mainly by charity, is probably the most successful, long-standing cancer research network on the continent – and Blay intends it to stay that way. "It is critical we involve more young investigators so that EORTC research groups do not lose momentum – and it's a great way to develop a career as they will become better known to colleagues in their own countries." The quality of younger researchers who do get involved at European level is good, but it is a self-selected group – "It is a challenge for oncologists to keep up with the latest in molecular biology."

Another area of fragmentation that concerns Blay is what he terms the 'double culture' of basic and clinical scientists when it comes to translational research. Unusually for a clinician, perhaps, he would like to see more invested on the basic side, while maintaining clinical levels. "Major clinical breakthroughs come from understanding molecular biology, but we have to bring the two groups together more." Biologists need to understand that, while they have complete control of experiments in their labs, they have to adapt to reality in the clinic, where say collection of specimens is subject to what surgeons and pathologists can provide, and ethical and legal constraints. Networking meetings for clinical and basic researchers are now key events in Lyon, he says.

Like many senior oncologists, Blay's own research interests have expanded rapidly during

his later years and he is probably one of Europe's most published lead and co-authors, with more than 300 papers, principally on sarcomas, GIST and immunotherapy, but also on public health issues such as breast and prostate cancer screening programmes. A quick glance at his CV though can miss the fact that in 1999 he moved from the cancer centre to head the oncology unit at the nearby Edouard Herriot university hospital, where in a nine-year spell he experienced being just another specialist competing for attention.

"When I arrived, some welcomed me but others said things like, 'I'm an organ specialist doing research on cancer – I don't need an oncologist' – and it was very challenging to convince people to work together as we built up an in-patient department for chemotherapy there. I had the higher mission though of merging its cancer activities and that of other hospitals in Lyon with Léon Bérard, and we have been quite successful, particularly in rare tumours. We now bring together physicians from different sites into a sarcoma board so we can allocate patients according to the best surgical specialists, for example." However, in countries where reimbursement is based on activity, and money can disappear when referrals to other hospitals are made, there can be major obstacles to setting up this type of treatment networking, notes Blay.

Since 2009, Blay has been back at Léon Bérard, and has the flexibility to devote at least a day a week to his EORTC work, along with clinical and research activities. He is studying very rare sarcomas, while his immunotherapy research has moved on to reconstituting the immune system rather than attacking the tumour itself. "It's completely different from the immunotherapy work of the 1990s," he says. The work has included showing that breast cancer cells 'subvert' the immune system to their own advantage.

He has long been a human dynamo, constantly on the move – colleagues speak of phenomenal drive and unlimited energy, despite him seemingly never eating lunch, which is very unusual in France. He is said to be a superb diplomat in the 'oncopolitics' of the European research community, taking on many organisational tasks with charm and tact (and never saying 'no'). Combined with his leading position in clinical and translational research, this makes him a key player across several fronts.

Close international colleagues include Paolo Casali in Milan and Allan van Oosterom in Belgium (both sarcoma experts) and Jaap Verweij, a top medical oncologist in Rotterdam. In France, mentors have included Clavel, and two now retired key cancer centre directors, Thierry Philip at Léon Bérard and Thomas Turz at Gustave-Roussy.

As if being in perpetual motion on the cancer front was not enough, Blay has a family of four children and finds time to also listen to a huge music collection and sometimes go snowboarding.

Will cancer research have a downhill run to success? Blay is certainly intent on moving things on as fast as possible. "I want to see true personalised treatment in selected groups in routine use in five years' time – that way we will really improve survival – and I want to see the EORTC and others doing more of the high-quality translational research we need to do this."

PIERRE HEUDEL

A close partnership. Blay's wife, Isabelle Ray-Coquard, chairs the gynaecological clinical research group of INCA, the French cancer research body, but she also shares Blay's interest in sarcoma and GIST

New approaches to treating gastro-oesophageal cancer

Robust evidence on the value of neoadjuvant chemotherapy, together with more effective imaging modalities, are opening up new options for diagnosis, staging, treatment and patient selection in gastro-oesophageal cancer. Andrés Cervantes looks at the implications for the management of this challenging disease.

The challenges of managing gastro-oesophageal cancer are illustrated by the case of a 50-year-old man with locally advanced oesophageal cancer. His main presenting symptom was dysphagia when eating solid foods. He had weight loss, no pain in the thorax or abdomen, no dysphonia or cough, no dyspepsia or gastro-oesophageal reflux. His performance status was considered to be 1.

Looking at his risk factors, the patient was a heavy smoker, he had significant – though moderate – alcohol consumption, and was obese, with a body mass index of 32.5 kg/m^2.

Physical examination revealed no lymph nodes in the patient's neck nor in the supraclavicular area; there were also no thoracic alterations, no hepatomegaly or ascitis, and no signs of pleural effusion. All these physical examination data indicate that the patient had localised disease. Having dysphagia only when eating solid foods indicated that the invasion of the oesophagus was not completed because the patient could swallow liquids without any difficulty.

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, Andrés Cervantes of the Hospital Clinico Universitario, Valencia, Spain, provides an update on the challenges of treating gastro-oesophageal cancer. He highlights the new treatment options and techniques for predicting tumour response that are changing the treatment of patients with this cancer. Florian Lordick of the Braunschweig Clinic, Germany, poses the wide range of questions sent in by participants during the e-grandround live presentation, which is summarised here by Susan Mayor.

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

Diagnostic tests

An oesophagoscopy indicated an ulcerated neoplastic lesion in the lower third of the oesophagus at 38 cm from the teeth, situated over an ectopic area of gastric mucosa, 3 cm long, without involving the gastro-oesophageal junction. This oesophagitis was related to gastro-oesophageal reflux. This description is very clearly a Barrett's oesophagus area transforming into a lower third oesophageal cancer.

The stomach and the duodenum were also explored because the tumour could have passed through the stenotic lesion, but they did not show any change. During the procedure, a biopsy was performed and this showed poorly differentiated and infiltrating diffuse adenocarcinoma of the oesophagus over Barrett's oesophagus.

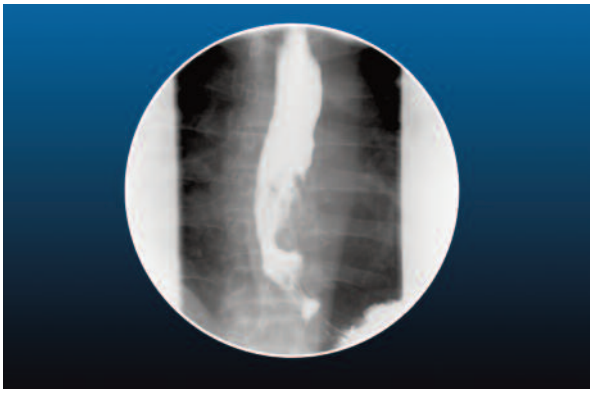
The oesophagogram was one of the most common diagnostic techniques performed some years ago, and we still perform this type of imaging. The image (see figure) shows some alteration of the mucosa of the lower third of the oesophagus, with irregular areas indicating a malignant tumour of the oesophagus.

A CT scan of the thorax, abdomen and pelvis showed no distant metastases; the lungs and liver were clear, and the only two findings were related to local regions. First, in the oesophagus, there was a thickness of the whole oesophageal wall at the lower third of the oesophagus. This was without any anatomical relation to the trachea or left bronchus. There was also enlargement of lymph nodes in the para-oesophageal area and in the upper mediastinum.

After doing the oesophagoscopy, the oesophagogram and a complete body CT scan, the clinical staging is considered cT3cN1cM0 stage 3a (where 'c' indicates clinical assessment), because the tumour has completely thickened the whole wall of the oesophagus. It is N1 because the enlarged lymph nodes are observed in the CT scan and cM0 because, clinically, there is no evidence of metastatic disease. We considered this patient to be at clinical stage 3a.

To summarise this, I would like to consider what was the classical approach to oesophageal cancer. First, the patient underwent surgical resection. After surgical resection, pathology assessment helped in the estimation of the risks. Postoperative treatment was based on the classical TNM stage. Postoperative chemotherapy was of either doubtful or no value, and postoperative chemoradiation was recommended by some experts.

DIAGNOSTIC OESOPHAGOGRAM



Oesophagrams should be used strictly for diagnosis and not for staging. The irregular dark area shows the malignancy

Source: Courtesy of Andrés Cervantes

Question: *What do you consider the standard procedures in staging oesophageal cancer today? Which examinations can be recommended as standard?*

Answer: *I think that oesophagoscopy is the main procedure for diagnosis, although this does not help to stage the patient. We would use a CT scan and then a PET scan, especially for a tumour located in the lower third of the oesophagus and at the gastro-oesophageal junction. I think CT and PET scanning are the critical tests. We do not use ultrasonographic endoscopy very often, except for patients with very small tumours – patients with T1 and T2 involving only the mucosa or muscular layer – but they are uncommon. In a patient at such an early stage, perhaps endoscopic ultrasonography could be of benefit in diagnosis.*

Lordick: *We use endoscopic ultrasonography to define the T stage. Would you say it is also good when you combine endoscopy and PET-CT scans? Would this be your standard approach?*

Answer: *That is right.*

Question: *In your case presentation, the patient had no major dysphagia. If the patient presents with dysphagia, do you insert stents or do you dilate the oesophagus before you start with any other treatment?*

Answer: *Assessing the nutritional status of a patient with oesophageal cancer is very important. This patient was presenting with no weight loss, indicating that although dysphagia was the main symptom, it was not presenting any problems. In patients presenting with major dysphagia we would try to do staging procedures very quickly because, when the disease is localised, improvement is common when you start chemotherapy. However, when we see a patient with disseminated disease, we try to start by implanting a stent first, because treatment is unlikely to be very successful and we prefer to focus on improving their nutritional status.*

Question: *What about the use of proton pump inhibitors with prokinetic drugs in order to prevent carcinoma of the oesophagus in patients with gastro-oesophageal reflux disease? Are you aware of data that show that oesophageal cancer can be*

prevented by the long-term use of proton pump inhibitors?

Answer: *I am not aware of any data that show that those pumps may prevent patients from developing oesophageal cancer.*

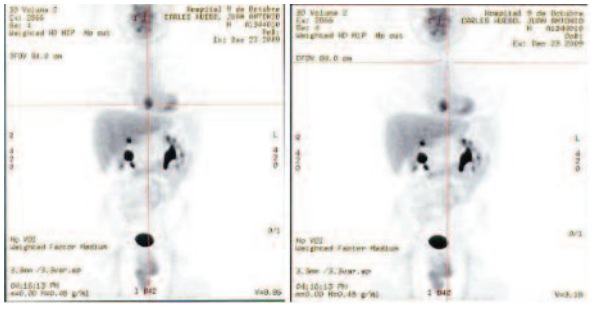
Current approaches to localised gastro-oesophageal cancer

A multidisciplinary approach should be adopted in the care of patients with localised gastro-oesophageal cancer. Clinical staging should include PET scanning for tumours located in the lower oesophagus or in the gastro-oesophageal junction.

The patient in our case study had a PET scan performed with labelled fludeoxyglucose (^{18}F), which confirmed the absence of distant metastases. This is a very important point because PET scanning is more sensitive even than current helical CT scans in detecting dissemination of the tumour. Approximately 18%–20% of patients without metastasis in the conventional workup are diagnosed as stage IV with a PET-CT.

The ^{18}FdG PET-CT scan showed a hypermetabolic area at the lower third of the oesophagus, with a maximum standardised uptake value (SUV) of 8.9 g/ml. Another metabolic area was observed at the upper mediastinum (SUV max: 3.4 g/ml), associated with the lymph glands (see below). This confirmed that this patient had locoregional disease involving the oesophagus and also locoregional lymph nodes.

^{18}FdG PET-CT SCAN FOR STAGING



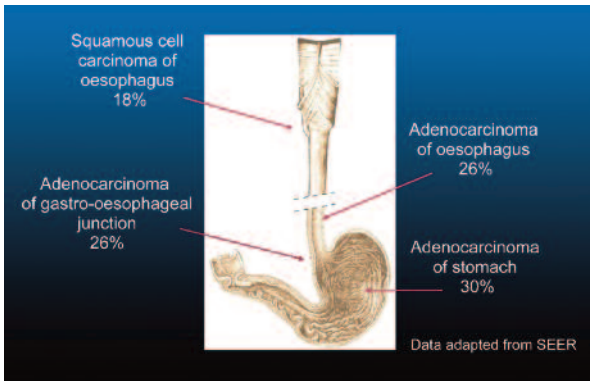
Areas of very high uptake of the ^{18}FdG show the tumour in the lower third of the oesophagus and reveal the involvement of lymph nodes in the mediastinal area

Source: Courtesy of Andrés Cervantes

Distribution of gastro-oesophageal tumours

Squamous cell carcinoma of the oesophagus is mainly located in the upper two-thirds of the oesophagus, and accounts for approximately 18% of cases. Adenocarcinoma of the lower oesophagus affects 26% of patients, while adenocarcinoma of the gastro-oesophageal junction accounts for a further 26%. Gastro-oesophageal tumours at these two sites are increasing in incidence and are common in developed countries – the US and Europe – where gastric cancer is not so common. Traditionally, gastric cancer was more common in Mediterranean countries, but its incidence is now decreasing, while tumours located around the junction and the lower section of the stomach are increasing. In this clinical case, smoking, alcohol and obesity are all related to the reflux disease, which could be the cause of the tumour.

DISTRIBUTION OF GASTRO-OESOPHAGEAL TUMOURS



These relative incidence data were adapted from the US Surveillance, Epidemiology, and End Results programme (SEER), and are likely to be different in other parts of the world

The Siewert classification of gastro-oesophageal junction adenocarcinomas is a surgical one: type I is when the tumour is located in the distal oesophagus (36% of patients); type II is true junctional disease (27%); and type III is when the bulk of the tumour is below or at the subcardial area (37%) (*Br J Surg* 85:1457).

Preoperative chemotherapy

Several studies have helped us in understanding that preoperative chemotherapy should be considered the standard of care.

A meta-analysis of randomised clinical trials of preoperative chemotherapy for oesophageal cancer by Gebski et al. (*Lancet Oncol* 8:226) showed clear, although limited, benefits (see p 16). Many of the studies were underpowered, with a very limited number of patients, and are now relatively old.

The MRC trial OE02 is important because it included 800 patients, making it the largest trial published so far in gastro-oesophageal cancer. It is also the most recent trial, published in the *Lancet* in 2002 (vol 350, p1727). The study included patients with all types of resectable oesophageal or cardia carcinoma,

including squamous carcinomas, adenocarcinomas and undifferentiated carcinomas (*n*=802). The patients were randomised to surgery alone or to the experimental arm of two courses of cisplatin (80 mg/m^2 on day 1) and 5-fluorouracil (1000 mg/m^2 continuous infusion days 1–4), given in a very conventional way and repeated after 21 days, with surgery performed immediately after the second course. It is important to note that two-thirds of patients had adenocarcinoma histology (66%) and one-third had squamous histology (31%).

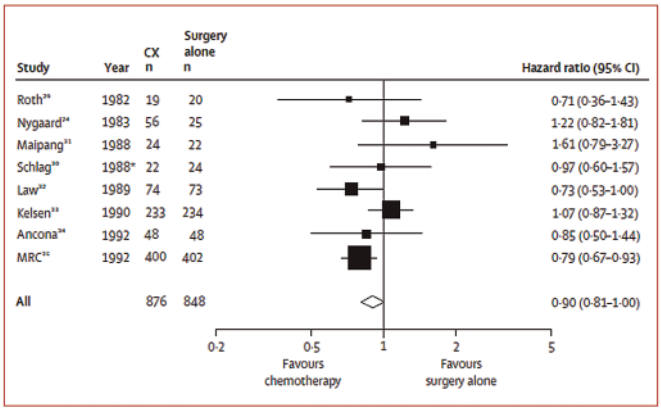
Results (see below) showed that median survival was improved by 3.5 months (13.3 vs 16.8 months), and overall survival after two years was improved by 9% (34 vs 43 months). Most types of histology benefited from the experimental approach (*Lancet* 350:1727). Long-term results – after 10 years of follow-up – have recently been published, indicating that the benefits of preoperative chemotherapy continued over the longer term (*JCO* 27:5062–5067).

The next trial I would like to discuss is the MAGIC trial. Although many people consider this trial as a gastric cancer trial, a group of patients with oesophagus and junction cancer were included. Patients were randomised to surgery only, or to preoperative chemotherapy with the classical British ECF combination of fluorouracil, cisplatin and epirubicin. Patients were given three courses of preoperative chemotherapy followed by three further courses after surgery. The quality of the trial is well established, and it has been published in the *New England Journal of Medicine* (vol 355, p11).

Final results indicate that median survival was improved by four months (24 vs 20 months) and two-year survival increased by 9% (50% vs 41%). The key finding was a 13% increase in five-year survival (36% vs 23%). Both progression-free survival and overall survival were significantly improved. This benefit applied to all patients, including those with stomach tumours, junction tumours and oesophagus tumours.

A further study of perioperative chemotherapy for localised gastro-oesophageal cancer, the French trial FNLCC 94012-FFCD 9703, has not yet been published in full (Boige et al, Abstract 4510, ASCO 2007). It randomised 224 patients to surgery alone or to three courses of platinum and fluorouracil (5FU 800 mg/m^2 on days 1–5), and did not include epirubicin, making it different to the British

META-ANALYSIS OF NEOADJUVANT CHEMO TRIALS

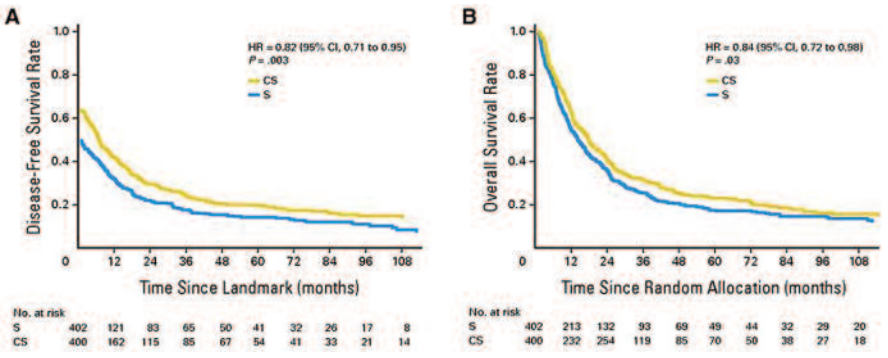


All-cause mortality estimates for neoadjuvant chemotherapy compared with surgery alone

Preoperative chemotherapy was shown to offer a slight advantage in this meta-analysis, which included studies dating back to 1982

Source: Reprinted from Gebski et al (2007) *Lancet Oncology* 8:226-234, with permission from Elsevier

UK MRC OE02 TRIAL



Ten-year results showed a sustained improvement in both disease-free and overall survival with preoperative chemotherapy

CS – neoadjuvant chemotherapy plus surgery arm, S – surgery alone

Source: WH Allum et al (2008) *JCO* 27:5062–5067. Reprinted with permission. ©2008 American Society of Clinical Oncology.

trial. Another difference is that two-thirds of the patients had gastro-oesophageal junction tumours, and only one-third had gastric tumours.

Results showed that perioperative chemotherapy improved progression-free survival and overall survival. Median survival increased by nine months and three-year survival by 10%, while five-year survival increased by 14%.

These three trials of perioperative chemotherapy for localised gastro-oesophageal cancer are all leading us in the same direction. They show the reduction in the risk of death at five years was 25% (in the Cunningham trial; *NEJM* 355:11) to 31% (in the French trial; Boige, ASCO 2007), indicating that perioperative chemotherapy may improve survival when given to patients with localised and resectable oesophageal or gastro-oesophageal cancer.

A meta-analysis of randomised clinical trials of preoperative chemoradiotherapy for oesophageal cancer (*Lancet Oncol* 8:226) indicates potential benefits, but also flags up some issues. There is a trend to higher mortality in patients treated with a combination of chemotherapy and radiation after surgery. Although this is now a commonly used approach in the US, my personal opinion, which is shared with others, is that in Europe chemotherapy without radiation could be the standard care for patients with lower-third, junction and gastric cancers, before surgical resection.

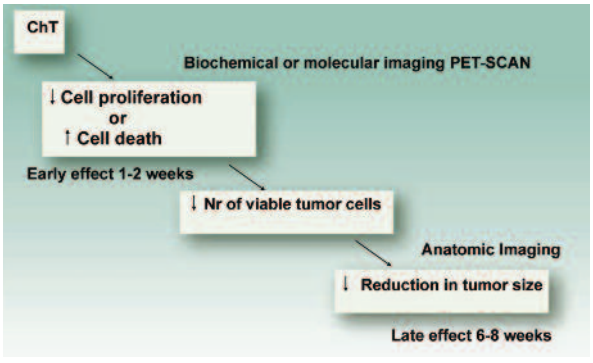
Question: *In which patients do you consider using neoadjuvant chemotherapy?*
Answer: *In all resectable patients except those clinically staged as cT1.*
Question: *Would you use neoadjuvant chemotherapy in T3 tumours and also when you see lymph nodes involved?*
Answer: *Yes, for any node-positive tumours, including T3 and T4, we would use preoperative chemotherapy.*
Question: *Do you use, or is it possible to use, capecitabine and oxaliplatin as part of the neoadjuvant chemotherapy?*
Answer: *Several trials performed in advanced disease have shown that oxaliplatin can be used safely and with good efficacy, substituting for cisplatin. Capecitabine could also substitute for fluorouracil. Going back to the clinical case we were reviewing, we recommended preoperative chemotherapy, and a combination of oxaliplatin and capecitabine was started. After the first course, the patient had complete resolution of dysphagia and a reassessment with PET-CT was performed after two weeks to assess the metabolic response.*
Question: *Do you think that chemoradiation is the preferred approach over chemotherapy alone, in neoadjuvant indications?*
Answer: *The only place in which chemoradiation could be better than chemotherapy is in patients with squamous tumours of the two upper-thirds of the oesophagus. Definitive chemoradiation can cure about 25% of these patients. Apart from this group of patients, as far as I know, there are no good randomised trials comparing chemotherapy with chemoradiation. The data we have from the meta-analysis compared chemoradiation with surgery alone. There are also some toxicity concerns. For this reason, I prefer to start with chemotherapy alone in patients with tumours that are resectable, and not use chemoradiation. There are several studies showing that chemoradiation is effective, and can result in an even higher proportion of patients with pathological complete remission than using chemotherapy alone. However, I think this strategy should be considered experimental, and should be explored in future phase III trials.*

Assessing tumour response to treatment

The classical way of assessing response to chemotherapy is anatomic imaging. After several weeks, or even months, of therapy we expect to see a reduction in tumour size. This could be seen as a very late effect, six to eight weeks after starting treatment. This is what we do at the moment, but we have to improve on this. We have to make the most of the opportunities we have now to include biochemical or molecular imaging. PET scanning is useful because it can detect an effect of therapy in reducing cell proliferation or in stimulating cell death. This effect can be seen as early as one to two weeks after treatment, so it can guide treatment decision making. Several groups have published data on this, and more work is ongoing.

A study by Ott and colleagues, looking at tailoring treatments based on metabolic response (Ott et al *JCO* 24:4692) included 65 patients with locally advanced adenocarcinomas of the gastro-oesophageal union who received preoperative cisplatin-based chemotherapy. They were assessed before the start of treatment and on day 14. Results show a clear difference in PET response, based

ASSESSING TUMOUR RESPONSE



New imaging modalities offer the potential to identify responders much sooner than relying on tumour shrinkage

on a reduction of at least 35% in the maximum standard uptake value. These patients do better than those not showing a significant response on PET. I think this is an important finding, although it is based only on retrospective studies.

In the patient in our case study, early reassessment with a PET scan performed two weeks after starting treatment showed a complete response, with no uptake of ^{18}FdG. Knowing that this patient was so chemosensitive, we decided to go on and give four more courses of the combination of capecitabine and oxaliplatin.

Results from the MUNICON phase II trial looking at the value of PET to assess early metabolic response and guide treatment of adenocarcinoma of the gastro-oesophageal junction confirmed the finding that patients with an early PET response that leads to several courses of chemotherapy do much better than those not showing a PET response, who go directly to surgery (*Lancet Oncol* 8:797–805). These data confirm the prognostic value of PET scanning in the assessment of response to treatment.

Surgical resection

The patient in our case study underwent thoracoabdominal surgery with a total oesophagectomy. An oesophago-gastrostomy was performed using Akiyama's technique, with extensive mediastinal and perigastric lymphadenectomy. During reconstruction using Akiyama's technique, an omentectomy was also performed.

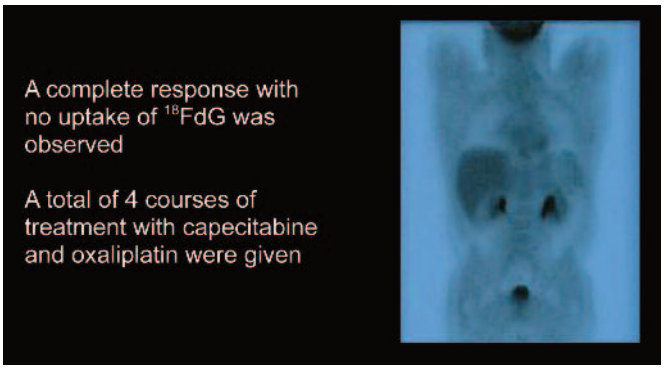
Pathology assessment and estimation of risk

It is very important to assess pathology to be able to estimate the risk for a particular patient. The main data from the case study's pathology report showed the patient had a moderately differentiated adenocarcinoma of the lower oesophagus. The tumour was infiltrated to the peri-oesophageal fat, so we considered this patient to have a ypT3 tumour (where 'yp' indicates pathological assessment after preoperative therapy). Perineural invasion was present, although none of the nine mediastinal nodes and none of the 13 perigastric nodes were involved. So this patient was ypT3 ypN0/22 M0 out of the 22 resected lymph nodes. In the omentum, no metastatic deposits were detected in the peritoneum. Overall, this patient was considered as a ypT3 ypN0/22 M0 patient.

RECOMMENDED APPROACH FOR LOCALISED OESOPHAGEAL CANCER

- Clinical assessment and staging
- Multidisciplinary team discussion
- Preoperative treatment in all patients with clinical stage II and III disease
- Surgical resection after chemotherapy
- Pathology assessment and the estimation of risk
- Postoperative chemotherapy?
- Participation in trials

PET AS A GUIDE TO TREATMENT



The MUNICON trial showed that metabolic response assessed early on a PET scan can help doctors identify which patients will benefit from preoperative chemotherapy

Source: Courtesy of Andrés Cervantes

Postoperative treatment

Many trials have been designed with pre and postoperative treatment. However, the postsurgery state of patients, including their nutritional status and the presence of surgically related complications, means that almost half of our patients cannot go through this final part of therapy. We decided against continuing chemotherapy to the patient in our case study on account of the changes to his nutritional status.

The patient is being followed up with clinical visits every three to four months for two years. He has no dysphagia, his trachea is working well and he can eat properly without any difficulties in swallowing. No postoperative chemotherapy was given due to the patient's poor nutritional adaptation and slow recovery after surgery. He lost around 20 kg in weight after surgery, although no steatorrhea or other signs of malnutrition were observed. There is no standard of care for follow-up, and this should be based on clinical signs and symptoms reported by the patient. We repeated a CT scan every six months for two years, and this patient has not shown any evidence of metastatic disease or signs of local relapse so far.

Conclusions

In conclusion, the patient in our case study was diagnosed with a locally advanced lower third oesophageal adenocarcinoma. Clinically, there was a T3 node-positive tumour with absence of metastatic disease. I would like to stress that a multidisciplinary discussion is essential for all cases. This case is a good example of the benefits of multimodality treatment. The surgical approach allowed an R0 resection, which is essential to offer the patient the possibility of long-term survival. A resectable oesophageal cancer should be treated with preoperative chemotherapy in a multidisciplinary team approach.

More, and better designed, clinical trials are needed to refine the optimal approach. I would encourage everyone to consider entering your patients into appropriate multicentre trials to provide more information on the optimal approach for managing oesophageal cancer for the future.

Florian Lordick (FL) of the Braunschweig Clinic, Germany, hosted a question and answer session with Andrés Cervantes.

Q: *When do you consider postoperative radiotherapy?*
A: That is a very difficult question. If the resection is R2 or R1, and there is evidence of microscopic or gross residual disease after surgery, then radiation could be considered as a palliative therapy. But we should balance the benefits of the radiation against the potential of inducing some other toxicities. I would be careful in selecting only those patients with residual disease after therapy for postoperative radiation. In general, it is not my standard of care.
Q: *What type of chemotherapy should be used? Is it necessary to include epirubicin in the treatment regimen?*
A: In the three trials indicating positive effects, two gave positive results for the benefit of chemotherapy without using epirubicin. Most data on epirubicin are from the British group and are well established findings, but we have other trials indicating that, even in the absence of epirubicin, there are benefits with chemotherapy. So the use of epirubicin is not a must in my opinion.
Q: *Given that early PET response is predictive, when the patient responds to chemotherapy can you go with definitive chemoradiation and avoid surgery?*
A: This approach has not been well studied in patients with lower-third adenocarcinoma. In general, it is considered that surgery may be better than radiation as definitive treatment in these patients. I would recommend definitive chemoradiation only for those patients with cancers located in the upper two-thirds of the oesophagus. Even in the presence of a good response on PET scan, I would recommend surgery as standard of care.
FL: I agree that in patients with adenocarcinoma of the distal oesophagus there is not yet a clear role for definitive chemoradiation. The standard approach today is surgery for patients presenting with resectable adenocarcinoma of the distal oesophagus and gastro-oesophageal junction. However, I think the hypothesis is justified and studies should be conducted to see whether there is a role for non-surgical treatment in very good PET responders.
Q: *Do you also use radiation without chemotherapy as preoperative treatment in oesophageal cancer?*
A: No, I think radiation alone should not be used as preoperative treatment in oesophageal cancer. There are data and recommendations in the current ESMO guidelines showing there is no indication for radiation alone, apart from palliative treatment in some advanced and unresectable disease, but not as neoadjuvant therapy.
Q: *Does neoadjuvant chemotherapy in oesophageal cancer improve survival?*
A: I showed a meta-analysis and, more definitively, three trials, that indicate short-term and long-term improved survival in patients with gastro-oesophageal cancer receiving preoperative chemotherapy. These three trials give evidence at level 1 that preoperative chemotherapy does improve survival in patients with oesophageal cancer.
FL: We should consider that this question came from India, where there may be more patients with oesophageal squamous cell cancers than in Europe. Maybe the questions asked in India are not answered by the trials presented and we need more studies in that part of the world.
A: The squamous situation is different. Only the MRC trial included patients with squamous cancer (31% of the total). However, there was a very good trial presented by Kelsen et al. in 1988 (*NEJM* 339:1979–1984) indicating that preoperative chemotherapy in patients with squamous disease is not so beneficial.
Q: *Do you agree that there are differences between the optimal management of patients presenting with squamous cell cancer and those presenting with adeno-*

carcinoma of the oesophagus?

A: Yes, I agree. For patients presenting with squamous cell cancer, the aetiology and biology are different, and the type of patient is different – it is more related to smoking. So, palliative care for these patients would be definitive chemoradiation and I would resort to surgery only if they do not respond or if the patient's tumour is still resectable. These types of disease are complicated.

Q: *Do you think there is enough evidence to use oxaliplatin instead of cisplatin in the preoperative setting?*

A: The data we have on oxaliplatin are very limited, so I do not think that this could be considered a standard of care. However, data from many trials show its advantages when oxaliplatin is substituted for cisplatin in the treatment of metastatic disease. Low-dose oxaliplatin is now easily accessible, and not as expensive as it was some years ago. Overall, I would not consider there is level I evidence to substitute oxaliplatin in locoregional disease, but for practical reasons I think we could use it.

Q: *After surgical treatment, do you always administer postoperative chemotherapy even in cases of yPT1 N0 and no more risk factors, after complete resection?*

A: I do not have the definitive answer to this question, but if a patient has a complete resection and is chemosensitive I do not see any reason not to use it, so long as the patient has adapted well after surgery and is keeping their weight stable without treatment. I try to treat all patients, if their pathology reports are good, with three more courses of postoperative chemotherapy. However, only half of patients are in a good enough condition to receive this type of treatment.

Q: *How many lymph nodes are required to consider that surgery was successful, and what do you do if there are only a few lymph nodes in the specimen. What is your approach?*

A: I am not aware of any guidelines indicating the number of lymph nodes we have to have in the resected specimen. But for the junction we should have more than 14 in order to get the right staging. When there is residual disease after chemotherapy and after surgery, the use of postoperative chemotherapy is indicated whatever the number of lymph nodes present.

Q: *Is it possible to insert a stent preoperatively if necessary?*

A: We never do that. This would only be considered in a patient with rapid worsening of dysphagia. I would try a nasogastric tube or just change therapy if a patient is sensitive to other drugs. But, in general, most patients improve after just a few days of chemotherapy.

International biobanking regulations: the promise and the pitfalls

Anna Wagstaff

Banked samples of human tissue, blood and serum linked to the patient's clinical data are the raw materials of modern cancer research. A single infrastructure for Europe's rapidly evolving biobanks is urgently needed. But finding agreement on the ethics, language and operating standards is proving quite a challenge.

Moving towards personalised cancer therapy is about finding answers to questions like: Is this colon cancer aggressive or fairly indolent? Which type of chemotherapy will this breast cancer respond to? Does this person need to take preventative measures to guard against a raised risk of cancer?

Finding those answers involves looking at samples taken from aggressive and indolent (or responsive and non-responsive) tumours and identifying a biological 'marker' or 'biomarker' that appears to differentiate the two. Further samples, from newly diagnosed tumours, are then needed to test, in a prospective study, whether such 'candidate' biomarkers really can predict the behaviour of the disease and can thus be relied on to help guide the clinician towards the right therapy for their patient.

The raw materials for all this work are large quantities of quality-controlled and well-catalogued biological specimens linked to information about the person from whom they came, their health status and the trajectory of the disease. A shortage of these raw materials will slow down progress in improving cancer treatments.

Responding to this need, the research community has been steadily building up 'biobanks' as repositories of data-linked human biological samples. Systematic banking of samples for research is becoming increasingly common at major cancer centres and university hospitals and is now mandatory in many. Biobanking samples for research is also specified as an essential activity for members of the elite Organisation of European Cancer Institutes (OECI).

A European network for data-linked frozen cancer specimens TuBaFrost, was set up in Rotterdam in 2003, and is now in the hands of the OECI. Specialist networks, such as Conticanet for connective tissue cancers, are building up their own banks to identify molecular subtypes. A number of countries, including Sweden and the UK, have also embarked on projects to develop population-based biobanks, which should enable researchers to study samples from cancer patients (and others) that were taken while they were still deemed healthy, to look for biomarkers of early detection or risk.

A considerable number of data-

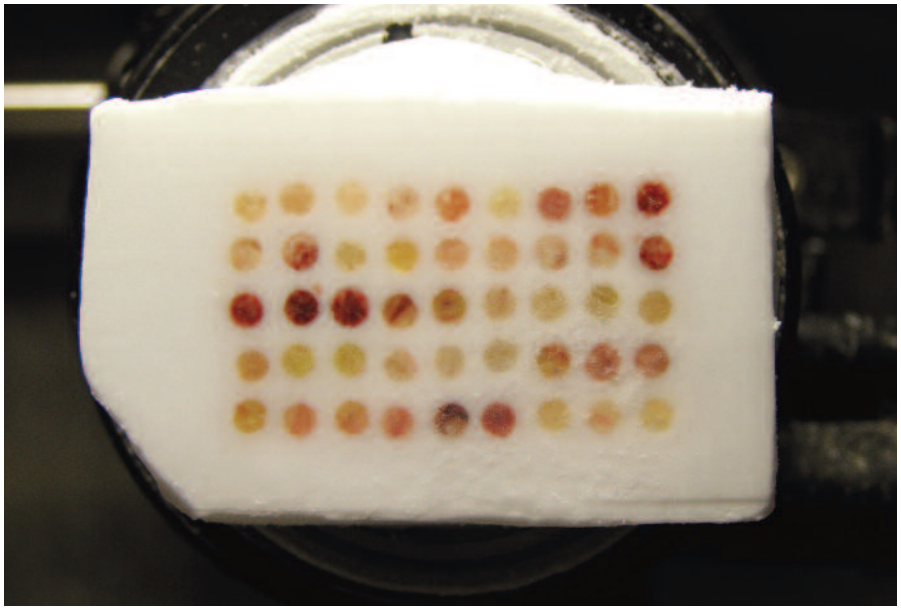
ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

linked biological samples have also been collected as part of specific studies. The MINDACT study, for example, collected and gene-profiled frozen samples as an integral part of the protocol, which aims to see how accurately the Mammaprint gene signature can predict who will benefit from adjuvant chemotherapy. Other collections come from 'correlative' translational research studies – ancillary protocols that research groups like the European Organisation for Research and Treatment of Cancer (EORTC) run alongside clinical studies, on the principle of 'no tissue, no trial'. This principle, put forward by ESMO's José Baselga – now Professor of Medicine at Harvard – holds that it is a waste of resources to organise a trial that answers the question: 'Is *a* better/no worse than *b*?', if it fails to gather biological samples that could answer the personalised therapy question: 'For which patients is *a* better/no worse than *b*?'

The blossoming of these biobanks is very good news, and yet their ability to serve the research community remains limited by their fragmentation. Each has grown up with its own set of norms, principles, quality

The blossoming of these biobanks is very good news, yet their value remains limited by their fragmentation

The principle that an individual should have a say over the use of their biological material is widely recognised



The raw material of cancer research. Large numbers of fresh-frozen tissue samples like these, linked to clinical data, hold the key to learning about the biological differences between cancers, and understanding what these differences mean for the way a given cancer behaves and thus the treatment strategies that will be most effective

standards and IT and legal frameworks, often in response to specific needs. The question is how to move to a more harmonised system that would enable any authorised researcher with a study proposal to instigate a single search request across all relevant biobanks, together with agreed rules, guidelines and principles governing the collection, storage, transfer and use of these data-linked samples. As if this were not challenge enough, it has to be achieved within the relevant national and European rules and regulations, including those on data protection and on the rights of the individuals from whom the samples are taken.

No consensus on consent

The principle that an individual should have some say over whether and how their biological material is used is widely recognised within research fields and the wider community, but is interpreted in a variety of ways. As a result, one breast cancer tissue sample may be available for use in any well-founded research study, whereas a similar sample biobanked elsewhere may have tight restrictions on its use. Consent may have been given purely for use in the study for which it was originally collected, or for additional specified studies, or perhaps with the proviso that use in any studies beyond those specified on the consent form would require approval from an ethical review board. In some cases, researchers may even be obliged to re-contact the donor to get a new consent. This disparity in conditions attached to the use of samples presents a potential obstacle where, for instance, a research centre from a country with stricter rules wishes to join an international biobanking system where tissues could be transferred for use in a country with more liberal rules.

Debates over personal data

Biological material, important though it is, makes up only half the research equation. The other half is data that describe the donor (age, gender etc) and disease (eg stage IIIb non-small-cell lung cancer), as well as data that allow researchers to draw conclusions about the significance of biological differences with regard to disease progression, response to treatment or perhaps adverse effects.

Though there is a European Directive on data protection, the laws and practices governing the storage and use of personal data for research vary widely across Europe – as has been highlighted by the battles that have had to be fought in some countries just to get the go-ahead to set up a basic cancer registry that could link a person's cancer diagnosis to their cause of death.

As with the consent issue, there is a broad consensus around a general principle: namely that patients have a right to keep their medical details confidential, and that biobanks may therefore only store anonymised data. There is less consensus, however, on what this means.

Some countries interpret it in the tightest possible manner – each donor is assigned a code that is used to identify their data and their biological samples, and the link between the donor and the code is then destroyed to preclude the possibility that someone could access the banked data to illicitly look at an individual's private medical records.

This is fairly disastrous for the purposes of research, because it means researchers cannot go back to the treating oncologists to get updates on how a patient's disease progressed or how it responded to various treatments. They cannot even go back to ask for additional information – on side-effects for example – that might have been available at the time of anonymisation, but was not deemed relevant.

Many countries, however, do accept 'two-way' coded data as 'anonymised', if there are sufficient safeguards. With two-way coding the patient's oncologist, or a third party, keeps hold of the code book, thus retaining the possibility for researchers to request further information about the donor. How easy that process is depends on how stringently the system is safeguarded. In the chain of tissue and data, double coding (coding additional to the one done at the source institution) may be required and permission to decode may involve complex and possibly bureaucratic procedures.

Such discrepancies between countries on the level of personal data protection presents another potential reason why some countries may not want their citizen's data to be internationally available through a biobank.

A PROLIFERATION OF GUIDELINES

Numerous guidelines and recommendations have been published regarding the ethical and social issues in biobanking.

- In 2003 UNESCO issued the International Declaration on Human Genetic Data. Among many other things, it set down the principle that "prior, free, informed and express consent, without inducement by financial or other personal gain, should be obtained for the collection of human genetic data," and that "Human genetic data, human proteomic data and biological samples linked to an identifiable person should not be disclosed or made accessible to third parties, in particular, employers, insurance companies, educational institutions and the family."
- In 2006 the Council of Europe issued its recommendation Rec(2006)4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin, which laid down more stringent conditions for consent, particularly for unspecified future research, than those currently in force in many EU member states.
- In 2009 the OECD issued its Guidelines for Human Biobanks and Genetic Research Databases, which appears to have been written principally with healthy volunteers in mind. The level of detail required in the consent forms seems inappropriate for cancer patients, from whom samples are taken within routine diagnostic and treatment procedures, when they will have many other things on their minds.
- In 2010 the Organisation of European Cancer Institutes (OECI) published its ethical and legal recommendations, From the Biobank to the Research Biorepository, with an emphasis on building public trust and support. They recommend that biorepositories take the form of charitable trusts or other 'neutral' bodies with a mission to act in the public interest, and that they develop policies for the development of patents from research carried out on samples … "with the aim of protecting the public interest to enjoy new technologies for health at reasonable costs."

A CASE FOR HARMONISATION?

Getting EU-wide agreement on a single set of rules governing consent and data protection – or indeed other social/ethical issues such as duties to publish the results of any research done using these samples, and who should own the intellectual property rights – may seem the obvious solution. The Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), an initiative to build an infrastructure for Europe's biobanks, is currently working on proposals to achieve this. Some, however, sound a note of caution. Evert-Ben Van Veen, an experienced medical lawyer at MedLawconsult in the Netherlands, points out that the Clinical Trials Directive was an exercise in harmonising rules and regulations across Europe – and look how that turned out.

Van Veen carried out extensive research on the various rules and regulations governing procedures for consent and data protection across Europe when the Erasmus Medical Centre in

"I realised that if you want to make such a model, you end up with the regulations of the strictest countries"

"Europe's approach to biobanking should be rooted much more firmly in solidarity-based values"

Rotterdam was in the process of setting up TuBaFrost in 2003. "The idea was that we would come up with a harmonised model for exchanging tissue: what would be accepted in one country would also be accepted in other countries." It wasn't long before a flaw emerged in the strategy. "I realised that if you want to make such a model, then you end up with the strictest regulations of the strictest countries, because what is accepted for the less strict will not be accepted by the stricter. That would be very harmful for research, especially for those researchers who have started their biobanks with lighter regulations."

The Council of Europe has, in fact, already agreed a 'Recommendation to Member States on Research on Biological Materials of Human Origin', Rec(2006)4, which Van Veen claims contains provisions considerably stricter than those operating in many European countries. The recommendation that any consent forms be "as specific as possible with regard to any foreseen research uses", for instance, appears to rule out asking patients to consent for their samples to be used in unspecified future research projects – an option widely seen as essential in cancer, where the rate of change in knowledge and techniques make it hard to foresee all possible research projects.

Any researcher wishing to use samples for a research project "not within the scope of prior consent", say the recommendations, should make "reasonable efforts" to contact the person in order to obtain consent to the (new) proposed use (with further conditions to be fulfilled if that fails). Given that the samples are coded, that many years may have elapsed since the original consent, and that it is cancer patients we are talking about here, this process would probably be not only complex and time-consuming, but may even cause distress to a cancer patient or family.

Were those recommendations given legal status, this would hinder efforts of the countries most actively promoting biobanking, some of which, the UK and Sweden for example, do give patients an option of allowing residual tissue to be used in future for unspecified research. Some even have an 'opt out' system, whereby patients are not asked for consent, but instead are given an opportunity to indicate that their tissue should not be used for research purposes. This system operates in Belgium and Denmark, with the Netherlands expected soon to follow suit.

Biobanking is a social activity

Van Veen is highly critical of what he sees as the 'paternalistic' and 'conflict-based' approach taken by most documents on regulating biobanking, including the OECD's 2009 Guidelines for Human Biobanks and Genetic Research Databases (see box, p25). They are, in his view, driven by the instincts of civil servants to regulate everything, they lack any democratic basis, and above all they fail to recognise that citizens don't just want protection, they also want, and will benefit from, progress in medical research. He says that patients are often very keen to be partners in research, pointing out that in Belgium and the UK, two countries where proposed legislation sparked wide public debate, the laws that were finally passed were much more research-friendly than the original drafts.

He believes Europe's approach to biobanking should be rooted much more firmly in the solidarity-based values that underpin the continent's healthcare systems, such that "the healthy contribute part of their income to the sick, the younger to the older, etc."

"What is wrong with expecting someone to contribute to observational research when it does not affect their personal lifeplan and other patients will profit in the longer run?" asks Van Veen.

This approach is apparent in the OECI recommendations for the operation of research bio-repositories, which says that, "to ensure compliance with the wishes of donors," every biobank should use the samples in the public interest. "In no way can samples be considered, or become, owned by private for-profit entities." It also recommends that every biobank should "disclose its rules, activities and results to the scientific community and the general public… to promote a culture of solidarity and consent to donations."

Rather than asking the EU to pass yet more rules and regulations, Van Veen suggests it should instead adopt a general framework for good research governance based on key principles consistent with a solidarity-based health system. These should encompass issues of transparency, accountability and the non-profit basis of biobanking, the right to opt out as a minimum, as well as "how the general results of research will be disseminated, 'conflict of interests' policies, how the issues of intellectual property rights are dealt with,

how the confidentiality of personal data of donors is maintained, etc." Above all, he argues, this should not become an extra bureaucratic layer.

This leaves the question of how countries with more strict conditions could agree to participate in an international biobank where samples may be used in countries with less stringent requirements. The answer, Van Veen suggests, is to use the 'coordinating principle' adopted by the TuBaFrost project, which states that, wherever the research samples are actually used, they must be handled in accordance with the regulations of the country where the tissue was taken from the patient and originally stored. This would permit unhindered exchange of biological samples without putting unwanted barriers in the way of biomedical research. Avoiding a new set of EU regulations would also make it easier for individual countries to review their own rules through their own democratic procedures.

A common language

If it is best to leave ethical and social details to countries, there are other aspects of biobanking for which the reverse is true. One big challenge will be establishing a common 'language' for cataloguing samples to ensure that what appears in the search results corresponds to what the researcher is looking for.

This issue has been preoccupying many cancer research leaders, including Angelo Paradiso, who is himself deeply involved in the effort to find biomarkers for early diagnosis and for predicting response to treatments. Paradiso is the coordinator for all of Italy's cancer centre biobanks, together with the Istituto Superiore Sanità in Rome, and he runs the biobank at the National Cancer Centre at Bari, southern Italy, which systematically collects and banks data and biomaterials from every patient. This system, he argues, is far more valuable than collecting samples only from specific trials, because it assembles samples from the entire cancer population, rather than only from patients selected by age, or disease stage or other criteria.

Paradiso recently completed an exercise that has introduced a single 'language' and software system throughout the network. He is now looking to work in collaboration with other national and pan-European networks to establish conditions for moving towards a similar level of harmonisation across Europe and beyond.

The term 'language' covers many issues that the clinical research community has wrestled with for years. Different hospitals may use different thresholds for judging a tumour to be ER-positive, or different tests for establishing the HER2 status. Even menopausal status may not be defined in the same way.

Paradiso mentions also the stage of disease: "If I want to compare the characteristics of my sample with others coming from other tumour banks, I have to classify the tumour stage, histological diagnosis and cytohistological grade in the same way."

Then there is the question of how far you go in defining a tumour for the purpose of a searchable catalogue? Even a relatively rare cancer type such as sarcoma is now known to consist of more than one hundred biologically distinct diseases (see cover story), and it is becoming increasingly apparent that different biologies behave very differently.

Standards for handling and storing

Agreement on basic quality standards and quality control of the collection, storage and transfer of samples is another essential element, so researchers can be confident that, no matter where the samples originated, their studies will not be confounded by poor-grade samples.

Sophisticated techniques for gene profiling or proteomic and metabolomic studies can be highly sensitive to small

Paraffin-embedded or fresh-frozen?

Fresh-frozen tissue is needed for screening approaches like gene expression profiling or proteomics, which are used to search for biomarkers or to learn about the mechanisms of disease. These techniques are highly sensitive and strict criteria are needed about collection and storage.

FFPE (formalin-fixed paraffin-embedded) blocks used in standard pathology are far less sensitive to discrepancies in the way they are collected and stored. They are useful because large collections already exist from trials going back decades.

The initial research behind the Oncotype DX multi-gene assay that gives risk scores for certain breast cancers was done using gene profiling in frozen tissue, but much of the validation work was done retrospectively on FFPE tissue blocks.

If samples are to be catalogued and exchanged across borders, there has to be an agreed classification system

EORTC is developing templates for what it considers to be the key information for different sample types

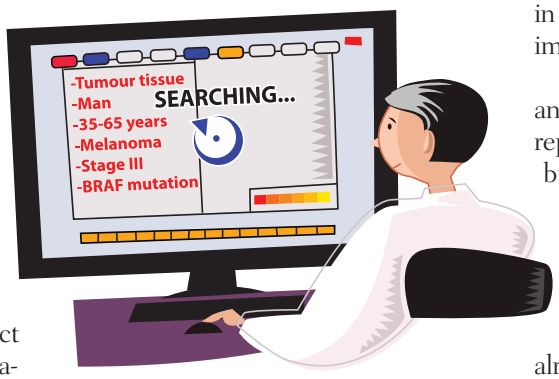
differences in samples. The minimum standards recommended by IARC/WHO in 2007 are widely accepted as a good starting point. However, they do not cover issues such as what drugs (not just cancer drugs) the patient may have been on at the time the sample was taken, or the techniques used for the sampling. Furthermore, these types of study all require fresh-frozen tissue, with the time from 'harvesting' to snap freezing being one of the quality parameters, and questions are now being asked about whether the time should be measured from the point of excision or from the point of clamping during the operation, as depriving the tissue of oxygen induces rapid changes. This in turn raises the question of how much you can ask of operating teams, for whom annotating samples is not their top priority.

Towards international biobanking

The goal of reaching agreement between Europe's biobanks might seem hopeless, given the disparities in practice and the difficult balancing act between cataloguing 'essential' information without demanding too much of the pathologists and data processors – not to mention the disparities in the software used to input that information. But Paradiso is confident it can be done. "When you talk about biobanks, you should talk about networks," he says. While harmonising every biobank for every disease in every European country might seem a big ask, if it is done network by network, working from the national level up, the task becomes a lot more manageable.

The framework for these networks has already been developed at a European level by the BBMRI in the form of 'hubs' that group different types of biobank at national and then European level. "Take Italy, you now have the hub for population-based biobanks, the hub for cardiovascular, for cancer, for genetic diseases and so on. This is the first level. The second is at the international level, where all national hubs take part, connected in a common platform, in which all kinds of communication is possible – within a hub and also between hubs."

As has happened in Italy, each of the hubs at national (first) level will of necessity work towards a common 'language'



and set of minimum data and quality standards, from the bottom up, with all of them hopefully following the international discussions and trying to move towards a harmonised system that could function internationally. "Discussion and agreement has to be reached, first at one level and then the next," says Paradiso.

To aid this process, he adds, there are already tools that make it possible to accept data from any of the software commonly used in hospitals and biobanks. Software, however, is no substitute for agreement between the major networks. To this end, the Bari Cancer Centre hosted a meeting for biobank networks last November, attended by representatives from more than 30 organisations in Europe, Asia and Africa. It was organised by the OECI together with ESO, under the auspices of the EORTC and endorsed by ISBER (the International Society for Biological and Environmental Repositories).

"The main aim," said Paradiso, "was to share experiences from all these groups, and to discuss the main possibilities for biobanking from a clinical perspective. What do biobanking organisations need in terms of minimum standards and minimum data requirements?"

These can be easy questions to answer, comments Jacqueline Hall, who represented EORTC at that meeting, but only if you know what study you want to carry out. "If you know, for instance, that you are going to be collecting a serum sample to be used for proteomics profiling, you know already what the goal is and you can already have in mind key variables you might want to collect about how that sample was taken from the patient or how it was processed, because there are known factors that can influence the proteomics profile.

"In the case of unspecified future use it becomes more tricky, because you have to find what is practical for the local pathologists and hospital staff to provide, and what is practical for managing the data here at EORTC HQ, and balance that against the needs of the research effort. As soon as you start

collecting more data it is more work and more cost. So we try to find a trade off."

Collecting samples is now a permanent concern for the EORTC and a priority for their research studies. In January the organisation released an updated policy on Human Biological Material Collection, Storage and Use, that covers sample collection for both specified and unspecified use (see Policy page at eortc.be). This policy includes making available for 'secondary use' the data-linked samples it holds in an independently run biobank facility in Milan, as well as at various institutions that participate in EORTC studies. Hall says it is also developing templates for what it considers to be the key information for different sample types. "We discuss these variables with the people involved in the studies, the pathologists who collect the samples and our own pathobiology group, in the context of international collaborations. We also look to information in the public domain about which variables people find important for different activities, and then we have an internal discussion to find out which will be the key variables for the different sample types in the context of that study."

With groups like this sharing experiences and discussing common positions on language, key associated data, and minimum quality requirements, the foundations are being laid for a biobank that can operate on a truly pan-European level. But Paradiso has set his sights on reaching further.

Present at the Bari meeting were representatives from Egypt, Tunisia, Israel and Jordan, all keen to develop biobanking in their countries. A follow-up meeting has been scheduled next year in Romania, with a focus on promoting a biobanking culture in central and eastern Europe, and beyond.

The best scenario is that the efforts being put in now will result in existing biobank networks gelling into an international system. As new biobanks join, this will transform the access researchers have to data-linked samples and significantly speed progress in understanding cancers and how to detect, diagnose and treat them.

For this to happen, guidelines and regulations must not only harmonise the biobanks. They must also inspire confidence in the public, in patients and in the clinicians and pathologists who are at front line of collecting samples, that the whole enterprise is based on the principle of solidarity, where the gains from these voluntary donations are disseminated and used for the public good.

BIOSOCIAL CITIZENS

Half a million people – around 1 in 50 aged between 40 and 69 – responded to the invitation to 'join the Biobank UK project' (www.ukbiobank.ac.uk). They attended 21 centres across England, Scotland and Wales to give blood, urine, saliva, and a variety of clinical measurements and filled out questionnaires on their lifestyle and medical history. Trust in the public service values of the NHS, which supports the Biobank, played an important role in motivating people to take part. The central message focused on the opportunity to take part in an exciting research project, and the idea that samples may be used for an unspecified purpose in future was presented as an opportunity rather than a threat: "In 10 or 20 years' time the things that we will be able to analyse in the samples may well be things that scientists have not yet thought about. The next generation of scientists, who might still be in primary school today, will actually use new tests and new methodologies to be able to unlock new secrets in terms of how we prevent diseases."

Guidelines and regulations must not only harmonise the biobanks, they must also inspire public confidence

The secret behind a successful clinical trial

Pinuccia Valagussa shares the insights gained from 40 years at the helm

➜ Simon Crompton

Good clinical trials are proposed by clinicians, have the potential for real patient benefit and increase knowledge about the disease. So says **Pinuccia Valagussa**, who forgets to mention another secret of success: having someone like herself in charge, who works closely with clinicians, keeps tight control over the quality of data, and is dedicated to helping more and more centres join trials.

The first thing that Pinuccia Valagussa says to me when I meet her in the reception of the Istituto Nazionale Tumori in Milan is that she doesn't want to do this interview. This is a little disconcerting, though she says it in a very friendly, polite manner. Then, thank goodness, she leads me down the corridors to her office, explaining that of course she will do it, so that she can get over important messages about clinical trials and current barriers to good research. It's just that the more she's thought about the interview, the more she's feared it.

The problem is that Valagussa, a woman who has been at the centre of some key trials in the recent history of cancer research, hates talking about herself. She agrees to interviews thinking it flattering, but then has second thoughts because, she says, she is a very private person.

Her dislike of the limelight isn't affectation. During most of our interview, Valagussa, who is director of the Operations Office for Clinical Trials at the Michelangelo Foundation in Milan, speaks openly and animatedly – discussing the qualities of good trials, the bureaucracy that stifles significant research, and some of the exciting studies she has been involved with over 40 years. She is all expressive hands, facial contortions and a combination of both that makes Italians uniquely able to express "that's how it goes", "what can you do?" and "I told you so" all in one go.

Yet when I venture into her background, motivations and influences, all that stops. "I really don't know what to tell you," becomes a regular reply.

Her demeanour is perhaps not unexpected given that she has had a central role in 350 papers on systemic adjuvant therapy for early breast cancer, treatment of malignant lymphomas and methodology in clinical trials, yet her name has rarely been first in lists of authors. Valagussa may be a lynchpin to some of the major advances in clinical oncology over four decades, and she may have received several awards (including an Italian Woman of the Year Award in 1997 and a City

ELIGIO PAONI

of Monza scientific merit award in 2005), but she works in the background.

She has run the Operations Office for Clinical Trials at the Istituto Nazionale Tumori in Milan since 1973, seeing its clinical trials office develop in 1999 into the Fondazione Michelangelo, a non-profit organisation devoted to advancing research in cancer. In 2007 she became a director of the foundation. The office where she has worked since the start is in the old part of Istituto Nazionale Tumori. The walls are covered with prints of impressionist paintings – the choice of renowned cancer doctor Gianni Bonadonna, who founded the Michelangelo Foundation. Despite having had a disabling brain haemorrhage in 1995, Bonadonna is still the heart and soul of the operation: his book-smothered office is next to Valagussa's, and he greets me warmly with a left-handed hand-shake.

Dedicated to clinical trials

Valagussa explains to me how the principle aim of the Michelangelo Foundation is to design and conduct clinical studies and translational research. Free of charge and independently, it assists clinical oncology investigators from the earliest planning stages. "We go through all the administrative burden, ask other sites to join the investigation, discuss the objectives and scheme of the study, go to the regulatory authorities and ethics committees, collect all the data, assess the quality of the data, plan and conduct the analysis, and prepare for presentation and publication."

The rigour the foundation applies to planning studies assures a quality of research that is far more likely to have an impact on clinical practice and patient care than studies that are poorly designed or never get off the ground because of

time-consuming administrative procedures. Valagussa's office ensures that nothing coordinated by them compromises its high standards.

"A good clinical trial is first of all one that is proposed by clinicians, because they have ideas. The hypothesis, if proved, must show a benefit that is clinically important and important to the patient. For example, is it important to start a very large study with the aim of finding a difference of no more than 3% between treatments *a* and *b*? You may improve the rate of survival but a new treatment may also have risks. There's a danger that such studies are like comparing Coca Cola with Pepsi Cola: is the goal really to benefit the patient?

"A good clinical trial improves knowledge of the disease, and it is important nowadays that when designing a clinical study you have to keep in mind that you will need to correlate it with a translational study. So you need to talk to your patients and explain the importance of them donating samples for future research."

Outstanding young investigator 1985. Valagussa's contribution to setting up some of the first big breast cancer trials was recognised with this prize awarded by the Italian Health Minister

An impressive track record

The research that Valagussa and her team have been involved in over the decades demonstrates the potential impact of well-planned clinical research. In the early 1970s, with Bonadonna, she coordinated the landmark trial showing that adjuvant CMF (cyclophosphamide, methotrexate and fluorouracil) provided significant survival benefits for women with operable breast cancer – a finding that has been confirmed in follow-up studies over 30 years. "It was quite a departure. We demonstrated to surgeons how patients could be cured with chemotherapy, so it began to change mentalities, and was the beginning of the multidisciplinary approach."

Another landmark trial occurred in the early 1970s, when Bonadonna designed a new combination chemotherapy for Hodgkin's disease known as ABVD (adriamycin, bleomycin, vinblastine and dacarbazine). With Bonadonna, she coordinated the trial that in 1974 showed the superiority of ABVD compared with the standard MOPP (mecloretamine, vincristine, procarbazine, prednisone) chemotherapy. ABVD is today still considered the gold standard for conventional chemotherapy in Hodgkin's disease.

In the late 1980s, she coordinated trials under Bonadonna and with the support of Umberto Veronesi, which challenged the classic indication of mastectomy for breast tumours of three centimetres or more, demonstrating that primary chemotherapy before surgery reduced tumour size, and that conservative surgery could be an effective and safe alternative to radical surgery. "In what was, and still is, a surgical centre, we were able to say: 'Please, now, we can all help our patients preserve their body integrity by starting

"A good clinical trial is first of all one that is proposed by clinicians, because they have ideas"

"We can all help patients preserve their body integrity by starting with chemotherapy followed by surgery"

with chemotherapy followed by surgery.' It took a while to convince people, but we managed it."

There's much more to come. She is currently planning a global trial of a new type of adjuvant therapy, involving groups from Italy, Britain and Australia, but the details as yet have to be kept under wraps.

There have been massive changes in the scope of trials into cancer drugs over the four decades that Valagussa has been at the Istituto Nazionale Tumori. She first came in 1969, a Red Cross volunteer nurse based at Monza Hospital attending a cancer course that the Institute was holding. Because she had studied languages at high school, spoke English and had attended courses in statistics while in Monza, she was asked by Veronesi to join the Institute as a scientific secretary.

"Nobody really told me what they wanted from me until my first day in the job, when Professor Veronesi told me I would be involved in trials. I didn't know what this meant. I never associated the word trial with medicine before."

Soon she was thrown into compiling information for Veronesi's trial on breast cancer surgery, and typing up Bonadonna's protocols for chemotherapy trials. The clinical trials operations office, officially set up to concentrate on medical oncology in 1972, was originally a small affair. It coordinated only single-centre studies for the Institute itself and had just three staff. Now there are 12 staff, coordinating studies in 35 centres around the world.

Going multicentre

Its growth can be traced to 1993, when Bonadonna decided to respond to requests from medical oncologists whom he had trained, and were now working elsewhere in Italy: they wanted to participate in some of the clinical studies he was running. "It was with some reluctance initially," says Valagussa, "because you are used to working within your own group, and it's not that easy to change. But it was an important step, because it meant we would be able to cooperate together according to certain rules, and it would allow patients from other regions of Italy to have good experimental treatments, based on sound clinical reasoning, without coming to Milan."

So around 15 medical oncologists from northern Italy got together for an exploratory meeting at the Michelangelo Hotel near Milan train station; they decided to stay in touch, and called themselves the Michelangelo group. They did indeed start multicentre trials, coordinated from the trials office of the Istituto Nazionale Tumori, and years later, when the work of the office became formalised into the new foundation, Bonadonna decided to continue with the Michelangelo name.

The move to international multicentre trials came in the mid 1990s, when Bonadonna was designing a new randomised trial to test classical adjuvant chemotherapy against neoadjuvant primary chemotherapy before surgery in cases of moderate- to high-risk breast cancer. One of the drug companies providing funding asked whether it would be possible to conduct it as an international trial. So a protocol was

A phenomenal partnership. The collaboration between Valagussa and Gianni Bonadonna, one of medical oncology's great leaders, has not just improved survival and quality of life for countless cancer patients but helped set the standards for clinical research

arranged and plans were made. And then Bonadonna had a brain haemorrhage.

"We had a big discussion in Paris with the investigators and the drug company, and we had to ask whether we could continue this adventure without Dr Bonadonna. Finally, Professor Luca Gianni, then director of medical oncology at the Istituto Nazionale Tumori, accepted the challenge. So in 1996, we started the internationalisation of our foundation. And once we did it, we knew we could do it again and again."

International trials suddenly presented Valagussa and her colleagues with new challenges for organising consistent protocols. Different countries had very different perceptions of what 'best conventional treatment' was. There were different technological levels – some centres participating in trials in the late 1990s did not even have routine access to the internet. Drug companies funding the trials had to be asked for more money to help less well-resourced sites participate.

Achieving quality data in these large trials is time consuming. "It's costly, but not just financially. It's not always easy to get investigators to send the right kind of data at the right time – they have their job to do in their clinic, after all. And you need to convince them of the importance of following rigorously all the safety procedures in your protocol. And if something doesn't look right to you in the data, you need to call the investigators and discuss it with them and provide advice. What qualifies our team is the clinical quality of the data. While the main priority of a drug company might be to ensure that all the right boxes in the study have been filled, and this might be done at the end of a study, our emphasis right from the start is to check the quality of the data. It's not so important that information is missing. It's important that what you have is good."

The burden of bureaucracy

But the biggest challenges have always been posed by bureaucracy. It's a problem that afflicts researchers in every country, but Valagussa believes international trials are battling against almost impossible odds to get off the ground. Even a specialist trials office such as her own struggles with the convolutions of red tape that drain time and money. If all goes smoothly in planning for a large study, it will take at least four years to complete enrolment and many more years to follow-up. In that time, other findings and developments may have made a study's original objectives obsolete. Valagussa says the situation is sometimes "nightmarish" for organisations like her own attempting independent research driven by the needs of patients.

"The regulatory authorities are all different in every country involved. You have to get your protocol cleared with them, and then present to the ethics committee, and then you have to select the participating sites. Nowadays, things are getting worse. For example, for a non-profit organisation like ourselves, conducting a non-profit study, it is not clear under European rules whether you, as the sponsor, have to pay for the drugs used in the study, even when they have been registered for the indicated use. It seems to be different in different countries.

"According to European regulations, sponsors have to provide a fee to the regulatory committee and a fee to the ethics committee. They often have to pay for all the drugs, and sometimes for extra patient examinations. If this continues, what is the future possibility of academics and institutes like our own conducting studies? They are just too expensive."

So it is inevitable that funding from commercial sources has to be accepted for many studies. Valagussa's office tries to help researchers find independent sources of funding, but these rarely cover the full cost of a study. Since much of the research is to establish new indications for drugs that have already been approved, drug companies are asked for support too. But Valagussa emphasises that there can be no drug company intervention in studies' design or objectives.

What could be done to make quality, independent multicentre research easier to accomplish? Valagussa shakes her head wearily. "I haven't any idea. We do need rules, and people to apply them, for the good of patients and the studies themselves. Years ago, we had few regulations, and

"It's not so important that information is missing. It's important that what you have is good"

"You have to believe you are doing your best for patients, and share the options you have with other countries"

that was wrong. But when you go to the bureaucrats, you always seem to be fighting a losing battle. You ask them, 'What do these words mean?' They have one interpretation. I have another. A third person has another. What can you do?" She tentatively suggests that one central European committee might help, so that separate authority wouldn't have to be sought from regulators in each country: but EU regulations are not famous for their clarity.

It's about patients

Despite all this, Valagussa is a great believer in international, multicentre trials. They bring benefits to a far larger group of patients than single-centre studies. "I think you have to believe you are doing your best for patients, and to share the options you have for treatment in your country with other countries. More patients benefit if you have several sites, working as if they are one specialised centre. You get a good exchange of information between investigators, and the focus is on improvement."

The patient, she emphasises, should drive everything. It's important to work with them before, during and after trials, often through patient organisations. User input into the design of consent forms is particularly important, she says. It is too easy to design consent forms that only clinicians understand – and even they sometimes find them difficult.

I wonder whether her background as a nurse has helped provide a patient-conscious counterpoint to the perspective of doctors in designing trials. She shrugs. Not really, she says. And as we begin to touch on her personal contribution and qualities, the answers begin to dry up. I learn that she is single, sees a great deal of her 10 nephews and nieces, and their 10 children, and likes travelling, reading thrillers and listening to classical music. But she doesn't wish to go into details about what makes her tick. "If you let me talk about protocols, that's fine. Otherwise, I stay quiet."

An internationalist. Valagussa goes out of her way to help new countries and new institutions participate in multicentre trials, even though this complicates her task of controlling the quality of the data collected. She is pictured here at a regional breast cancer conference in Uruguay, 1999

Actually, what motivates her has become obvious as we talked about her work, and about the debt she feels to Bonadonna for his confidence in her since her earliest days at the Institute. "I've always appreciated that I've been able to talk openly with all the clinicians I've worked with – just sensing that we were, and are, a team, working together out of scientific curiosity. We all have this same challenge ahead of us, framing the clinician's perspective in the right way so that we can test what we think according to the correct methodologies."

And sometimes, when the hard data show something really exciting, the shy person who wants to keep the personal out of the professional can't help acknowledging her personal investment in the work. "When you start a study, your main priority has to be not to harm our patients for the sake of a scientific idea. But when you get the initial results, sometimes you cannot help being excited. You get a leap inside, and say: yes, we are on the right road. We have not solved it, but we are on the right road."

Hypoxia modification with radiotherapy for bladder cancer

Mary Gospodarowicz

The outcomes in bladder cancer treated with radiotherapy are suboptimal. Recently, Hoskin et al. reported improved survival in patients with bladder cancer treated with radiation therapy with concurrent hypoxia-modification therapy. These results are promising but must be viewed in the context of previous studies and alternative treatment approaches.

The management of muscle-invasive bladder cancer continues to be controversial; there is no solid evidence that overall survival has improved in the past two decades. The most common approach for bladder cancer management is radical cystectomy; bladder-conserving approaches with radiotherapy are far less frequently used. The major challenge in the latter approach are the limitations of radiotherapy due to the proximity of dose-limiting organs including the bladder, rectum and adjacent small bowel. A number of approaches have been developed using radiation-sensitising chemotherapy to improve local control.[1] In addition, hypoxia is present in most solid human tumours and attempts to overcome its effect have been tried in head and neck cancer and, to a lesser extent, bladder cancer.[2,3]

In a recently published paper, Hoskin et al.[4] report the results of a prospective randomised trial comparing the efficacy of external-beam radiotherapy with and without concurrent carbogen and nicotinamide. This trial was based on previous phase II trials that used a similar approach, that is, hypoxia modification. In the present trial,[4] 333 patients were randomly assigned to either radiotherapy alone (55 Gy in 20 fractions over 4 weeks or 64 Gy in 32 fractions over 6.5 weeks) or radiotherapy with concurrent carbogen (2% carbon dioxide and 98% oxygen at 15 l/min for 5 min before and during radiotherapy) and oral nicotinamide (60 mg/kg administered 1.5–2 hours before each fraction of radiation). Patients were stratified by centre and their characteristics were well balanced except for a slightly higher proportion of patients with T3 tumours (23.9% vs 18%) in the radiotherapy-alone arm. The primary endpoint of the study was cystoscopic local control at six months. The secondary endpoints included the

nature REVIEWS CLINICAL ONCOLOGY
This article was first published in *Nature Reviews Clinical Oncology* 2011 vol.8 no.3, and is published with permission. doi:10.1038/nrclinonc.2011.5, www.nature.com/nrclinonc

overall survival rate and local-relapse-free survival. The results showed improved overall survival at five years in the cohort receiving radiotherapy, carbogen and nicotinamide (50% vs 39%).[4]

The results of this trial are surprising because no previous phase III trial of radiotherapy in bladder cancer has showed improved overall survival, including large randomised trials. The results are difficult to interpret because the primary trial endpoint of improved cystoscopic local control was not achieved. In bladder cancer trials, the use of local tumour control as an endpoint is problematic because many patients do not have follow-up cystoscopies owing to the development of progressive distant disease or comorbidities.[5] Moreover, the higher rate of salvage cystectomy in the radiotherapy-alone group suggests improved local control in the combination arm (13 vs 23 salvage cystectomies). However, in terms of survival, the higher rate of salvage cystectomy should have compensated for the lower local control in radiotherapy-alone patients. The cohort treated with radiotherapy alone had more deaths unrelated to bladder cancer (29 vs 24 patients); therefore, it is difficult to be certain that the treatment intervention caused the overall survival benefit. The trial used CT to define clinical target volumes but no details were provided regarding the verification of treatment delivery.[4]

There are considerable problems with the reproducibility of radiotherapy delivery to bladder cancer that are mostly related to variation caused by bladder filling between fractions and during treatment.[6] Trials of image-guided and adaptive approaches to overcome this problem are ongoing. The difficulties in imaging the actual tumour, rather than the bladder, pose additional problems that some investigators have tried to overcome by injecting lipiodol around the tumour to facilitate real-time image guidance.[7,8]

The majority of patients with muscle-invasive bladder cancer are managed with radical cystectomy and pelvic lymph-node dissection, while those who are poor surgical candidates are referred for external-beam radiotherapy. A number of investigators have tried to popularise bladder conservation strategies based on combined modality approaches with concurrent chemotherapy and radiotherapy. Unfortunately, little progress has been made in this area in the past two decades. Trials performed in the 1980s and 1990s showed superiority of concurrent cisplatin and radiotherapy when compared with radiotherapy alone.[9,10] However, the single-agent cisplatin had no impact on distant-metastasis rate and, therefore, no survival advantage.[10] Studies of adjuvant multiagent cisplatin-based chemotherapy showed a very modest survival impact.[9] A surgical approach is generally preferred as it defines the microscopic disease extent in the primary tumour and regional lymph nodes. Radical cystectomy offers improved local control for tumours confined to the bladder, and pelvic lymph-node dissection has been shown to cure a proportion of patients with involved pelvic lymph nodes. Unfortunately, the price is the loss of natural bladder function, and although modern continent diversion techniques offer improved quality of life, the long-term effects of surgical management are imperfect.[9]

Bladder preservation strategies are much more complex than the standard surgical approach and require close cooperation between urologists and radiation oncologists with regards to patient selection, response assessment and ongoing management. The best candidates for bladder preservation have small T2 tumours with no coexistent carcinoma *in situ*.[5] Optimal survival has been achieved with immediate salvage cystectomy in patients who do not achieve local control or relapse owing to muscle-invasive disease. The small proportion of bladder cancer patients considered for radiotherapy hinders clinical trials in this area. Most studies are small and require a prolonged accrual phase. The approach in the Hoskin et al.[4] trial merits attention and further study, especially in patients not fit for more aggressive approaches. However, as the Hoskin et al.[4] study shows, distant failures continue to be a major problem in this group of patients. It is important to note that the approach taken does not address the issues of micrometastatic disease and, therefore, is unlikely to have a major impact on overall survival.

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

Practice points

- Bladder cancer management remains a challenge for radiation oncologists; attention to patient selection, optimal treatment planning and delivery is important
- There is a need for studies of adaptive radiotherapy delivery approaches
- The role of hypoxia modification merits further study
- Participation in clinical trials of combined modality approaches is encouraged

Author affiliations: Princess Margaret Hospital, University of Toronto, Canada

An 18-gene signature (ColoPrint) for colon cancer prognosis

Iain Tan and Patrick Tan

ColoPrint is an 18-gene expression signature designed to predict disease relapse in patients with early-stage colorectal cancer (CRC). We discuss the potential impact of ColoPrint on clinical practice, and its contribution to our knowledge of CRC molecular heterogeneity.

Many oncologists are familiar with MammaPrint (Agendia, Amsterdam, The Netherlands) and Oncotype DX (Genomic Health, Redwood City, CA, USA), two multi-gene assays used to predict disease relapse and guide adjuvant therapy decisions in patients with early-stage breast cancer. Recently, both companies have published gene-expression classifiers for predicting disease relapse in early-stage colorectal cancer (CRC).[1,2] Here, we discuss the potential clinical and scientific impact of one of these classifiers – ColoPrint (Agendia).

CRC is the third leading cause of global cancer mortality. Outcomes for patients with early-stage CRC are heterogeneous, with five-year survival rates ranging from 72% to 83% in stage II disease and from 44% to 83% in stage III disease.[3] In the past two decades, randomised trials have demonstrated a survival advantage for patients treated with surgery and adjuvant chemotherapy,[4] particularly those with stage III disease. However, in these trials, many patients were cured by surgery alone, suggesting that it might be possible to omit chemotherapy in selected patients. Clinical guidelines currently recommend observation for stage I disease and adjuvant chemotherapy with a combination of a fluoropyrimidine and oxaliplatin for those with stage III disease.

In stage II CRC, the benefit of adjuvant chemotherapy is contentious, with ASCO recommending the integration of clinical risk criteria to select patients for adjuvant therapy.[5] Identifying molecular markers that can inform therapeutic decisions, such as the need for treatment and type of adjuvant therapy, would be tremendously useful. To address this challenge, Salazar et al.[1] analyzed fresh-frozen tumour tissues from 188 patients with stage I to IV CRC using Agilent gene-expression microarrays. By correlating the expression of more than 40,000 genes with metastasis-free survival, they identified an optimal set of 18 genes that was used to construct the ColoPrint prognostic classifier. In an independent validation series of 206 patients with stage I to III CRC, 60% of patients were classified as 'low risk', with a five-year relapse-free survival (RFS) rate of 87.6%. The remaining 40% 'high-risk' patients exhibited a RFS rate of 67.2% (HR=2.5; 95% CI 1.33–4.73; P=0.005). In multivariate analyses, ColoPrint remained one of most significant prognostic factors (HR=2.69; P=0.003), and in stage II CRC, ColoPrint was superior to the ASCO criteria for the assessment of cancer recurrence risk (HR=3.34; P=0.017). The authors concluded that, compared with conventional clinicopathological criteria alone, ColoPrint provides more accurate information on the risk of recurrence and may facilitate selection of low-risk patients who can be spared chemotherapy.

While these results are encouraging, it

nature REVIEWS CLINICAL ONCOLOGY

This article was first published in ***Nature Reviews Clinical Oncology*** 2011 vol.8 no.3, and is published with permission. doi:10.1038/nrclinonc.2010.229, www.nature.com/nrclinonc

is prudent to interpret them in the context of an early discovery study. Several gene-expression classifiers for predicting CRC relapse have been described,[6,7] but none have achieved clinical utility. It is worth noting that studies relying on fresh-frozen tissue (for example ColoPrint) typically have modest sample sizes and cannot benefit from archival material collected from randomised clinical trials. As a comparison, Oncotype DX (colon), the parallel CRC prognostic classifier developed using formalin-fixed paraffin-embedded tissues, was tested in more than 1800 patients from four adjuvant trials.[2] Therefore, further retrospective validation of ColoPrint in large independent cohorts is clearly required. Fortunately, a prospective study, PARSC (Prospective study for the Assessment of Recurrence risk in Stage II Colorectal patients using ColoPrint) has already been initiated to evaluate the performance of ColoPrint in the classification of patients in the clinical setting.[8]

The potential for gene signatures to influence treatment decisions depends on the disease stage. Molecular markers are most likely to impact the management of stage II disease, where the need for adjuvant chemotherapy is already based on assessment of clinical risk features. Molecularly, microsatellite instability (MSI) status is a marker of good prognosis in patients with stage II CRC and may be associated with a lack of benefit from adjuvant fluoropyrimidine therapy.[9] Indeed, most MSI high (MSI-H) patients were identified as 'low risk' by ColoPrint. However, the 48% discordance observed between ColoPrint and the ASCO clinical risk criteria[1] suggests an additional discriminative value of ColoPrint beyond clinical characteristics. Stage II patients identified as 'low-risk' by ColoPrint exhibited an excellent five-year survival similar to that seen for stage I disease, raising the possibility that ColoPrint may identify stage II patients for whom chemotherapy can be avoided. That said, we must remember that good prognosis does not necessarily mean lack of benefit from adjuvant therapy. For example, Oncotype DX (colon) has not been shown to be predictive in stage II CRC, despite its prognostic significance.[2] Further studies should also be performed to establish if ColoPrint is purely prognostic or whether it is predictive of treatment benefit as well.

In stage III CRC, adjuvant chemotherapy is the standard of care. In our opinion, oncologists are highly unlikely to omit chemotherapy altogether in medically fit patients with stage III CRC unless the data supporting excellent prognosis in molecularly low-risk patients is very compelling. The study by Salazar et al.[1] cannot address the role of ColoPrint in stage III disease, since there were only 62 patients with stage III disease and there was a trend towards inferior RFS in high-risk patients (P=0.1). Nevertheless, a validated prognostic signature for stage III CRC patients might still be useful to identify low-risk patients for whom oxaliplatin chemotherapy might be omitted and who might be treated with a fluoropyrimidine alone. Moreover, with the exception of oxaliplatin, stage III CRC has demonstrated notable failures for drugs that were efficacious in the metastatic setting, such as bevacizumab, cetuximab and irinotecan. Given the curative intent of treatment in stage III CRC and the vast investment into these completed trials, it might be fruitful to search for molecular markers predictive of selective benefit for therapies that otherwise do not provide an advantage in an unselected population.

The present study also broadens our knowledge regarding the inherent molecular heterogeneity of CRC.[1] Using unsupervised clustering techniques, three molecular subgroups were identified that had different survival outcomes. These groups were differentially enriched for *BRAF* activating mutations and MSI-H, suggesting unique underlying biologies. Notably, only the largest subgroup (n=110) was used to develop the prognostic signature. Given the distinct biological makeup of these three groups, it is plausible that the prognostic impact of ColoPrint is specific to the biological subgroup from which it was developed, analogous to the questionable prognostic value of Oncotype DX in HER2-positive breast cancer.[10] Salazar et al.[1] do not provide prognostic information of ColoPrint in the three biological subgroups – this should also be addressed in a future study. Investigations addressing the relationship of ColoPrint to other molecular markers (for example, 18q loss of heterozygosity, *KRAS* mutation status and CpG island methylation subtypes) are also warranted.

In conclusion, Salazar and colleagues are to be commended for their promising findings that ColoPrint might provide additional prognostic information beyond clinicopathological criteria in early-stage CRC. We eagerly await the results of the ongoing clinical trial seeking to prospectively validate ColoPrint.

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

Practice point

In colorectal cancer, novel molecular markers such as gene-expression signatures offer the potential of improving upon current prognostic models that are based on clinical criteria. However, widespread acceptance of these markers will necessitate identifying opportunities where they directly influence clinical management decisions.

Author affiliations: Department of Medical Oncology, National Cancer Centre, Singapore (I Tan). Cancer and Stem Cell Biology, Duke–NUS Graduate Medical School, Singapore (P Tan)

NEWSROUND

Selected reports edited by Janet Fricker

Treatment by gynaecologic oncologists improves outcome in endometrial cancer

➜ Journal of Clinical Oncology

Patients with endometrial cancer treated by gynaecologic oncologists were more likely to undergo staging surgery and receive adjuvant chemotherapy in advanced cancer, a US study has found. The researchers also reported a higher five-year disease-specific survival among endometrial cancer patients with stage II–IV disease who were treated by gynaecologic oncologists.

Over the last decade the number of annual deaths from endometrial cancer has doubled in the US. Studies of patients with ovarian cancer have shown that those receiving care from gynaecologic oncologists underwent more thorough staging surgery and received more chemotherapy in high-risk disease. This, in turn, led to improved survival outcomes. Despite a lack of evidence for survival benefit for patients with endometrial cancer, the American College of Obstetrics and Gynecology recommends that these patients should also be referred to gynaecologic oncologists.

In the current study, John Chan and colleagues from the University of California at San Francisco, undertook to determine the influence that care by gynaecologic oncologists had on both the type of treatment and the survival of patients with endometrial cancer. Between 1988 and 2005 the investigators obtained data from the Medicare data bases and from the Surveillance, Epidemiology and End Results (SEER) programme. The speciality of the treating surgeon was found by linking their unique provider identification numbers in the data bases to information collected by the American Medical Association. Kaplan–Meier and Cox proportional hazard methods were used for analyses.

Results show that of the 18,338 women identified with endometrial cancer in the data bases, 21.4% received care from gynaecologic oncologists (defined as group A); while 78.6% were treated by other clinicians (defined as group B).

Women in group A were older, with 49.6% in group A aged over 71 years compared to 44% in group B (P=0.001); they had more lymph nodes removed, with 22% in group A having more than 16 nodes removed compared to 17% in group B (P<0.001) they presented with more advanced cancer, with 21.9% in group A having stage III–IV cancers versus 14.6% in group B (P<0.001); they had higher-grade tumours (P<0.001) and they were more likely to receive chemotherapy for advanced disease, with 22.6% in group A receiving chemotherapy versus 12.4% in group B (P<0.001).

For women with stage II–IV disease, the five-year disease-specific survival (DSS) of group A patients was 79% versus 73% for group B (P=0.001). For stage III–IV disease, women in group A had a five-year DSS of 72% versus 64% in group B (P<0.001). However, no association with DSS was identified among women with stage I cancers. On multivariable analysis, younger age, early stage, lower grade, and treatment by gynaecologic oncologists were all found to be independent prognostic factors for improved survival.

"Directed care by gynecologic oncologists was associated with more extensive lymph node resection and subsequent adjuvant therapy. Most importantly, care provided by gynecologic oncologists improved the survival of those with high-risk (stages II to IV, grade 2 and 3, and high-risk histologies) disease," write the authors, adding, that to their knowledge this is the first population-based study to have analysed the impact that gynaecologic oncologist care has on endometrial cancer patients.

Nearly 80% of endometrial cancer patients in the study, stress the authors, did not receive care from gynaecologic oncologists. "Clearly, further research is needed to identify the

disparities in endometrial cancer treatment and potential barriers to accessing subspecialty care," they write.

Limitations to the study included a lack of information on the extent of residual disease after cytoreductive surgery for advanced disease, lack of central pathology review, unknown types and cycles of adjuvant chemotherapy and unspecified treatment for recurrent disease. "Without central pathology review, it is possible that a change in grade of disease may affect the results of this study," write the authors.

■ J K Chan, AE Sherman, DS Kapp et al. Influence of gynecologic oncologists on the survival of patients with endometrial cancer. *JCO* doi 10.1200/JCO.2010.31.2124, published online 24 January 2011

Choice of surgeon is a significant influence on outcome in DCIS

→ JNCI

The most important determinants of outcomes for women with ductal carcinoma *in situ* (DCIS) are associated with tumour margins, whether or not they received radiotherapy, whether or not they underwent mastectomy, and the treating surgeon, a retrospective US study has found.

"An important implication of our work is that surgeons may play a critical role both in the surgical treatment choices made by patients (and in the receipt of radiation therapy). Because these are the most important factors in predicting outcomes the substantial variation by surgeon suggests that the quality of DCIS care could be improved," write the authors Andrew Dick and colleagues from the RAND Corporation (Pittsburgh, PA), a non-profit-making institution, with the remit to improve policy and decision making through research and analysis.

The goal for treating DCIS, or non-invasive breast cancer, is to reduce the likelihood of developing invasive breast cancer while respecting patient preferences for treatment options, which include breast conserving surgery alone, breast conserving surgery followed by radiation, and mastectomy. Since DCIS is non-lethal, physicians' attitudes regarding optimal management and patient preference may play a role in treatment decisions.

To determine the comparative effectiveness of treatment strategies, and identify key factors associated with variations in outcomes, Dick and colleagues conducted a retrospective study of 994 women diagnosed with DCIS between 1985 and 2000. The investigators identified subjects through two large tumour registries: the Monroe County (New York) tumour registry, and the tumour registry at the Henry Ford Health System in Detroit. Margins were defined as positive (when cancer cells extended to the edge of the resected tissue); negative (when cancer cells were more than 2 mm away from the edge of the tissue); or close (when cancer cells were present within 2 mm of the edge).

Results showed that the overall differences in predicted five-year disease-free survival rates were 0.993 for mastectomy, 0.945 for breast-conserving surgery with radiation therapy and 0.824 for breast-conserving surgery without radiation therapy, with all the differences found to be statistically significant (*P*diff <0.001 for each of the differences). Similarly, each of the differences at 10 years was statistically significant (*P*<0.001).

In all the treatment groups, except breast conserving surgery without radiation therapy, the rates of recurrence were statistically significantly different according to margin status, with positive margins found to be associated with substantially higher recurrence rates. Furthermore, variation by surgeon accounted for 15%–35% of the subsequent ipsilateral five-year recurrence rates, and for 13%–30% of 10-year recurrence rates.

"Although variation by surgeon could be generated by patients' preferences, the extent of variation and its contribution to long-term health outcomes are troubling," write the authors, adding that further work is required to determine why women with positive margins receive no additional treatment and why margin status and receipt of radiation therapy vary by surgeon. Additionally, they add, there is currently no consensus on what constitutes a negative margin.

In an accompanying commentary, Beth Virnig and Todd Tuttle of the University of Minnesota ask how patients should go about selecting health providers, in the knowledge that up to 35% of the variation in outcomes is based on their choice of physician, but that there are no actionable characteristics that can be taken into account.

One solution, they suggest, would be to publish the scores for all physicians performing breast cancer surgery in a particular area. "With this approach, it would not matter why one physician had higher or lower recurrence rates or positive margin rates, the rates would simply be reported so that women could take this into account when selecting a provider," they write.

The challenge, they add, will be for the professional community to identify factors that are associated with the unexplained physician variability and to use that information to promote identification of high-quality providers or quality improvement activities.

■ AW Dick, MS Sorbero, GM Ahrendt et al. Comparative effectiveness of ductal carcinoma in situ management and the roles of margins and surgeons. *JNCI* 19 January 2011, 103:92-104

■ B Virnig, TM Tuttle. Random physician effect and comparative effectiveness of treatment for ductal carcinoma in situ. *ibid*, pp 81–82

Protocols needed to cut delays in giving antibiotics for febrile neutropenia

→ British Journal of Cancer

A study providing detailed insights into the management of chemotherapy-induced febrile neutropenia in a UK Cancer Network shows that while the condition is generally recognised early and managed appropriately,

improvements are needed in the timely administration of antibiotics. The prospective study, the authors believe, highlights the need for introducing network-wide clinical care pathways to improve outcomes.

Febrile neutropenia (the development of fever in patients with abnormally low levels of neutrophil granulocytes) is a complication of chemotherapy associated with considerable morbidity and mortality. The UK National Chemotherapy Advisory Group (NCAG) – set up to provide advice on the delivery of high-quality chemotherapy services to the National Cancer Director and Department of Health – have produced guidelines on febrile neutropenia, recommending 'treat and transfer' arrangements (if hospitals do not have appropriate facilities), and an arrival to delivery time of antibiotic administration for neutropenic sepsis of less than one hour.

"The NCAG recommendations provide a framework for a process of assessment, decision to treat, informed consent and prescription of chemotherapy, and emphasise the importance of detailed standardised consent forms and the involvement of senior trained oncology medical staff ," write the authors of the study, Simon Chowdhury and colleagues from Guy's & St Thomas' NHS Foundation Trust (London, UK).

In this study, Chowdhury and colleagues undertook a prospective study of all the cases of chemotherapy-induced febrile neutropenia in the South West London Cancer Network between May and August 2007. Data recorded at seven hospitals serving a population of 1.4 million people included demographics, treatment histories, management of febrile neutropenia and outcomes.

Results showed that, in all, 71 admissions for febrile neutropenia were reported, involving 64 patients, with seven patients admitted on two separate occasions. Fifty-nine per cent of patients (*n*=38) were female and 41% (*n*=26) male, with a median age of 60 years. Of note, one-third of patients with febrile neutropenia in the study were older than 65 years, which the authors suggest supports the notion "that increasing age is an independent predictor of development of febrile neutropenia." The seriousness of the condition was underlined by the fact that three of the patients (4.2%) died as a direct consequence of neutropenic sepsis.

Forty-five patients (63%) were admitted directly to a specialist oncology or haematology ward, while 21 (30%) were seen first in the accident and emergency departments. The median time from arrival to nursing assessment was 10 minutes (range 0–135 mins), and the median time to first assessment by a clinician was 40 minutes (range 0–230 mins). The median time from arrival to administration of an antibiotic was 135 minutes (range 15–550 mins), with only 9 out of 50 patients receiving antibiotics within 60 minutes.

"Our study has provided an important and detailed insight into the incidence and management of chemotherapy-induced febrile neutropenia in a representative cancer network in the United Kingdom," write the authors, adding that the area that most needs to be addressed is the time interval between arrival at the hospital and treatment.

"To achieve this, physician and nursing protocols to standardise and streamline clinical care pathways for the whole network are under consideration," write the authors, adding that it is hoped that the recommendation for NICE to provide a nationwide policy for management of neutropenic sepsis will lead to the introduction of a standardised approach both within and across networks.

One issue, add the authors, is that peripheral hospitals may not be staffed with 24-hour oncology services, making it crucial that these sites have access to well-designed protocols and expert consultant advice. Furthermore, patient education regarding what to do in the event of a chemotherapy-induced complication is fundamental to ensuring people receive prompt appropriate care.

■ M Okera, S Chan, U Dernede. A prospective study of chemotherapy-induced febrile neutropenia in the South West London Cancer Network. Interpretation of study results in light of NCAG/NCEPOD findings. *Br J Cancer* 1 February 2011, 104:407–412

IMRT spares head and neck cancer patients dry mouth symptoms

➔ Lancet Oncology

Sparing the parotid glands of patients with head and neck cancer by using intensity modulated radiotherapy (IMRT) reduces the incidence of xerostomia (a dry mouth due to lack of saliva), reports the phase III UK PARSPORT study.

While radiotherapy is the main non-surgical treatment for squamous-cell carcinoma of the head and neck, radiation-induced xerostomia is a commonly reported late side-effect. Lack of saliva affects speech and swallowing, and can accelerate dental caries. In comparison with conventional radiotherapy, IMRT, which allows focused radiation delivery to tumours, can reduce irradiation of the parotid glands.

In the current study, which took place at six UK centres between January 2003 and December 2007, Christopher Nutting and colleagues from the Institute of Cancer Research (Sutton, UK), randomised 94 patients with histologically confirmed squamous carcinoma (T1–T4, N0–N3, M) to parotid sparing IMRT (*n*=47) or to conventional radiotherapy (*n*=47). In both groups, the primary tumour and involved lymph nodes were treated with 65 Gy, delivered in 30 daily fractions, five days a week. The investigators undertook measurement of salivary flow prior to radiotherapy, at week 4 of treatment, and then at 2 weeks and 3, 6, 12, 18 and 24 months after radiotherapy.

Results at 12 months show that grade 2 or worse xerostomia symptoms occurred in 74% of patients given conventional radiotherapy versus 38% of patients given IMRT (P=0.0027). At 24 months, grade 2 or worse xerostomia occurred in 83% of patients given conventional radiotherapy versus 29% given IMRT (P<0.0001).

At 12 months, unstimulated saliva flow from the contralateral parotid glands was noted in 47% of patients treated with IMRT versus none treated with conventional radiotherapy (P<0.0001), while at 24 months unstimulated saliva flow occurred in 44% of patients in the

IMRT group versus none in the conventional therapy group (P=0.0068).

The only recorded acute adverse event of grade 2 or worse that differed significantly between the treatment groups was fatigue, which occurred in 41% of patients given conventional radiotherapy versus 74% given IMRT (P=0.0015). Significant differences were also noted in stimulated saliva flow from the contralateral parotid at 12 months (P<0.0001). The estimated two-year overall survival was 76% with conventional radiotherapy versus 78% with IMRT.

"Our trial has shown a clinically and statistically significant reduction in xerostomia, improved salivary flow, and improved quality of life, and this strongly supports a role for IMRT in head and neck squamous cell carcinoma," conclude the authors, adding that the results of the PARSPORT trial are likely to be generalisable to all head and neck tumours for which conventional radiotherapy is used. It is possible, they say, that further reductions in severe xerostomia could be achieved by additionally sparing the submandibular and mucosal minor salivary glands.

Fatigue was unexpectedly found to be greater in patients treated with IMRT. This, say the authors, could be due to greater radiation doses being delivered to non-tumour tissues.

One limitation of the study, they add, is that it was not possible to mask the treatment from patients or clinicians due to the differences in treatment delivery. "However, results that relate to multiple secondary endpoints support the primary analysis and the size of the observed effect is unlikely to be due entirely to assessment or reporting bias."

In an accompanying commentary, Andy Trotti from the Moffitt Cancer Center (Tampa, Florida) and Avi Eisbruch from the University of Michigan Medical Centre (Ann Arbor) say that future work should systematically explore the prioritisation of different components of the salivary gland system, since a clinical benefit of sparing the submandibular glands can be obtained over the parotid glands. "The parotid glands provide watery saliva during eating, which is largely replaceable by consuming more water or lubricants. The submandibular, sublingual, and minor salivary glands provide mucinous saliva, associated with the resting sense of moisture and dry mouth symptoms." Further possibilities, they add, include gland repair or regenerative strategies with stem cells, acupuncture, or acupuncture-like stimulation.

■ CM Nutting, JP Morden, KJ Harrington et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* February 2011, 12:127–136

■ A Trotti, A Eisbruch. Reducing xerostomia through advanced technology. *ibid* pp 110–111

Cannabis improves cancer patients' appetites and sense of taste

➔ Annals of Oncology

The active ingredient of cannabis improved the appetite and sense of taste of patients with advanced cancer, but had no effect on their calorie intake, a US proof of principle study has found.

Loss of appetite is common among cancer patients, both due the cancer itself and to treatment affecting people's sense of taste and smell. As a result, they experience decreased enjoyment of food, which in turn can lead to weight loss, anorexia, reduced quality of life and decreased survival. For a long time health professionals thought nothing could be done and advised cancer patients to 'cope' with chemosensory problems by eating bland, cold and odourless food. More recently, however, the potential of delta-9-tetrahydrocannabinol (THC) – the main psychoactive ingredient in cannabis, which is thought to increase appetite via endocannabinoid receptors – has been recognised. Studies have shown that THC increases appetite in animals, healthy humans and patients with acquired immunodeficiency syndrome (AIDS), but its ability to have an effect in cancer patients has not been consistently reported.

In the current study – conducted in two Canadian cancer centres in Edmonton and Montreal – Wendy Wismer and colleagues from the University of Alberta (Edmonton, Canada) hypothesised that THC may favourably alter the chemosensory perception of cancer patients.

In the randomised placebo-controlled phase II double-blind pilot study, which took place between May 2006 and December 2008, 21 patients with advanced cancer (excluding brain cancers) who had been eating less as a result of their illness for two weeks or more, were randomised to receive THC (n=11) or to placebo (n=10). The active capsules contained 2.5 mg of THC, with patients asked to take them once a day for the first three days, then twice a day thereafter, with the option to increase the dose to a maximum of 20 mg a day. Treatment ran for 18 days. Questionnaires were conducted before, during and at the end of the trial.

From questionnaires, researchers found that 73% of THC-treated patients reported an increased overall appreciation of food compared with 30% of patients receiving placebo, and that 55% said that the medication "made food taste better", compared with 10% taking placebo (P=0.04). Half of the patients who reported odours to be unpleasant at baseline no longer found odours offensive with THC treatment (P= 0.083).

Although no difference was found in the total number of calories consumed by the two groups, the THC-treated patients tended to increase the proportion of protein they ate, and 55% reported that savoury foods tasted better, whereas no patients in the placebo group reported an increased liking for these foods. In addition, THC-treated patients reported better quality of sleep (P=0.025) and relaxation (P=0.045) in comparison the placebo group.

"Our pilot study demonstrates that THC, compared with placebo, improved and enhanced chemosensory perception, altered micronutrient preference, appeal of savory foods, appetite, relaxation, and quality of sleep for advanced cancer patients with chemosensory alterations," write the authors, adding that the data will assist in the development of larger phase II trials by facilitating sample size calculations.

Inevitably, they add, questions are raised about the ability to blind THC treatment based on

its well-known psychoactive characteristics. "However, the timed administration of low doses and the lack of differences in AEs [adverse events] between treatment groups suggest that this problem was likely minimal," write the authors.

■ TD Brisbois, IH deKock, SM Watanabe et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol* doi:10.1093/annonc/mdq727, published online 22 February 2011

Study shows occult metastases have little effect on outcome

➜ New England Journal of Medicine

No additional clinical benefit is obtained by evaluating women with breast cancer for occult metastases, a US study has concluded. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial found that the detection of occult metastases could not be regarded as a discriminatory predictor of cancer recurrence.

Clinicians have debated for some time whether breast cancer patients whose lymph nodes initially test negative for disease, but who have occult metastases (detected after further evaluation), are at greater risk of recurrence and might benefit from more aggressive treatment. The standard approach, endorsed by ASCO and the American College of Surgeons, is to slice sentinel nodes at 2.0-mm intervals and stain samples with haematoxylin and eosin (H&E). However, controversy continues over whether pathologists should be looking at more frequent intervals in order to find hidden cancers.

Donald Weaver and colleagues from the University of Vermont College of Medicine (Burlington, USA) undertook the B-32 trial in which 5611 women with no clinical evidence of metastatic disease in the armpit were randomly assigned to sentinel lymph node biopsy plus axillary dissection or sentinel lymph node biopsy alone.

In the current sub-study, the 3887 patients in whom metastases were not detected underwent further evaluation. Tissue blocks from the negative sentinel nodes were sent to a central laboratory for evaluation of additional sections that were 0.5–1.00 mm deeper in the block relative to the original surface. The deeper analysis included routine use of (H&E) testing and immunohistochemical staining.

Occult metastases were detected in 15.9% of the patients whose initial sentinel node biopsy tested negative for cancer. Isolated tumour cells (≤0.2 mm) accounted for 11.1% of the metastases followed by micrometastases (>0.2–≤2.0 mm, 4.4%), and macrometastases (>2.0 mm, 0.4%).

Log-rank tests indicated a significant decrease in overall survival (P=0.03); disease-free survival (P=0.02); and distant-disease-free interval (P=0.04) between patients in whom occult metastases were detected and patients in whom occult metastases were not detected.

However, the five-year Kaplan–Meier survival estimates for overall survival were 94.6% for patients in whom occult metastases were detected versus 95.8% for patients in whom occult metastases were not detected; for disease-free survival they were 86.4% versus 89.2%; and for distant-disease-free survival were 89.7% versus 92.5%.

The multivariable analysis identified several other factors that influenced outcomes: older age and larger primary tumour size adversely affected outcomes, whereas systemic chemotherapy, endocrine therapy and radiation therapy significantly improved outcomes.

Perhaps the most interesting interaction, say the authors, was with endocrine therapy, indicating that occult metastases are associated with oestrogen-receptor-positive tumours (considered a favourable prognostic factor) and that endocrine therapy markedly reduces the risk of a poor outcome.

"Occult metastases were an independent prognostic variable in patients with sentinel nodes that were negative on initial examination; however, the magnitude of the difference in outcome at five years was small (1.2 percentage points)," write the authors, adding that their findings argue against analysis of additional tissue levels or routine immunohistochemical analysis for sentinel-lymph-node evaluation.

One limitation of the study, they say, is that no analysis would be able to detect all the occult metastases.

Although the difference in survival between women with and without occult metastasis was small at five years' follow-up, the investigators believe the study "warrants continued follow-up and analysis".

■ DL Weaver, T Ashikaga, DN Krag et al. Effect of occult metastases on survival in node-negative breast cancer. *NEJM* 19 January 2011, 364:412–421

Corrections and clarifications

ISOPP's founders

In the cover story on Klaus Meier, published in the Jan-Feb issue, we reported that Meier founded the International Society of Oncology Pharmacy Practitioners (ISOPP).We would like to clarify that it was Helen McKinnon of New Zealand who came up with the idea of founding ISOPP in 1988, and she was elected ISOPP's first president in 1997. Meier was part of the board that initiated and developed the notion of ISOPP becoming an incorporated society in 1993, and he turned that notion into reality, setting up ISOPP as an incorporated society under German law in 1996.

Myriad's gene patents

It was a federal district court that overturned some of Myriad's BRCA patents in March last year, and not the Supreme Court, as was incorrectly reported in the article on Promoting genetic literacy, in the Jan-Feb issue of *Cancer World*. Myriad is now appealing the decision in a hearing that started on April 4th. It's chances of succeeding will have been dented by a re-evaluation of past policy conducted by the US Justice Department, which has filed a brief asking the appeal judges to uphold parts of the ruling that overturned several of Myriad's patents on the BRCA genes.

Cutting unnecessary deaths from cervical cancer

Collective effort aims to narrow eleven-fold gap between worst and best in Europe

Peter McIntyre

Given how preventable cervical cancer is, setting up robust screening programmes must feature as a key element in Europe's strategy for cutting deaths from cancer. But as this six country initiative is finding out, it takes time, resources and attention to detail. Sharing experiences and learning from the model Finnish screening programme has been key to making progress.

It is ten years since the European Union started to focus attention on fighting inequalities in cancer between countries, using the twin tools of comparison of data and solidarity between country programmes.

Perhaps nowhere has that inequality been shown more clearly than in cervical cancer, where incidence and mortality in some European countries are five times higher than those with the best organised screening programmes. This translates into tens of thousands of extra deaths of women across the whole of Europe, often women in middle age who are active economically and key family members.

What makes this tragedy the more unacceptable is that cervical cancer is in most cases preventable or curable. Despite the high profile that vaccines against HPV infection have achieved, the missing ingredients are the old-fashioned public health virtues that go to make up population-based screening. The gap is in planning, organisation, training and perhaps political commitment.

There is also lack of knowledge and a sense of distrust on the part of some women that inhibits them from going for check-ups.

The net result is that women are four times more likely to develop cervical cancer over the course of a lifetime in Estonia, Lithuania or Slovakia than in Finland, while in Lithuania and Romania they are eight to eleven times more likely to die from cervical cancer (Globocan 2008 data – see box, p 60).

The latest stage in a European programme aimed at fighting cancer inequalities, EUROCHIP 3, was launched by the European Commission in September 2008, with cervical cancer as a major focus.

The five countries officially included in efforts to transform screening systems are Bulgaria, Estonia, Latvia, Lithuania and Romania. They were chosen not simply because the figures were amongst the worst, but because teams of professionals were already beginning to address the problem, and there was something to build on. Poland, although not included in EUROCHIP 3, is working alongside these countries to improve its own figures.

Together, these countries constitute a base for testing current knowledge on how to implement and manage

A pilot screening programme in Cluj county Romania. *Left:* Women of all ages queue up beside the mobile screening unit in one of the county's 356 villages. *Below:* Local GPs were trained in carrying out smears and breast examinations as part of the pilot; some of them have now taken responsibility for this work, while others are still assisted by the mobile unit. Almost 80% of women in this region aged 25–64 years had never previously had a Pap test

screening programmes to achieve acceptable coverage and quality standards with medium or low levels of healthcare resources.

Developing effective screening

The key planks for screening programmes are that they invite women in a target age range (usually 30–59 years old) at regular intervals for high-quality Pap smears that are accurately read, and that they follow up women who do not attend or who have unusual smears, and ensure high-quality treatment. To ensure the Pap smears are of good quality and accurately read, screening programmes also require training for gynaecologists, general practice doctors (GPs), nurses and laboratory staff, as well as systematic monitoring and evaluation.

To close the gap in public awareness and promote atten-dance, public information and advocacy are needed. Some of the countries on this list do not even have a word for screening in their own languages.

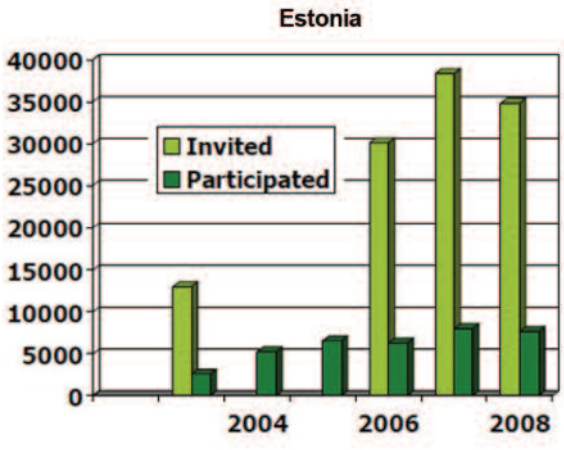
Leading this EUROCHIP work package is Ahti Anttila, who is the research director of the Finnish Mass Screening Registry, which has become the system by which the rest of the world judges itself. Finland was the first country to institute a screening programme, in 1962. No-one paid much attention until, in 1976, a paper in the *American Journal of Epidemiology* demonstrated that the incidence of cervical cancer was 80% lower amongst women who had been screened than in the rest of the female population.

Although, the main inequalities in cervical cancer are between 'old Europe' and the countries of central and eastern Europe, Anttila points out that there are also still inequalities within other countries that lack a screening programme. "There are big countries like Germany and Belgium where some of the target population is still missing. Some women have screening much too frequently, whereas there could be a proportion, let us say about 20% of the target population, who are underserved or never screened." It's clear that much more needs to be done to ensure European countries adhere to the current EU recommendations and guidelines on screening, he adds.

"Some women have screening much too frequently, whereas some are underserved or never screened"

Women wanted a personal letter inviting them to screening and to be able to phone for an appointment

ATTENDANCE IS STILL A PROBLEM



EUROCHIP's Estonian participants have been exploring why attendance rates for cervical cancer screening remain at low levels despite the number of invitations going up

Source: Department of Epidemiology and Biostatistics, National Institute for Health Development, Tallinn, Estonia

Estonia

With a population of 1.34 million, Estonia is the smallest country in the EUROCHIP group, and it was one of the first to get a screening programme up and running, with nationwide screening for women aged 30–59 starting in 2006. Estonia was motivated by a disturbing trend that saw the incidence of cervical cancer double in the 30- to 49-years age group between the early 1980s and 2000–2006.

Pap smears are taken by trained midwives at 19 clinics around the country. However, despite efforts to organise the system, take-up has been disappointing, with only 15% of women attending. Meanwhile about 50% of the target group of women have had private smear tests outside the screening programme. Anttila points out that, due to the absence of a screening registry, it has not been possible to check on the quality of these smears or what follow-up treatment women have been offered.

Epidemiologist Piret Veerus, from the National Institute for Health Development in Tallinn, has overseen a study to find out why women do not attend.

She found that women wanted a personal written letter inviting them to screening and to be able to phone for an appointment at a time that suited them. Information levels were high amongst the Estonian majority, but fewer than half of the Russian minority even knew that a screening programme existed.

Veerus would like to see a health education programme in schools to alert young women to the risks of early sex and multiple partners, but says they also have to do more to convince older women to attend. "According to the experience from other countries, we know that only the tests that have been given during organised screening with a proper follow-up of good quality will decrease the numbers of women who are diagnosed with cancer."

Latvia

Latvia had a 'compulsory' system of gynaecological examination in the 1980s, but the incidence of cervical cancer rose once this was abandoned in 1989. Cancer rates are especially high in the rural population and a third of the women who are diagnosed have stage III or IV disease. A quarter of women die within a year of diagnosis.

An opportunistic screening programme was launched in 2005, and a full screening programme in 2009, but so far only a quarter of the women who are invited attend.

Only 1 GP in 50 provides gynaecological care for their patients, and a survey in 2003 suggested that three-quarters of girls and women aged 15–49 did not trust their GPs to do so.

Ilze Viberga, a gynaecologist at Riga

Three-quarters of girls and women aged 15–49 did not trust their GPs to provide gynaecological care

Stradins University, says that this has to change if the Latvian programme is to succeed, and she is currently conducting a study of doctors' knowledge and attitudes.

"The general practitioner is not very interested in this screening programme, because they think it is the job of gynaecologists, and the gynaecologists expect more from the general practitioners," she says, adding, "We have to change this philosophy so that women can go to a general practitioner, because it does not matter who is going to take this test. Taking a smear does not need specialist skills; it is just simple training. If the result is not good, then the gynaecologist has to be involved in the treatment process."

Lithuania

In Lithuania, where screening started in 2004, the response has been a little better, but still less than half of women (44%) attended the first round of screening, with the lowest returns in rural areas. Ruta Kurtinaitiene, a gynaecologist at Vilnius University, says there is a need for a centralised system of call and recall, with a personalised letter to every woman.

"I think we have a problem with lack of knowledge and a psychological barrier. I think a woman is scared to come to a gynaecologist. She does not understand that you need a Pap smear every three years even if you do not have any disorders or problems with gynaecology. Our early study shows that if you send a private letter to the woman, the attendance rates double."

Research conducted by her colleague Jolita Rimiene for her doctoral dissertation indicated a need for better training in how to do a Pap smear. She found that 5%–12% of Pap smears were evaluated as 'inappropriate content' or 'inadequate' for cytological evaluation, and that up to half the cells collected from the patient never get onto the slide and are discarded with the test instrument.

Quality control. Jolita Rimiene demonstrated the need for better training in Lithuania, as up to 12% of Pap smears were too poor to be evaluated

Bulgaria

With a population of 7.6 million people, Bulgaria is as big as Estonia, Latvia and Lithuania put together, and with a larger population, screening becomes even more of a challenge. The old Bulgaria had a strong tradition of prophylactic health checks, but no organised screening programme, and when the country began to suffer economic hardship in the 1980s and 1990s, even this fell apart. Until the late 1980s cervical cancer mortality rates were comparable with many EU countries, but incidence doubled between 1984 and 2004 for women aged 30–49, and the mortality rates rose 2.5 times.

In May 2009, a national Campaign for the Early Detection of Cancer was approved, under which a million women would be reached with information and 200,000 women tested throughout the country in 2012. However, the economic crisis has stalled moves towards a truly national programme.

Yulia Panayotova, from the Bulgarian Health Psychology Research Centre, says there is still a lack of political commitment, but she is optimistic that a national programme may begin in two to three years. This early detection programme includes 'STOP and GO for a Check-up', designed to improve infrastructure, increase capacity and prepare society for population-based screening programmes for cervical, breast and colorectal cancers. Improving capacity will include establishing a screening registry and a call-recall system.

Panayotova still feels some frustration at the delays. "Every day a woman is dying from cervical cancer in our country. It is obvious that the best way is to have an organised programme. There are many people who are taking it seriously but unfortunately we still don't have a programme, which means that the policy makers are not taking it seriously enough."

Romania

Romania has the highest death rate from cervical cancer in the whole of Europe. In 2006, the crude mortality rate was 20.9 per 100,000 women.

Florian Nicula, Head of Epidemiology at the I Chiricuta Oncological Institute in Cluj-Napoca, received the Pearl of Wisdom award, along with his colleagues, for a regional pilot screening programme in Transylvania. This saw screening coverage increase from less than 1% to 20% in Cluj county, and similar improvements in another five districts.

This programme has produced a 'proven in Romania' model that can be introduced into the rest of the country.

His team rang to say that they would have to stay overnight in the village, because the queues were so long

In particular, it has demonstrated that women in rural areas – always the most difficult to reach – do indeed want high-quality screening.

Nicula recalls how he sent out a mobile team to a village in a local rural area where staff visited women community leaders, convincing them to back the screening initiative. These women agreed to encourage the women in the community to attend a mobile screening unit, and took a lead by being the first to attend. Later in the day he took a phone call from his team to say that they would have to stay overnight in the village, because the queues were so long outside the van.

Even so, the 20% success rate is still far too low says Nicula. "The women responded very well, but we couldn't invite all the women we should, because of logistical and financial problems. The national programme was supposed to start last year as a roll out of the regional pilot programme, but because of the resources crisis we had to delay the start."

A report on Romania produced for the European Cervical Cancer Association points to a lack of political will. "The project has made good progress in raising the political priority of cervical cancer prevention in Romania… However, the majority of politicians still do not understand the complexity of the programmes required to achieve good results nor the resources that must be committed to the implementation of these programmes."

Building on this regional success, Romania has appointed the Cluj team as the National Management Unit with responsibility to coordinate 21 county units across the country and responsible for quality control for the entire programme.

Daniela Coza, epidemiologist at the I Chiricuta Oncological Institute, says that this needs to be a national priority. "It is a huge problem for Romania, as we have the highest number of new cases and mortality in Europe and one of the highest in the world. It affects women of active ages and women in middle- and lower-income groups. We have been struggling with this matter for a long time. Romania has to do something for the most at-risk women."

Poland

Taking action alongside EUROCHIP is Poland, which with its population of 38.1 million aims to screen 3 million women a year. However, even after three years, the National Cervical Cancer Screening Programme attracts only a quarter of the women who are invited.

Arkadiusz Chil, from the Kielce Oncology Centre, says, "Every year, cervical cancer is diagnosed in 4000 women in Poland and half of them die because of it. These numbers speak for themselves, which is why we set up our cervical cancer programme. The real problem is that cervical cancer is diagnosed too late in advanced stages."

Magdalena Bielska-Lasota from the Independent Unit of Oncological Education, at the Maria Skłodowska-Curie Institute of Oncology in Poland, says that Polish women lack confidence in the system. "The programme is organised very well from an administrative point of view and it is supposed to work, but the failure of the screening is that we have a very low attendance.

"There are a few reasons in my opinion. One is that there is a crisis with trust in the system and trusting the doctors. Women are scared because they may have an examination which does not have good quality assurance and may give false-negative or false-positive results. My message to women is to press our government and the doctors to keep the quality to the levels set by the European guidelines."

There has been a big effort to train doctors, midwives and nurses. By 2010, 7900 professionals had been trained, as well as 1284 'opinion leaders' who, it is hoped, will convince women to attend.

Lack of faith in the system is not just a problem for Poland, but a common theme in these countries. EUROCHIP, in collaboration with the European School of Oncology, organised media training for key staff in each country to help specialists become more comfortable in developing and delivering key messages through the media.

HPV vaccination

The complicating factors for countries trying to set up screening services now are the HPV vaccines which hold out such promise for the next generation, but also have the potential to demobilise efforts for improving existing screening services. The cost of the vaccines in the first few years of their availability has also been a constraint in the new member states, where resources are particularly stretched.

If given to girls before sexual activity begins, they have the potential to

Going for a check-up. This mobile unit covers the villages of Swietokrzyskie province in Poland, providing both breast and cervical cancer screening. The system is well organised but more work needs to be done on building awareness and trust, in order to improve take-up rates

dramatically reduce the incidence of HPV and therefore cervical cancer.

One problem is that it is unlikely that the benefits will start to be felt for 15–20 years, and the full population-wide impact would take 50 years or more. Implementing an HPV vaccination programme is no substitute for organising an effective screening system. The vaccine is of little value to the population of women who have already become sexually active, as it cannot eradicate the virus where it is already present, or stem the growth of an incipient cancer. And despite very impressive results in clinical trials, they have not yet proven themselves in country programmes.

Romania decided to provide the vaccines free for girls aged 11 years old, and started a school-based campaign of vaccination. But the European Cervical Cancer Association reported that the take up was as low as 4% – well below even the worst screening programme results.

Florian Nicula accepts that the vaccine could in theory prevent almost all the cervical cancers if it reached enough girls at the right age. In practice, however, in Romania they have been left with stockpiles of the vaccine, which they are now trying to use through a new information campaign. "The parents did not agree to their daughters having the vaccine," he said. There is clearly a need to investigate the public health aspects of the HPV vaccines; including which implementation models would be best for a high coverage and acceptance.

Arkadiusz Chil from Poland sees the vaccine as a distraction from the main challenge. "The vaccine is not an alternative to cytology. We cannot fight cancer without regular cytological examination and that must be clearly stated."

It takes time to get it right

There are no short cuts to establishing effective screening programmes, says Ahti Anttila – careful planning and attention to detail are important at every stage.

"Even in small country, it takes about two years to plan everything, taking into account the current activities in healthcare and how the screening could be integrated. One cannot go directly to full national screening in a short time because it is so complicated to get all the parts of the chain into the right order."

The bigger the country, the greater the challenge. Romania, has a target population of 6 million women, and even if they were only invited for screening every five years, that means 1.2 million invitations a year, probably resulting in a million screening tests and 30,000 colposcopies [an investigative diagnostic procedure usually performed where abnormalities have been revealed by the smear test]. Staff have to be trained at every step of the way, expanding from

"My message to women is to press our government and the doctors to keep to the European quality guidelines"

In Romania they have been left with stockpiles of the vaccine, which they are now trying to use

pilot areas, so that they in turn become reference centres to coordinate training and organisational activity in other regions. "For small countries like Estonia, Latvia and Lithuania one could do everything in 5–10 years. For a large country like Romania it could be even more than 10 years."

Anttila points out that even in Finland they still do monitoring and evaluation. "The Finnish programme started in 1962 and has continued for almost 50 years, but every year we still collect data. The cancer burden is extremely low when screening works well, but this systematic monitoring and learning has to be part of it." The Finns are also proactively studying potential new methods for cervical cancer prevention, such as HPV screening or HPV vaccinations.

With the EUROCHIP work package due to conclude at the end of 2011, the organisers are to ask the European Commission for more time to address screening problems, which would allow time for Bulgaria and Romania to further develop their pilot schemes. Andrea Micheli, leader of EUROCHIP from the Italian Istituto Nazionale Tumori in Milan, believes the work constitutes a vital step towards reducing cancer inequalities across Europe and so reducing the overall burden of cancer.

Anttila says they should not step back now. "We do not yet have screening programmes of high quality. We cannot say we have them, and it has not been adequately resolved. I don't think the EU would want to give up.

"All these countries have made a start and need to consider what more to do. Then, political commitment will come, as we've seen happen in countries like England, and everything will work very effectively. Maybe it takes even more than 10 years, but I think the information that EUROCHIP has shared in the countries and scientific communities takes us one step further."

Screening is a major focus of the recently launched European Partnership for Action Against Cancer, he adds, which reinforces the political will to make progress on this front at the highest political level of the Union.

Micheli also believes that the data and experiences being provided by these countries is like gold dust. "The most precious element we had in EUROCHIP was the availability of data to allow comparisons amongst all the countries of Europe. Through solidarity and networking, countries are now sharing experiences on best practice and developing screening programmes at lower cost than if they were tackling this alone."

MORE ON CERVICAL CANCER AND EUROCHIP

- Further details about the state of cervical cancer screening in the countries covered by the EUROCHIP cervical cancer programme can be found in: F Nicula et al. (2009) Challenges in starting organised screening programmes for cervical cancer in the new member states of the European Union. *Eur J Cancer* 45:2679–2684
- Articles on the cervical cancer status of each EUROCHIP country can also be found on the *Tumori* website at http://www.tumorionline.it/index.php?archivio=yes&vol_id=516
- The huge gap in cervical cancer incidence and mortality between the original 10 EU member states and the 15 that joined later was first documented by Marc Arbyn and colleagues in 2007, using data from 2004 (*Ann Oncol* 18:1708-1715; available in full online at http://annonc.oxfordjournals.org/content/18/10/1708.full)
- Updated incidence and mortality figures, from 2008, were published last year: J Ferlay et al. Globocan 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. International Agency for Research on Cancer (2010). http://globocan.iarc.fr
- Progress in the EUROCHIP 3 work on cervical cancer can be found at http://www.tumori.net/eurochip/wp.php?page=4

"It takes time because it is so complicated to get all the parts of the chain into the right order"