Eric Van Cutsem:

closing in on GI tumours

Marc Beishon

Eric Van Cutsem has been at the forefront of developing new molecular therapies for gastrointestinal cancers, but he's not relying on finding that magic bullet. He advocates a many-fronted attack, combining genetic counselling with screening and specialist multidisciplinary care, and he believes that specialist GI oncology units, like his centre in Leuven, are the way to deliver that strategy.

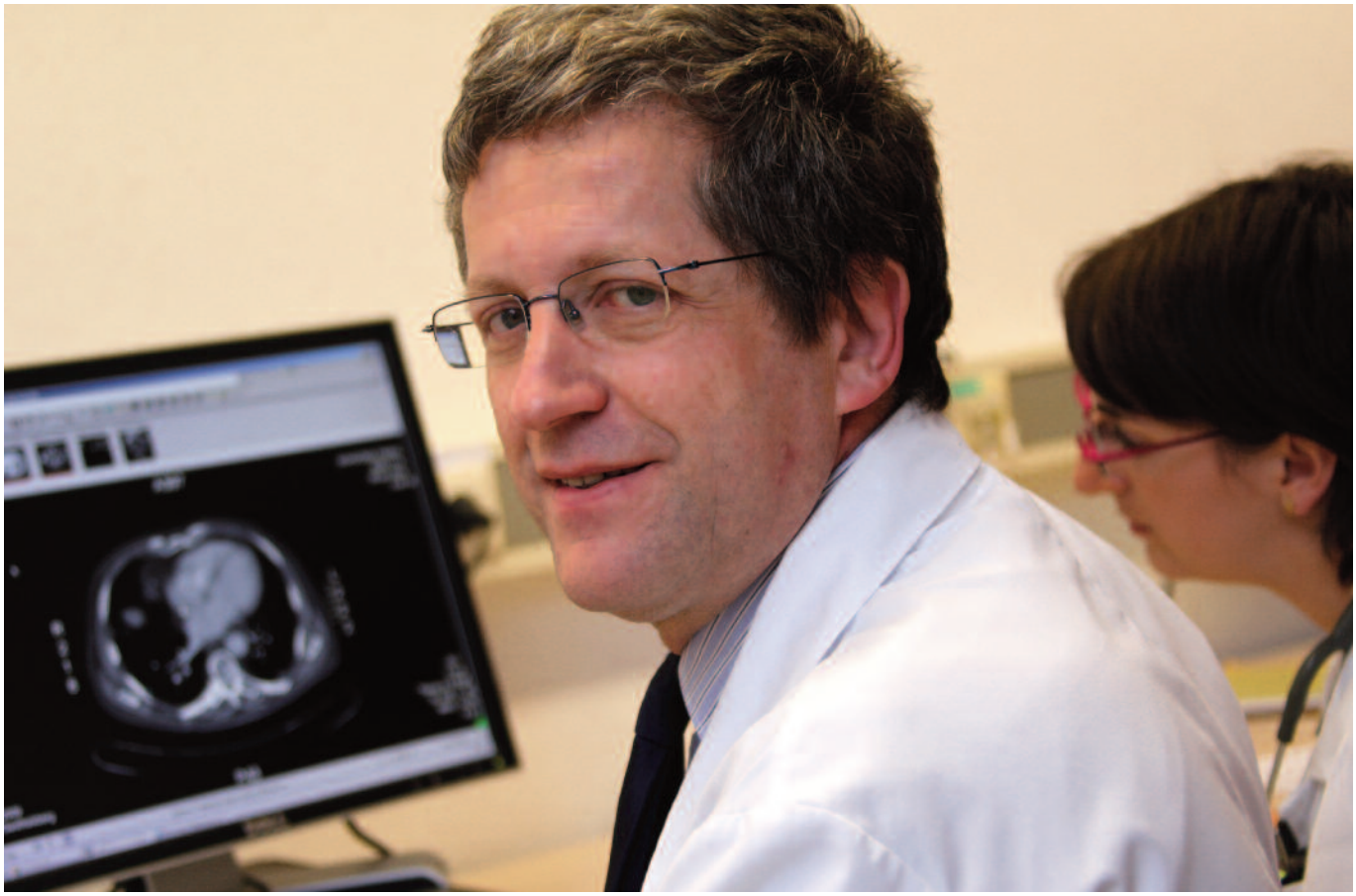
Looking ahead to the end of an already distinguished career, gastrointestinal (GI) oncologist Eric Van Cutsem can see two possibilities. "After I retire we could eventually see a new definition of colorectal cancer – a rare disease that occurs only in unscreened populations. Or failing that ideal, I do expect substantial progress in targeted therapies for advanced colon cancers. I am sure we will see a shift from merely prolonging survival to curing certain groups, well before I retire."

Whatever is going to cut the burden of this big killer – and all the other less frequent diseases of the GI tract – Van Cutsem can lay claim to one of the earliest and most well-known multidisciplinary GI centres in the world. He heads the digestive oncology unit at the University Hospital Gasthuisberg in Leuven, Belgium, and is also a professor of internal medicine. He has spent the last 15 years building the profile of GI oncology and developing and pushing a young team involved in patient care and an array of research projects.

"When we started on a specialist structure for GI and also for other organ-specific tumours, we were certainly one of the European leaders in integrating clinical and research activity around the needs of patients," he says. "In GI today, we have everything from familial heredity advice to leading a regional screening programme, and from the latest functional imaging techniques using PET and MRI to all the new molecular agents, plus also specialist surgeons and radiation oncologists. Multidisciplinary care has been crucial for our organisation and care programme. You just can't have that sort of breadth in general medical oncology practice."

There are close parallels between developments in colorectal cancer and breast cancer in terms of advances in genetic understanding, surgical advances and application of new cytotoxic and molecular agents. But breast has outstripped GI in the development of many specialist units with true multidisciplinary expertise. As Van Cutsem says, "A unit is only as strong as its weakest link."

While certified GI oncology centres may be some way off – but a definite aim – he is promoting the development of integrated expertise in a punishing schedule around the world. Not only is he one of the founders of the World Congress on Gastrointestinal



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Cancer – the leading conference in this field – he is also channelling his expertise into the GI activities of the major cancer societies, an increasing number of specialist groups and an endless round of educational and committee meetings that means he's working most weekends – as well as often from 8.00 in the morning to midnight during the week.

GI oncology covers one of the most complex groupings of tumours, everything from the upper oesophagus to the anus plus the pancreas, liver and other organs. This makes it particularly challenging. "Of course we have people specialising in aspects of GI oncology in various ways around the world. But there are common links. It covers all aspects, from endoscopy and gastroenterology to a detailed knowledge of tumour biology. It makes sense to group them together for training purposes, in particular. Postgraduates and fellows need to see the entire picture before they themselves specialise."

While all aspects of GI oncology are in his remit at Leuven, Van Cutsem is known internationally for cutting-edge research in targeted treatments. Early experience of trial work with new cytotoxic agents in the 1990s paved the way for the addition of drugs such as cetuximab (Erbitux), bevacizumab (Avastin) and now trastuzumab (Herceptin) in both advanced disease and adjuvant settings, and he is a regular top platform and plenary speaker. Notably, at last year's ASCO (American Society of Clinical Oncology) conference, he made a case for testing colorectal patients for a gene mutation (KRAS), and this year his work with a group studying the application of trastuzumab to gastric (stomach) cancer was again one of the most widely mentioned of the ASCO presentations.

"Well, this year's ASCO was at first glance not what I call a 'premier cru' year, but if you look more carefully some excellent progress was reported. We are seeing a lot more about the molecular pathways that can lead to more personalised

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care. Certainly, a good example is the trastuzumab study – the one I presented on how we may be able to start to personalise treatment for gastric cancer – and the other that caught my attention was not in my field but in breast cancer, where there is a new class of targeted agent aimed at so-called triple-negative disease."

The GI congress in Barcelona followed shortly after ASCO, and is the event where both science and practice are explored in depth, according to Van Cutsem. "Since Mario Dicato and I started it in 1999, the strength of the congress has been its multidisciplinary nature, and it became a joint venture with ESMO (European Society for Medical Oncology) in 2004, but we also partner with a range of other bodies such as the European School of Oncology, the European Oncology Nursing Society and now Europacolon, the advocacy organisation. Our focus is educational and about translating science into practice."

The ESMO/World GI congress this year brought in 3,500 people – more than last year. "Attendance at many meetings was down this year – maybe it was swine flu or the recession – but we saw an increase," says Van Cutsem. "I do think it is the quality of our programme and the interaction between education and science – I ask people what we can improve and usually don't get an answer."

He is clearly very proud of the congress and highly motivated by the educational side of his work. But the fact that GI oncology has only relatively recently benefited from major international meetings, and now also some specialist societies, shows how long this major cancer group had been in fairly slow motion. The way in for Van Cutsem to be at the forefront of most of the key developments was to look for opportunities to develop oncology from within gastroenterology. The problem-solving, hard-work ethic he was imbued with during his upbringing also played a role.

"I grew up in a scientific environment. My father was a drug development researcher in industry and worked with Paul Janssen, founder of Janssen Pharmaceutica, which has four drugs in the WHO list of essential medicines," he says. "I had many hours of discussion with them as a student, and was left in no doubt that you need a good character and hard work to succeed." Given that Paul Janssen has – posthumously – been awarded the title of 'most important Belgian scientist' by a science magazine, it is no surprise that he is one of Van Cutsem's key influences.

Choosing medicine for the usual reasons of combining human interest with scientific research, Van Cutsem went into internal medicine and gastroenterology, having preferred the complexity and greater human interaction over more mechanical subjects such as cardiology, and he also had no thought of moving into lucrative private practice. In fact, bar some spells abroad during training, he has spent both his student years and his entire career so far at Leuven, thanks to the continuing opportunities that have opened up in this small but prestigious university city – medicine at Leuven, he notes, is generally ranked among the elite in Europe, up with Cambridge and Oxford in the UK and Karolinska in Stockholm.

"I did general gastroenterology for the first few years – my head of department then was known as the 'pope of the oesophagus' for motility work [work on swallowing disorders], and I did a PhD on electrical activity in the stomach with Jozef Janssens, one of my mentors and dean of the faculty of medicine at Leuven. But I was already interested in oncology, and as we were already a big gastroenterology centre there was room for me to move to focus exclusively on cancer, very quickly."

Becoming clinical head of digestive oncology within gastroenterology in 1994, Van Cutsem set about populating the unit with the multidisciplinary input that has put it among Europe's leaders in both treatment and research. An early initiative was starting to advise people on hereditary risk

factors for colorectal cancer – and today he is chairman of the Belgian familial adenomatous polyposis association. Trial work then moved to the new cytotoxic agents, oxaliplatin (Eloxatin) and irinotecan (Campto), and to early work with targeted agents, especially bevacizumab, cetuximab and panitumumab (Vectibix). "We have led and taken part in many pivotal studies here – our advantages are integration with preclinical research at the university, the knowledge and ability to collaborate and the reputation of Leuven as a centre."

Morphologic imaging, functional imaging and preclinical work in GI cancer have also developed, at varying speeds, and more research is now being done on topics in radiation oncology and surgery. But Van Cutsem emphasises as one of the key features of GI oncology at Leuven that it has developed alongside other gastroenterology specialisms – inflammatory bowel diseases, motility and hepatology – and outpatients are triaged into the right group. Two other organ-based groups follow the same model at Leuven, namely pulmonary and gynaecological specialisms.

Van Cutsem considers that the advantages of developing oncology in this way are considerable, with the best of both worlds – of a large teaching hospital and a dedicated cancer centre, converging around the organ and the patient.

As a gastroenterologist himself, Van Cutsem also carries out endoscopies, so is well equipped to follow patients through the journey from diagnosis to end-of-life care. "I can remove polyps during colonoscopies, but I do not of course carry out any real surgery." But taking a step forward – to population-based screening for colorectal cancer – could prevent many people entering this journey in the first place, and indeed screening is a major research and implementation interest for him. The questions are: how far we can realistically take this proven intervention and in what ways?

"I'm currently leading the screening programme in the Flemish part of Belgium, where we are first

Visitors. Van Cutsem and his wife Anne showing colleagues Arnaud and Gillian Roth and Josep and Anna Tabernero around the beautiful university city of Leuven

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carrying out a pilot in the Antwerp area. It is based on the occult stool test that looks for blood – and if we find it we will then do a colonoscopy. But we are also doing some science by testing abnormal cells that come from polyps and cancers – working with a company that provides such a test and integrating it into the clinical setting." The pilot will also try to cover first-degree relatives of people with colorectal cancer. The French-speaking part of Belgium, meanwhile, is proceeding with a programme based on a different blood stool test (guaiac-based).

The challenge of population screening, he adds, is to generate high levels of participation and develop an effective structure and organisation. There is broad consensus on the age range to include in screening – from age 50 to 75, which follows European Union recommendations, although the UK is a notable exception in targeting only the higher-risk group of 60- to 69-year olds in its programme. "You can make a more dramatic impact in cutting incidence if you screen everyone by colonoscopy between 50 and 60, and repeat after 10 years," says Van Cutsem, noting that people with a clean colon at age 50–55 are at low risk of developing cancer in later years.

But getting people to take part in colorectal screening is difficult. In Germany, Van Cutsem mentions that in one area where an insurance company offered a colonoscopy – which requires unpleasant preparation – uptake is only about 5%–10%. Take-up rates of faecal occult blood test are higher in some countries and health systems, but this test can only reduce mortality, not incidence. "Realistically, in Belgium we estimate we can cut mortality by 15%–20% – not enough maybe, but with deaths from colorectal cancer of up to 4,000 a year at present, that will be a major achievement."

It would be a major achievement too across Europe, but wearing his various European 'hats', and having had discussions with the European Health Commissioner, Van Cutsem notes that healthcare systems across the continent are too fragmented and the EU has no power to impose evidence-based screening on Member States. Currently, only 12 countries in the EU are running or establishing population-based screening programmes for colorectal cancer, and the EC has reported that Europe needs "to intensify and double cancer screening".

And this autumn the EC is launching the European Partnership for Action against Cancer, with the hugely ambitious aim of achieving "100% population coverage for screening for breast, cervical and colorectal cancer", as well as developing a more coordinated approach to cancer-related research across the EU. Given the autonomy of national health systems, Van Cutsem feels the screening aim will be a very long way off, and he adds that the goal of uniting research efforts can only be realised by the often-discussed idea of a European cancer institute.

"America's National Cancer Institute [NCI] is not the Holy Grail and I'm not in favour of centralising everything, but a European equivalent really is the least we should we aiming for. What is dangerous for now is that we just have too many small and underpowered trials running in several countries on key questions such as the value of different targeted therapies in first-line treatment, or even just on issues such as oral versus intravenous drugs."

The European Organisation for the Research and Treatment of Cancer (EORTC), for which Van Cutsem has chaired the GI group, could provide a

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A family man at work. Giving a speech at the University offices, with wife Anne and daughters Céline and Inès

research framework for Europe, he comments, but it lacks the funding and also the power to tackle bureaucracy. "Its international trial work has been too slow, but criticism is rather unfair as it receives no central funding from the EU, relying instead on industry, legacies and ironically some money from the NCI."

Much of the effort he would like to see accelerated relates, naturally enough, to the work he is known for in personalised medicine and translational research. With the dismal outlook for metastatic colorectal patients, he has been among the first to investigate the addition to standard cytotoxic regimens or single-use of the monoclonal antibodies cetuximab and also panitumumab, which targets the EGFR (epidermal growth factor receptor), commonly expressed in colorectal cancer.

The KRAS story – which is still in its early stages – is one of the key current translational research questions, as once it was understood that the status of the KRAS gene is critical to the action of these antibodies, initial patient selection is now possible, and the search is on to unravel the 'downstream' pathways that could further refine who will benefit most. Van Cutsem's forte is conducting trials that lead on, and validate, the actions of new agents, such as in the CRYSTAL study (cetuximab combined with irinotecan in first-line therapy for metastatic colorectal cancer).

"What we now know is that 40% of patients have a mutated KRAS gene and will not benefit from the antibody – it is only the 'wild type' or normal KRAS patients who will benefit, but then not all of them, which is why KRAS is just the beginning and we are looking at downstream factors such as BRAF and PI3K mutations and ligand expression, which have been identified in small studies. We have to validate these markers in larger trials."

Although the effect of new agents is still modest, there is clearly enough evidence now to recommend that neither cetuximab nor panitumumab should be given to patients with the mutated KRAS gene, says Van Cutsem. In Europe, these drugs are only approved for use in patients with EGFR-expressing KRAS wild-type (non-mutated) metastatic colorectal cancer. "The test is very cheap

"Generally, we have been a good 10 years behind colorectal in looking at gastric tumours"

compared with the drug cost, and I consider the CRYSTAL trial and related work as one of my major achievements. But we're already moving on – shifting the trial paradigm from retrospective analysis, which was the important first step in personalisation, to integrating prospective trial data in the future."

Van Cutsem expects that following the full gene sequencing of colorectal cancer, it will be found to comprise several distinct subtypes. Certainly, the KRAS 'on/off' status is already spawning a lot of research for effective drugs, with many in the phase I pipeline (including possible inhibitors for the mutated version). Europe, he adds, is playing a leading role in such translational research, as groups there "tend to take a more pragmatic approach and there is less emphasis on basic science."

Other research he highlights is on anti-angiogenesis, using bevacizumab, where the gains are also modest, and there has been a big recent disappointment of a US trial that failed to reach statistical significance. "But again we are looking for markers that are predictive for Avastin, and we have here one of the leading researchers, Peter Carmeliet, who also works at Leuven. The work is quite advanced and we have some new results to present this autumn." (See also *Cancer World* July–August 2009 for an article on the outlook for angiogenesis, page 60, and also a summary of Van Cutsem's CRYSTAL trial, page 47).

Work on the most common tumour, colorectal, is much more advanced than most of the GI cancers, but Van Cutsem made the ASCO headlines again this year with a study, ToGA, on gastric cancer and trastuzumab. Gastric cancer causes the second highest number of global cancer deaths after lung cancer, and new approaches for advanced disease are badly needed.

"This is joint work led by my team, a group in Korea and Roche, the drug maker. Generally, we have been a good 10 years behind colorectal in looking at gastric tumours, although the higher incidence in Asia means there has been more interest there. But I'm sure it will evolve in a similar way." The HER2 receptor was found to be positive in 22% of tumours from patients with advanced gastric cancer in the ToGA trial, a similar level to breast cancer, leading to a relevant prolongation of survival when adding trastuzumab to standard chemotherapy.

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Van Cutsem also highlights the increasing role of functional imaging using PET and MRI to look at factors such as blood flow, drug response and the composition of tumours. Hurdles to integrate them into clinical practice are high, he comments, but with several PET scanners at Leuven alone, there is a good deal of research in train. He also emphasises advances in removing liver metastases that would have been inoperable before, in patients receiving chemotherapy plus targeted agents.

In the absence of a pan-European strategy, various initiatives are emerging

to help plug networking gaps in GI oncology, and Van Cutsem has some involvement with most of them. One is PETACC (Pan-European Trials in Adjuvant Colon Cancer), which he says is having 'moderate success' in conducting some large trials with partners such as the EORTC and the national groups. PETACC-8, for example, is looking at cetuximab to reduce relapse after stage III cancer. "But there is no central funding and we have to start again with each project – we have not yet been as successful as the Breast International Group [BIG]."

Other initiatives include the European Neuro-Endocrine Tumour Society (ENETS), which covers a rare group of cancers in which Van Cutsem has a special interest, and the European Union Network of Excellence for Gastric Cancers, which held its first meeting last year .

He is also the medical director of Europacolon, a colorectal advocacy organisation founded in 2004, which he says is starting to make some headway, but is limited by a lack of staff and funds. "I also feel that advocacy bodies generally should focus on all aspects of prevention, treatment and care, and not only prioritise access to drugs, as they then become targets for drug companies to try and influence healthcare decisions."

If Van Cutsem remains frustrated by slow pan-European progress, he is encouraged by recent moves in his home country, although it is only catching up with others. "Not only have we recently recognised medical oncology as a specialty, as well as specific oncologic competencies, but we now have a cancer plan that has developed from a White Paper I helped to draw up with others. Already, we have a small federal cancer institute and €15 million released for translational research, some of which we are benefiting from at Leuven. Another early success of the plan is funding psychosocial support for cancer patients around our hospitals – this was previously an unmet need and, where it was available, was paid for out of other budgets."

Looking to the global effort, Van Cutsem says that while there are still some enduring differences in opinion and guidelines about treating GI cancers, there is growing consensus. "There are still differences in adjuvant treatment for gastric tumours and on the chemotherapy for metastatic gastric cancers among Europe, Asia and the US. Europe has shifted to preoperative chemoradiotherapy in rectal cancer, and the US is now also following this approach. In the adjuvant treatment of pancreatic cancer, the standard in Europe is six months of chemotherapy, whereas in the US it is often chemo- plus radiotherapy, but that's based on weak evidence. The use of intravenous over oral drug delivery is also a difference."

With science and treatment, as in all the many activities across the spectrum of GI oncology, Van Cutsem says he tries to be a 'consensus figure' in helping colleagues to reach decisions. "But it can be difficult sometimes. We have to fight for quality in the face of political influence, including at European level."

There are no concrete plans yet for the European institute that would help, he notes, but there is no doubt he will be at the centre of the discussions with colleagues from ESMO, ECCO, EORTC and other organisations. The European Commission is, however, about to ask for proposals for a European Research Area network (ERA-Net) for translational cancer research in Europe.

The consensus at home is that any free time is spent with his three daughters and his wife Anne, a psychologist who counsels and registers patients with hereditary colon cancer – "my main source of energy, inspiration and support". This can be a tough call with the demands for his professional input. The belief that cancer research – as in most walks of life – is largely perspiration, with added inspiration, is deeply ingrained.

But Van Cutsem never doubts that we will see an inspiring combination of screening, multidisciplinary care and research, real team work and targeted agents, playing out in new cures for certain patients, more people suitable for surgery and a much higher profile for GI oncology.

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