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## Pulling together

the case for prostate cancer units

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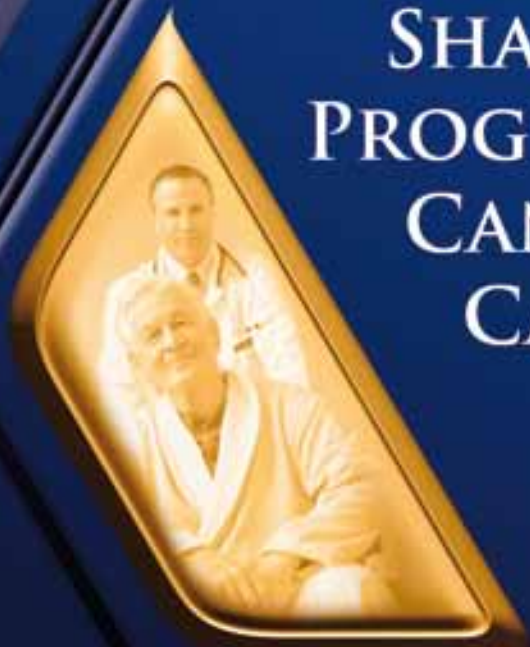
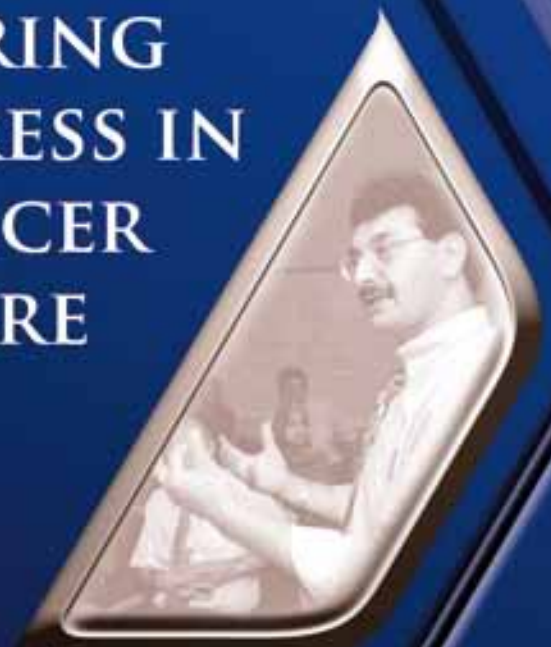
European School of Oncology

Learning to care

# Sharing Progress in Cancer Care





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# Personalising treatments: lessons from history

Stephan Tanneberger, Guest editor

Stephan Tanneberger was Director of the Central Institute of Cancer Research of the Academy of Sciences of the German Democratic Republic from 1974 until 1990. He spent much of his later career with the Bologna-based Associazione Nazionale Tumori, developing their local and international work supporting home-based palliative care services.
*h.s.tanneberger@gmx.de*

Fifty years ago, when I was just starting out in cancer medicine, our team at the cancer centre attached to Berlin's Academy of Sciences began our attempts to individualise chemotherapy treatments. We knew that response to different drugs varied enormously between patients, so we invented the 'oncobiogram' to try to select, in advance, the best treatment for each one. Modelled on the 'antibiogram' for selecting antibiotics, we cultivated biopsies (cell culture/organ culture), which we then treated with the different drugs *in vitro*. We evaluated the efficacy of this selection procedure in clinical trials, and the results were encouraging.

Less encouraging was what we learnt about the extreme heterogeneity of tumours in space and time. Our collection of more than a thousand of these cultures of human tumours showed individuality with respect to detailed histology, mitotic index, DNA synthesis, drug sensitivity and more. In a programme that spanned ten years, we realised then that the existence of a single 'cancer state-specific cell defect' is nothing more than a scientific illusion.

'Personalised' or 'precision' medicine is often seen as a purely 21st century concept that is just in its infancy. A better understanding of the historic context could help inform more realistic expectations about what it will be able to deliver.

The annual rate of publications on cancer chemotherapy doubled between 1997 and 2014, alongside an expansion in expensive new anticancer drugs. But the reported results do not show convincing clinical progress. Given the biological diversity and continuing evolution of tumours, it is perhaps not surprising that patients cannot be cured using a single targeted therapy. Even today's sophisticated technologies still give us only a snapshot of the dynamic carcinogenic process.

Cancer is an error of cell division induced by avoidable carcinogens or unavoidable body aging. It is an inherent part of our biology. Targeted treatment remains a concept continually pursued, rather than realised, and realistically speaking, we may never see a definitive breakthrough.

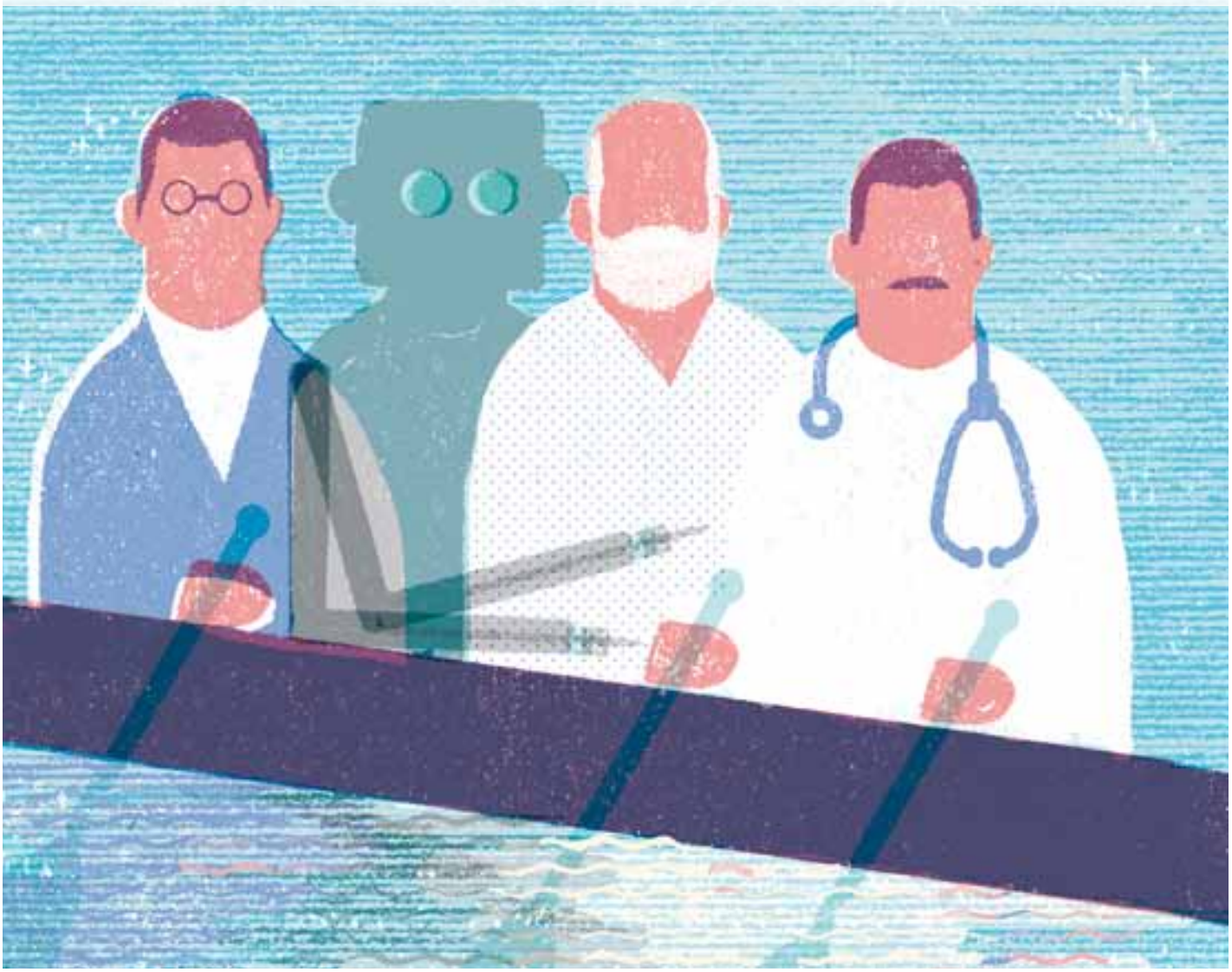
Yes, the immune system is intriguing and a new generation of immune checkpoint inhibitors hold interesting potential. However, it has not evolved to eliminate tumours, but rather to control 'minimal deviations' of cell division at the start of carcinogenesis. There are other interesting approaches that also need to be explored, and in a time of great dreams of cancer therapeutics, we should not forget cancer prevention.

Oncology does need personalised medicine. But a renewed focus on the patient, their needs and feelings, must be central to that personalisation. Our patients, many of whom are old, may have other needs more important than access to highly sophisticated drugs.

My plea, particularly to the new generation of colleagues, is: when you look at someone's tumour to understand its driver mutations, don't forget to also look in their eyes, understand the person, and 'personalise' that human being in the room with you. This we call *eubiosia* – a 'good life', a human right for all, including those of us suffering from cancer.

# Pulling together: the case for prostate cancer units

People with cancer need their care managed by a team of specialists who work together and learn and improve together. **Simon Crompton** reports on efforts to achieve such a collaborative approach in delivering prostate cancer care.



There are few easy decisions in prostate cancer. Many men's experience of diagnosis, treatment and beyond is characterised by lack of clarity about the best management options, worry about potentially life-changing side effects, and enduring uncertainty about prognosis. A 2014 review in *BMJ Open Oncology* found that anxiety reached clinical levels in more than one in four men on diagnosis, one in seven during treatment, and more than one in six after treatment.

But it wasn't like that for Jobst Plog, a 74-year-old retired director of a broadcasting company, who has little bad to say about his cancer journey while at the Martini Clinic in Hamburg, Germany. Before having a nerve-sparing radical prostatectomy, he was advised about options, offered his choice of treating physician and treatments, and was then given the opportunity to attend a pre-treatment multidisciplinary conference.

"Physicians and the entire staff at the clinic work as a team, using their range of experience and specialisations in an organised process," he says.

A diagnosis of prostate cancer brings choices, which take careful explanation because each option is based on uncertainty and involves a complex risk–benefit analysis. Treatments such as surgery and radiotherapy may bring a greater likelihood of cure, but they produce hugely varied side effects from patient to patient. Some men are left with life-changing complications such as incontinence and impotence.

Around two in ten men have long-term urinary incontinence following prostatectomy, but the likelihood varies according to age, physical fitness, surgical technique and where the surgery is conducted. The Martini Clinic, for example, claims its database shows that more than nine in ten of its patients are fully continent after treatment, compared to a German average of between five and six in every ten (Harvard Business Case Collection 2014, case 714-471).

Less aggressive approaches such as active surveillance, which rely on careful monitoring, reduce the risk of side effects and overtreatment – but leave the risk of cancers growing and becoming harder to treat.

Whichever way you look at it, patients can often be left with an anxiety-inducing gamble. Finding the right option for them requires clear understanding and impartial expert advice from the sum of the professionals involved in their care – not just a single urologist or radiation oncologist. And it was the multidisciplinary pooling of expertise at the Martini Clinic that helped Plog weigh the pros and cons, and left him confident he was doing the right thing.

**Finding the right option requires impartial expert advice from all the professionals involved**

He was told about the treatment options and also provided with detailed printed information. And he was involved in all the joint decision-making about the type of treatment he should receive.

"There were no surprises during my treatment because I was well informed and prepared," he says.

## Specialist, multidisciplinary, audited units

What distinguishes the Martini Clinic, and 96 other centres in Germany, from the vast majority of units treating cancer in Europe is that they are certified prostate cancer units – centres characterised by specialisation, multidisciplinary collaboration and independent audit.

It is a model that a range of opinion leaders, led by the European School of Oncology and Europa Uomo – a coalition of prostate cancer patients' groups – see as the future of prostate cancer care in Europe. Its over-riding principle is that no surgeon, radiation oncologist or other professional should treat prostate cancer unless they specialise in it, and no single professional should be directing treatment on their own. The patient should be informed, involved and supported.

It is the logical way to go, according to Riccardo Valdagni, Director of the Radiation Oncology 1 and the Prostate Cancer Programme at Milan's Istituto Nazionale Tumori and also coordinator of ESO's Prostate Cancer Programme.

"If we look at the experience with breast cancer, it is clear that our evolution will be towards a system of certified and accredited prostate cancer units," he says. "That means independent bodies checking the quality of services."

As Valdagni suggests, the idea of the prostate cancer unit hasn't come out of the blue. A similar model has been promoted – and gradually implemented – for breast cancer care across Europe. Responding to evidence of widely varying survival rates, two European Parliament resolutions in 2003 and 2006, and declarations on the fight against breast cancer in 2010 and 2015, called on member

Exploring all the options. Patients seen by the Prostate Cancer Unit at Milan's Istituto Nazionale Tumori have an initial consultation with the full range of specialists, including a urologist, radiation oncologist, medical oncologist, psychologist and nurse

states to ensure that all women in the European Union have access to treatment in specialist breast units, certified according to quality criteria set down by the European Society of Breast Cancer Specialists.

There is evidence that five-year survival is around 18% higher among women treated in a specialist breast unit (*BMJ* 2012, 344:1e9). Indeed, research in breast and other cancers shows that such specialist multidisciplinary centres produce the highest treatment success rates and best patient experience. High concentrations of specialists and a high volume of patients develop skills and quality. And multidisciplinary care brings quicker treatment, better individualised care and support, and better adherence to evidence-based guidelines.

## The case for prostate cancer units

Multidisciplinary specialist management has become widely accepted as the best means to optimise experience and outcomes for patients for many years. But the argument to have it at the heart of prostate cancer care is particularly strong.

Here, the 'best' means of diagnosing and treating localised disease can attract intense debate: the benefits and drawbacks of different diagnostic tests; the relative merits of surgery, brachytherapy, radiotherapy and surgery; the right time for active surveillance and watchful waiting; the role and timing of new drugs. All need to be carefully balanced to meet each individual's needs and priorities.

Multidisciplinary prostate cancer units provide a structure where urologists, radiation oncologists, medical oncologists and psychologists specialising in prostate cancer collaborate to decide the best treatment and care options.

Germany has been encouraging cancer centres with this specialist multidisciplinary approach since 2003.

## Requirements for a European Prostate Cancer Unit

A multiprofessional task force of internationally recognised opinion leaders, representatives of European scientific societies and patient advocates gathered to set criteria and standards for prostate cancer units. The result, published as a position paper in *Critical Reviews in Haematology & Oncology* last year, describes the relevant, feasible and applicable core criteria for defining prostate cancer units, and represented a consensus on 40 mandatory and recommended standards and items, including the following:

**European Prostate Cancer Units**

- are structures, with on-site interdisciplinary and multiprofessional teams and infrastructures, that are able to provide interdisciplinary and multiprofessional curative and supportive care for patients from newly diagnosed through to follow-up, rehabilitation and care of patients with advanced disease
- must manage a minimum volume of patients (set at 100 patients/year for the unit, 50 radical prostatectomies/year for surgeons, 50 radical or adjuvant treatments for radiation oncologists and a patient load of 50 for medical oncologists)
- need not be a geographically single entity, but patients must be managed and followed up under the guidance of a single interdisciplinary and multiprofessional team, for all immediate and deferred treatments and observational protocols (active surveillance, watchful waiting)
- should be allowed to network and outsource services, including adjuvant and palliative therapies as well as psychological support, to entities formally collaborating with the prostate cancer unit, to complete the path of care.

**Education and research**

- Prostate cancer units should provide interdisciplinary and multiprofessional continuous education on all aspects of prostate cancer care, including research.
- They should actively aim to enrol patients in clinical trials and research.

**Guidelines/protocols**

- Evidence-based written guidelines used for diagnosis and management of prostate cancer at all stages should be clearly identified.
- Protocols should be agreed by the core team members; new protocols and protocol amendments should be discussed in the core team.

**Documentation and audit**

- A minimum set of variables should be recorded electronically in a database: diagnosis, pathology, surgical treatments, radiotherapy, brachytherapy, adjuvant treatments, observational strategies, palliative treatments, clinical outcomes and follow up, including side effects and complications.
- Data must be available for audit.
- Minimum outcomes for mandatory quality indicators should be achieved.
- Performance and audit figures must be produced yearly and set alongside defined quality objectives and outcome measures.
- Internal audit meetings should be held at least twice a year to review quality indicators and amend protocols as necessary.

*The full list of standards and requirements can be seen in* Critical Reviews in Haematology & Oncology *vol 95, pp 133–143.*

It has done it through a system of certification administered by Deutsche Krebsgesellschaft, the German Cancer Society – first for breast cancer, then for colorectal cancer and then, in 2008, for prostate cancer. By 2014, one-third of all prostate cancer patients in Germany were treated at a certified prostate cancer centre.

Each centre needs to fulfil a catalogue of requirements and publish quality indicators to receive certification. The requirements were developed by a commission of experts from professions and disciplines specialising in prostate cancer and German patient advocacy groups. They were taken into account when ESO's Prostate Cancer Units Initiative in Europe developed 40 new standards for prostate cancer units, which were published last year in *Critical Reviews in Haematology & Oncology* (see box).

The German framework, then, is providing inspiration for the new European evolution of prostate

cancer treatment. But what insights does it provide into the experience and effectiveness of specialist, multidisciplinary units?

An analysis of the German Cancer Society's 2014 annual report of 92 urology departments certified as prostate cancer centres shows that all treat more than 100 primary cases of prostate cancer each year: throughput is an important quality indicator. The number of radical prostatectomies has decreased over time, indicating that approaches aiming to minimise overtreatment are increasingly valued.

Between 2010 and 2013, the proportion of patients on active surveillance increased more than six-fold, from 2.5% to more than 16%. And the proportion of patients receiving psycho-oncologic care more than doubled, from 8% to 17%.

"We defined our measures to reflect quality," says Simone Wesselmann, head of the certification department of the German Cancer Society. "An auditor from the independent OnkoZert institute visits each centre, examines processes there, speaks to all the people involved and discusses the results of the quality indicators. This gives you a means of judging."

**It is this constant measurement and reporting that most distinguishes prostate cancer centres**

Certification, she says, is all about transparency for the patient – making quality of care visible, and providing a basis for national and international comparison. The main criterion for comparing centres will never be length of survival, says Wesselmann, even if it were possible to measure.

"That's not the aim of certification,"she says. "If you want to gain the trust of the patient, you must be able to say that within this year, this doctor achieved these high-quality standards.

"You cannot say that if one patient dies after 13 years and another dies after 15 then the difference is down to the quality of their surgery, or the care they received. For certified centres that would be a superficial measure. We want to be trusted by the patient – to be able to tell him that we know what this doctor did last year, that he's had so many re-sections for a particular operation, or so many critical events."

These are the things that matter for patients, says Wesselman. "It's about being totally transparent."

No one claims that the German system is perfect. Wesselmann acknowledges that patients' own reports of outcomes for different therapies could be included in the indicators: the German Cancer Society is investigating this as part of a new study into the patient experience, which will be funded by the men's health charity Movember. And a recent paper in *Der Urologe* reviewing the 2014 report of German prostate cancer centres noted that data about potency and continence following all treatments was lacking.

Patient groups have, however, been a driving force behind certification of German prostate cancer centres, and representatives do believe that the patient experience is improving as a result of certification.

Günter Feick, chairman of the German prostate cancer patients' organisation Bundesverbandes Prostatakrebs Selbsthilfe, is also a member of the certification commission for German prostate cancer centres. He says that around a quarter of the total number of hospitals treating prostate cancer in Germany are now certified. The important differences between the certified and non-certified centres, says Feick, lie in management systems, structural requirements, audit, and collaboration with prostate cancer patient groups.

"The multidisciplinary organisation is very important to us," he says. "The patient always has the oncologist, the urologist, the radiation oncologist, the pathologist, the psychological team, the social management team all together as one organisational unit, all following a certain path of treatment and communication together, in a procedural flow described in the requirements.

"It's important that, three years after their initial certification, centres are visited by an independent team of experts, including a patient representative, to see on-site whether what they are doing still fulfils the initial requirement.

"Each of the centres is required to be in cooperation with a prostate cancer patient support group. Because of this, not only are we part of the certification process, but we also have representatives within the centres.

"Patient representatives are also involved in the annual audit. So this is a system where the patient has maximum influence, where the patient is treated in a structure, process and reporting system which you find in no other clinical organisation."

It is this constant measurement and reporting that most distinguishes prostate cancer centres from the rest, according to those involved with the

## "What's measured improves"

The German Cancer Society certifies prostate cancer units on the basis of their performance, on a wide range of indicators, including the following measures of interdisciplinary collaboration:

- Case presentation in pre-treatment conference — through urology (primary cases)
- Case presentation in pre-treatment conference — through radiotherapy (primary cases)
- Participation of core disciplines in post-therapy conferences — urology (diagnostic + surgical)
- Participation of core disciplines in post-therapy conferences — radiotherapy
- Participation of core disciplines in post-therapy conferences — urologist or medical oncologist
- Participation of core disciplines in post-therapy conferences — pathology
- Presentation at post-therapy conference — primary cases
- Presentation at post-therapy conference — all patients with initial manifestation of a recurrence and/or distant metastasis
- Psycho-oncologic care (at least 30 minutes) (primary cases)
- Social service counselling (primary cases)
- Participation in research study

The full list includes indicators of interdisciplinary collaboration, specialism and adherence to clinical guidelines.

German certification system. Once you do that, how good (or bad) you are becomes transparent – and the force to improve becomes irresistible. As Feick says: "What's measured improves."

This amounts to much more than the vague commitment to involving and informing patients that might come from non-certified centres, he says. The certification requirement that patients should be present, if they wish, at the pre- and post-treatment conferences with the entire multidisciplinary team, makes decision-making without patient involvement virtually impossible.

The German Cancer Society's report of indicators from all prostate cancer centres shows that 98% of patients who initially presented to a urologist attended a pre-treatment conference in 2013.

## The challenge of change

Specialist centres where men with prostate cancer are managed through a multidisciplinary team have been established in some countries besides Germany, and some are now applying the ESO criteria. Their experiences are pointing to some of the challenges, as well as some of the opportunities, that come with introducing prostate cancer units.

In the Netherlands, for example, the official ending of national health insurance in 2006 enabled insurance companies to centralise treatments in specialised centres to increase efficacy and quality. The Prostate Centre at the Erasmus Medical Centre in Rotterdam started in October 2010, and is the first organised multidisciplinary prostate cancer unit in the Netherlands.

There is as yet no authoritative evidence that abiding by the requirements outlined in the ESO initiative (*Crit Rev Haematol Oncol* 95:133–143) improves patient experience or outcomes, says Chris Bangma, Professor and Chairman at the Department of Urology at the Erasmus Medical Centre. "Of course, our questionnaires show we have high patient satisfaction," he says. "We also know that we are reducing unnecessary biopsy by 30% because of risk-reducing protocols agreed between specialists. It's the result of close collaboration and agreed procedures. But there is as yet is no comparable data to show that it is better."

What is clear, says Bangma, is that setting up a truly multidisciplinary expert system is no minor undertaking. Re-organising structures, funding, working methods and professional

hierarchies, takes time. For some professionals, it involves letting go.

"It's all about creating trust," says Bangma. "Some people think they're working towards something, other people want their income or salaries or patients or whatever. That is what you have to avoid."

Elsewhere, there have been concerns that traditional urology structures in some countries are a barrier to the multidisciplinary outlook of prostate cancer units. Last year, the long-serving Secretary General of the European Association of Urology (EAU), Per Anders Abrahamsson, told *Cancer World* that urologists – traditionally surgeons – could no longer work independently of other specialists in the cancer field and had to work as part of multidisciplinary teams. He expressed EAU support for the concept of prostate cancer units.

**Re-organising structures, funding, working methods and professional hierarchies takes time**

## Investing in nurses

But the concept of true multi-disciplinary working, with skilled and specialist nurses at the heart of clinical care, is still a challenge to some, according to Lawrence Drudge-Coates, a urological oncology nurse specialist at King's Hospital London and Chair of the European Association of Urology Nurses.

"If prostate cancer units are to be a reality throughout Europe," he says, "there has to be a recognition from urologists that there needs to be investment in specialist urology nurses – and an agreed skill mix where nurses are not just part of a support team, but actively, clinically involved in patient care. It's about a change of attitude, realising that nurses have to be engaged on an equal level."

In the UK, specially trained urology nurse specialists form part of a multidisciplinary urology cancer team, and see all newly diagnosed patients. This is a mandatory requirement, laid down by the standard-setting National Institute for Health and Care Excellence (NICE). The NICE requirements, concentrating prostate-specialist professions, means that the UK effectively has a system of prostate cancer units.

For the patient, says Drudge-Coates, there are enormous benefits. "In the UK model, nurses are pivotal in ensuring continuity in patient care, from the point of referral when prostate cancer is first suspected, and then all along that patient pathway. They have more contact with the patient than any other individual in the team, and have the skills to tackle many aspects of patient care, patient questions, follow-up, and also providing key clinical input."

Research conducted at King's College Hospital found that a nurse-led assessment clinic for suspected cases of prostate cancer cut waiting times to further tests from eight to four days. And nine out of 10 men said they were very satisfied at having nurses involved at this early point of contact, saying they gained a clear understanding of the diagnosis process.

However, there are huge variations in nursing skills, status and autonomy in Europe. In some countries, such as the UK, Ireland, Scandinavian countries and the Netherlands, specialist nurses have clinical autonomy and work alongside urologists. In others, their clinical input is virtually zero. In the absence of any European directives for standards in urological cancers – as there have been for breast cancer – it is hard to see nurse specialists in urological cancers becoming widely available, says Drudge-Coates.

"Prostate cancer units may be able to function without them, but in those countries that don't have nurses working at that level, you have to ask what can we can do to raise skill levels so that centres can call themselves prostate cancer centres."

In setting down its 40 requirements for prostate cancer units, ESO's Prostate Cancer Units Initiative in Europe acknowledged the need to set standards at an "attainable medium level" to make them applicable across Europe.

The prostate cancer unit skill mix requirements specify, as part of the core team, "one or more nurses dedicated to or specialised in urology", where "dedicated to" is defined as devoting at least 75% of their working time to genito-urological oncology. Among their specified roles, they are required to be available at clinics for people who are newly diagnosed, "to provide additional information and support as required". Candidates for accreditation as Prostate Cancer Units will therefore have to show their nurses have the knowledge and skills to fulfil that role.

## Making it happen

The example of breast units in Europe, though inspiring for prostate cancer, is not necessarily encouraging. The target set by the European Parliament was that all

women in Europe should have access to a specialist breast centre by the year 2016. But according to Europa Donna, the European breast cancer patients coalition, that was instrumental in gaining EU guidelines on specialist breast units, progress has been slow. And the need to improve breast cancer services through specialist units has not been accepted by all stakeholders.

"There are still many countries where no breast units exist that in any way conform to the guidelines and there is a risk that there are now entities calling themselves breast units without meeting many of the standards outlined in the guidelines," said Susan Knox, Europa Donna Chief Executive Officer, in an article in *Breast* last year.

She told *Cancer World*: "We continue to advocate for the implementation of specialist breast units across Europe. We are now working on highlighting the need for specialist breast unit implementation at the upcoming European Breast Cancer Conference, where a survey will be presented indicating the status of implementation today and a manifesto addressing this issue will be released."

The next steps for the Prostate Cancer Unit Initiative in Europe, then, look to be deliberate ones. Gathering support for the concept, gaining wide agreement for the quality indicators, and establishing an independent accrediting body won't happen overnight.

"Putting together the actors could take a while," says the Chair of the Prostate Cancer Unit at Milan's Istituto Nazionale Tumori, Riccardo Valdagni. "But we understand the process and the nature of our evolution is that, if people support the idea of multidisciplinary working, the rational way to go will be someone independent accrediting prostate cancer units."

The prostate patients' coalition Europa Uomo, which has supported ESO's European prostate cancer unit initiative from the start, now sees the main challenge as inequalities in Europe. "We absolutely support prostate cancer units as the gold standard," says current chairman Ken Mastris.

"From the patient point of view, the current experience is that the professional you first see is the person who controls your treatment. And in some countries the urologist is still regarded as God. It's important that we break down that kind of barrier to a multidisciplinary approach. At the same time, you have to recognise that the gold standard may not be easily achievable for the next five to ten years."

**"In some countries the urologist is still God. We need to break that barrier to a multidisciplinary approach"**

Following the example of breast cancer, Mastris believes that EU guidelines for prostate cancer services are essential. Europa Uomo's Call to Action on prostate cancer across Europe, published in 2013, called for prostate cancer care to be coordinated and managed by a multiprofessional team within a certified centre or network of excellence. Europa Uomo sent a copy to every Member of the European Parliament, asking for support. So far, the response has been thin.

"We want to see the issue addressed more in the European Parliament," says Mastris. "The priority should be: don't treat the cancer but treat the patient. We need more personalised medicine, more communication, patients being guided through their journey – before, through and after treatment. Communication between professionals is so important for that."

## Prostate Cancer Units Network

In January 2016, ESO and the patient advocacy coalition Europa Uomo launched a new network designed to help those centres working on the prostate cancer unit model share information and spread understanding. The objective is to gather a European consensus about the need for prostate cancer units, and then build an international system to accredit them. More information about its aims and how to join can be found at www.prostatecancerunits.org.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# Is this the end for the microscope?

New generations of precision digital scanners are threatening to replace the tool that has been the iconic symbol of pathology for so long. **Maria Delaney** reports.

Glass slides containing tissues and cells are sitting in piles on a shelf in the pathology lab. They wait here until the consultant picks up a stack and carries them to a microscope for analysis. An analogue system in a digital world.

Well that's how Michael McKenna sees it. He is clinical lead for pathology services in Altnagelvin Hospital, Northern Ireland, and wants to move their system from slides to screens. "We want to report off the screen because this makes it more efficient and productive," says McKenna, who is currently trying to find a mechanism to scan slides and report them through their existing picture archiving and communication (PAC) system.

There are a number of pathology labs in Europe that have already gone digital. LabPON, a large pathology lab in the Netherlands, is one such early adopter. Linköping Hospital in central Sweden is another.

Three years ago all of the histology samples at Linköping were digitised, and they now scan just under 200,000 slides every year. Instead of looking at slides through a microscope, Arrigo Capitanio, consultant pathologist at the hospital, analyses scans of the slides on a high-resolution screen.

He notes that many fields have improved with digitisation and feels that the same is true for pathology. "A trainee in radiology can't imagine that all the instruments they are currently using didn't exist just 30 years ago," he says.

Linköping has six slide scanners: four for clinical slides, one for large histological sections, and one dedicated to research. They run day and night to allow almost real-time scanning. A variety of suppliers are involved, including Hamamatsu and Aperio for the scanners, as well as SECTRA for the digital platform/viewer.

One of the biggest benefits to working digitally, says Capitanio, is that he can "ask a colleague in New York by email or Skype to look at the slide and discuss the case". This means pathologists can get much greater access to expert opinion without having to delay their report.

## Pathologists can get much greater access to expert opinion without having to delay their report

Without a scanner, obtaining a second opinion takes much longer. First you write an email or letter to the relevant colleague, then you post the slides. Capitanio remembers hoping that the slides would not be broken


when they arrived. Other hazards include the slide being delayed *en-route* or sometimes disappearing on its return journey. "It's quite a big difference," he says.

At Altnagelvin Hospital, the PACS system for radiology was implemented as part of a huge project that involved two datacentres and 27 hospitals across Northern Ireland (NI). Known as NIPACS, and using a platform developed by SECTRA, the system not only digitised radiology requests and consultations within each hospital, but also linked all the hospitals within the system. Brendan Devlin, radiologist at Altnagelvin, was one of the driving forces behind its implementation.

Shortly after getting the system, Devlin remembers sitting at his desk and receiving a message from his colleague in a hospital 100 kilometres away. "He was asking me to give a second opinion on a CT liver and since the message is automatically linked to the examination, within a few minutes I was able to send a message back." Before NIPACS this type of request would have taken days or weeks, says Devlin. "It's all to do with speed, efficiency and quality."

Devlin, who now also works with SECTRA to promote digital platforms, believes that "all medical images should be treated with the same robust storage and sharing facilities," and says NIPACS can offer that. As he points out, pathology is just one area producing images. Others include medical photography, diabetic retinopathy, dermatology, cardiology, and ultrasound.

## Closer scrutiny

When pathology joins radiology on NIPACS in Altnagelvin, Devlin feels it will be the quality of scrutiny the report receives at the multidisciplinary team meeting where the real impact will be felt. "It revolutionises them in terms of an effective discussion of the patient's case," he says, because, if all the images are available, the team gets the opportunity to interrogate and confront.

Devlin himself likes to be challenged and forced to justify what he's written, which he sees as a matter of quality assurance. "It's not just a question of reading my report," he says.

This has certainly been the experience at the LabPON pathology labs in the Netherlands, according

Maria Delaney

Brendan Devlin at his workstation in Altnagelvin

## NIPACS: a national virtual department

One of the largest RIS/PACS (radiology information system/picture archive and communication system) projects ever undertaken worldwide was conducted in Northern Ireland, where 27 hospitals were connected by a system called NIPACS.

Provided by SECTRA, this digital platform caters for more than 1.4 million patient examinations a year. All radiology images captured in the participating hospitals are stored in a central archive in Belfast.

The vision of NIPACS includes a virtual radiology department across Northern Ireland, full availability of images and reports, a system to revolutionise dispersed networked care and minimisation of training issues and clinical risk.

The assignment of a unique "Health & Care" number to every individual in Northern Ireland was a key factor supporting its implementation, says Brendan Devlin, former lead radiologist of NIPACS. "Robust identification is the cornerstone of these integrated systems because you can't afford to put the wrong images in the wrong place," he says, pointing in particular to the huge medico-legal implications.

The NIPACS service was launched in 2009 after many years' preparation. The new technology costs £31mn (€40mn) over 10 years.

to Alexi Baidoshvili, pathologist and project director of the digital pathology team. Multidisciplinary team meetings, he says, work much better when digital files are used. Other advantages he lists include faster consultation, the ability to compare a number of slides, a cleaner work environment, and better logistics.

Notable by its absence from that list, however, is the quality of the images themselves, which Baidoshvili argues is not quite as good as microscopy. "It's always a choice," he says, arguing that the marginally poorer quality is more than compensated for by the improvements in the diagnosis process and logistics. The problem will be solved in the near future, he says, as "scanners become better every year."

Capitanio denies there is a problem at all. The important point is to be able to recognise the subject, he says. He uses George Clooney and Naomi Campbell as examples, asking whether it is easier to recognise them in person or by looking at a photo.

The tissues and the changes present in the histological preparation can be recognised perfectly in a good-quality scan, he says. "In other words: it is diagnostic."

## Making the change

Implementing major change to complex procedures rarely goes smoothly, particularly when IT systems are involved. Capitanio, in Sweden, says the main problem in his lab was the transition from the microscope to the computer for the pathologists. "Some simply don't want to do it."

The turning point for many came when they experimented with the digital system. "Colleagues who were sceptical at the beginning now work very well digitally, and some also became quite enthusiastic," he says, though he adds that some are sticking with the "glasses" (glass slides).

This works in Linköping, as the pathologists receive both the digital and glass slides for analysis, which Capitanio says is needed, because in around 3% of digital slides the scan is not perfectly in focus, despite the quality control. "Rather than send everything back, I look at the microscope, because there is a turnaround time to respect," he says.

At his hospital, the change to digital also required a major reorganisation of the whole histology lab to standardise the method of production needed to produce high-quality scanned images. Some of the practical problems Linköping encountered were coverslip precision, drying of the slides before scanning and, for smaller histology blocks, correct positioning of the section on the slide.

McKenna in Northern Ireland says he does not expect such a major reorganisation will be needed at the Altnagelvin pathology lab, because it already functions in a very linear fashion, so it should be simple to add a scanning step at the end of their current method. The lab is also based in a new building within the hospital, which has space for new machines. When it was originally designed, the pathologist explains, "they already knew that technology was advancing and a lot of the things that we normally did manually would be replaced by technology platforms, which tend to have quite a substantial footprint compared to a human."

McKenna points to a corner of the lab where the slides are currently stacked, to show where he intends to locate the machines he will need. But he recognises that not all labs have been built with new technology in mind, and this could pose a problem. "Some labs will need to invest in infrastructure if their building is too small," he says, in which case, "it's not just about procuring a piece of equipment, it's also about knocking down a wall or building an extension."

Getting to grips with the requirements of digital technology can also be a bit of a learning curve, according Baidoshvili, who says they have had to change the server at LabPON three times since the system went live last July. "Every time we use more scanners, or more pathologists start with digital diagnosis, the server becomes slow," he says.

Currently they use four scanners, as well as two backup scanners, and process 300,000 slides per year. They are using the Philips Digital Pathology Solution for both their scanners and digital platform/viewer.

The changes in working practices also brought new work-related health hazards, with some pathologists developing repetitive strain injury – inflammation in the arm and shoulder – from spending all day moving images around with a mouse.


Scrutiny: The ability to share images across the Internet, compare different slides, and magnify particular areas – as Alexi Baidoshvili from LabPON in the Netherlands is pictured doing here – all contribute to raising the quality of discussion at multidisciplinary team meetings

Baidoshvili notes that using a microscope all day is also known to cause problems, but he didn't want to create new problems with digitisation. Working in partnership with Philips, they created additional user interfaces, such as a touchpad, and Baidoshvili

**"Colleagues who were sceptical at the beginning now work very well digitally, and some became quite enthusiastic"**

says that he now protects himself from RSI by alternating between devices over the course of a day and also using both hands.

Devlin recognises the problem and says ergonomics was also an important issue in the Northern Ireland project. He sits at a work station that can tilt and be raised or lowered to suit him, and he uses an ergonomic multi-button mouse to control the PACS and minimise use of the keyboard.

"You're not uncomfortable, you're not distracted," says Devlin. His own work station is in a dark room with wall panels to muffle sound. A number of work stations are also housed in a communal reporting room for easier communication with colleagues and to facilitate second opinions. "It's all part of better quality," he says.

As far as McKenna is concerned, the switch to digital can't come fast enough. He is looking forward, above all, to moving from Vernier scales on a microscope to clicking a mouse. Measurement is really "tiresome and cumbersome" at the moment, he explains. "With a digital image, the ruler is there and you just pull it from point to point." This is not only easier, he says, but also improves accuracy and enables pathologists to leave a record of the measurement.


## A resource for research

In addition to the clinical applications of digital pathology, slides are currently being scanned for research purposes. The European Organisation for Research and Treatment of Cancer (EORTC) has a number of projects which are doing just that.

Pathology review for the INNOVATION trial (http://tinyurl.com/eortc-innovation), includes scoring tumour regression after neoadjuvant treatment of HER-2 positive, resectable gastric cancer. This will be done using scanned slides which will be viewable by the review panel members via the Internet.

The EVIDENCE trial (http://tinyurl.com/eortc-evidence) will scan the slides for quantitative, digital assessment to calculate the percentage of residual viable tumour cells at the site of the primary lesion in early-stage non-small-cell lung cancer.

The EORTC is also planning to set up a digital platform for review of scanned slides as part of their new Screening Patients for Efficient Clinical Trial Access (SPECTA) programme. Edit Szepessy, a translational researcher at the EORTC, says this will be particularly valuable for their thoracic and rare cancers projects: SPECTAlung and SPECTArare.

## Digital futures

Digital pathology in Linköping and LabPON is only for histology to date. As Capitanio explains, this is because the tissue or tumour section lies on the glass, so single-level scanning with a focus depth of about one micron is enough for this type of specimen.

Cytology samples, by contrast, are made up of cells from fluids such as urine or sputum, or from the abdominal cavity or around the lungs. Micro-focusing is needed to analyse these cells, which involves changing the focus level, second by second, to see different levels in the slides. "To do this digitally, it is necessary to scan several levels and then to use software to see all these levels," says Capitanio. This consumes a lot of time and data, so it cannot be used for routine diagnosis with current technology.

Cytology samples are, however, already being scanned at Linköping for the purposes of teaching, documentation and research. A number of companies are working on new types of scanners that can do this automatically.

Arguments for cost saving with digitisation mainly involve process improvements for the pathologists, rather than reducing workload in the lab. In fact scanning is an extra step on top of the normal slide-making process. This is in contrast to radiology, which can remove the film-making process and associated costs when moving to digital images.

One cost saving that falls outside of the norm is storage. "You don't have to store the glass slide because, if you scan the image, the image is stored for as long as legally required," says McKenna. This means the glass slide could be disposed of after a shorter period of time.

This saves money, as the cost to store the glass slides "is increasing every day," according to Capitanio, whereas digital storage costs are reducing. In his previous job at University College London Hospitals, costs for storage were so high that the slides were sent on a lorry to Wales.

There are many arguments and lines of thought about the future of pathology, but why should labs move from microscopes to screens? Capitanio has a simple answer. "Why not? We're in the digital era."

For Baidoshvili, the question is already out of date. His focus is on where digital pathology is going next. His first goal is to become completely digital, including cytology, he says. When that is accomplished, the plan is to focus on image analysis, which Baidoshvili says is the future of pathology.

He is collaborating with other labs in the Netherlands, as well academic hospitals and Philips, to create software to use in their daily diagnostics. This will make their work much faster and more accurate, according to the digital enthusiast.

Back in Northern Ireland, McKenna sits back at his desk with a microscope on one side and a computer on the other. Glass slides in position and ruler in hand, he turns to the analogue machine. Perhaps not for much longer.


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# Ana Maria Forsea: getting from here to where we want to be

With no data from a reliable registry, and no functional national cancer plan, Romania is destined to continue suffering some of the worst cancer rates in Europe. **Vlad Mixich** tells the story of one dermatologist who is doing her best to break her country from endlessly re-living the same crisis.

On her tenth birthday, Ana Maria Forsea told her parents that she wanted to be a scuba diver when she grew up. She was told that she would have to give up on this dream because there was nowhere in the country for her to learn. Romania was a communist country at the time – all borders were closed, people bought their daily bread ration with food coupons, hospitals had no heating, and power cuts could hit at any time, even during surgery. At Forsea's school, like all other schools, a portrait of President Ceaușescu hung on the walls of every classroom, and children could be punished if they said what they were thinking out loud.

Then in 1989 the Berlin Wall fell, and everything changed overnight. Every single thing. The country where Forsea lived her teenage years had become chaotic but fascinating: no rules, no borders, no more parents telling their kids that they had to give up on their childhood dreams. "When I turned 18" – four years after the fall of the communist regime – "I wanted to be the best at whatever I would be doing and I wanted to be needed," says Forsea. "I wanted my actions to matter, to have meaning to other people." She got into the best school of medicine in the country, and this was the starting point in the journey of one of the pioneers in European dermato-oncology.

Even locals find it difficult to make any sense of the Eastern European dynamics in the '90s, but all locals, be they Polish, Romanian or Hungarian, will summarise those days in two words: openness and transition. Forsea had her full share of both. But in 1994, the Romanian medical studies tradition was still strongly influenced by communist mentalities. The first health ministers after 1989 had also held important positions under the communist regime. Of all the sectors that needed to be reformed in Eastern Europe, the health system was and still is the hardest to change.

What made a difference was that Western European countries provided a lot of scholarships to young people on the other side of the continent. One of these gave Forsea the chance to spend her first student summer doing practical training at the Saint-Luc hospital in Brussels, Belgium. "That was the place that set the paradigm for me of what caring for patients and nursing means," Forsea reminisces.

All photos: Ioana Moldovan

"The way that nurses cared for the patients, the way that patients were greeted with smiles, and supported all the way to get better. It was a mind-setting experience."

As a student, Forsea spent additional elective semesters in Bristol, UK, and Lyon, France, and says these experiences reinforced her conviction that she needed to go to learn from the best, where she could learn most. "In places where they let you learn, they support you in your learning and they encourage you to practise. A place where knowledge and information are not personal assets to be locked away safely somewhere, but things that you have to share." This approach to gaining and sharing information was to be a defining aspect of her future life.

On graduating from the Bucharest School of Medicine, the second top student of her year, Forsea started a PhD at the Dermatology Department of the Freie Universität in Berlin, emerging two years later with a *summa cum laude* thesis on melanoma. The time she spent there, under the mentorship of Constantin Orfanos and Christoph Geilen, were decisive, she says, in her development as a passionate dermatologist and a committed researcher.

But when she returned to Romania to start practising as a dermatologist, she found that the realities of everyday life were brutally different. "I kept seeing advanced tumours, discovered late in the process, and people who died useless deaths. So that was when the concept of early detection in cancer became crucial. It stopped being a mere slogan and it became a necessity, a matter of practical urgency."

**"That was when the concept of early detection in cancer stopped being a mere slogan and became a practical urgency"**

It is estimated that melanoma kills more than 20,000 Europeans yearly. But there are significant differences between Western and Eastern Europe. In the West, up to 70% of newly diagnosed melanomas are less than 1 mm thick, whereas in countries like Romania or Bulgaria, that is

true in less than 25% of cases. One reason is that, in many Eastern European countries, the density of doctors in city hospitals is twice as high as the national average, while large rural areas lack physicians and diagnostic facilities. Another reason, says Forsea, is the lack of awareness about skin cancer. "And there is a wide gap between what people know they should do and what they actually do in practice. Most people don't know what they have to do in the first place, but even the few who do know still don't do it."

Forsea understood that to improve early detection rates in skin cancer, a lot of things had to be done right. "People need to become aware that they have a problem, then they must get out of their homes and go to the doctor, then they must be scheduled for a medical consultation, the doctor in question must understand what the issue is, must be able to make a diagnosis and then, once diagnosed, the patient must be sent where treatment is available."

In Eastern European countries like Romania, this flow is often broken. This is partly because the healthcare budgets in eastern countries are much smaller than on the other side of the continent, but it is also because of management

**"Then I discovered that there simply was no data, that I couldn't provide any statistics"**

shortcomngs and cultural differences, which Forsea believes need more attention. "In Romania, there are popular beliefs that may not exist in other countries. People are afraid to have a suspicious-looking mole removed because they know of an uncle who died after doing so. But this belief is actually lethal, because the removal of the mole would have saved a life," Forsea explains.

So 10 years ago, Forsea set about establishing a foundation that aimed at challenging these misperceptions and improving skin cancer awareness. But in looking for office space she came up against another cultural barrier: stigma and taboo. "The owner of one building said 'Oh no! No cancer in my building, it gives off negative vibes.' These beliefs and customs vary from one country to another. So when I set up this foundation, I did it precisely because people died in vain, out of ignorance."

Forsea used to believe that this low level of medical awareness was part of the Eastern European specificity, but what she heard from European patients' conferences taught her differently. "It was mind-blowing for me to hear similar things everywhere, from the North to the South, from the East to the West. I kept hearing that many doctors are not sufficiently trained to detect melanoma early on and to take preventive measures. That people are not educated enough to know when they need to go to the doctor. I was already familiar with such problems in Eastern Europe, but I was less prepared to hear this in the UK for example. That cases of melanoma are diagnosed late, that the doctor did not pay enough attention to a mole that their patient was pointing out."

## Looking for data

Forsea started to ask herself some questions, "It was a researcher's knee-jerk reaction." She tried to identify the obstacles that block the prevention and early detection process. This, as she emphasises, meant looking for data. "No data, no research. You are left with a crystal ball."

The search for data led to the Harvard School of Public Health in the United States, where Alan Geller, one of the leading experts on early detection and prevention of skin cancer, is based. So in 2011, that is where Forsea went. She spent a year there, researching with Geller and his team how to build an adapted strategy to improve early detection of melanoma in Eastern Europe. "He said to me, 'OK, we're building strategies that need to be adapted to Eastern Europe, but let's see first where we are and where we want to go from here,'" remembers Forsea from their first encounters.

Based on her practice experience, she thought it would be easy to collect the baseline data on skin cancer. "But then I discovered that there simply was no reliable data for Eastern Europe, that I couldn't provide any statistics matching what I knew from practice. In my career as both researcher and practitioner, that was the moment when I stumbled upon the problem of cancer registries for the first time."

Cancer registries collect and statistically analyse data on cancer cases. The more complex the data, the more valuable the resulting statistics are. But in the absence of objective and complete data from these registries, "One simply cannot develop any strategy, any plan or intervention to reduce the cancer burden in a specific geographical area," says Forsea, adding that the data are also needed to assess whether a strategy is useful, whether it should be a priority and, most importantly, to assess retrospectively whether or not it worked.

Yet, so far, only 29 out of the 41 European countries have quality population-based cancer registries. Some countries, such as Poland, only have local registries that cover about 10% of the population. In nine countries, located in Europe's

eastern half (Romania, Hungary and Greece included), the national cancer registries might exist legally, but do not function at a sufficient quality, so that in international statistics the data from these countries are only estimates.

"We do not know what our melanoma patients look like," says Forsea. "We don't know how many they are. We don't know how late they are diagnosed. We don't know if their risk factors are the same as in Germany, or how long they survive. We do know that in neighbouring Bulgaria, melanoma survival is 49% compared with 87% in Western Europe." A 2014 report addressed by the European Commission to the European Parliament underlines that "at present, these registries supply the majority of epidemiological data on cancer but, most of the time, they are not managed by sufficient staff or they are not adequately planned."

The problem sticks out immediately from a glance at current statistics. While death rates from melanoma are comparable in Western and Eastern Europe, the rate of registered new diagnoses in Central and Eastern Europe is less than half that in the western part of the continent. Such anomalies persist when looking at data from some neighbouring countries: Germany reports four times the incidence of melanoma compared to Poland, and the same difference is reported for Romania and Hungary. "It is obviously a question of diagnosing and reporting the data," Forsea concludes.

This has serious consequences, all the more so for Eastern European countries, where the need for accurate data to maximise the impact of health policies is all the greater because financial resources are so limited.

Remembering a conference of South-Eastern European cancer registries, Forsea describes the situation as an Alice in Wonderland stance:

*"Would you tell me, please, which way I ought to go from here?"*

*"That depends a good deal on where you want to get to," said the Cat.*

*"I don't much care where…" said Alice.*

*"Then it doesn't matter which way you go," said the Cat.*

*"…so long as I get somewhere," Alice added as an explanation.*

*"Oh, you're sure to do that," said the Cat, "if you only walk long enough."*

In Romania, there are eight regional cancer registries, but only one provides data that are of sufficiently quality to be taken into consideration in European statistics. There are many reasons for this – first and foremost the high degree of legislative and political instability. In the past 25 years,

Romania has had no fewer than 25 health ministers, and the ministerial orders that regulate these registries have been amended several times in recent years. Very often, these amendments are inconsistent and result in discontinuities in organisation, financing and information. For instance, it is not yet very clear who coordinates the registration at national level or how institutions that are responsible for organising these registries can be made to implement the necessary actions.

## Looking for allies

Forsea emphasises that the European Union did make a considerable effort to provide member states with a set of detailed guidelines on how to design their cancer control planning and set up quality cancer registries. She also commends the vision of Vytenis Andriukaitis, the European Health Commissioner, that "investment, investment, and once again investment is the way to fight against cancer" (*Cancer World* Sept–Oct 2015). Yet, the EU itself also lacks political consistency. Countries such as the Netherlands, who now hold the EU presidency, frequently cite healthcare as an example of where the subsidiarity principle should

apply, as they claim this is an area that member states can organise perfectly well themselves. Yet, as Forsea remarks, the disparities signalled by all European statistics and mapping clearly point to the fact that not all member states are perfectly capable of organising their healthcare.

"We must take a step forward and move from mapping to benchmarking. Starting from the indicators already put forward by the Commission, there should be a set of measurable minimum standards to allow us to concretely monitor the progress made. An external audit system would also be useful. The mapping and the analyses done so far – and they do represent a huge effort – rely mostly on the self-evaluation of member states. Objective and independent control mechanisms are crucial to improving the status quo. This type of control is not an intrusion or a coercion, it is a way to identify the problem, help allocate resources to the highest priorities, and support member states to take necessary action where they most need it."

Making people aware of the problems and empowering them to take action on them is also crucial, says Forsea. "People are unaware of the threat that lack of data means – that they die in vain, without their case being counted. Their suffering is not at the moment quantified in data that could contribute to the prevention of similar cases in the future."

Forsea speaks with passion, which shows from the lively sparkle in her eyes, and the determined set of her jaw. She is a product of the European medical school: Bucharest, Brussels, Bristol, Lyon and Berlin. At present, Forsea runs the largest survey conducted among European dermatologists. More than 8000 doctors have responded to questions about their practice of dermoscopy for skin cancer early detection. Her quest to bring data to the light and to improve the prevention of melanoma and the care of patients is one she will not give up easily, but she needs more allies, more support.

"Cancer registries are not an isolated issue", she says. "They are part of a cancer control continuum that needs to be planned in the long run. Otherwise it's always yet another Groundhog Day. We keep re-living in the same present over and over again, the same crisis, the same desperate urgency to do something right here, right now."


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# Accelerating progress in immunotherapy

The concept is attractive, the results in some patients have been stunning, but what will it take to extend these impressive responses to wider groups of patients? **Peter McIntyre** reports.

There is a growing sense of confidence that immunotherapy will deliver long-term survival to an increasing number of cancer patients, including some people with advanced and metastatic disease.

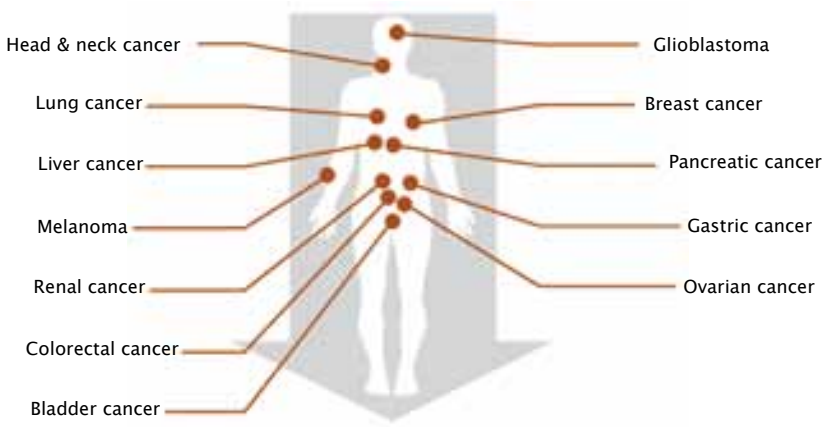
The percentage of cancer patients with advanced melanoma who have a prospect of long-term survival roughly doubled from around one in five on ipilimumab to more like two in five on the newer range of checkpoint inhibitors that combat the ability of tumours to switch off the T-cell response. Early data from patients with other tumours, such as non-small-cell lung cancer (NSCLC) and bladder cancer, also indicate important survival benefit among patients who respond.

Trials and clinical use suggest that a percentage of patients can be kept alive in the long term. Some patients with advanced melanoma are still alive ten years after they started treatment with ipilimumab, and the newer anti-PD1 and anti-PD-L1 therapies are expected to extend this still further.

For patients who do respond, the impact on quality of life can also be dramatic. One study showed quality of life for patients with advanced NSCLC even rising above the levels for the general population.

It is predicted that combinations of more than one immunotherapy, and combinations of immunotherapies

## Not just for melanoma




Immunotherapies work across a wide range of cancers, but only for a minority of patients

with chemotherapy, targeted therapy or radiotherapy will improve survival in an ever wider number of cancers, though potentially at the cost of serious toxicity.

The sense of excitement is palpable. There are currently more than 1,200 trials for cancer immunotherapies listed on clinicaltrials.gov, mainly for therapies that seek to block the tumours' defences, but also for chimeric antigen receptor (CAR) therapies that engineer T cells to attack the tumour and are designed provide a memory effect and long-term protection.

However, there are significant obstacles to developing immuno-therapies that work for more patients in a wider range of cancers.

The European Medicines Agency and the Brussels-based Cancer Drug Development Forum convened an international summit in February 2016, where leading global experts in immunotherapy discussed how to amass the evidence that will convince regulators and health technology assessment (HTA) bodies to approve these treatments for more indications and patients. The meeting attracted researchers, clinicians and patient representatives, from Europe and North America, with strong representation from pharmaceutical companies and the participation of the US regulators, the FDA.

Much of the current excitement is focused on a class of drugs that inhibit PD-L1 (programmed death ligand 1), which plays a key role in protecting cancers from attack by the body's immune system. The protein, which is expressed by cancer cells, switches off T cells by binding to the PD-1 marker on the cell's surface.

In a keynote address, Ira Mellman, Vice President of Research Oncology at Genentech, said that this new class of drugs represents a paradigm shift in treatment. "What you can achieve, albeit as yet for a relatively small number of patients, using immunological approaches is unlike almost anything I have seen in the past with respect to other types of cancer therapies in major disease indications."

But he also emphasised how much there is still to learn about how these therapies function and in whom. The current excitement, he argued, is being driven largely by clinical data, which has outpaced basic scientific understanding of how these therapies work.

"Exciting as these agents are, they really only benefit a small minority of patients in all but the most responsive indications such as melanoma, which can be 30–40%. Almost all the other indications are in the order of 10–20% as single agents. Well tolerated and highly effective, but not everybody benefits."

### Fast and furious

Paolo Ascierto from the Istituto Nazionale Tumori in Milan argued for adopting a "fast and furious" approach to testing combinations and identifying the right sequencing, dosage, and length of treatment for the right patients to increase the response rate and reduce the impact of side-effects. The potential prize, at least in advanced melanoma, he says, could be a further doubling of the proportion who survive for the long term, from 40% to 80%.

Traditional approaches to trial

design, it was widely agreed, are simply too slow and inflexible. As Samir Khleif, Director of the GRU Cancer Center, in Augusta, Georgia, put it: "The elephant in the room is the 300 years and multi trillion dollars [it could take] to be able to reach where we want to reach."

For patients with advanced cancers, the "fast and furious" approach certainly resonates with their need for urgent progress. The challenge is how such an accelerated approach can deliver the level of evidence on efficacy and value required by regulators and payers.

## Balancing ethics and evidence

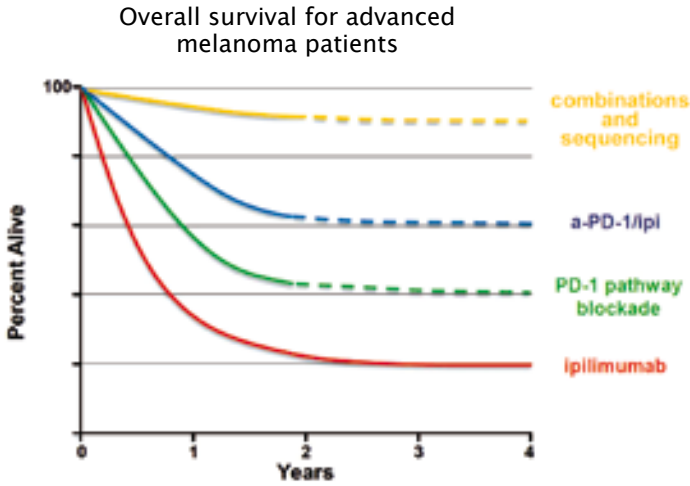
Immunotherapy agents are already being trialled in combination with one another, and with chemotherapy, radiation therapy and small molecules, with the potential for much higher response rates, especially in those who have low levels of PD-L1.

Many early results continue to both excite and impress, despite some serious toxicity issues. An ongoing combination study in patients with non-small-cell lung cancer, for instance shows that almost 40% of patients who are PD-L1 negative respond, compared with just 5% on monotherapy.

But these early indications of success raise problems of their own, as Ramy Ibrahim, immunotherapy clinical vice-president for AstraZeneca, pointed out.

"It will be very difficult to enrol to a monotherapy arm when the early data is suggestive of limited activity of monotherapy. When we start thinking of a randomised trial with a monotherapy arm of a CTLA4 inhibitor, patients are reluctant to consent to such a study design," he said.

## Today, tomorrow and the future




Combinations of checkpoint inhibitors could see long-term survival rates of up to 60% in some cancers, while the hope is that clever combinations and sequencing could raise this to 80% and beyond. However, this is not yet within grasp

*Adapted from Walter J Urba, ASCO 2013*

Vagn Erik Jesperson, a 13-year survivor of NSCLC and co-founder of the Danish Lung Cancer Patients Association, posed a question to the meeting about the ethics of conducting trials where early results had shown such major differences between the trial arms. "How do you feel about that when you make [such] clinical trials?" he asked.

Using adaptive designs that allow a trial arm that was proving to be inferior to be dropped was seen as one way to mitigate this problem. There would be a cost, however, in terms of losing data that could help get approval and reimbursement for the novel therapy.

Khleif suggested that learning from pre-clinical research in the lab will help rule out combinations that are unlikely to work. "The biology is very important. We need to think about the optimum response before we put millions of dollars into what we need to take it forward and invest."

Ibrahim agreed that animal models can guide the search for combinations and dosages. "The biology is very complex when we start looking at combinations. We need to find the relevant animal model that can help us, so we don't end up spending 300 years trying to figure out which is the right combination to take into the clinic."

> "The elephant in the room is the 300 years ... [it could take] to reach where we want to reach"

But as Bernard Fox, from the Earle A. Chiles Research Institute in Oregon, pointed out, mouse models can only take you so far. "The biology of the tumour in a mouse and its interaction with the immune system is fundamentally different from what you find in a human. I would encourage

regulatory agencies and companies to be thinking about innovative clinical trials with small numbers of patients studied aggressively and in depth to learn as much as you can about what happens."

More investment is also needed in basic science to better understand the mechanisms of the immune response, said Fox, singling out in particular the need for a microbiome equivalent of The Cancer Genome Atlas (TCGA), which could help define the role played by the body's microbiota.

## Finding the right endpoints

Choosing the best indicators, or 'endpoints', to demonstrate, within an acceptable timescale, that a novel therapy is more effective and brings more patient benefit than its comparator is always tricky. With immunotherapies, those problems seem to have become even tougher, because of the unique way in which they kick in.

Overall survival – showing that patients live longer – has traditionally been the gold standard in pivotal clinical trials. However, as new therapies are trialled in different doses and combinations, and trials often allow patients on one arm to cross to another if they progress, once survival times go beyond 18 months it becomes extremely difficult to demonstrate that differences in overall survival are attributable to a particular treatment.

To get around this problem, trials of other types of cancer therapy are increasingly using progression-free survival as a surrogate for overall survival. This doesn't work so well with immunotherapies, as checkpoint inhibitors often elicit an initially slow (or no) reaction followed by a long survival curve for a percentage of patients.

The RECIST criteria for judging progression by monitoring the size of tumour lesions is of little use in these circumstances. Even experienced clinicians can be fooled, for instance, when a head and neck cancer treated with pembrolizumab appears to grow alarmingly before an equally dramatic regression.

Current trials of immunotherapies are therefore taking place without any agreement on what should be used as a surrogate for overall survival, at least in advanced disease.

The story of ipilimumab is instructive. The anti CTLA4 antibody passed through three different companies and underwent six clinical trials over 10 years before it was shown that it extended patients' lives. The problem was finding a clear parameter of response that could be documented. The pivotal study was expected to last three years but Bristol-Myers Squibb (BMS) had to extend it a further 1.5 years to gather enough data for marketing approval.

**Trials are taking place without any agreement on what should be used as a surrogate for overall survival**

Tai-Tsang Chen, Executive Director of Global Biometric Sciences (part of BMS), says it might be sufficient in future to follow only the earliest trial entrants to get long-term follow up, and use 'milestone survival' for the rest to indicate survival rates 'x' years after treatment begins.

Finding effective endpoints for immunotherapies "presents one of the most important challenges we have as a field," says Dan Cheng, who leads work on immunotherapy at Genentech. "These drugs have a powerful effect on overall survival, but probably all of these studies will be confounded by massive use of immunotherapies in multiple lines."

He talked about the "immune-modified RECIST criteria" Genentech has introduced into randomised trials to study detailed efficacy patterns and get a sense of whether they predict survival. "One of the big questions would be to work in partnership with health authorities to the point where we all feel confident enough with a new endpoint like this to use it for actual approval in the future," he said.

### *Quality of life*

David Cella, Director of the Institute for Public Health and Medicine at Northwestern University, Chicago, highlighted the importance of measuring quality of life endpoints. As survival gets longer and harder to measure, the focus will turn more to the quality of that survival.

Long-term successful treatment carries its own quality of life challenges, he added: "It is one thing to have short-term horrible diarrhoea – it is quite another to have it for two or three years. Some of the long-term treatment can be intolerable."

He also pointed to a potential correlation between quality of life and survival. "In advanced disease, early change in quality of life scores of just about anything you measure is predictive of survival. There is a case there that patients know something – particularly the change. There have been a lot of studies in lung cancer, colon cancer, breast cancer, where patients who get better early on in therapy live longer, and patients who get worse early on don't live as long."

Cella suggested that analysing how changes in different symptoms and quality of life indicators, measured just before and shortly after progression, correlate with overall survival could help identify markers that can predict survival.

## Finding the right patients

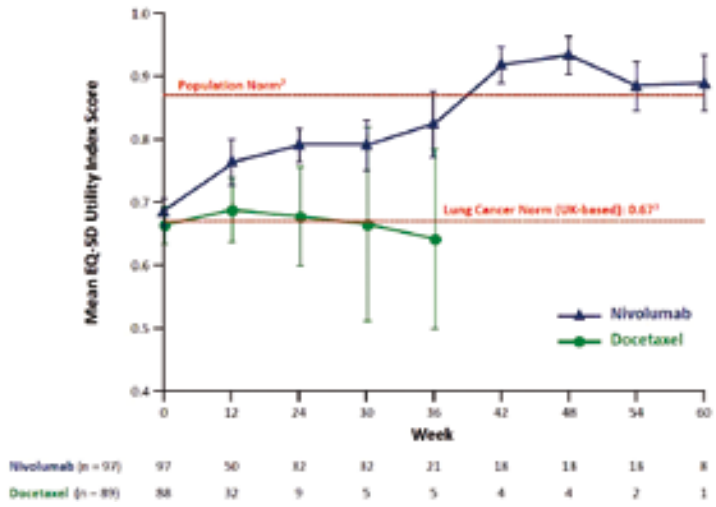
Immunotherapies currently work well in only a small minority of patients. Finding biomarkers that can predict which patients will benefit is proving surprisingly challenging. Contrary to expectations, the presence of CTLA4 or PD-L1 in tumour cells – both targets for checkpoint inhibitors – does not seem to be a reliable guide to the immune response.

One thing that is clear, according to Genentech's Mellman, is that, "Everyone who responds to PD-1/PD-L1 therapies are individuals who have some level of pre-existing immunity which you can objectively measure with increasing degrees of accuracy." Patients who do not respond to immunotherapy either have dysfunctional responses so that T cells never get beyond the periphery of the tumour or "an immune desert" where no T cells at all confront the tumour, he said.

Resolving this issue will be important, not least because the FDA and EMA are becoming increasingly insistent that new cancer therapies be accompanied by validated biomarker tests that indicate in whom they should be used.

Heinz Zwierzina, from the Early Clinical Trials Unit at Innsbruck, who chairs the Cancer Drug Development Forum, argues that it is also an issue of ethics and affordability. "If we treat the 'wrong' patients with a drug that does not work and may cause side effects, we may lose time in treating patients with the right drug," he said, adding that, "Our healthcare systems will be in serious trouble if we cannot define sub-populations of patients."

## Quality of life




A study of patients treated with nivolumab for advanced non-small-cell lung cancer indicated that, among long-term responders, patient-reported quality of life scores returned to population norms at 36-42 weeks (M Reck et al, ECCO-ESMO 2015, Abstract 3011). The study was exploratory, and involved a very small number of patients
*Courtesy of Martin Reck, LungenClinic Grosshansdorf*

The size of the problem can be seen in the striking difference between the cut-off points used in different clinical trials to define 'PD-L1 positive', ranging from 1% in a trial of pembrolizumab for melanoma, to 5% for a trial of nivolumab in non-small-cell lung cancer and 50% for pembrolizumab in non-small-cell lung cancer.

Mira Pavlovic-Ganascia, a dermatologist who coordinated the European Network of Health Technology Agencies (EUnetHTA) for two years, says this discordance makes it impossible for regulators and HTA bodies to compare biomarkers. "It is really frustrating that people use different expression cut-off levels and say it is positive. What are we meant to do with this?"

Francesco Pignatti, who leads cancer drug evaluation for the EMA, says that they cannot ignore the complexities, but have to find a way to be able to compare data. "It is entirely plausible that the relationship does not have a natural threshold telling us there is a single cut off where you can exclude or include patients in the label. It is perhaps a dynamic type of marker across different tumour sites or tumour types. The relationship might be a linear one not a binary cut off."

Imposing an arbitrary cut-off point, he argued, would be seen as desperately unfair by patients whose PD-L1 marker falls on the wrong side of a dividing line, and could encourage off-label use. On the other hand, leaving it to patients and clinicians to decide could mean that everybody ends up on the drug, regardless of benefit. "How much confidence is there across the European Union about shared decision-making once it ends up on the label?"

## EMA to sponsors: Talk early talk often

The European Medicines Agency and the Food and Drug Administration have both adopted a proactive approach to discussing the shape of trials with pharmaceutical companies during the design stage and a willingness to accept 'breaking news' evidence after a licence application has been submitted.

The 'breakthrough' designation introduced by the FDA in 2012, and the 'adaptive pathways' approach piloted by the EMA in 2014, both aim to speed the development and review of new drugs for serious diseases where preliminary data indicate they might be substantially better than what is currently available.

In both cases, the emphasis is on early and frequent access to discussion and advice, and a 'rolling review' to help steer the drug (or combination) through the most efficient development pathway.

Pembrolizumab (Keytruda) was the first immunotherapy to be granted breakthrough designation by the FDA in 2013, and was approved for use in patients with advanced melanoma in September 2014. EU approval for the same patient group came in the summer of 2015.

Roger Dansey, head of oncology clinical development at developers Merck (MSD), said that the EMA and its human medicines committee had demonstrated "enormous flexibility and willingness" to accommodate data as it emerged from a trial that was simultaneously assessing clinical benefit and dosage. "We are in a hurry because patients are in a hurry. There is an enormous unmet need. We were very appreciative of that degree of flexibility."

Bristol-Myers Squibb reported similar flexibility when they applied for marketing authorisation for nivolumab (Opdivo) in advanced squamous non-small-cell lung cancer. Catherine Weil, from BMS Belgium, said, "We submitted the confirmatory study data during the review based on large survival advantage. The boundaries had been clearly crossed and the result was positive. It was very, very collaborative I would say. For squamous non-small-cell cancer patients there has not been a new drug approved in the past 20 years or so. The sense of urgency was really shared."

## The reimbursement hurdle

Marketing approval is one thing – getting the therapy to patients is another. Patrick Hopkinson, director of health economics and outcomes research at BMS UK, said the average time from approval to an agreement for reimbursement for cancer therapies is just over 8 months in France, 9 in Germany, 10 in Italy, almost 11 months in England and just over a year in Spain. In some other EU countries it is even longer.

Francesco De Lorenzo, President of the European Cancer Patient Coalition (ECPC), said that delays in introducing treatment amount to a form of rationing. ECPC is calling for a strengthening of current efforts to coordinate aspects of HTA assessments across member states by introducing a single assessment of relative clinical benefit that would be legally binding across Europe.

Hopkinson argued that HTA bodies need to take a broad view of clinical benefit given the potential for immunotherapy to transform patient outcomes. "We are on the cusp of a revolution in terms of therapies launched or to be launched. Current frameworks for value assessment in many HTA bodies especially for cancer medicines are not built for this class and type of therapy."

He said the willingness of the FDA and EMA to give accelerated approval on the basis of early evidence was very encouraging, but there could be a mismatch with the criteria HTA bodies required for their assessments. "Time is of the essence if you are a lung cancer patient – 80% of patients are dying within 12 months."

Mira Pavlovic-Ganascia, former coordinator of EUnetHTA, agreed that some of the mortality data from trials was "amazing". She argued, however, that HTA bodies want a broader set of data to evaluate "added clinical benefit", with the main clinical endpoints being how a patient "feels, functions or survives".

They also need data that can inform national policy on where the treatment fits within the overall treatment pathway and how this differs between patients according to whether their disease is progressing fast or slow.

They are therefore looking for something more meaningful than early data on progression-free survival, and they become "extremely nervous", for instance, when asked to assess results of a trial using a non-authorised dose of pembrolizumab for NSCLC.

Many countries are, however, looking at various forms of managed entry agreements and risk-sharing arrangements that can allow new medicines to be marketed on the basis of promising early data, while additional data about its value in actual clinical practice are being collected.

## A wider horizon

Although it is checkpoint inhibitors causing the excitement today, other forms of immunotherapy could

## Accelerating progress in immunotherapy: the challenges

**Ethics v evidence.** Patients don't want to be put on lengthy trials where early data indicate big differences between trial arms. Adaptive trial designs, and investing resources up front to learn as much as possible through many short exploratory trials with small numbers of patients, will be important.

**Endpoints**. Finding surrogates that can be measured early on and predict for survival is a priority. Currently there is no agreement on surrogate endpoints. Changes in specific and measurable aspects of how a patient feels is one area for exploration.

**Side effects.** Monotherapy has shown impressive improvement in quality of life among responders in diseases associated with a very high symptom burden. However, combinations of immunotherapies carry a high risk of serious toxicity. This needs to be overcome, particularly if immunotherapies are to be used long term or as adjuvant therapy.

**Personalisation**. Finding biomarkers that predict who will benefit is turning out to be very difficult. More basic understanding is needed of exactly how immunotherapies work.

**Reaching patients.** Working with HTA on managed entry and risk-sharing agreements to secure early access to new treatments while gathering robust information on value remains a challenge.

become significant tomorrow, building on new and emerging techniques. One under development is the use of mRNA and peptide-based anti-cancer vaccines based on antigen profiling of the individual tumour. Another uses CAR-modified T cells to attack the tumour. This seems to be highly effective in leukaemias but can also be highly toxic.

One small study (so far unpublished) in February 2016 reported 94% complete remission in patients with acute lymphoblastic leukaemia, along with some very severe side effects. A wave of immunotherapy trials will report at ASCO in Chicago in June.

Meanwhile, patients are increasingly seeking access to the new wave of immunotherapies. Aleksandra Filipovic, a clinical fellow at Imperial College London, said that the private sector there had started using the latest checkpoint inhibitors within weeks of FDA approval, with patients treated on the NHS now also able to use them through the early access programme.

"The way these drugs have moved forward in the past year and a half – the speed is absolutely staggering. The question we have answered is that the drugs work. Tumours that have been very difficult to treat are now finding their answer in immunotherapies," she said.

The greatest response rates had been seen in lymphoma, mesothelioma, patients with mismatched repair deficient colorectal cancer and melanoma. Responses of 20% or more have also been reported in patients with advanced NSCLC, heavily pre-treated triple negative breast cancers and gastric cancers.

Filipovic agrees that many questions remain about how to select the most suitable patients, how best to combine therapies, how long to give them for, how to best assess likelihood of response as early as possible and how costs can be met. The main story, however, is that these treatments are offering hope to patients in great need. "It is a space that is exploding at the moment."

# From evidence to practice in multidisciplinary cancer care

## ECCO2017 European Cancer Congress, 27–30 January 2017 Amsterdam

I am pleased to introduce ***ECCO2017 – European Cancer Congress***, the multidisciplinary evidence-based meeting for all cancer types, addressing all oncology disciplines and related healthcare professions. ECCO2017 will have a direct impact on daily clinical practice.

Focusing on phase III data, this scientific meeting will put the new evidence into perspective for a multidisciplinary audience by critically reviewing it in expert panels. Leading oncologists will address the value of these potentially practice-changing treatments by reviewing their clinical benefits and cost. Experts, patient advocates and the audience will determine whether the data really do support changes in clinical practice.

Recognising the discrepancies between what happens in real life and in a clinical trial setting, the congress will give centre stage to real world data showing the impact of treatment and care.

This focus on clinical practice will provide delegates with concrete, up-to-date knowledge through a multidisciplinary tumour board format, and give them the opportunity to participate in identifying practice-changing developments.

The Educational Committee has prepared a comprehensive educational programme covering topics from using evidence-based information to guide decisions on treatment options to understanding health economics and outcome research. There will be strong focus on immunotherapy and personalised medicine.

Based on ground-breaking research, the programme will also look at evolving healthcare systems and the future of cancer treatment, with particular regard to access to innovation, disparities in cancer care and the diminishing oncology workforce. Given the increasing role that primary care looks set to play in secondary cancer care, ECCO2017 will invite community care physicians, oncologists and patient advocates to discuss this evolution.

Regulatory sessions on newly approved drugs and innovation in local regional treatment will gather regulators, HTA bodies, academia, industry and patient advocates.

ECCO2017 will shed light on ECCO policy initiatives, centred around the oncology workforce and quality cancer care, making sure cancer is at the top of the EU public health agenda.

ECCO is an open forum for its members. The first day of ECCO2017 will feature societies' meetings for their members and the oncology community: the European Oncology Nursing Society (EONS), the European Organisation for Research and Treatment of Cancer (EORTC), the European School of Oncology (ESO), the European Society of Surgical Oncology (ESSO), the European Society for Therapeutic Radiology and Oncology (ESTRO), and the European Society for Paediatric Oncology (SIOPE).

Reaching a global audience, ECCO2017 has an extensive media programme for scientific media worldwide. Submit your practice-changing data for global visibility:

| | |
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| *Abstract submission opens:* | *25 April 2016* |
| *Registration opens:* | *15 April 2016* |
| *Early registration deadline:* | *27 June 2016* |

I thank ECCO member societies, the ECCO Patient Advisory Committee, and leading experts, for designing this innovative scientific programme.

ECCO2017 will change the paradigm of oncology, be part of this change!

***ecco-org.eu***

Peter Naredi – President of the ECCO Board of Directors (2016/2017) and Professor of Surgery and Chairman of the Department of Surgery at the Sahlgrenska Academy, University of Gothenburg since 2013

# Endoscopy in gastrointestinal oncology

Once used primarily to detect large polyps and tumours, endoscopy has now become an essential tool for early diagnosis, curative treatment and palliation for gastrointestinal cancer.

*This is an edited version of a presentation delivered by Michael Häfner, from St. Elisabeth Hospital, Vienna, Austria, as a live webcast for the European School of Oncology. It is edited by Susan Mayor. The webcast of this and other e-sessions can be accessed at e-eso.net.*

Endoscopy is used in gastrointestinal (GI) oncology in diagnostic, curative and palliative settings. In diagnosis, it is used to detect lesions, facilitate macroscopic classification of tumours and enable biopsy and fine-needle aspiration to collect tissue samples. In curative treatment it is used to resect early cancer by endoscopic mucosal or submucosal resection and thermal ablation. In palliation it is used mainly for stent implantation, but also for percutaneous endoscopic gastrostomy.

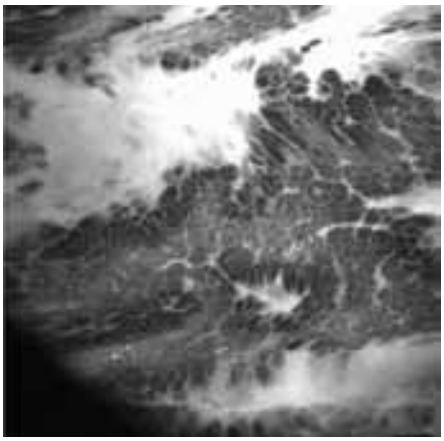
## Endoscopy in diagnosis

In the early days endoscopy was used mostly for diagnostic procedures with the goal of finding tumours – mostly large polyps and tumours at an advanced stage. The development of more advanced technologies over recent years has led to a paradigm shift, and endoscopy has moved on to the detection of small, flat, early malignant or precancerous lesions. The benefit is that there are now several interventions to cure these conditions, including resecting early lesions by endoscopic techniques.

Technological developments, including high-resolution endoscopy and zoom endoscopy, enable clinicians to examine lesions more closely, for example assessing the vascular pattern in dysplasia in Barrett's oesophagus. Novel technologies, such as confocal laser endomicroscopy and autofluorescence, now allow the detection and characterisation of minute lesions that can otherwise be difficult to see. This is crucial because mucosal cancer can be cured by means of endoscopic resection in many cases.

The figure overleaf shows an example of real-time pathology using confocal endomicroscopy, which is typically carried out using a probe during endoscopy, such as during endoscopic retrograde cholangio-pancreatography (ERCP) in the bile duct. In this case the procedure was carried out during gastroscopy with a dedicated endomicroscopy endoscope in a patient with Barrett's oesophagus. The image shows a leakage in the bright area, which is the contrast agent given intravenously, and a distortion of the mucosal cells that indicates Barrett's cancer. The benefit

## Real-time pathology



Confocal endomicroscopy reveals leakage of contrast agent (*bright area*) and a distortion of the mucosal cells – enough to diagnose a Barrett's cancer without the need for biopsy
*Courtesy of Michael Häfner*

of this technique is that it offers real-time histopathology while examining a patient, without taking a biopsy. Based on these findings, we were able to plan our therapeutic intervention. Only a few centres in the world currently have this technology, but it is an exciting development for the future.

## What to look for

To actively find lesions it must be clear what we are looking for. Classifications are usually considered rather boring, but they can be very useful in endoscopy. The figure below shows the Paris endoscopic classification for superficial neoplasia, which applies in all of the organs that can be reached with an endoscope: the oesophagus, stomach and colon.

### *Enhancing images*

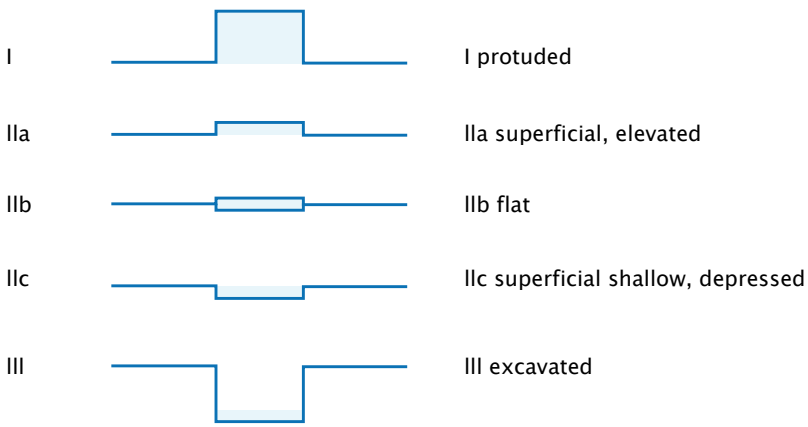
There are several techniques for enhancing endoscopic images. Flat lesions can be very difficult to detect, so considerable knowledge of macroscopic features is needed. The endoscopic picture can be enhanced using optical or electronic manipulation, with techniques such as virtual chromoendoscopy, or use of a dye in chromoendoscopy. The goal is to enhance contrast and improve the detection of lesions and allow for their characterisation, including assessment of surface patterns. Virtual chromoendoscopy makes use of the fact that modern endoscopes are basically computers that allow manipulation of colours, essentially providing 'Photoshop' for endoscopy. Other techniques use optical filters that enhance the contrast and make blood vessels and surface patterns more visible, enabling us to spot very discrete lesions.

The figure on page 39 (*top left*) shows a completely flat lesion on virtual chromoendoscopy, which makes lesions easier to see by changing their colour. This was a squamous cell cancer of the oesophagus that was extremely important to diagnose, because endoscopic submucosal resection cured this early cancer with no need for surgery. Lugol's staining shows the lesions much more clearly as the unstained areas. The case illustrates that it is important to know what you are looking for, or you may miss subtle lesions.

If these technologies are not available, various dyes can be used to improve image visualisation throughout the gastrointestinal tract. This can facilitate detection and also characterisation of a lesion. They include:

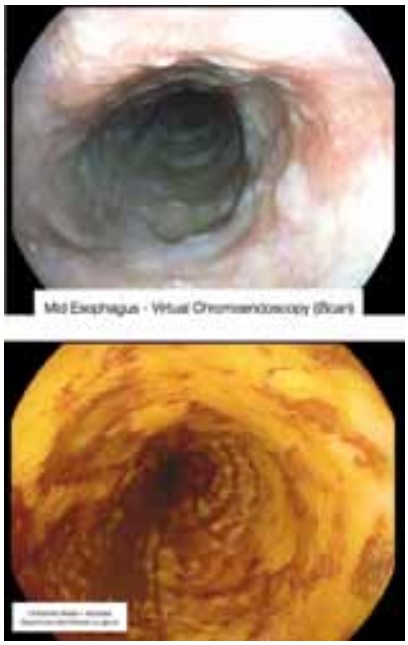
- **Lugol's staining.** This is iodine based (so it is important to be aware of the risk of allergy), and is used for the detection of oesophageal squamous cell cancer. It is also used for screening high-risk patients, such as smokers or patients with a history of alcohol abuse.
- **Acetic acid (vinegar).** This reacts with the surface of the mucosa and makes the surface pattern, or pit pattern, of a lesion much more visible. It is applied to detect dysplasia in Barrett's oesophagus.
- **Indigo carmine.** This can be considered the 'Swiss Army knife' of gastrointestinal endoscopy, and is widely used throughout the gastrointestinal tract. The blue colour stains depressed areas and increases the contrast. It also makes surface structures, surface patterns and the margins of a lesion more visible (see page 39 *top right*). The spread and surface pattern information can help distinguish benign from malignant lesions.

Modern imaging technology makes it possible to reliably predict the




The Paris endoscopic classification of superficial neoplastic lesions.
*Source:* Participants in the Paris workshop (2003) *Gastrointest Endosc* 58:S3–S43
Reprinted with permission from Elsevier

## Enhancing images



Mid-oesophagus scan using virtual chromoendoscopy (*above*) and Lugol's staining (*below*) in the same patient – *Courtesy of Michael Häfner*

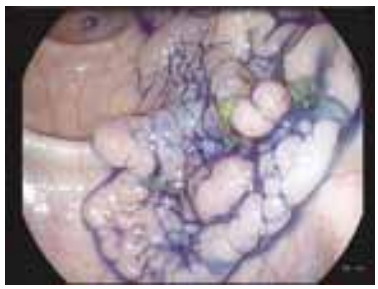
histopathology of lesions. Macroscopic classification, with the help of contrast enhancement, is important for making decisions during endoscopy on whether to resect a lesion, take a biopsy, refer for surgery or leave a lesion because it has no risk of malignancy. Commonly, classifications are used for (early) oesophageal cancer, (early) gastric cancer and lesions in the colon. The oldest and most widely used classification, Kudo's Pit Pattern (see figure *right*), has been developed for colon polyps. Certain types of patterns are clearly associated with neoplastic lesions and others with non-neoplastic lesions, providing further information for decision-making during endoscopy without having to wait for pathology results.

### *Fine-needle aspiration*

Not everything is accessible for direct biopsy. Tissue sampling from deeper layers, for example submucosal lesions, is usually unsuccessful with standard biopsies. Some lesions cannot be reached at all because of their nature or location, such as lesions in the lymph nodes or outside the gastrointestinal tract, such as the pancreas. In these situations, endoscopy-guided fine-needle aspiration is a relatively easy way to obtain tissue samples. It is ultrasonography based and enables operators to puncture tissue and obtain pathology specimens. However, results can vary considerably depending on operator experience, the presence of a cytologist, who can advise when enough material has been obtained, and the choice of needle.

*Question: Would you consider taking a biopsy in early malignant lesions?*
*Answer: It is important to recognise early lesions because taking a biopsy is not generally recommended due to the risk of making resection more difficult. It is best to resect flat lesions immediately or mark for a colleague who will resect them. You can biopsy any polypoid lesion safely without having consequences for endoscopic resection.*

## Macroscopic classification of lesions



Staining with indigo carmine shows up the margins of the lesion and its surface patterns well enough to reliably predict the histopathology – in this case a laterally spreading tumour with granular type pit pattern type IV
*Courtesy of Michael Häfner*

## Endoscopy in curative therapy

Use of endoscopy in curative treatment of gastrointestinal oncology is a very recent development. In the past, the standard treatment of gastric cancer was surgical, but endoscopic techniques have been developed so that endoscopic mucosal resection (EMR) of early cancers is now the standard approach. The first attempt

## Kudo's Pit Pattern classification

| | | |
|---|---|---|
| Type I | Round pit (normal pit) | non-neoplastic |
| Type II | Asteroid pit | non-neoplastic |
| Type IIIs | Tubular or round pit that is smaller than the normal pit (Type I) | neoplastic |
| Type IIIL | Tubular or round pit that is larger than the normal pit (Type I) | neoplastic |
| Type IV | Dendritic or gyrus-like pit | neoplastic |
| Type VI | Irregular arrangement and sizes of IIIL, IIIs, IV type pit pattern | neoplastic |
| Type VN | Loss or decrease of pits with an amorphous structure | neoplastic |

*Source:* S Kudo et al. (1996) *Gastrointest Endosc* 44:8–14
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## Barrett's cancer pre- and post-EMR

*Courtesy of Michael Häfner*

at endoscopic treatment was reported in Japan in 1974, where it was used to treat a polypoid-type gastric cancer. Subsequently, EMR techniques have been developed to resect flat gastric lesions. You can usually resect lesions of up to 1.5–2 cm in one piece. However, this technique is unsuitable for larger lesions, which have to be resected piecemeal or with a newer technique called endoscopic submucosal dissection (ESD). This has, theoretically, no upper limit on the size of the lesion that can be resected.

Endoscopic mucosal resection was developed initially for the treatment of mucosal gastric cancer in Japan. It is currently used for lesions in the oesophagus, where it is used in Barrett's oesophagus, in the stomach and the colorectum. The main drawback of this method is the limited size of specimens that can be resected *en bloc;* but, on the positive side, it is fairly quick to learn and is safe. A commonly used technique is cap-EMR, in which saline, and sometimes dye, is injected into the submucosa. The artificial polyp created is sucked into the endoscope cap and cut with a snare. Complications are rare and include bleeding (5%), perforation (very rare) and strictures, which are also rare but may occur, for example, in circumferential EMR in the oesophagus. The figure *top left* shows a Barrett's cancer pre- and post-EMR.

Endoscopic submucosal resection overcomes this limitation, allowing for *en bloc* resection of larger lesions if certain criteria are met. It is now considered the treatment of choice for intramucosal gastric cancer and oesophageal cancer, especially for squamous cell cancers, and is superior to conventional EMR in terms of the curative and recurrence rates.

Endoscopic submucosal dissection (ESD) is a new development in therapeutic endoscopy, which allows the direct dissection of the submucosa and enables large lesions to be resected *en bloc*. ESD is not limited by resection size and is expected to replace surgical resection, at least in well-defined indications (*J Gastroenterol* 2006, 41:929–942). However, it is associated with a higher incidence of complications than standard EMR procedures, is much more complicated to perform than EMR and requires a high level of endoscopic skill.

### *Indications for treatment*

The most important indications for endoscopic treatment of early gastric cancer are determined by considering the risk of lymph node metastasis, technical problems and whether to resect the tumour *en bloc*. The conventional criteria for endoscopic resection of early gastric cancers, which were proposed by the Japanese group, are:

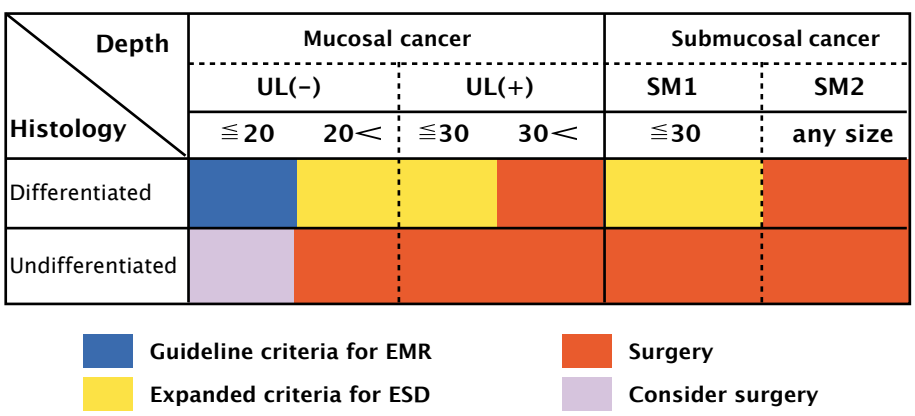
- highly differentiated adenocarcinoma
- intramucosal cancer
- size of the lesion less than 20 mm
- no endoscopic findings of ulceration
- no lymph node involvement or metastasis seen on computed tomography.

Lesions that meet all these criteria should be considered for *en bloc* resection by conventional EMR methods because of the low risk of lymph node metastasis.

Extended indications for EMR have recently been proposed, based on surgical data. Gotoda et al. reported that lesions meeting the following extended criteria have no, or minimal, risk of lymph node metastasis (*J Gastroenterol* 2006, 41:929–942):

- no size limitation for intramucosal differentiated cancers without ulceration that have no lymphovascular invasion
- less than 3 cm in diameter for ulcerated differentiated intramucosal cancers without lymphovascular invasion
- less than 3 cm in diameter for differentiated cancers (extension into the submucosa <500 μm)

## The risk for lymph node metastasis in gastric cancer




*Source:* T Gotoda, H Yamamoto and RM Soetikno (2006) *J Gastroenterol* 41:929–942
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without lymphovascular invasion
- less than 2 cm in diameter for undifferentiated intramucosal cancers without ulceration.

EMR can be performed, sometimes in an outpatient setting, in patients meeting these criteria, and it provides a very effective way of treating patients. The figure at the base of page 40 presents a graphical representation of the criteria, illustrating that EMR and ESD can be used for small lesions, nonulcerated lesions, and lesions limited to the mucosa. Patients with other types of lesions should be considered for surgery.

### *Endoscopic submucosal dissection technique*

Endoscopic submucosal dissection (ESD) involves applying a submucosal injection, which can be with saline or glycerol, although we prefer to use hyaluronic acid for more complicated procedures because the cushion it forms in the submucosal layer is longer lasting. ESD knives are available in different shapes, including the IT knife, which is designed to reduce the risk of perforation. Haemostasis devices, such as the coagrasper that coagulates blood vessels in the submucosa, are required because bleeding is common, as for EMR. In addition, devices are needed for closing perforations. These may include conventional clips or OTS clips, which can close larger perforations.

A 2011 study of ESD from the French working group of 16 centres, each with one endoscopist performing ESD, analysed data from 188 consecutive patients (mean 6 per centre, range 1–43) (*Endoscopy* 2011, 43: 664-670).

The cancers treated with ESD were: stomach (*n*=75), oesophagus (*n*=27), duodenum (*n*=1), caecum (*n*=3), right-sided colon and transverse colon (*n*=8), sigmoid (*n*=3), and rectum (*n*=72). The mean size of lesions treated was 26 mm, with the largest being 150 mm. Most lesions were high-grade dysplasia or mucosal cancer (71.2%). *En bloc* resection was performed in 77.1% of cases, which was a little bit worse than figures from Japan, and the R0 resection rate was 72.9%. The mean duration was 105 minutes and the complication rate was 29.2% (34 perforations, which is high, and 21 cases of bleeding), with most resolved conservatively.

The number of ESD procedures being carried out is increasing, and their duration and complication rates are decreasing with growing experience. In my unit we performed 50 ESD and EMR procedures in 2014.

## Endoscopic submucosal dissection of a gastric cancer

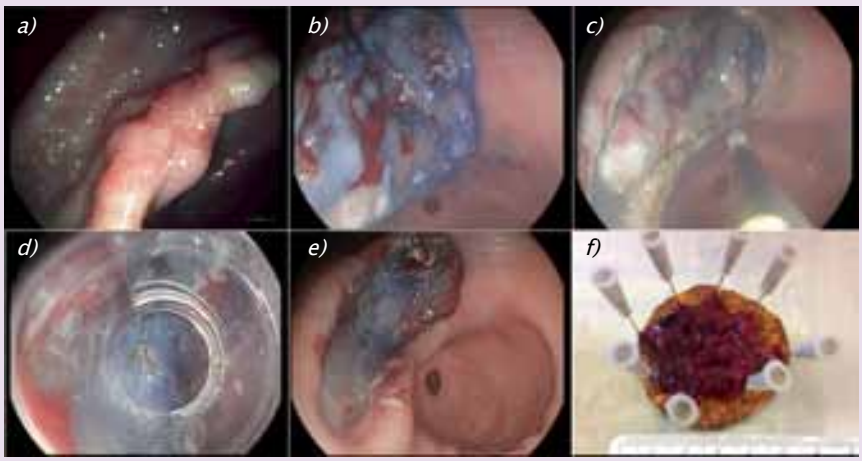


Figure a) shows a clearly suspicious stage IIa–c lesion in the stomach, which had been biopsied in the referring hospital and found to be a gastric cancer. We marked the outer margins and administered a submucosal injection of hyaluronic acid (b), creating a cushion that gave enough space to enable us to resect the lesion in the submucosal layer and in one piece. The next step was to cut around the lesions (c), with indigo carmine used to stain the lesion margins, before mounting the cap (d) and continuing to resect in the submucosal layer and remove the lesion (e). Pathology showed the tumour was limited to the lower third of the mucosal layer, was highly differentiated and there was no lymph node involvement (f). The patient was cured of her gastric cancer by this endoscopic dissection procedure.

## Palliation

The goal of endoscopic palliation is to offer minimally invasive therapy to reduce a patient's suffering and to avoid surgical interventions. Common procedures include bile duct drainage, implantation of endoprostheses in other areas of the gastrointestinal tract, and endoscopic feeding tubes (percutaneous endoscopic gastrostomy, PEG). Although endoscopic palliation is commonly performed, some indications, such as colonic stenting, have to be chosen carefully.

### *Stenting*

Stenting is a very important method for palliation in endoscopy. Stents are most commonly used in the bile duct

## Take home messages

"Seeing in endoscopy" has changed considerably over the last few years. Detection of premalignant lesions or early cancer has become the pinnacle of diagnostic endoscopy.

High- and low-tech image manipulation allows for precise characterisation of a lesion based on its macroscopic appearance.

Endoscopic resection techniques such as submucosal dissection can replace surgery in carefully selected patients.

Endoscopic palliation should be considered as a minimally invasive option in patients with advanced oncologic diseases.

as a palliative measure in unresectable tumours, such as tumours of the pancreas or cholangio-carcinoma. Plastic stents are cheap and widely available but suffer from limited patency, for example biliary stents last for about three months. Metal stents are expensive, but have much longer patency. However, in the case of covered stents they can't be removed. Other common indications for stenting include oesophageal cancer, duodenal obstruction due to pancreatic cancer and, in rare cases, colon cancer.

### *Percutaneous endoscopic gastrostomy (PEG)*

Common oncological indications for endoscopically placed feeding tubes include:

- oro-pharyngeal and oesophageal malignancy with inability to eat
- prolonged stomatitis after radiation therapy for oropharyngeal cancer
- oesophageal fistula and perforation.

A PEG should be considered if prolonged enteral feeding is required for a period of longer than three weeks. PEG placement is generally considered to be relatively safe. Complications such as infection occur quite frequently, but can be avoided by giving a single injection of an antibiotic.

*Question: In times of limited resources, which patients are best for endoscopic palliative treatment?*

*Answer: As a rule of thumb, I would suggest patients who are fit enough to go home after palliative interventions are good candidates. Conservative methods may be preferred for patients in their final days, because of the risk of complications and the limited potential for gains in quality of life and survival time. We discuss options with the patient and their relatives and come to a decision together.*

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# Affordable cancer care: a global mirage?

Richard Sullivan is Director of the Institute of Cancer Policy and Conflict and Health Programme at Kings Health Partners Comprehensive Cancer Centre. He will address a specific challenge in global cancer care in each issue of *Cancer World*.

One of the great myths peddled about cancer control is that it is intrinsically affordable. Nothing could be further from the truth. Preventing and treating cancer is the pinnacle of the health system's mountain. It is the most demanding disease domain to address in health systems planning, as well as being highly sensitive to all the socio-cultural determinants of health. Those of us 'inside' the cancer tent take for granted these interdependencies, but to the 'outside', including most policy makers, cancer is a 'black box'. This is a huge challenge to rational economic and fiscal policy-making. As the Institute of Medicine noted in its *Delivering Affordable Cancer Care in the 21st Century* report, "cancer is such a prevalent set of conditions and so costly, it magnifies what we know to be true about the totality of health care systems. It exposes all of its strengths and weakness."

There are some eye-watering numbers around economic productivity losses due to cancer, particularly premature mortality and morbidity. Lung cancer costs Europe more than €10 billion every year in premature mortality, far outstripping the costs of direct cancer care of around €4.5 billion. And we know from the Lancet Oncology Commission on Global Cancer Surgery that a failure to deliver more surgical workforce, the backbone of cancer care, will cost low-income and emerging powers $7 trillion of cumulative GDP losses by 2030. The Global Taskforce on Radiotherapy also estimates similar losses. The point is not the huge figures, it's that failure to invest in systems for cancer care is going to seriously impact development. Yet we are faced with a range of serious paradoxes.

The first is the cold hard fact that many countries are failing miserably to invest in basic healthcare. Affordable and equitable cancer care cannot be built on sand, and this is just the situation facing many countries now. It's all very well to sign up to Universal Health Coverage, the Sustainable Development Goals and National Cancer Control Plans, but in low-income and emerging powers only a handful of countries have a total health expenditure above the threshold needed to build a cancer system (about 6% of GDP, and more than $100 per capita). The economies of Asia typify the problems affecting many countries: low domestic healthcare spending that is increasingly being backstopped by private health expenditure (*Lancet* 2011:377:863–872). In some Asian countries, such as Laos, Philippines and Cambodia, the private sector now makes up more than two-thirds of total health expenditure.

Should this matter though? The short answer

is yes it does. Only countries with dominant public sector financing, such as Thailand, can deliver equitable and sustainable economic policies to build cancer care. The sad fact is that the mantra from the World Bank and most of the overseas aid donors is that public fiscal policy in cancer is not that important, and gaps can be filled by business, contrary to the evidence from studies such as *Global Health 2035* (*Lancet* 2013, 382:1898–1955). Economic sustainability in cancer control is also in serious doubt in many places. For example, take a stable African country like Uganda. As it stands, around half of the Sustainable Development Goal indicators are currently underperforming (World Bank Group. *Country Diagnostics* Jan. 2015).

The other equally pressing issue is how to protect individuals and families from catastrophic health expenditure. Here too the picture is none too rosy. The Asean costs in oncology study (ACTION) looked at the economic impact of cancer on 9513 patients diagnosed with cancer between March 2012 and Sept 2013, who were recruited from private and public hospitals and cancer centres across eight Asean countries. It found that, one year after diagnosis, 29% had died and nearly half (48%) had suffered financial catastrophe, defined as having to pay more than 30% of their annual income in healthcare costs (*BMC Medicine* 2015, 13:190). The fact is that out-of-pocket expenditures are ruining families. In many countries social health insurance, such as AUGE in Chile and RSBY in India, are also not keeping up with what it actually costs to deliver good basic cancer care in the public sector. A radical overhaul is urgently needed, but with so many competing needs, cancer's place in universal health coverage is not assured.

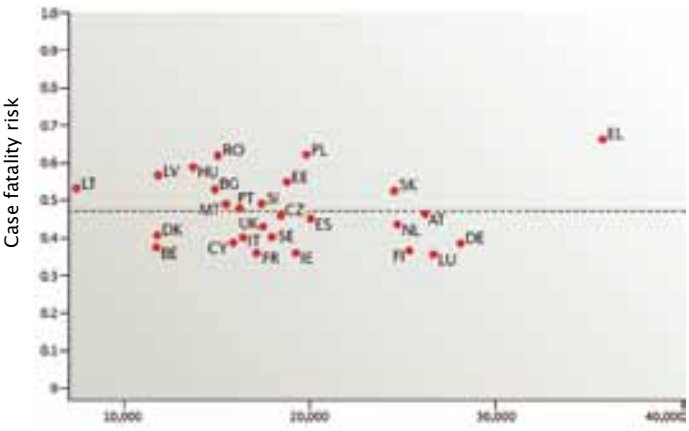
**Only countries with dominant public sector financing can deliver equitable and sustainable cancer care**

The last paradox reflects a deep-seated failure to square trade and investment liberalisation with the needs of public health. The evidence is overwhelming that these are serious drivers of the burden of non-communicable diseases, yet the proliferation of bilateral and regional preferential trade agreements, without any in-built public health protection, will simply drive up cancer risk factor exposure (*Globalisation & Health* 2014, 10:66). Development money today is being traded off against economic losses in health tomorrow.

If this all sounds depressingly familiar, it is. Talking about the cost of cancer is really a debate about how we are going to manage to pay for our healthcare. High-income countries like France are now having to spend more than €11 billion every year to achieve the outcomes their populations enjoy. Yet the needs of the elderly and chronically ill are not being met (*Value in Health* 2010, 13:552–556).

What we do know is that there is no straightforward investment–impact model. Increasing expenditure does not lead automatically to better outcomes without serious structural, organisational and cultural engineering (*Nat Rev Clin Oncol* 2016, 13:137). Irrespective of base funding, too much cancer care is poor value or the focus of corruption. However, just adopting high-income mechanisms for priority setting does not work. Context matters too much, and different ideological and normative values will need very different economic and fiscal strategies, as Thai colleagues have pointed out (*Value in Health* 2009, S26–S30). But this is not an excuse for ignoring the basic building blocks. Fund your health system properly. Invest in a strong public sector system for caring for cancer patients, and protecting them financially. And ruthlessly ensure the quality and fiscal probity of services from both public and private sector.

## Some cancer systems get more for their money than others




Healthcare costs per incident case adjusted for price differentials (€, 2010 – 2011)

This graph, which plots cancer patients' risk of dying against the per patient spend, shows that some EU countries spend almost three times as much as others for comparable outcomes (e.g. Belgium v Germany)

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**1.** Aapro MS, et al.; Eur J Cancer. 2011; 47: 8–32. **2.** Sandoz data on file, US Brand name: Zarxio® (filgrastim-sndz). **3.** Zarzio® Summary of Product Characteristics. **4.** Gascón P, et al.; Support Care Cancer 2013; 21(10): 2925–2932. **5.** Verpoort K, Möhler TM. Ther Adv Med Oncol 2012; 4(6): 289–293. **6.** Salesi N, Di Cocco B, et al.; Future Oncol 2012; 8(5): 625–630. **7.** Bonig H, et al.; Transfusion 2015; 55: 430–439. **8.** Gascón P, et al.; Cancer Rev 2015; 75: P5-15-19. **9.** www.sandoz.com; accessed 26 May 2015. **10.** Sorgel F, et al.; Biodrugs 2010; 24(6): 347–357. **11.** Gascon P, et al.; Ann Oncol 2010; 21(7): 1419–1429.


**ABBREVIATED Prescribing Information. Zarzio® (Filgrastim).** Zarzio® (Filgrastim) Abbreviated Prescribing Information. Please refer to the Summary of Product Characteristics before prescribing Zarzio®. Zarzio® is a recombinant human Granulocyte-Colony Stimulating Factor (G-CSF). **Presentations:** 30 MIU/0.5 ml and 48 MIU/0.5 ml solution for injection or infusion in pre-filled syringe. **Indications:** Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. Mobilisation of peripheral blood progenitor cells (PBPC). In children and adults with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of ≤0.5 x 10⁹/l, and a history of severe or recurrent infections. Treatment of persistent neutropenia (ANC ≤ 1.0 x 10⁹/l) in patients with advanced HIV infection. Please refer to the Summary of Product Characteristics for full prescribing indications. **Administration:** Zarzio® should only be given in collaboration with appropriate and experienced specialist centres with the necessary facilities. If required, Zarzio® may be diluted in glucose 50 mg/ml (5%) solution; see Summary of Product Characteristics for details. *Established cytotoxic chemotherapy:* Subcutaneous injection or intravenous infusion (over 30 mins). *Patients treated with myeloablative therapy followed by bone marrow transplantation:* Intravenous short-term infusion (over 30 mins) or a subcutaneous or intravenous continuous infusion over 24 hours. *Mobilisation of PBPC:* Single day subcutaneous injection (5-7 consecutive days) or subcutaneous continuous infusion over 24 hours. *Severe chronic neutropenia (SCN)/HIV infection:* Subcutaneous injection. **Dosage:** For the approved indications the typical dosage range is from 0.1 MIU/kg/day to 1.2 MIU/kg/day. For the detailed instructions on dosage, please refer to the Summary of Product Characteristics. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions:** Special warnings: Zarzio® should not be used to increase the dose of cytotoxic chemotherapy beyond established posology regimens. Zarzio® should not be administered to patients with severe congenital neutropenia who develop leukaemia or have evidence of leukaemic evolution. Established cytotoxic chemotherapy. *Malignant cell growth:* Zarzio® is not indicated for use in patients with myelodysplastic syndrome or chronic myelogenous leukaemia. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia. Caution should be taken in patients with secondary acute myelogenous leukaemia (AML). Safety and efficacy of filgrastim administration in *de novo* AML patients <55 years with good cytogenetics (t(8;21), t(15;17), and inv(16)) have not been established. *Leucocytosis:* White blood cell counts should be performed at regular intervals during therapy. If leukocyte counts exceed 50 x 10⁹/l after the expected nadir, Zarzio® should be discontinued immediately. For PBPC mobilisation, Zarzio® should be discontinued or reduced if the leukocyte counts rise to >70 x 10⁹/l. *Risks associated with increased doses of chemotherapy:* Intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurologic, and dermatologic effects (please refer to the Summary of Product Characteristics of the specific chemotherapy agents used). Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia. *Other special precautions:* In patients with reduced precursors, neutrophil response may be diminished (see Summary of Product Characteristics for details). There have been reports of Graft versus Host Disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (refer to Summary of Product Characteristics). Mobilisation of PBPC. *Prior exposure to cytotoxic agents:* After extensive myelosuppressive therapy, Zarzio® may not show sufficient mobilisation of PBPC to achieve the recommended minimum yield or acceleration of platelet recovery (see Summary of Product Characteristics for details). *Assessment of progenitor cell yields:* Results of flow cytometric analysis of CD34⁺ cell numbers vary depending on the precise methodology used, therefore, recommendations of numbers based on studies in other laboratories need to be interpreted with caution (see Summary of Product Characteristics for details). *Normal donors prior to allogeneic PBPC transplantation:* Only to be considered in normal donors for the purpose of allogeneic stem cell transplantation. Thrombocytopenia has been reported very commonly in patients receiving filgrastim. Platelet counts should therefore be monitored closely. Transient thrombocytopenia following G-CSF administration and leukapheresis has been observed (see Summary of Product Characteristics for further details). Zarzio® should be discontinued or the dose reduced if the leukocyte counts rise to >70 x 10⁹/l. Donors who receive G-CSFs for PBPC mobilisation should be monitored until haematological indices return to normal (see Summary of Product Characteristics for details). Transient cytogenetic modifications have been observed in normal donors following G-CSF use. Spleen size should be carefully monitored. A diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal pain or shoulder tip pain. *Recipients of allogeneic PBPCs mobilised with Zarzio®:* Immunological interactions between the allogeneic PBPC graft and recipient may be associated with an increased risk of acute and chronic GvHD when compared with bone marrow transplantation. SCN. *Blood cell counts:* Thrombocytopenia has been reported commonly in patients receiving filgrastim. Platelet counts should be monitored closely, especially during the first few weeks of therapy. Consideration should be given to intermittent cessation or decreasing the dose in patients who develop thrombocytopenia. Other blood cell changes occur, including anaemia and transient increases in myeloid progenitors, which require close monitoring of cell counts. *Transformation to leukemia or myelodysplastic syndrome:* Special care should be taken in the diagnosis of SCNs to distinguish them from other haematopoietic disorders. Complete blood cell counts with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approx. every 12 months - see Summary of Product Characteristics for details). *Other special precautions:* Causes of transient neutropenia, such as viral infections should be excluded. Splenic enlargement is a direct effect of G-CSF, and spleen size should be monitored regularly. Regular urine analyses should be performed to monitor haematuria/proteinuria. The safety and efficacy in neonates and patients with autoimmune neutropenia have not been established. HIV infection: *Blood cell counts:* ANC should be monitored closely, especially during the first few weeks of Zarzio® therapy (see Summary of Product Characteristics for details). *Risk associated with increased doses of myelosuppressive medicinal products:* Regular monitoring of blood counts is recommended (see Summary of Product Characteristics for details). *Infections and malignancies causing myelosuppression:* The effects of G-CSF on neutropenia due to bone marrow infiltrating infection or malignancy have not been well established (see Summary of Product Characteristics for details). Other special precautions: Pulmonary adverse reactions such as interstitial pneumonia have been reported following G-CSF treatment, and patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. Monitoring of bone density may be indicated in patients with underlying osteoporotic bone diseases who undergo continuous therapy with Zarzio® for more than 6 months. Physicians should exercise caution when considering the use of Zarzio® in patients with sickle cell disease and carefully evaluate the potential risks and benefits of treatment (see Summary of Product Characteristics for details). Capillary leak syndrome has been reported after G-CSF administration and patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions. Excipients: Zarzio® contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use Zarzio®. In order to improve the traceability of G-CSFs, the trade name of the administered product should be clearly recorded in the patient file. **Interactions:** Use is not recommended in the period from 24 hours before to 24 hours after myelosuppressive cytotoxic chemotherapy. Preliminary evidence from a small number of patients treated concomitantly with G-CSF and 5-fluorouracil indicates that the severity of neutropenia may be exacerbated. Possible interactions with other haematopoietic growth factors and cytokines have not yet been investigated in clinical studies. Lithium is likely to potentiate the effect of G-CSF. **Pregnancy and lactation:** There are no or limited data in pregnant women available. There are literature reports where the transplacental passage has been demonstrated. Animal studies show no evidence of teratogenicity. Zarzio® should be used in pregnancy only if the expected benefit outweighs the potential risk to the foetus. Use whilst breast-feeding is not recommended. **Effects on ability to drive and use machines:** Zarzio® has no or negligible influence on the ability to drive or use machines. **Undesirable effects:** In cancer patients, the most frequent undesirable effects were musculoskeletal pain which was mild or moderate in 10%, and severe in 3% of patients. GvHD has also been reported. In PBPC mobilization in normal donors the most commonly reported undesirable effect was musculoskeletal pain. Leucocytosis was observed in donors and thrombocytopenia following G-CSF and leukapheresis was also observed in donors. Splenomegaly and splenic rupture were also reported. Some cases of splenic rupture were fatal. In SCN patients the most frequent undesirable effects attributable to G-CSF were bone pain, general musculoskeletal pain and splenomegaly. Myelodysplastic syndromes (MDS) or leukaemia have developed in patients with congenital neutropenia treated with G-CSF (see Summary of Product Characteristics for details). Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥ 1/1000 to < 1/100) in cancer patients undergoing chemotherapy and healthy donors undergoing peripheral blood progenitor cell mobilisation following administration of G-CSFs (see Summary of Product Characteristics for details). In clinical studies in patients with HIV, the only undesirable effects that were consistently considered to be related to G-CSF administration were musculoskeletal pain, bone pain and myalgia. **List of excipients:** Glutamic acid, sorbitol (E420), polysorbate 80, water for injections. **Shelf life:** 36 months. **Special precautions for storage:** Store in a refrigerator (2°C–8°C). Keep the pre-filled syringe in the outer carton in order to protect from light. Within its shelf-life and for the purpose of ambulatory use, the patient may remove the product from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 72 hours. At the end of this period, the product should not be put back in the refrigerator and should be disposed of. **Nature and contents of container:** Pre-filled syringe (type I glass) with injection needle (stainless steel), with or without a needle safety guard, containing 0.5 ml solution. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex; see Summary of Product Characteristics for details). Pack sizes of 1, 3, 5 or 10 pre-filled syringes. Not all pack sizes may be marketed. **Legal category:** Medicinal product subject to restricted medical prescription. **MA numbers:** EU/1/08/495/001, EU/1/08/495/002, EU/1/08/495/003, EU/1/08/495/004, EU/1/08/495/005, EU/1/08/495/006, EU/1/08/495/007, EU/1/08/495/008, EU/1/08/495/009, EU/1/08/495/010, EU/1/08/495/011, EU/1/08/495/012, EU/1/08/495/013, EU/1/08/495/014, EU/1/08/495/015, EU/1/08/495/016. Availability of pack sizes may vary between individual EU member states. **MA holder:** Sandoz GmbH, Biochemiestr. 10, A-6250 Kundl, Austria. Further information is available from: Sandoz International GmbH, Industriestr. 25, 83607 Holzkirchen, Germany. Additional information may be obtained also from your local Sandoz office. **Last revision of text:** December 2014

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# Improving care for patients with rare cancers

## *Are European reference networks the answer?*

As the European Commission issues its first call for proposals to set up European reference networks, **Anna Wagstaff** asks: how can these cross-border healthcare structures improve the quality of care received by the almost half a million Europeans who are diagnosed with a rare cancer each year.

Nobody wants to be told that their 15-year-old daughter has a cancer that cannot be removed without cutting out her entire stomach. But when the medical team – at one of the top children's hospitals in the country – also tells you that they've never seen anything like it before and don't know exactly how to treat it, that is a very lonely and frightening place to be.

That is certainly how Jayne Bressington felt six years ago. The surgeons, who had aborted an operation to remove the growth after seeing how far it had invaded the young teenager's stomach, had taken an informed guess that it could be a gastro-intestinal stromal tumour (GIST) – a rare type of sarcoma, which is itself a rare cancer, and is most commonly found in 50- to 70-year-olds. Tests revealed they were in the right area: it was a rare form of GIST, known as a paediatric-adolescent wild-type syndromic (PAWS) GIST – which was more a description than classification, being a GIST that occurs in young people and does not have either the KIT or PDGFRA mutation, which characterise 85% of all GISTs. So an extremely rare cancer.

The advice was to agree to the removal of her daughter's stomach. Bleeding from the tumour was causing severe anaemia that could be controlled only through regular transfusions, and would eventually be life threatening. It had to come out.

Bressington was not keen. Like many people in similar situations, she turned to the Internet. She would have given anything at that point to have been directed to a PAWS-GIST centre of excellence in the UK, or indeed anywhere in Europe – somewhere that specialised in treating young people like her daughter, had experience caring for similar patients, and was engaged in research. But she found no such place.

Happily, thanks to a tip-off from one of the doctors who'd been doing some research of his own, Jayne and her daughter did find what they needed in the US. The only PAWS-GIST clinic in the world convened twice a year at the National Institutes of Health in Bethesda, Washington DC, flying in specialists from different disciplines from all over the country to consult with patients who found their way there.

Jayne Bressington brought two things back with her from that clinic. The first

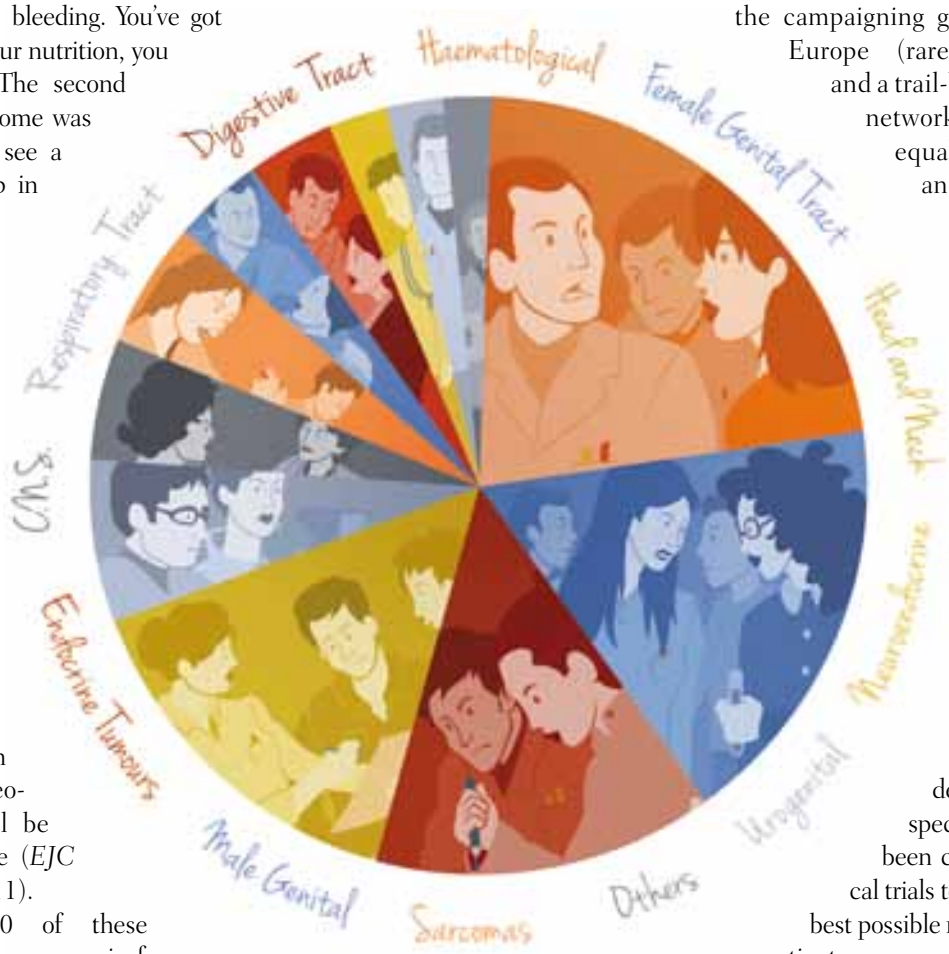
was the confidence to say "no" to surgery. The advice from "the most knowledgeable people in the world," had been categorical: "Resist at all costs having your stomach removed. You have to find every way possible to stop the bleeding. You've got to grow, you need your nutrition, you need a stomach." The second thing she brought home was a determination to see a similar clinic set up in the UK.

## European Reference Networks

There are almost 200 different types of rare cancer (defined as fewer than 6 cases per year per 100,000 people), and every year, more than half a million people in Europe will be diagnosed with one (*EJC* 2011, 47:2493–2511).

Around 120,000 of these will be cancers that are seen in fewer than 1 person per 100,000. Many of those affected scour the internet, as Jayne Bressington did, to find doctors and centres with the expertise to give them the best possible chance of surviving with a good quality of life. Many will not find what they are looking for.

Their chances of finding a specialist centre may considerably improve, however, thanks to an EU policy promoting the setting up of European reference networks, which formed part of the 2011 cross-border healthcare directive. The idea is to harmonise and improve the standard of care available to patients with rare diseases across Europe by building networks that link designated centres of expertise within and between the member states.

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The 12 groups of rare cancers. Research by the EU-funded RareCare project identified almost 200 types of rare cancer. A consensus exercise carried out by Rare Cancers Europe grouped these into 12 families, each of which, they argue, needs its own European reference network

How these networks will work in practice remains to be seen. The first call for proposals was issued by the European Commission in mid-March. As healthcare is beyond the competence of the European Commission, power to approve or reject proposals has been put in the hands of a 'Board of Member States', which will deliberate on the first round of proposals sometime after the summer deadline, and make its decision. Paolo Casali, chair of the campaigning group Rare Cancers Europe (rarecancerseurope.org), and a trail-blazer in rare cancer networking, is waiting with equal measures of hope and trepidation.

## Hopes and fears

When it comes to networking to improve the care of people with rare cancers, no-one does it better than the paediatric oncologists. Every paediatric cancer is a rare cancer, and for decades this group of specialist clinicians have been collaborating on clinical trials to learn how to get the best possible results for their young patients.

In recent years, specialists in other forms of rare cancers have begun to follow their lead and have used EU funding to set up their own networking projects. Casali himself played a key role in setting up the Concatinet network, which linked teams in a number of European countries with expertise in diagnosing and treating more than 25 types of connective tissue cancers known as sarcomas.

Casali's biggest hope for European reference networks is that they will dovetail with rare disease communities like his that are already organising

themselves and their work – his biggest fear is that they won't.

One serious concern is that the Board of Member States has failed to grasp how many people are affected by rare cancers. "Using a conservative definition, rare cancers are 20% of new cancer cases. Clearly they are at the heart of the field of oncology. This must be properly understood or the networks will fail," Casali warns.

A consensus exercise carried out by Rare Cancers Europe succeeded in sorting almost 200 types of rare cancer into a minimum of 12 family groups, each with its own community of experts, reference institutions and patients. The signals coming from the Board of Member States, however, is that they are looking to keep the total number of rare cancers networks very low – maybe two or three.

This might mean a single network for paediatric cancers, as has already been set up in the form of a three-year pilot project (see box), and one for haematological cancers, possibly grouped with other rare diseases of the blood. The expectation seems to be that the entire spectrum of adult solid rare cancers would be taken care of by a single network, even though each involves different communities and institutions, requires different approaches to diagnosis and management, and the specialists in Europe are already working together within their specific communities.

Casali accepts that it might be possible to organise subnetworks within one big network, but argues that this would add an unnecessary and bureaucratic layer of complexity. Specialists in sarcomas already work with one another and constantly meet at conferences and other forums, as do people specialising in head and neck cancers or endocrine tumours, and so forth, he says, so it makes sense to set up reference networks that mirror this reality.

The other big concern for Casali is research. Linking care and research has become a mantra throughout the cancer community, but nowhere is this more important than for rare cancers, where the evidence base for diagnosis and management is sorely lacking, and the small size of patient populations makes it imperative to recruit every patient possible into trials, or at least ensure that the details from each patient's history contributes to building up new knowledge.

When pressed on this issue at a meeting on European reference networks called by the European Commission last October, however, the Commission was very clear: the primary purpose of reference networks is to provide care – they are not intended for research.

But Casali argues that the two can and should go hand in hand: "Care can be well accomplished without giving up the goal of research."

**Linking care and research has become a mantra throughout the cancer community – nowhere is this more important than for rare cancers**

The heavy focus on care is reflected in the structure of the networks, where only healthcare institutions can join as designated centres of expertise. Professional bodies that develop clinical practice guidelines, such as ESMO, and research organisations such as the EORTC – which is currently setting up a rare cancers screening platform to improve access to trials – will probably be relegated to operating on the fringes of the networks.

"Why not acknowledge and build on the reality of the networking that the oncology community has already built over recent decades?" asks Casali, "rather than acting as if oncology networking in Europe is a blank slate."

## Making the networks work

Even in the worst case scenario, Casali recognises that the European reference networks will mark an important step forward, because centres joining the networks will be endorsed by governments. This means that patients will have somewhere in Europe to turn to that has been endorsed by its government, and is linked to a formal European network.

It also creates conditions for building networks within countries, and promoting policies on referral or shared care to ensure that the diagnosis and care of patients with rare cancers is handled by professionals with the greatest expertise, and not by the first doctor they encounter. "Clearly some health systems work better on rare cancers than others," says Casali, "This could lead to a kind of harmonisation, because governments are involved."

That said, the rare cancers community is not intending to sit idly by to see how these networks develop, says Casali. Rare Cancers Europe has been instrumental in getting agreement to set up a European Joint Action on Rare Cancers, "with the overarching aim of helping shape European reference networks in the best way possible for member states."

The Joint Action is going to have to move pretty quickly, given that the networks have already been defined and the first call for proposals has been issued. However, there is a lot still to play for in how these networks will operate in practice.

Because the Joint Action group includes representatives from many member states, it should offer the chance to look at how European reference networks can meet varying needs and priorities in different countries.

Casali, for instance, based in Italy – population 60 million – sees European reference networks more in terms of "networks of [national] networks". Italy records 2000 new sarcoma cases each year, so the role of its national hub will be to ensure that patients diagnosed anywhere in the country benefit from expert diagnostics and care planning, rather than discussing routine cases across borders.

Slovenia, by contrast, with its population of 2 million, can expect to see closer to 100 cases a year, spread between many different types of sarcoma, diagnosed at different stages and in patients with different needs and priorities. Slovenian sarcoma specialists may well value the opportunity to discuss cases with experts in other countries. They may be less interested, however, in building a national network, as care of complex or rare cases is largely concentrated in Ljubljana's Institute of Oncology.

Tanja Čufer, Professor of Oncology at the University of Ljubljana, would like the Joint Action to raise the issue of access to clinical trials in other EU countries, which she sees as crucial for people with rare cancers, and is not covered by the reference networks' remit. She points out that, "There are more and more small countries, and more and more rare cancers," and says a solution must be found.

She gives as an example, ROS-positive lung cancer, which makes up just 1% of non-small-cell lung cancers. "There is no routine care, so these patients need access to clinical trials in larger countries, because we don't have clinical trials for all these rare cancers in such a small country."

Winning the argument on cross-border access to trials, she hopes, may be easier once you have accredited centres and European networks to make the case.

Patient advocacy groups have their own priorities. For Paulina Gmaj, who is active in the Polish sarcoma patient advocacy group Stowarzyszenie Pomocy Chorym na Mięsaki Sarcoma, having a government-designated centre of expertise is not the big issue. Poland does have an institution that acts as a reference centre – the problem is it has only one (for adult patients), serving a population of almost 40 million spread across a very large country. For her, the major obstacles include late diagnosis due to poor awareness among the public and GPs; lack of accurate information for patients and poor doctor–patient communication; and poverty, which limits access to best care. In Poland, she says, many people can't afford to travel for appointments within the country, let alone across borders.

Gmaj believes that effective European networks could do a lot to address at least some of these needs. They could, for instance, develop patient friendly information for advocacy groups to disseminate (including information about clinical trials for those who can afford to pay). They could also give patients access to second opinions, and help harmonise standards of care.

**"There is no routine care, so these patients need access to clinical trials in larger countries "**

In Belgium, the problem is almost the reverse. Véronique de Graeve, President of the NET & MEN advocacy group for patients with neuroendocrine tumours and multiple endocrine neoplasia, says that Belgium has several centres and

## The paediatric pilot

Reference networks are being been piloted in paediatric oncology. The three-year ExPO-r-Net project (European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment – http://expornet.siope.comsbox.com/), was launched in 2014 to build a European Reference Network for Paediatric Oncology.

It has started:

- tackling technical and legal (privacy and medical liability) issues involved in conducting cross-border tumour boards
- identifying the types of patient who need a particular concentration of resources or expertise, where European networking could be most valuable
- setting up a partnering scheme to improve access to high-quality healthcare in countries where that is not available due to low case volumes and/or lack of local resources – the emphasis is on moving information, not the patient, wherever possible.

ExPO-r-Net involves 18 core partners and more than 50 collaborating professional partners (professionals, hospitals, institutes) from 17 countries, as well as parents and patients.


The world's second PAWS-GIST clinic. Jayne Bressington (*far right*), who was instrumental in making it happen, is pictured with (*from right to left*) Dochka Davidson (sarcoma specialist nurse), Richard Hardwick, (upper GI tract surgeon), Ramesh Bulusu (clinical oncologist, and clinical lead for the PAWS-GIST clinic), Palma Dileo (medical oncologist specialising in sarcoma) and Jason Bossert (formerly project manager).

European reference networks could help ensure patients with rare cancers like PAWS-GIST have a government-accredited reference centre somewhere in Europe they can turn to. But their impact on boosting research and spreading best practice will depend on how well they dovetail with the way rare cancers communities already work together.

professionals with expertise in NETs (less so for MENs), but that patients often don't know where to find them. "Even general practitioners don't really know where to refer their patients so the best care can be given," she says, "because we still don't have official national lists with experienced or recognised NET doctors or centres." The government, she adds, is in the process of setting up a patients' portal to provide relevant information to both patients and professionals.

de Graeve's concerns are that the European reference network model, with its emphasis on centres of expertise, could lead to pressures for services to be more centralised than they need to be. "An isolated NET reference centre is not the way we see it in Belgium," she says. "I prefer the 'shared care' between reference centres and peripheral hospitals… you need to respect what people are used to."

## Room for manoeuvre?

There are, in short, plenty of views and opinions about how European reference networks should function. But will the rare cancers community really be able to influence how they develop in practice?

If the PAWS-GIST story in the UK is anything to go by, the answer is an unequivocal yes. On her return from the US, Bressington started her quest to found a similar specialist clinic in the UK with a Google search for "Dr+GIST", which came up with 33 names in the UK. Together with a patient advocate from GIST Support UK, she wrote to them all, saying, "We're in this terrible situation. Nobody knows what's ailing our daughters, and there is no treatment. We want to set up a focus group in the UK."

Eleven responded; one of them, Ramesh Balusu at Addenbrookes in Cambridge, saying he would be happy to lead the initiative. Four years of frenetic activity followed, raising funds, setting up a tissue bank, sorting out a registry and increasing the pool of patients from the three they started with to 70. They also set up a PAWS-GIST collaborative research initiative – a multidisciplinary team effort that aims to improve care and find innovative treatments for patients with this rare cancer.

If you Google PAWS-GIST from anywhere in the world now, you will find your way to the world's second PAWS-GIST clinic (www.pawsgistclinic.org.uk), which convenes four times a year, has so far seen 40 patients, and is about to be written into the latest edition of the UK national guidelines for diagnosing and managing GIST. Patients across Europe get in touch, and specialists approach Balusu at conferences to talk about setting up something similar in their own countries. A few weeks ago, PAWS-GIST received its first requests for seed funding to kickstart two research projects – "A dream come true," says Bressington.

So what would Bressington look for in a European reference network? "It would have to be able to help transform the situation from where we are now to where patients need to be," she says, "ie a system that naturally facilitates research – a network of GIST registries, which includes mutational status; mutational testing as standard; a network of GIST tissue banks; a network of agreed specialist centres focusing on PAWS-GIST patients in collaboration with their local physician."

It doesn't sound quite what the Commission has in mind. But as we await the responses to the first call for proposals, there is still much to play for. With determined players like Bressington on the field, there may still be a chance to ensure that the reference networks provide what people with rare cancers really need.

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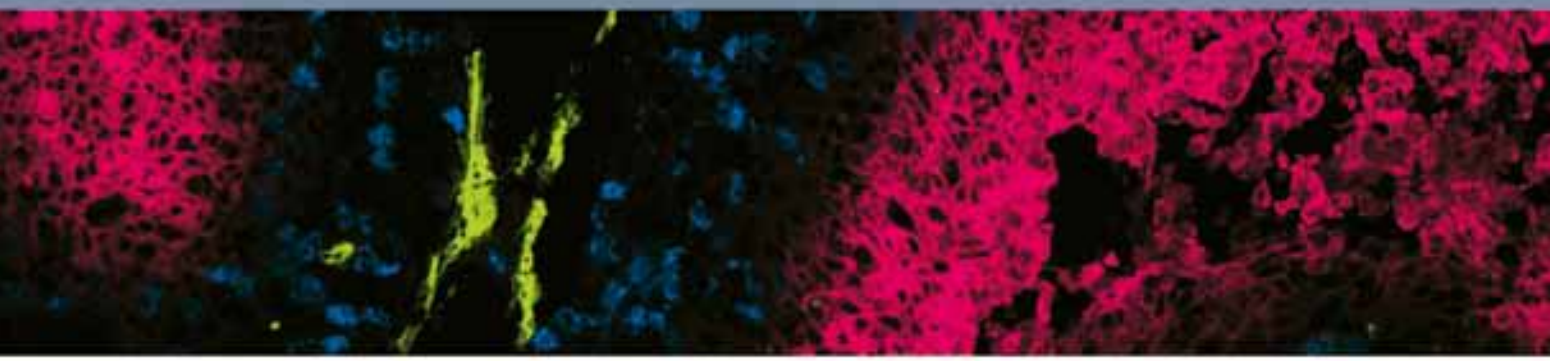

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# Novel approaches to pancreatic cancer

With a five-year overall survival of less than 5%, there is an urgent need to explore new treatment paradigms for pancreatic cancer, including targeting stroma cells, cancer stem cells and metabolic pathways. **Ignacio Garrido-Laguna** and **Manuel Hidalgo** outline the current standard of care and review promising novel treatments.

*This is an abridged version of I Garrido-Laguna and M Hidalgo (2015) Pancreatic cancer: from state-of-the-art treatments to promising novel therapies.* ***Nat Rev Clin Oncol*** *12:319–334. It was edited by Janet Fricker and is published with permission* ©*2015 Nature Publishing Group. doi:10.1038/nrclinonc.2015.53*

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Surgery is still the only curative treatment for pancreatic cancer; however, therapeutic strategies based on initial resection have not substantially improved the survival of patients with resectable disease over the past 25 years. Presently, more than 80% of patients suffer disease relapse after resection.

## The state of the art

### *Resectable disease*

More effective chemotherapy backbones are currently being tested in the adjuvant setting (nab-paclitaxel plus gemcitabine, APACT trial) and FOLFIRINOX (PRODIGE study).

## Neoadjuvant therapy

Potential advantages for neoadjuvant therapy include increasing negative margin (R0) resection rates, improving surgical selection, earlier treatment of micrometastatic disease, and enhancing chemoradiotherapy delivery.

Single-institution studies suggest neoadjuvant treatment increases the rate of R0 resections. Such findings contrast with a retrospective analysis of resections of pancreatic ductal adenocarcinoma between 1992 and 2011, which showed no R0 margin differences between upfront resection and neoadjuvant treatment (*World J Surg* 2014, 38:1184–95).

Meta-analyses have consistently failed to demonstrate neoadjuvant survival advantages. A lack of consensus over which tumours are borderline resectable influenced results.

Predictive biomarkers of response to gemcitabine or 5-fluorouracil (5-FU) are urgently needed.

## Unresectable disease

The ECOG 4201 trial demonstrated a modest improvement in survival

for chemoradiotherapy compared to gemcitabine, but with increased toxicity (*JCO* 2011, 29:4105–12). The FFCD/ SFRO study, however, suggested detrimental overall survival for chemoradiotherapy versus gemcitabine therapy (*Ann Oncol* 2008, 19:1592–99).

The rationale for the detrimental effects of chemoradiotherapy comes from a study showing enhanced invasiveness for cancer cells co-cultured with irradiated fibroblasts due to activation of MET and MAPK signalling pathways (*Cancer Res* 2004, 64:3215–22).

The SCALOP trial demonstrated that capecitabine is superior to gemcitabine as a radiosensitiser (*Lancet Oncol* 2013, 14:317–326).

Clinical trials are needed to validate biomarkers to identify patients less likely to benefit from chemoradiotherapy. The RTOG 1201 trial is currently testing nab-paclitaxel plus gemcitabine followed by chemoradiation. This study stratifies patients according to *SMAD4* status. The hypothesis is that patients with preserved *SMAD4* may benefit from intensification of local therapy.

### *Advances in metastatic disease*

Over the past decade, single-agent gemcitabine has been the standard of care in metastatic pancreatic ductal adenocarcinoma, with multiple trials failing to show that adding targeted therapies improves survival.

Two positive trials have been reported in advanced-stage pancreatic cancer. The PRODIGE-III trial showed better survival (HR 0.57) with FOLFIRINOX over gemcitabine (*NEJM* 2011, 364:1817–25), while the MPACT study showed nab-paclitaxel plus gemcitabine delivered better survival (HR 0.72) than gemcitabine (*NEJM* 2013, 369:1691–1703).

## Novel treatment opportunities

Given the poor clinical outcomes for pancreatic ductal adenocarcinoma, novel strategies are needed.

### *Drugs targeting pancreatic cancer cells*

**Cytotoxic agents.** To tackle the desmoplastic response in pancreatic ductal adenocarcinoma, where dense fibrous tissue grows around tumours, novel formulations of classic cytotoxic agents are currently under development.

MM-398, a nanoliposomal formulation of irinotecan, was recently approved by the US FDA, in combination with 5-FU, for patients with metastatic pancreatic cancer refractory to gemcitabine. The NAPOLI-1 study showed a modest improvement in survival (8 weeks) with the combination compared to 5-FU alone (*Ann Oncol* 2014, 25:ii105–ii117). It is unclear whether MM-398 will provide any benefit to patients who have received first-line therapy with nab-paclitaxel and gemcitabine, as such patients were not included in the study.

TH-302, a releasing DNA-alkylating agent activated under hypoxic conditions, recently failed to provide any added survival benefit to gemcitabine in the MAESTRO trial (Van Cutsem et al. Abstract #193 ASCO GI 2016).

The 'synthetic lethality' strategy holds some promise in patients with aberrations in DNA-repair pathways. A basket study tested olaparib in patients with germline *BRCA1/2* mutations in *BRCA*-associated cancers. The response rate in patients with pancreatic cancer ($n$=23) was 21%.

**RAS pathway inhibitors.** Activating *KRAS* mutations are found in more than 90% of pancreatic ductal adenocarcinomas. Inhibition of oncogenic RAS signalling might be achieved by multiple mechanisms including blocking RAS protein transport to the cell membrane, and inhibiting oncogenic RAS activity directly or indirectly through targeting downstream pathway components.

Owing to the complexity of directly targeting *KRAS*, efforts have focused on downstream components of the RAS pathway, such as MEK. Unfortunately, clinical trials with MEK inhibitors (trametinib or pimasertib) have provided disappointing results. Inhibition of ERK has shown promising activity in preclinical models. A phase 1b study will be testing BVD-523 (an ERK inhibitor) in combination with nab-paclitaxel and gemcitabine (NCT02608229) in patients with advanced pancreatic cancer.

**Janus kinase inhibitors**. High throughput gene-expression analysis showed enrichment of the JAK–STAT pathway in pancreatic cancer (*Pancreas* 2014, 43:198–211). A randomised phase II study failed to show survival benefit when ruxolitinib (a JAK inhibitor) was added to capecitabine. In a small subset of patients with markers of systemic inflammation, a modest improvement in survival was identified. Two phase III trials evaluating capecitabine plus ruxolitinib in second-line advanced stage pancreatic ductal adenocarcinoma are ongoing.

**Drugs targeting tumour metabolism.** To survive hostile desmoplastic microenvironments, cancer cells reprogramme metabolic pathways to metabolise 10 times more glucose than normal. In addition, cancer cells process glucose through high rates of glycolysis and anaerobic conversion of pyruvate to lactate (Warburg effect). Nutrient deprivation

also activates autophagy, enabling cancer cells to utilise internal fuel sources. Hydroxyl-chloroquine, an autophagy inhibitor approved for malaria, is being evaluated in a neoadjuvant setting and advanced-stage disease in combination with nab-paclitaxel plus gemcitabine.

**PI3K–mTOR pathway inhibitors.** Mutations in *PIK3CA*, encoding part of the PI3K subunit, have rarely been reported in pancreatic ductal adenocarcinoma. While two phase II trials failed to demonstrate therapeutic activity for rapalogues targeting mTOR (the downstream effector of PI3K–AKT signalling), a case report in a patient with *STK11*-positive pancreatic cancer showed a response to everolimus. In future, next-generation DNA sequencing could identify patients most likely to respond to mTOR inhibitors.

### *Drugs targeting stromal compartments*

A growing body of evidence suggests that crosstalk between malignant epithelial cells and surrounding stroma results in cancer cell proliferation, survival and resistance.

**Hedgehog inhibitors.** A phase II trial did not observe progression-free survival benefits when the SMO inhibitor vismodegib was added to gemcitabine in patients with chemonaïve metastatic pancreatic cancer. Vismodegib is currently being evaluated in combination with nab-paclitaxel and gemcitabine. The clinical failure of HH pathway inhibitors in pancreatic cancer may be better understood in light of preclinical evidence suggesting pathway inhibition releases tumour restraining influences of the stroma.

**Enhancing drug delivery using hyaluronidase.** Hyaluronic acid, a glycosaminoglycan extracellular matrix component, is enriched in the hypovascular stroma of pancreatic ductal adenocarcinoma. Degradation of hyaluronic acid might overcome physical barriers, enhancing drug delivery. In a phase II study, the addition of PEGPH20 (a recombinant human hyaluronidase) to nab-paclitaxel and gemcitabine resulted in increased response rate and progression-free survival in *post-hoc* analysis (Hingorani et al Abstract #4006 ASCO 2015).

### *Drugs targeting cancer stem cells*

The concept of cancer stem cells driving tumour growth remains controversial. Expression of cancer stem cell markers in pancreatic ductal adenocarcinoma specimens was associated with shorter survival. In patient-derived xenograft models, treatment with drugs targeting cancer stem cells increased survival. However, as cancer stem cells frequently represent less than 1% of total tumour cells, drugs targeting cancer stem cells are unlikely to result in objective responses. Nevertheless, in advanced-stage pancreatic ductal adenocarcinoma, several drugs inhibiting signalling pathways associated with cancer stem cells are being tested in combination with chemotherapy.

### *Immunotherapy*

Pancreatic cancers are characterised by immune-suppressive microenvironments believed to be orchestrated by multiple cell types recruited to the tumour, including cancer-associated fibroblasts, myeloid-derived suppressor cells, and tumour infiltrating lymphocytes. Disrupting immunosuppressive networks might provide new treatment opportunities.

**Monoclonal antibody immunotherapies.** Cancer cells evade natural immune responses by modulating T-cell signalling and inducing immune tolerance. While monoclonal antibodies targeting the checkpoint inhibitor PD-1 and its ligand PD-L1 have proved effective in non-small-cell lung cancer and melanoma, responses have not been observed in pancreatic cancer. Furthermore, ipilimumab, an anti-CTLA4 monoclonal antibody, failed to show significant activity in advanced-stage pancreatic ductal adenocarcinoma.

A different approach is through activation of CD40, a member of the tumour necrosis factor receptor superfamily present in tumour-associated macrophages. Gemcitabine combined with a CD40 agonist promoted accumulation of tumouricidal macrophages, leading to stromal collapse and tumour regression.

**Cancer vaccines.** GVAX pancreas is an allogeneic whole-cell vaccine generated from pancreatic cancer cell lines that have been modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF induces chemotaxis of dendritic cells to the injection site, which phagocytose tumour cells and subsequently present tumour antigens to T cells, eliciting an immune response against the tumour.

A phase II trial in metastatic pancreatic cancer reported a two-month improvement in overall survival for GVAX–cyclophosphamide and CRS-207 (an attenuated *Listeria monocytogenes* strain given as a boost vaccine) compared with GVAX–cyclophosphamide alone. In a different study, increased expression of PD-1/PD-L1 was noted following resection in patients treated with GVAX. Such studies suggest there may be roles for combining GVAX and immune-checkpoint inhibitors.

**Chimeric antigen receptor T cells.** A first-in-man study examining the safety of genetically modified T cells engineered to express chimeric antigen receptors recognising tumour antigens (CAR T cells) led to anaphylaxis and

## Take home message from the authors

Ignacio Garrido-Laguna (*left*) is from the Department of Internal Medicine, Division of Oncology, and Center for Investigational Therapeutics, at the Huntsman Cancer Institute, University of Utah, USA. Manuel Hidalgo (*right*) is from the Gastrointestinal Cancer Clinical Research Unit, Clinical Research Programme, at the Spanish National Cancer Research Centre (CNIO), Madrid, Spain.

"Even in the early stages, pancreatic ductal adenocarcinoma is a systemic disease. This is supported by *in vivo* models as well as clinical data showing that up to 60% of patients relapse within six months of resection. Better systemic treatments are needed in adjuvant settings, as well as different treatment strategies allowing early treatment of systemic disease (neoadjuvant therapy). For patients with locally advanced unresectable disease, where the role of chemoradiation is controversial, more effective induction chemotherapy backbones must be tested. For patients with more advanced disease, targeting different tumour compartments, such as the stroma, seems critical. The growing field of immunotherapy could open new treatment opportunities in this lethal disease.

**Clinical implications**

We would like to see an increasing number of neoadjuvant trials to elucidate the role of early systemic treatment. At a time when the value of care is critical for the sustainability of health care systems across the world, we need to consider whether drugs that provide modest survival benefits (days for erlotinib and weeks for MM-398) deliver any added value to patient care at current costs.

**Future studies**

In the adjuvant setting it will be interesting to follow up the results of the APACT and PRODIGE studies to discover whether more effective chemotherapy backbones impact on survival in patients with resectable disease. We also need to identify biomarkers to assist treatment decisions. It is also critical to elucidate whether patients with grade 2 ECOG performance status (Karnofsky score 70) benefit from nab-paclitaxel plus gemcitabine. The MPACT study did not find a survival benefit in this subgroup, and there is a potential for harm with gemcitabine doublets in frail patients.

For patients with advanced disease, early results from immunotherapy clinical trials enrolling pancreatic cancer patients were disappointing. The stroma in this disease is predominantly immunosuppressive leading to exclusion of CD8+ effector T lymphocytes. Overall this leads to a tumour phenotype characterised by immune system ignorance. Work in preclinical models shows that, even when only premalignant lesions (PanIN) are identified, the immune response is impaired. Treatment strategies that increase T-cell infiltration of tumour sites have shown promising results in preclinical models and are currently undergoing clinical testing in early-phase clinical trials. In addition, recent preclinical work demonstrates that loss of PTF1A, a regulator of acinar differentiation, is needed to facilitate oncogenic acinar to ductal reprogramming by KRAS. One could envision that the use of preclinical models such as Ptf1a cKO; $KRAS^{G12D}$ may facilitate the identification of neoepitopes as new targets to develop immunotherapies in this disease.

Lastly, use of next-generation sequencing and liquid biopsies need to be further investigated in this disease."

cardiac arrest in one patient, although clinical activity was seen in a patient with pancreatic ductal adenocarcinoma. A phase I study is evaluating meso-CAR T-cell therapy in advanced-stage pancreatic cancer.

**Indoleamine-2, 3-dioxygenase inhibitors.** Expression of the tryptophan-catabolising enzyme indoleamine-2, 3-dioxygenase (IDO) is associated with poor outcomes, with expression increased in metastases. Tryptophan metabolites are toxic to T cells and contribute to an immunosuppressive microenvironment by increasing regulatory T cell numbers. An ongoing phase Ib trial is testing the IDO inhibitor indoximod combined with nab-paclitaxel plus gemcitabine in advanced pancreatic ductal adenocarcinoma. Preliminary results from this study showed delayed and durable responses (Bahary et al. Abstract #452 ASCO GI 2016).

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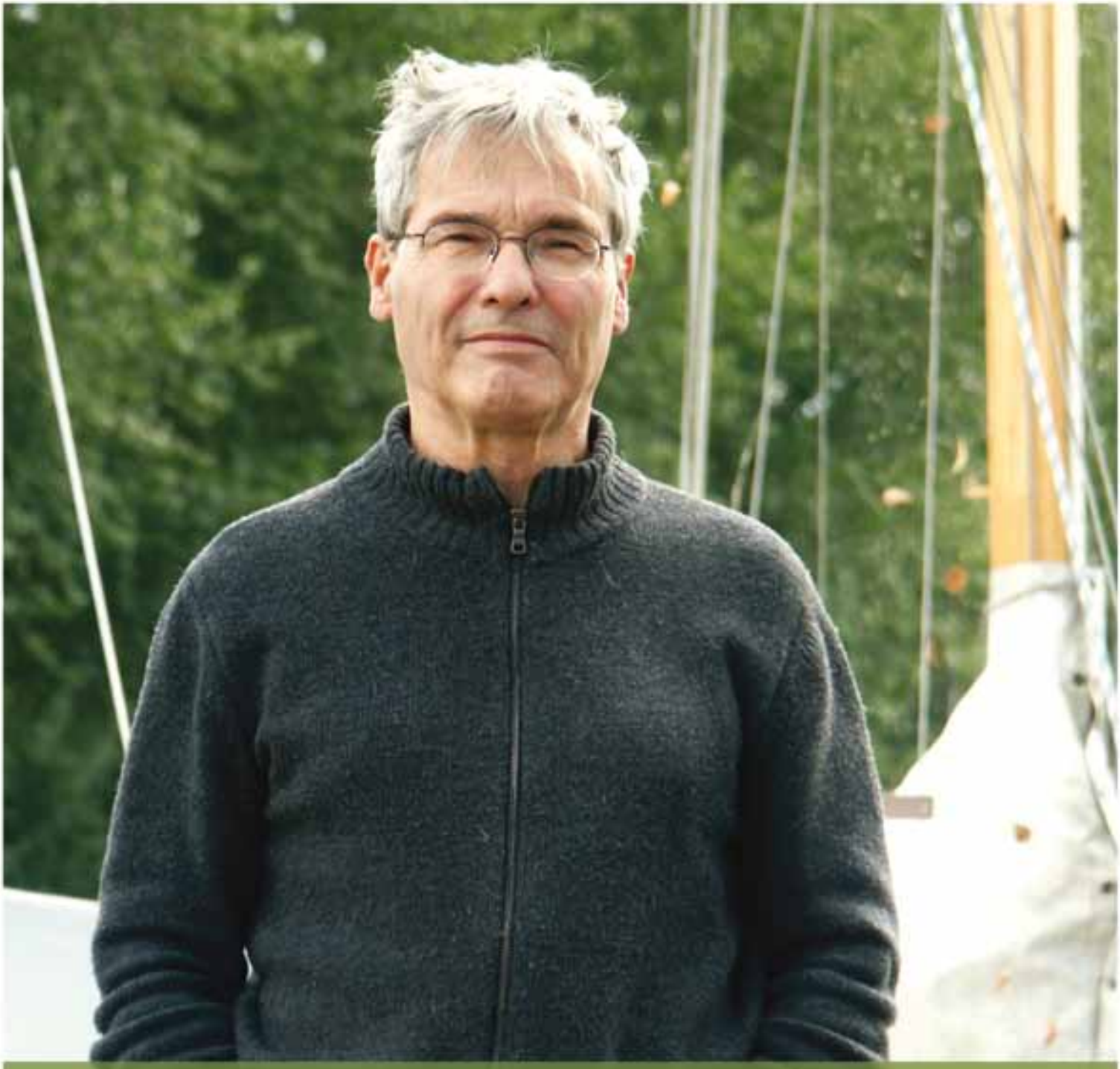

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# How doctors die

## *It's not like the rest of us, but it should be*

This hard-hitting blogpost by **Ken Murray,** a retired Los Angeles family doctor, helped open up discussions about why doctors routinely administer treatments to dying patients that they would adamantly refuse for themselves.

Years ago, Charlie, a highly respected orthopaedist and a mentor of mine, found a lump in his stomach. He had a surgeon explore the area, and the diagnosis was pancreatic cancer. This surgeon was one of the best in the country. He had even invented a new procedure for this exact cancer that could triple a patient's five-year-survival odds – from 5% to 15% – albeit with a poor quality of life.

Charlie was uninterested. He went home the next day, closed his practice, and never set foot in a hospital again. He focused on spending time with family and feeling as good as possible. Several months later, he died at home. He got no chemotherapy, radiation, or surgical treatment. Medicare didn't spend much on him.

It's not a frequent topic of discussion, but doctors die, too. And they don't die like the rest of us. What's unusual about them is not how much treatment they get compared to most Americans, but how little. For all the time they spend fending off the deaths of others, they tend to be fairly serene when faced with death themselves. They know exactly what is going to happen, they know the choices, and they generally have access to any sort of medical care they could want. But they go gently.

Of course, doctors don't want to die; they want to live. But they know enough about modern medicine to know its limits. And they know enough about death to know what all people fear most: dying in pain, and dying alone. They've talked about this with their families. They want to be sure, when the time comes, that no heroic measures will happen – that they will never experience, during their last moments on earth, someone breaking their ribs in an attempt to resuscitate them with cardiopulmonary resuscitation (that's what happens if CPR is done right).

Almost all medical professionals have seen what we call "futile care" being performed on people. That's when doctors bring the cutting edge of technology to


bear on a grievously ill person near the end of life. The patient will get cut open, perforated with tubes, hooked up to machines, and assaulted with drugs.

All of this occurs in the Intensive Care Unit at a cost of tens of thousands of dollars a day. What it buys is misery we would not inflict on a terrorist. I cannot count the number of times fellow physicians have told me, in words that vary only slightly, "Promise me if you find me like this that you'll kill me." They mean it. Some medical personnel wear medallions stamped "NO CODE" to tell physicians not to perform CPR on them. I have even seen it as a tattoo.

To administer medical care that makes people suffer is anguishing. Physicians are trained to gather information without revealing any of their own feelings, but in private, among fellow doctors, they'll vent. "How can anyone do that to their family members?" they'll ask. I suspect it's one reason physicians have higher rates of alcohol abuse and depression than professionals in most other fields. I know it's one reason I stopped participating in hospital care for the last 10 years of my practice. How has it come to this – that doctors administer so much care that they wouldn't want for themselves? The simple, or not-so-simple, answer is this: patients, doctors, and the system.

## What it buys is misery we would not inflict on a terrorist

To see how patients play a role, imagine a scenario in which someone has lost consciousness and been admitted to an emergency room. As is so often the case, no one has made a plan for this situation, and shocked and scared family members find themselves caught up in a maze of choices. They're overwhelmed.

When doctors ask if they want "everything" done, they answer yes. Then the nightmare begins. Sometimes, a family really means "do everything," but often they just mean "do everything that's reasonable." The problem is that they may not know what's reasonable, nor, in their confusion and sorrow, will they ask about it or hear what a physician may be telling them. For their part, doctors told to do "everything" will do it, whether it is reasonable or not.

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The above scenario is a common one. Feeding into the problem are unrealistic expectations of what doctors can accomplish. Many people think of CPR as a reliable lifesaver when, in fact, the results are usually poor. I've had hundreds of people brought to me in the emergency room after getting CPR. Exactly one, a healthy man who'd had no heart troubles (for those who want specifics, he had a 'tension pneumothorax'), walked out of the hospital.

If a patient suffers from severe illness, old age, or a terminal disease, the odds of a good outcome from CPR are infinitesimal, while the odds of suffering are overwhelming. Poor knowledge and misguided expectations lead to a lot of bad decisions.

But of course it's not just patients making these things happen. Doctors play an enabling role, too. The trouble is that even doctors who hate to administer futile care must find a way to address the wishes of patients and families. Imagine, once again, the emergency room with those grieving, possibly hysterical, family members. They do not know the doctor. Establishing trust and confidence under such circumstances is a very delicate thing. People are prepared to think the doctor is acting out of base motives, trying to save time, or money, or effort, especially if the doctor is advising against further treatment.

Some doctors are stronger communicators than others, and some doctors are more adamant, but the pressures they all face are similar. When I faced circumstances involving end-of-life choices, I adopted the approach of laying out only the options that I thought were reasonable (as I would in any situation) as early in the process as possible. When patients or families brought up unreasonable choices, I would discuss the issue in layman's terms that portrayed the downsides clearly. If patients or families still insisted on treatments I considered pointless or harmful, I would offer to transfer their care to another doctor or hospital.

Should I have been more forceful at times? I know that some of those transfers still haunt me. One of the patients of whom I was most fond was an attorney from a famous political family. She had severe diabetes and terrible circulation, and, at one point, she developed a painful sore on her foot. Knowing the hazards of hospitals, I did everything I could to keep her from resorting to surgery. Still, she sought out outside experts with whom I had no relationship.

Not knowing as much about her as I did, they decided to perform bypass surgery on her chronically clogged blood vessels in both legs. This didn't restore her circulation, and the surgical wounds wouldn't heal. Her feet became gangrenous, and she endured bilateral leg amputations. Two weeks later, in the famous medical center in which all this had occurred, she died.

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It's easy to find fault with both doctors and patients in such stories, but in many ways all the parties are simply victims of a larger system that encourages excessive treatment. In some unfortunate cases, doctors use the fee-for-service model to do everything they can, no matter how pointless, to make money. More commonly, though, doctors are fearful of litigation and do whatever they're asked, with little feedback, to avoid getting in trouble.

Even when the right preparations have been made, the system can still swallow people up. One of my patients was a man named Jack, a 78-year-old who had been ill for years and undergone about 15 major surgical procedures. He explained to me that he never, under any circumstances, wanted to be placed on life support machines again.

One Saturday, however, Jack suffered a massive stroke and got admitted to the emergency room unconscious, without his wife. Doctors did everything possible to resuscitate him and put him on life support in the ICU. This was Jack's worst nightmare. When I arrived at the hospital and took over Jack's care, I spoke

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to his wife and to hospital staff, bringing in my office notes with his care preferences. Then I turned off the life support machines and sat with him. He died two hours later.

Even with all his wishes documented, Jack hadn't died as he'd hoped. The system had intervened. One of the nurses, I later found out, even reported my unplugging of Jack to the authorities as a possible homicide. Nothing came of it, of course; Jack's wishes had been spelled out explicitly, and he'd left the paperwork to prove it.

But the prospect of a police investigation is terrifying for any physician. I could far more easily have left Jack on life support against his stated wishes, prolonging his life, and his suffering, a few more weeks. I would even have made a little more money, and Medicare would have ended up with an additional $500,000 bill. It's no wonder many doctors err on the side of overtreatment.

But doctors still don't over-treat themselves. They see the consequences of this constantly. Almost anyone can find a way to die in peace at home, and pain can be managed better than ever.

Hospice care, which focuses on providing terminally ill patients with comfort and dignity rather than on futile cures, provides most people with much better final days.

Amazingly, studies have found that people placed in hospice care often live longer than people with the same disease who are seeking active cures. I was struck to hear on the radio recently that the famous reporter Tom Wicker had "died peacefully at home, surrounded by his family." Such stories are, thankfully, increasingly common.

Several years ago, my older cousin Torch (born at home by the light of a flashlight – or torch) had a seizure that turned out to be the result of lung cancer that had gone to his brain. I arranged for him to see various specialists, and we learned that with aggressive treatment of his condition, including three to five hospital visits a week for chemotherapy, he would live perhaps four months.

Ultimately, Torch decided against any treatment and simply took pills for brain swelling. He moved in with me.

We spent the next eight months doing a bunch of things that he enjoyed, having fun together like we hadn't had in decades. We went to Disneyland, his first time. We'd hang out at home. Torch was a sports nut, and he was very happy to watch sports and eat my cooking. He even gained a bit of weight, eating his favorite foods rather than hospital foods. He had no serious pain, and he remained high-spirited.

One day, he didn't wake up. He spent the next three days in a coma-like sleep and then died. The cost of his medical care for those eight months, for the one drug he was taking, was about $20.

Torch was no doctor, but he knew he wanted a life of quality, not just quantity. Don't most of us? If there is a state of the art of end-of-life care, it is this: death with dignity. As for me, my physician has my choices. They were easy to make, as they are for most physicians. There will be no heroics, and I will go gentle into that good night. Like my mentor Charlie. Like my cousin Torch. Like my fellow doctors.

This blogpost was first published in 2011 on Zócalo Public Square (http://www.zocalopublicsquare.org/), a not-for-profit Ideas Exchange affiliated to Arizona State University. It is republished here with permission .
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