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"In the labyrinth of rare cancers" by Nicolò Assirelli

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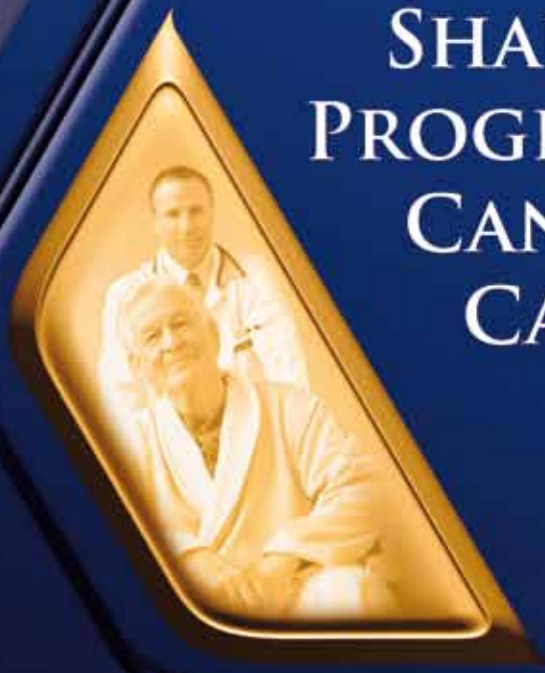
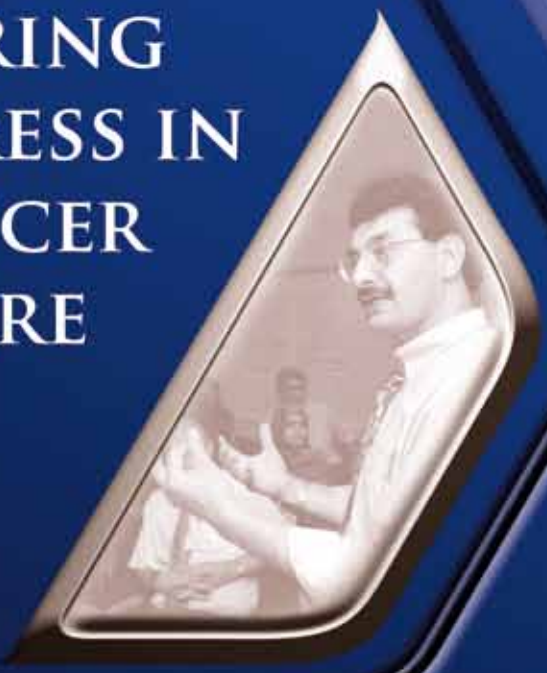
Learning to care

Sharing Progress in Cancer Care





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We're researching the history of recent oncology: *What's in it for you?*

Alberto Cambrosio & Peter Keating Guest Editors

Alberto Cambrosio is a Professor of Social Studies of Medicine, at McGill University, Montreal, Canada. Peter Keating is a Professor at the Department of History, University of Quebec at Montreal, Canada

The history of medicine has often been reduced to hagiography – a celebration of past events lacking critical scrutiny. The contemporary history of oncology, with its 'breakthroughs' and 'disruptive' innovations, has likewise been exposed to such 'Whiggish' approaches, which assume that history follows a path of inevitable progression and improvement. Historians have long rejected this cheerleader role, but we are nonetheless reliant on the goodwill of busy clinical researchers to grant us lengthy and often repeated interviews and to provide us with other relevant material. So it's fair enough that prospective informants occasionally ask us the question: "what's in it for me?"

Let us provide two possible answers.

A number of experts have expressed concerns about the 'cycle of hype' and 'promotional enthusiasm' surrounding precision medicine, and the premature adoption of genomic techniques. A thorough social and historical analysis of the dynamics of clinical research provides a much-needed, realistic basis for exploring these issues. It is not enough to enact a few rules designed to prevent unwarranted claims, as bioethicists tend to do. We need to understand the forces and undercurrents that create such potential problems, and this is precisely the kind of analytical work we pursue.

The same can be said, more broadly, of the major transformations that have affected clinical cancer research in the last two decades. Clinical trials can no longer be reduced to mere testing machines, but qualify as clinical experimental systems, i.e. devices for learning about the pathogenesis of cancer – a fact that undermines the traditional distinction between research and care. As a precondition for a meaningful discussion of the social and political aspects of these transformations, we need to develop a clear understanding of the situation, and this cannot be done without empirical, conceptually informed clarifications of the evolving nature of clinical research practices.

Having studied the development of clinical oncology from World War II to the present, we noticed that our work was becoming increasingly complex as we approached the new century. Drug companies, which used to play a relatively minor role vis-à-vis academic research in oncology, are now major players, and their involvement has become more closely entwined with their commercial strategies, and thus more opaque.

The speed of change has accelerated. While in the past we could interview members of an institution or research team and be fairly confident that we had a relatively durable overview of their research programme, these days a single lab can regularly undergo major conceptual and technological changes within a three- to five-year period.

The research landscape is fragmenting. In the past, a few major organisations (such as the EORTC in Europe and the US National Cancer Institute) covered a great deal of the clinical cancer research terrain. Nowadays, a growing number of hybrid, public–private consortia, initiatives, and networks occupy the field, complicating the task of providing a coherent, comprehensive overview of the domain.

In our different ways, oncologists, historians, and social scientists share these problems, which is another reason for engaging in productive dialogue.

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Ending the isolation

A guide to developing national rare cancer networks

European Reference Networks can only work if member states designate and develop their own accredited specialist centres that can network across borders. **Simon Crompton** talks to some of the policy makers, clinicians and patient advocates who are making it happen.

"Don't speak about things you know nothing about." Medical oncologist Lisa Licitra remembers the message being constantly driven home to her by teachers at school. Yet throughout her career she, like other cancer clinicians, has been faced with having to do exactly that.

"Patients with rare cancers want precise answers to their questions after diagnosis," she says. "But what do you do if you're uncertain of the data on a cancer, and you're not sure of the best way forward? Maybe you shouldn't even convey your uncertainty to the patient. Sometimes the uncertainty is so high that it's best to just treat in the most appropriate way you can. But in your heart you know there is nothing there supporting your decision."

Licitra today is one of Italy's foremost authorities on head and neck cancers, Director of head and neck medical oncology at the Istituto Nazionale Tumori, Milan, and Associate professor of medical oncology at the University of Milan. But she freely acknowledges that even she has been left uncertain by untypical tumours. It's hard, she says, for doctors who are supposed to be experts to say that they don't know. Yet patients deserve answers.

This is not an uncommon experience. There are more than 300 rare cancers which – as rare cancer campaigning organisations continually point out – adds up to them not being very rare at all. Together, rare cancers account for 22% of all cancer cases diagnosed.

Diligent clinicians respond with a frenzy of activity: squeezing more information from pathologists, entering into long discussions at multidisciplinary meetings and scouring PubMed, reports, books and the World Health Organization classification for clues and information. "This is all very time-consuming," says Licitra. "And then, at the end, you still don't know if what you're doing is the best course. And the uncertainty for patients remains."

Text books and diligence are not the answer. Building knowledge and expertise requires opportunities to pool the experiences of similar patients with rare cancers, compare thoughts on best practice, develop research projects together. This can't happen in one centre, or often even in one country.

"The value of networking at European level depends on strong national networks that are still largely non-existent"

EU policy makers have recognised that this is an area where crossborder collaboration can play an important role. In March this year they launched their flagship European Reference Networks (ERNs) – with one specifically covering rare solid adult tumours, called EURACAN. In addition, there are ERNs for paediatric cancers, genetic tumour risk syndromes and haematological diseases including cancers.

The move has been welcomed by the rare cancer community. But as the policy rolls out, it is becoming increasingly clear that the value of networking at European level depends on strong national networks that are still largely non-existent.

This is a concern of the Joint Action on Rare Cancers (JARC) – a collaboration for EU stakeholders and policy makers to set a European agenda to improve diagnostics and care for people with rare cancers.

"We have to make sure that the ERNs are a network of networks," argues Paolo Casali, co-ordinator of JARC, whose partners include ministries of health, cancer control programmes, universities, public health institutions, cancer registries, oncological institutes, patients' associations and other professional societies.

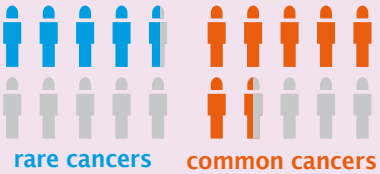
"Things can't happen on a European level unless they're happening at a national level. The European Commission is very much in agreement with this. And then the issue is that to have national networks, you need national governments and regions to be very much involved and motivated across the EU. This is a difficulty."

Rare cancers patient advocate Kathy Oliver agrees that if people with rare cancers across Europe are to receive timely diagnosis and appropriate treatment, then pan-European aspirations in themselves are not enough. Infrastructure also needs to grow within each individual country.

"Certainly the arrival of the European Reference Networks demonstrates that there is a will throughout Europe, which is very heartening from the patient perspective," says Oliver, who is Chair of the International Brain Tumour Alliance and a founding member of Rare Cancers Europe. "But it's not just a matter of deciding something, and then it will be done.

"You need the resources to create proper durable links between existing centres of expertise. You need good solid cancer plans that include guidelines on treatment, care and support of people with rare cancers. You

Improving services to improve survival



Five-year survival for rare cancers is 47% compared with 65% for more common cancers, reflecting deficiencies in early and correct diagnosis and effective treatment. This burden looks set to grow as the increasing fragmentation of 'common' cancers into molecular subgroups will effectively increase the numbers of rare cancers.

need multidisciplinary teams and you need quality research and standards. These things have to be achieved on a national level with solid and sustainable foundations."

So how do you build standards of diagnosis and care nationally? JARC representatives are now looking at what lessons can be learnt from the progress some countries are making in defining expert centres, ensuring access to expertise for all patients with rare cancers, and establishing clinician buy-in to a system of referral.

Establishing national consensus on expertise

Josep Maria Borras, professor of public health at the University of Barcelona and a JARC advisor, believes that progress in establishing networks of expert reference centres for rare cancers in Spain provides hope that other countries can do the same. Spain has a regionally organised health system but, after an initiative to identify reference centres of expertise in several regions, the country has now established national networks for sarcoma and childhood cancers.

It wasn't always a simple process. "The problem is that sometimes hospitals self-declare as reference centres without any kind of evidence," he says. "What you need to establish are requirements for the minimum number of patients receiving treatment for a particular cancer annually, a demonstration that outcomes are good, a research commitment."

"You need solid cancer plans with guidelines on treatment, care and support of people with rare cancers"

With rare cancers, these requirements pose special problems. "How do you demonstrate that results are good, when typically the number of rare cancers receiving treatment in one hospital is very low? That makes evaluation, and finding differences in outcome, very difficult." The solution in Spain, says Borras, has been to make the big hospitals the reference centres, and encourage smaller hospitals to refer to them.

But this in turn can present human challenges. "How do you convince hospitals with smaller numbers of patients to send to bigger hospitals? There is a level of recognition that others can do the job better than you, but at the same time, there is an issue of… let's say self-esteem. There are human emotions involved."

The solution, he says, is establishing a clear national consensus on the criteria for what constitutes a centre of expertise for particular rare cancers. And this won't work unless it is agreed by all parties: clinical experts, representatives of scientific societies, patient representatives, health service managers, politicians.

Borras acknowledges that the criteria established will – at least at first – be to some extent arbitrary. The required number of sarcoma cases treated annually, for example, was set at 60 – but current evidence provides very little consensus about the correct thresholds. Nonetheless, a national accreditation and audit process is now underway in Spain, co-ordinated by the Ministry of Health.

Any reference system for rare cancers, says Borras, is bound to have shortcomings. The important thing is to have a national will, driven by policy, and then put into practice by achieving consensus between regions and all the parties involved.

Achieving universal access to expertise

If Spain demonstrates the importance of a top down approach to improving access to expert rare cancer services, France has moved the concept considerably further. A national cancer control plan for 2009–13 required the certification of adult rare cancer reference centres, and has resulted in the establishment of 15 national clinical networks, recognised by the Institut National du Cancer (INCa). Each national network is comprised of national reference centres and regional or interregional centres of competence.

These networks were initially

approved through a process of self-assessment and independent external assessment, using quantitative and quality indicators to assess whether stated missions had been achieved.

"The important thing is a national will, driven by policy and put into practice by achieving consensus "

The result is not simply a network of national expert centres. The aim is to ensure that every single rare cancer patient has access to optimum care. So within each network, every new case is discussed at a virtual national expert multidisciplinary tumour board, held using Webex online meeting tools. And each network has a national database that is providing new clues to the best treatment, which can be tested in trials.

The French network for thymic (thymus gland) tumours, for example, consists of two co-ordinating centres – Hospices Civils de Lyon and Institut Gustave Roussy, Paris – and 12 regional centres. Representatives from all the centres gather at a web-based tumour board twice a monthly, bringing together national expertise in surgery, medical oncology, radiation oncology, radiology and pathology, to discuss each new diagnosis, and each patient who requires a new treatment strategy. It works to French guidelines adapted from the 2015 ESMO clinical guidelines for thymic cancers.

"We have a systematic pathological review of all cases," says Nicolas Girard, senior attending physician in the thoracic oncology service of the Hospices Civils de Lyon. "We have found a 7% rate of major discrepancies between the initial diagnosis and the final diagnosis after pathological review. This will be an error in the stage or tumour type that modifies management for the patient."

The benefit goes beyond accurate diagnosis. "Because we use the guidelines, and because of the way we analyse patient history and situation, we now have management that is more consistent from patient to patient. Surgeons from the network have clearly progressed – there's a lot of discussion at the boards about surgical technique and optimal approach."

And because the networks provide access to larger numbers of patients, oncologists can finally target rare cancer patients for trials. Each network has an associated database – there are 2,000 patients in the new thymic tumour database.

"It's a tool for sending patients for

A network for rare adult cancers

The European Reference Network for rare adult solid cancers, EURACAN, aims to pool the expertise of 67 accredited rare cancer centres across 18 countries, using them as the basis of an integrated network of information, services and expertise covering the EU area.

It classifies rare adult cancers into 10 domains:

- Sarcoma of the soft tissue, bone and viscerae (Sarcoma)
- Rare neoplasm of the female genital organs and placentas (Rare GYN)
- Rare neoplasm of the male genital organs, and of the urinary tract (Rare GU)
- Neuroendocrine tumours (NET)
- Rare neoplasm of the digestive tract (Rare GI)
- Rare neoplasm of endocrine organs (Endocrine)
- Rare neoplasm of the head and neck: salivary gland tumours, nasopharyngeal cancer, nasal and sinonasal cancers, middle ear (Rare H&N)
- Rare neoplasm of the thorax: thymoma, mediastinum and pleura (Rare Thoracic)
- Rare neoplasm of the skin and eye melanoma (Rare Skin/Eye melanoma)
- Rare neoplasm of the brain, spinal cords (Rare Brain)

The European Commission wants European Reference Networks to reach all EU countries within five years, providing a referral system to ensure at least 75% of patients are treated in an accredited centre. It is seeking to improve patient survival, produce communication tools in all languages for patients and physicians, and develop multinational databases and tumour banks.

For more information see bit.ly/EURACAN

Clinician-driven network development: the ENET experience

Action taken by expert groups putting together criteria for reference centres, treatment guidelines and some basic quality indicators for networks can drive national and international development.

This is what happened in neuroendocrine tumours. Martyn Caplin, professor of gastroenterology and neuroendocrine tumours at the Royal Free Hospital in London, was involved in a European neuroendocrine tumour group instigated in the mid-1990s by Kjell Oberg from Sweden, Michelle Mignon from France and Bertram Widenmann from Germany. In 2000, when he realised there was "nothing in the UK for neuroendocrine tumours," he started a UK neuroendocrine specialist group and a linked patient support group.

This led to the identification of expert specialists and centres in the UK, and the publication of UK guidelines for the management of neuroendocrine tumours in 2004. The interest generated within such 'enthusiast' specialist groupings provided momentum to found a European Neuroendocrine Tumor Society (ENETS) in 2004. In turn ENETS developed a system of auditing centres of excellence throughout Europe. Today, there are 37 centres of excellence in Europe, eight of them in the UK (www.enets.org/coe_map.html).

"It's a robust system of approval," says Caplin, "looking at standard operating procedures, care pathways, pathology procedures, and adherence to ENET standards of care and guidelines." Centralised frameworks are needed, he adds, if only to ensure that rare cancers move up the priority list throughout a health service. "Otherwise you are relying on the goodwill of one or two people to take it on."

clinical trials in Paris or Lyon," says Girard. "We are in the process of publishing many data from this prospective database, on radiotherapy, chemotherapy, pathological review and so on. The database is really useful for long-term follow-up. We started in 2012, so now we have a five-year follow-up for the first patients. It will be an incredible tool for better understanding of recurrences."

The benefits are not just for thymic cancers. Bertrand Baujat, a head and neck cancer surgeon at Hôpital Tenon, Paris, says that it is now unusual for any French doctor not to refer head and neck cancers to the national network, at least for advice or pathology review. There are 5,000 head and neck cancer patients on their database, so more information on which to assess treatments and prognosis.

"For example, in salivary gland cancer there's been no consensus on whether we should remove the nodes or not. Now we can provide recommendations based on our database. We know that in this kind of cancer we had ten people with node metastasis, and now we recommend doing the node dissection in the neck section systematically. This makes a difference to the patient."

For Isabelle Ray-Coquard, gynaecological cancer specialist at the Centre Léon Bérard, Lyon, the beauty of the French networks has been that patients don't always have to be physically referred to an expert centre, sometimes hundreds of miles away. "If they can be managed at regional level it's clearly helpful for the patient and the physician in charge," she says.

Is France a template?

Is the French system replicable in other countries? Certainly, say those involved, but it needs top-down commitment, manifested in a national cancer plan backed by law and funding.

"None of this would have been possible without a national initiative to start it," says Bertrand Baujat. "We needed the money so that we could set up the infrastructure." Around €1 million was allocated over four years to establish a national network for head and neck cancers. It paid for setting up co-ordination systems, a database, clinical research technicians and other set-up costs. It receives annual government funding of €190,000.

Isabelle Ray-Coquard says that setting up the infrastructure required for

Patient-driven policy and guidelines development: the sarcoma experience

European patient organisations for rare cancers can play a significant role in setting quality standards and templates for policy development. Last year, Sarcoma Patients EuroNet (SPAEN) – an international network of sarcoma, GIST and desmoid patient advocacy groups – launched a set of recommendations for service development, providing a clear statement on what sarcoma treatment and services should look like.

It includes pathways and recommendations for diagnosis, primary treatment and advanced disease, and is available at bit.ly/SPAENpathway

According to Markus Wartenberg, co-author of the paper and SPAEN Chair, the paper is already informing the certification of sarcoma centres in Germany – and will help guide their practice once established. SPAEN will be collecting information from its members on the extent to which it is influencing service development in other countries too.

"I think this is our way forward," he says. "To produce service recommendations, guidelines and also position papers with recommendations on certain issues in treatment. This could be part of a collaboration process on a national level between patient organisations and experts."

This February, SPAEN also launched a Sarcoma Policy Checklist, drafted by an expert group to help policymakers close the gap in access to high-quality information and care for sarcoma patients across Europe. It describes five key areas where policy makers should focus their efforts to have the most impact on care for sarcoma patients:

- designated and accredited centres
- greater professional training
- a multidisciplinary approach
- incentives for research and innovation
- rapid access to effective treatment.

The document also provides examples from six countries to show the extent to which these recommendations have been implemented. The document is available in English, Spanish, Italian, French and German at bit.ly/SPAENpolicychecklist

these kinds of rare cancer networks is not as expensive as people imagine. "I think it is feasible," she says. "We work with around €200,000 a year for gynaecological cancers, so that we can organise at national level. If you look at what misdiagnosis and unnecessary treatments cost, it is clearly more than organising a national network."

But Baujat, who is involved with JARC and represents the French head and neck cancer network in EURACAN, is concerned that lack of funds will hold back the creation of a Europe-wide rare cancer network. And if other countries cannot replicate the kinds of national networks of expertise seen in France, then "harmonising standards" across Europe will actually mean an extra burden placed on one or two expert centres.

"It's true that, in France, we are a few years ahead of other countries because of our national plan," he says. "And there are other countries, like Italy and the Netherlands, which are being quite active on a regional level. But there are countries where there is nothing for rare cancers. So harmonising quality of care across Europe is such a big project. I'm worried that for countries like France, EURACAN will mean double work. Developing things at a national level is a good place to start. But there's no money in EURACAN to support this."

"It is unusual for any French doctor not to refer head and neck cancers to the national network at least for advice or pathology review"

This is a worry too for Martyn Caplin, founder and Vice Chair of the European Neuroendocrine Tumor Society, ENETS, which has set up a

system of auditing centres of excellence throughout Europe (see box p 8).

"There's no ERN funding that comes to individual hospitals, so no-one is sure what the next stages are. We have to take things forward in terms of meeting the ERN criteria for standards of care, teaching, access to multidisciplinary teams and so on."

He worries particularly about patients in countries with less sophisticated and more fragmented health services. "First of all, a lot of patients will still be getting a delayed or wrong diagnosis. Then, they will be referred to their local oncologist, who may not be aware of where to refer for specialist treatment – or may not even want to refer them on. Part of the process needs to be for governments to state that it's in the best interest of patients that they are sent to identified centres. But there are geographic issues related to that – patients separated from their families, travel costs. There are a lot of practical issues to be sorted."

A bottom-up approach

A way forward for some countries might be that forged in the field of sarcoma in Germany where, despite a fragmented health system, patients have linked with clinicians to provide a national momentum for change (see box p 9). Faced with problems of incorrect diagnosis, lack of authoritative information about experts in sarcoma, and centres self-declaring themselves as "expert", the patient organisation Das Lebenshaus e.V. linked with the German Cancer Society and medical experts to establish a certification system for sarcoma centres.

The system is currently built on meeting organisational criteria such as number of patients treated and use of multidisciplinary teams. As with other new certification systems for rare cancer units, independently monitored quality indicators are, as yet, a pipe dream. "But this is the aim," says Markus Wartenberg, Senior Manager of Das Lebenshaus e.V, which supports patients with GIST, sarcomas and kidney cancer.

"The certification system is the first step to identifying 20–25 centres in Germany that are able and willing to move forward in the field of sarcoma." The next step, he says, will be to create a real force for change by formally bringing sarcoma patients and expert clinicians together in a single German Sarcoma Foundation. "This is a very valuable development to raise awareness. Building common power between patients and experts is the way to build an infrastructure and move forward."

Service improvements in rare cancers can be achieved from the bottom up, rather than the top down, he says. "It's a question of whether or not you want to put your energy into a national battlefield to convince politicians that they need to do more for rare cancers. We decided to build from the bottom up, and try and make sarcomas something like a lighthouse for the rest of the rare cancer community to follow."

National responses to the EU lead

Despite the lack of funding to help countries develop their own reference centres and networks, Paolo Casali points out that European Reference Networks are having a positive effect on services in individual countries, by the mere fact of their existence.

"What I've come to realise is that the main meaning of these European mechanisms is national, rather than international," he says. "The ERNs are already forcing national governments to do something in their countries. For example, the process of selecting centres to join the ERNs was the first time some governments took political responsibility for explicitly endorsing centres for rare cancers."

"It was the first time some governments took responsibility for endorsing centres for rare cancers"

This was the case in Italy where, as a result of government and regions selecting rare cancer centres for the ERN, they are now discussing the possibility of establishing a formal rare cancer network. This follows many years of efforts by Casali and his colleagues in the clinician-led Italian Rare Cancer Network to connect centres, but without a formal accreditation system.

"We hope the selection process for our national network will mimic to some extent what is happening for the ERNs," says Casali, "so it is as if the European action is giving rise to a virtual cycle of improvement nationally."

Finally, he says, he sees the prospect of services for rare cancers improving at national and European level. "I didn't expect it, because I saw some countries slowing down the process through bureaucracy and so on. But once you've started a process at European level, involving all the rare diseases communities on finding a framework, then the process is very difficult to slow down."

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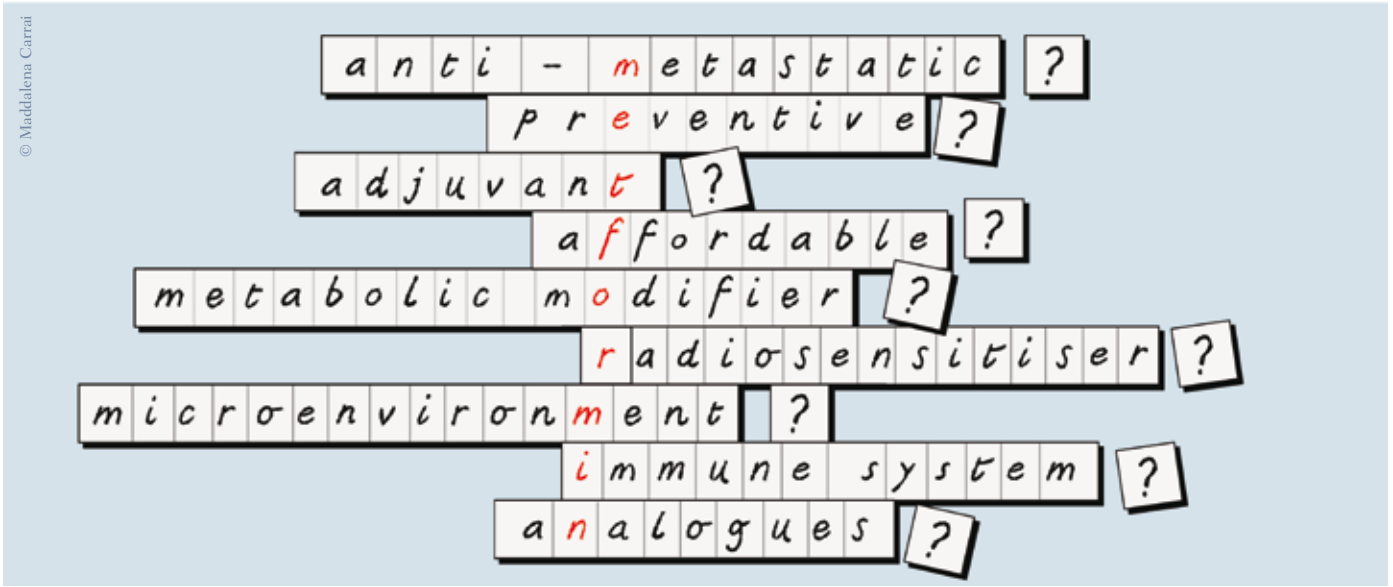


Building the clinical evidence on metformin and cancer

Population studies, mouse models, and mechanistic studies all show that metformin, a cheap well-tolerated diabetes drug, impacts in some way on how some cancers develop and progress. **Anna Wagstaff** talks to clinicians and researchers building the evidence on what it can deliver in the clinic.

In the early 2000s diabetologists began reporting an unusually low rate of cancer among their patients who were treated with metformin.

What happened next seemed to follow a 'false-dawn' pattern that has become all too familiar in the history of cancer research. A series of epidemiological studies came out showing large effect sizes, some showing cancer rates more than halved in metformin users – results that wiser heads cautioned were simply "too good to be true". But then attempts to back up the findings with lab studies confounded the sceptics: whether used against cancer cells in petri dishes or against tumours in mice models, metformin did indeed inhibit cancer growth.

"That was the golden period," says Michael Pollak, whose lab at the McGill translational research centre in Montreal, Quebec, was one of those tasked with carrying out the research. "It appeared that we had independent evidence from population studies and lab studies that projected that metformin had a bright future in treating cancer, at least in diabetics and even in patients without diabetes."

As the excitement rose, so did the number of studies. But then uncertainty began to creep in. Research done to confirm the early epidemiological reports found no evidence, or conflicting evidence, of a protective effect. And while the findings of the lab studies were found to be robust, questions emerged about dosing levels: was the anticancer activity occurring at drug levels higher than those that are – or ever could be – achieved in humans?

In 2015, hotly awaited results from one of the few robust ran-

domised controlled trials of metformin, used in patients with advanced pancreatic cancer, showed no impact on survival (*Lancet Oncol* 2015, 16:839–847). The golden period was over.

Metformin is special

The discovery of new anticancer agents is always welcome, but in the case of metformin, there were additional reasons for excitement. The drug is off patent, simple to manufacture and therefore cheap, so global access would not be a problem. Its side effects are known from decades of use by people with diabetes, and they are well-tolerated. Indeed some 'side-effects' – if that is the right term in the context of cancer treatment – may be positively beneficial. This is because the drug is active against metabolic syndrome, which is associated with chronic conditions such as diabetes, obesity, atherosclerosis and cardiovascular disease. This aspect takes on particular importance when seen in the context of the changing diets and lifestyles, and consequential rising rates of obesity and metabolic syndrome, that are thought to be a factor in the current global cancer epidemic.

All of that may be irrelevant to oncology if the drug does not actually work against cancer in humans. Yet the way that metformin performs in restricting cancer cell proliferation in preclinical tests cannot be ignored.

Metformin seems to work at a whole organism level principally by lowering the insulin levels. This could be relevant for the subset of cancers that are growth-stimulated by insulin. But it also works directly on the tumour, by modifying the characteristic energy metabolism of cancer cells in a way that Pollak says is "very, very interesting" – not least because energy metabolism is one of the characteristics that distinguishes cancerous from normal cells, and is important in sustaining their ability to survive and proliferate.

In short, despite the disappointing results of the pancreatic cancer trial, the mechanisms and potential clinical benefit of this drug deserve to be explored further. As Pollak says, "Pancreatic cancer is a pretty hard nut to crack. That doesn't mean there is no area where it may be of some use. But the best case scenario – that metformin will be effective against a wide range of cancers – is unlikely to be achieved… The overarching message is that we are now into the subtleties."

He suggests that there could be a rationale for conducting trials that focus on areas like the colon and the liver (including prevention of liver metastases), because metformin is known to accumulate in higher levels in these organs – indeed it has already been shown to decrease polyp growth in a phase III trial of people who had undergone polypectomy (*Lancet Oncol* 2016, 17:475–83). Focusing metformin trials more generally on cancer types associated with metabolic syndrome and obesity could also make sense, says Pollak.

Would an adjuvant trial make sense?

Ruth Langley, a medical oncologist and programme leader at the UK Medical Research Council clinical trials unit, spends much of her time amassing and analysing different types of evidence to assess whether it is strong enough to justify running a clinical trial.

She is the key instigator behind the Add-Aspirin trial, which is following up evidence from clinical, preclinical and mechanistic studies to try to get a clear answer on whether taking low-dose aspirin as an adjuvant therapy can lower the risk of recurrence in people treated for a range of common cancers.

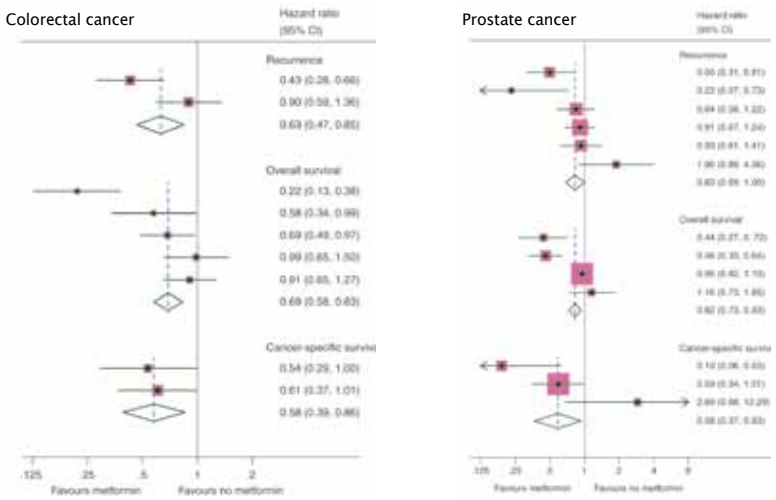
Most recently, she and her team have been examining the evidence around metformin, to assess whether there is sufficient evidence – and enough support among clinicians and funders – to think about trialling the drug in a similar, adjuvant, setting.

Their 'homework' included carrying out a meta-analysis of research reporting cancer outcomes for individual tumour types in metformin users compared with non-users – focusing on the results for patients with early-stage cancers (*Ann Oncol* 2016, 27:2184–95). The findings come with all the usual caveats about observational studies, with some additional ones – not least that the metformin users will all have been suffering from diabetes, which could affect cancer outcomes independently of the metformin.

The results do nonetheless add to the total body of evidence available. They indicate that, taken in an adjuvant setting by patients treated for early-stage colorectal cancer, metformin appears to be associated with significantly better recurrence-free, overall and cancer-specific survival. Significant or borderline significant benefit for all three measures was also seen among patients treated for early prostate cancer, particularly those treated with radiotherapy, though there was a lot of heterogeneity between studies (see figure overleaf).

No significant benefits were seen in either urothelial or breast cancer. The latter finding may temper expectations around the outcomes of the MA.32 Canadian Cancer Trials Group phase III randomised trial of metformin vs

Could metformin work as an adjuvant?



A meta-analysis of studies comparing outcomes between metformin users and non-metformin users for cancers treated curatively at an early stage found that, in colorectal cancer (*above left*), metformin use was associated with longer recurrence free survival, overall survival and cancer-specific survival. For men with early-stage prostate cancer, metformin was also associated with significant, or borderline significant, benefits in all three outcomes, but there was significant heterogeneity between the studies (*above right*). The data also suggest that prostate cancer patients treated with radical radiotherapy may benefit more from metformin. In breast and urothelial cancer, no significant benefits were identified.

Source: C Coyle et al (2016) *Ann Oncol* 27:2184–95. Republished under a Creative Commons licence

placebo in early-stage breast cancer, which is one of the few robust trials of metformin in an adjuvant setting, and is due to report sometime in 2020. Langley is keen to emphasise that epidemiological studies are often not confirmed in clinical trials.

The MRC clinical trials unit has not taken any decision yet on whether or not to try to launch a trial of metformin in an adjuvant setting, but Langley, with her experience of the aspirin story, believes there may be some good arguments for doing so.

"One of the things I feel about these potential repurposed agents is that we know, because most of them are used every day – metformin for diabetes, aspirin for heart disease – that they don't make a large amount of tumour disappear. But it is plausible that they affect the microenvironment such that, if you have a very, very small volume of cancer – right at the beginning of a primary cancer or one or two cells from a metastasis – they change the microenvironment such that the growth isn't established."

This seems to be what is happening in the case of aspirin, Langley argues, because the doses used in most of the epidemiological studies supporting the Add-Aspirin trial "suggest it is acting on platelets, and the microenvironment, not directly on the tumour."

Another reason that could tip the balance in favour of trialling metformin as an adjuvant treatment is that a large platform study is already up and running. The Add-Aspirin trial has been randomising patients treated for early breast, colorectal, prostate, and gastro-oesophageal cancer to aspirin (100mg or 300mg) or placebo for two years now (bit.ly/AddAspirin-protocol). If an additional metformin arm – or arms – were to be run on the same trial platform, in at least some of the same cancers, this would be an efficient use of resources.

This 'smarter' approach to conducting clinical trials, using a single platform to evaluate multiple primary treatment hypotheses, was developed by the Director of the MRC clinical trials unit, Mahesh Parmar, and has always been part of the strategic concept behind the Add-Aspirin trial, says Langley (*Clin Trials* 2017, 14:451–61).

"Despite calling the trial Add-Aspirin, we always thought we might evaluate other agents." If they do add further arms (metformin is only one of a number of possibilities), they'll have to change the name to 'the Add trial' or the 'Adjuvant trial' she says.

The fact that the Add-Aspirin trial is now opening up in India could be seen as a third argument in favour of adding a metformin arm. Cancer prevention, including secondary prevention, needs to be a priority in countries where expensive high-tech treatments are accessible to only a privileged few. Collaborating with the trials network run by India's recently established National Cancer Grid (*Indian J Med Paediatr Oncol* 2014, 35:226–7), to explore the value of cheap generics like aspirin and metformin in that population, makes obvious sense in terms of global cancer control.

None of which, Langley emphasises, rules out the possibility that metformin could also be of interest in other settings, including advanced disease. She mentions as an example the

STAMPEDE trial – one of the great success stories of the MRC clinical trials unit's 'multi-arm, multistage' trial platforms, for patients with prostate cancer who are starting on androgen deprivation therapy. The trial compares a single standard-of-care arm against a rolling panel of exploratory treatments added to standard of care, and has recently started randomising patients to added metformin.

Can metformin perform in advanced prostate cancer?

Finding better solutions for men with advanced prostate cancer has become something of a speciality for Silke Gillessen, who is co-lead of the STAMPEDE metformin comparison.

Like Langley, Gillessen and all the STAMPEDE triallists spend a lot of time weighing up evidence to make intelligent decisions about the most likely options to move into large clinical trials – and with some notable successes. The metformin arm of STAMPEDE is the tenth arm to run against a single continuously recruiting control arm, in a trial that has already notched up two important changes in the standard of care for men with advanced prostate cancer, first with docetaxel and more recently with abiraterone (*Eur Urology* 2016, 70:906–8).

Gillessen believes that prostate cancer is a likely place to see a benefit from metformin, not least because it reduces insulin levels, which could be important for a number of reasons. "Insulin has been shown to upregulate intracellular testosterone levels and secreted androgens sufficient to activate the androgen receptor – a very important receptor in prostate cancer," says Gillesen, "It acts directly on prostate cancer cells and can also activate pathways involved in progression to castration resistance."

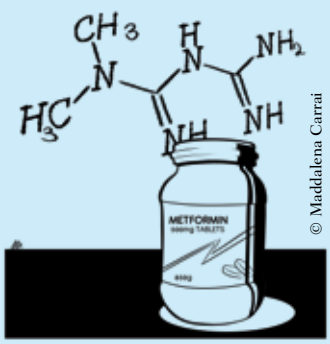
Hyperinsulinaemia also causes activation of insulin-like growth factor (IGF) signalling pathways, which has been associated with prostate cancer progression in preclinical models, she adds, while metformin has been shown to block AMP kinase, which is involved in a signalling pathway known to be important for prostate cancer. "So there is a lot of preclinical evidence to suggest that metformin has anti-proliferative effects in prostate cancer."

These findings, she argues, are backed up by the overall weight of evidence from population studies, including a relatively recent study of almost 4,000 diabetic men who were diagnosed with prostate cancer, which found that "cumulative duration of metformin treatment after prostate cancer diagnosis was associated with a significant decreased risk of prostate cancer-specific and all-cause mortality in a dose-dependent fashion," (*JCO* 2013, 31:3069–75). Those findings, says Gillessen, support the idea that metformin can work in patients who already have cancer, and not just in a prevention or adjuvant setting.

Whether or not that anti-cancer benefit shows up in the clinical trial only time will tell. But even if it doesn't, Gillessen believes that metformin could still improve both quality and length of life for her patients. This is because the androgen deprivation therapy that is the standard of care is believed to raise their risk of developing insulin resistance, high blood sugar levels, obesity, and high cholesterol, which may in turn raise their risk of diabetes and cardiovascular disease.

So potentially metformin could do "two really fantastic things," says Gillessen. "one is the anti-cancer effect, and the other is mitigating the metabolic effects of androgen deprivation therapy." Unlike the other STAMPEDE arms, the primary outcome measure by which metformin will be judged is all-cause survival, to capture both the anti-cancer effects and the wider health benefits.

Mechanisms of anti-cancer action



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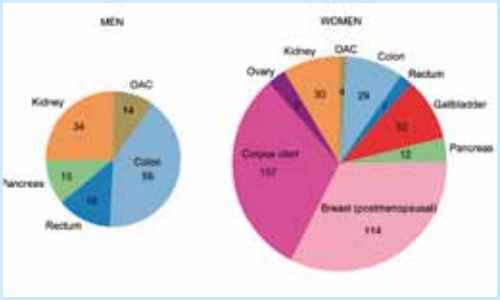
Metformin affects multiple key processes related to cell growth, proliferation, and survival. The drug's effects on these processes stem from both metabolic and intracellular-signaling activity. First, metformin decreases the amount of glucose produced by the liver and reduces the bloodstream level and cellular uptake of insulin. In turn, the reduced insulin stimulation results in reduced activation of insulin receptors on cell membranes, triggering a cascade of intracellular molecular effects, such as the downregulation of the Ras/Raf/MEK/ ERK and PI3K/AKT/ mTOR signaling pathways. One or both of these pathways are often activated in many types of cancer cells. In addition, metformin appears to upregulate AMP-activated protein kinase, a key molecule in glucose and insulin regulation and also an inhibitor of mTOR.

For further information see, for instance: I Pernicova & M Korbonits (2014) Metformin—mode of action and clinical implications for diabetes and cancer. *Nat Rev Endocrinol* 10: 143–156

Obesity, insulin resistance, metabolic syndrome and cancer incidence

A population-based study led by the International Agency for Cancer Research (*Lancet Oncol* 2015, 16:36–46) showed that 3.6%, or almost 481,000, of all new cancer cases in 2012 were attributable to excess BMI (BMI≥25kg/m^2).

Cancers attributable to excess BMI accounted for 5.4% of all cancers in women – almost one third of which were post-menopausal breast cancer, with another one third cancers of the corpus uteri.



Estimate of the number of cancers (in thousands) attributable to excess BMI in 2012
OAC – oesophageal cancer
Source: M Arnold et al. (2015) *Lancet Oncol* 16:36–46.

Among men, cancers attributable to excess BMI accounted for almost 2% of all cancers, with colon cancer accounting for a little under half (43%).

A review of the evidence on the links between insulin resistance, diabetes and cancer (*Curr Diab Rep* 2013, 13:213–22) cited "multiple meta-analyses and other large cohort studies published over the past year", supporting an association between the presence of insulin resistance (type 2 diabetes and metabolic syndrome) and an increased incidence of many types of cancer, including colorectal, hepatic, pancreatic, breast, endometrial, and urinary tract malignancies.

Michael Pollak, who has led preclinical work exploring the impact of metformin on cancer, argues that focusing metformin trials on cancer types associated with metabolic syndrome and obesity could be a sensible way to go in developing clinical evidence.

Not surprisingly perhaps, the trial is proving a hit with patients, and Gillessen is confident they will accrue their target of 1,800 patients by the end of 2019 – greatly helped by the multi-arm, multi-stage design, "which means we can open several arms and lose fewer patients onto a control arm." She hopes to be able to report early results by the end of 2024.

Is radiotherapy where metformin will prove its value?

Alan Dal Pra, assistant professor of radiation oncology at the University of Miami Miller School of Medicine, shares Gillessen's enthusiasm for learning more about what metformin can do for men with prostate cancer.

His priority is to follow up intriguing results from population and preclinical studies that seem to indicate a particular benefit when the drug is used in combination with radiotherapy.

He too mentions the 2013 *JCO* study of 4,000 diabetic men treated for prostate cancer, which showed an association between cumulative dose of metformin and a significantly decreased risk of dying of that cancer, but points out that the decrease was a lot higher among the one in four men who had been treated with radiotherapy. "For the radiotherapy cohort, there was a 48% decrease in prostate-cancer specific mortality," says Dal Pra.

Those results form part of a body of evidence that has convinced him and colleagues at SAKK (Swiss Group for Clinical Cancer Research) to launch PROMET, a randomised phase II trial that will look at the benefit (measured by time to progression) of adding metformin to salvage radiotherapy for patients whose PSA rate has started to rise after radical prostatectomy. The trial will be carried out in collaboration with the GETUG group (Groupe d'Etudes des Tumeurs Uro-Génitales).

A more recent study of 2,500 patients with local or locally advanced disease treated with curative radiotherapy (including diabetics on metformin, diabetics not on metformin and non-diabetics) showed that metformin was associated with improved biochemical (PSA) control and decreased incidence of castrate-resistant prostate cancer, distant metastases and prostate-specific cancer mortality (*Eur Urol* 2013, 63:709–16).

These and other epidemiological studies – with all the many caveats – are backed up by evidence from mechanistic studies, including one conducted by Dal Pra and colleagues in the Koritzinsky Lab in Toronto, looking *inter alia* at the impact metformin has on cancer cell metabolism, and potential therapeutic implications (*Clin Cancer Res* 2013, 19:6741–50).

"We showed, in preclinical cells and animal models, that metformin results in tumour reoxygenation, leading to increased radiotherapy response," says Dal Pra. The relationship between hypoxia and resistance to radiotherapy has been known about for many years, he adds, but so far efforts to address

the problem by increasing oxygen delivery to the cells have not gained significant clinical traction. Metformin, by contrast, changes the way the cells consume oxygen, and may be more effective at combatting radioresistance, he suggests.

Interestingly, when the impact of metformin on oxygen consumption was assessed *in vitro* in a panel of different cancer cells, says Dal Pra, "while there was a significant dose- and time-dependent decrease in oxygen consumption in all cell lines, the prostate cancer cell line showed the biggest impact."

We'll know more about what this could mean for patients undergoing salvage radiotherapy after prostatectomy when the findings are reported from Dal Pra's SAKK 08/15-PROMET trial, which has recently started recruiting.

He worries, however, that the efforts of people like himself and his trial colleagues to learn more about exactly how and where metformin could play its most effective role in treating cancer may be hampered by lack of co-ordination.

Who will take the lead?

Alan Dal Pra says he is aware of more than 20 phase II trials currently looking at metformin and radiotherapy, including one in non-small-cell lung cancer, and others in cervical cancer, brain tumours, rectal cancer (as a neoadjuvant) and more. Searching the terms cancer+metformin on clinicaltrials.gov throws up 68 phase II or phase III studies currently recruiting.

If this were a patentable new drug, says Dal Pra, these trials would probably be part of a joined up strategy designed to learn about what would be the best way to prove its value in cancer. In the absence of such a joined up strategy, he worries that unhelpful variations in doses, durations, patient populations, endpoints and biomarkers could limit what can be learned from pooling data, and biological samples will end up scattered around repositories with no common structure.

Dal Pra would love to see greater collaboration in the collective effort to gather the evidence for the clinical use of metformin in oncology – it's something he says he discussed with Michael Pollak when the idea of the PROMET trial was conceived, but no one has yet stepped up to take a lead.

As for Pollak, he doubts that many more major metformin trials will be embarked upon until the results of some ongoing robust phase III trials have reported, including the MAST trial, looking at whether metformin can delay progression of low-risk prostate cancer for men who opt for active surveillance, and the MA.32 randomised trial of metformin vs placebo in early stage breast cancer, both of which are expected to report sometime in 2020.

The one exception, he suggests, would be a decision on adding a metformin arm to the Add-Aspirin trial – particularly for colorectal cancer. "That trial would really be looking at a situation where the evidence is a bit better, because of the accumulation of the drug in the colon, the association of colon cancer with metabolic syndrome, and the known adverse effect of weight."

Pollak remains hopeful that metformin will indeed prove its value in some cancer settings. But he is also interested in efforts to develop analogues that would work in a similar way to metformin, with improved pharmacokinetics that would allow higher doses to reach cancer cells throughout the body. One of the first cancer clinical trials of a metformin analogue – IM-156, from the American Houston-based biotech Immunomet – is set to start in Korea in the first half of 2018. Other companies, including San Francisco-based Enlibrium, also have plans to evaluate metformin derivatives for use in oncology.

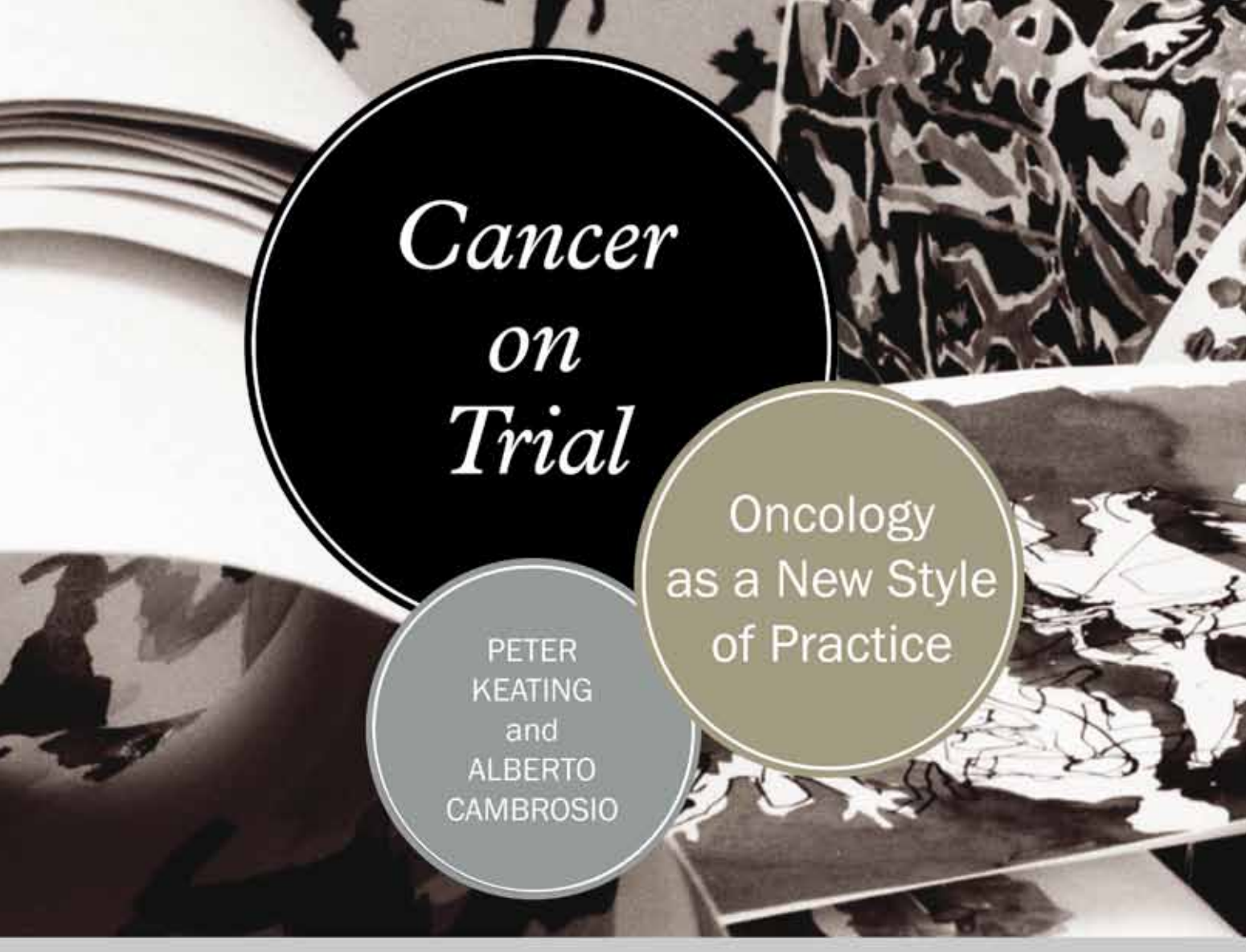
He worries that efforts to learn about how best to use metformin against cancer may be hampered by lack of co-ordination

Recent research from Japan suggesting a possible immunological mechanism for metformin is now adding new layers of interest to this intriguing drug, with mouse model studies showing that its anti-cancer activity does not work in immune-deficient mice (*PNAS* 2015, 112:1809–14).

Indeed Pollak's own lab has recently reviewed studies showing the impact of metformin on the gut microbiome, which is itself linked to diabetes and obesity, and also plays a role in immune and inflammatory systems (*Diabetologica* 60:1662–67).

So as happens so often, says Pollak, disappointment that metformin did not turn out to be a panacea that benefits all cancer patients is spawning new areas of research, delving into the subtleties to learn about the specific settings where metformin does have a role to play, or how to adapt the drug to work more effectively. "This is a field that is keeping a lot of people busy."

To comment on or share this article, go to bit.ly/cw80-metformin



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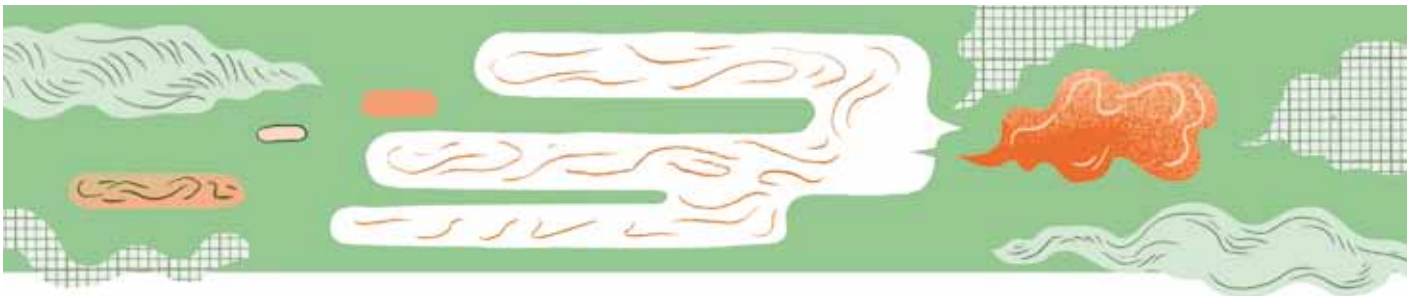


Omar Youssef: cosmetic surgery is not just a Western luxury

Training Egypt's breast surgeons in techniques of plastic surgery is giving survivors a better quality of life and transforming women's attitudes towards the disease. Having proved it is possible in his own country, Omar Youssef is now helping other developing countries do the same, as **Anna Rouillard** reports.

Breast cancers in Egypt are more deadly than they are in the West. They strike at a younger age – around ten years younger than the average in Western countries. They are more aggressive. And they are picked up later – six in every ten new patients are diagnosed with locally advanced disease.

So training Egypt's breast surgeons in how to achieve the most aesthetically pleasing outcomes for their patients might not be considered an obvious priority. And yet it is – thanks in large part to Omar Youssef, professor of surgical oncology at the National Cancer Institute in Cairo.

In recent years he has been part of a cultural revolution that he believes has "changed the face of breast surgery in Egypt," inspiring breast surgeons to consider reconstruction as an essential part of their job and helping patients regain their confidence after treatment. It is also changing the whole way women think about the disease, says Youssef, which could help improve survival rates because they are less fearful of asking a doctor about suspicious lumps.

"Cultural taboos around cancer have been declining in Egypt in recent years, but denial is very common in the Middle East – far more so than in the West," he says. "While awareness of the importance of breast self-examination has improved a lot over the past 10 years, when a woman finds a lump herself, she often goes into denial about the possibility of it being something dangerous. Unfortunately, tumours may be ignored for so long that by the time the patient sees a doctor the disease has progressed to an advanced stage, requiring major treatment."

Until the late 1990s, Egyptian women undergoing surgery for breast cancer would, for the most part, undergo partial or radical mastectomies with little or no reconstruction afterwards. "Breast reconstruction was sporadic, with only one or two cases per year in the whole country," says Youssef. "At this time we didn't have the expertise in our country to perform it."

Youssef was adamant that Egyptian women should have access to the kind of aesthetic surgery that women in the West were receiving. His determination led him to Milan, where a fellowship in the department of plastic and reconstructive surgery at the European Institute of Oncology gave him the chance to learn the necessary skills and expertise.

"I was absolutely delighted to be offered this fellowship," he says. "It was 1998, I had just finished my surgical oncol-

ogy training in Cairo, and was developing an interest in reconstructive surgery. Having the opportunity to train in a world-class institute determined the course of my career as an oncoplastic surgeon."

Oncoplastic surgery is the combining of plastic surgery techniques with breast cancer surgery. It aims to ensure an aesthetically appealing result to breast surgery, and includes breast reshaping, such as lifting, reduction, augmentation, remodelling, fat injection and implants, and using skin flaps from other areas of the body to correct defaults.

"These techniques are not used in very early disease, but rather when there are larger tumours," says Youssef. "Conventionally we would have removed the whole breast, but now, thanks to plastic surgical techniques, we can keep the breast by doing some reduction or remodelling and preserving an appealing shape at the same time as removing the diseased tissue."

In many cases, he adds, both breasts are operated on. "Working on both sides guarantees the best aesthetic result, and also gives us the chance to take a biopsy from the other breast." Breast reduction is commonplace, and reducing the volume of both breasts may also lower the risk of future cancers, he says.

There are also downsides to working on both breasts, however. "Of course it is a more lengthy operation and requires longer postoperative care, and sometimes causes the patient some anxiety," says Youssef, but most women are very pleased to have a reduction in the volume of their breasts.

The advantages of a more aesthetic outcome may seem self-evident, yet on his return to Cairo after finishing his fellowship, Youssef found his patients somewhat reluctant to contemplate anything beyond the need to remove the cancer.

"While lumpectomy and mastectomy were seen as necessary, life-saving operations, reconstruction was perceived as superfluous extra surgery, and the benefits were not really appreciated," says Youssef. "It took a lot of persuading for my patients to appreciate that reconstruction could be achieved in the same operation as the removal of the tumour, and that they would come away from the operation with a very natural look and feel."

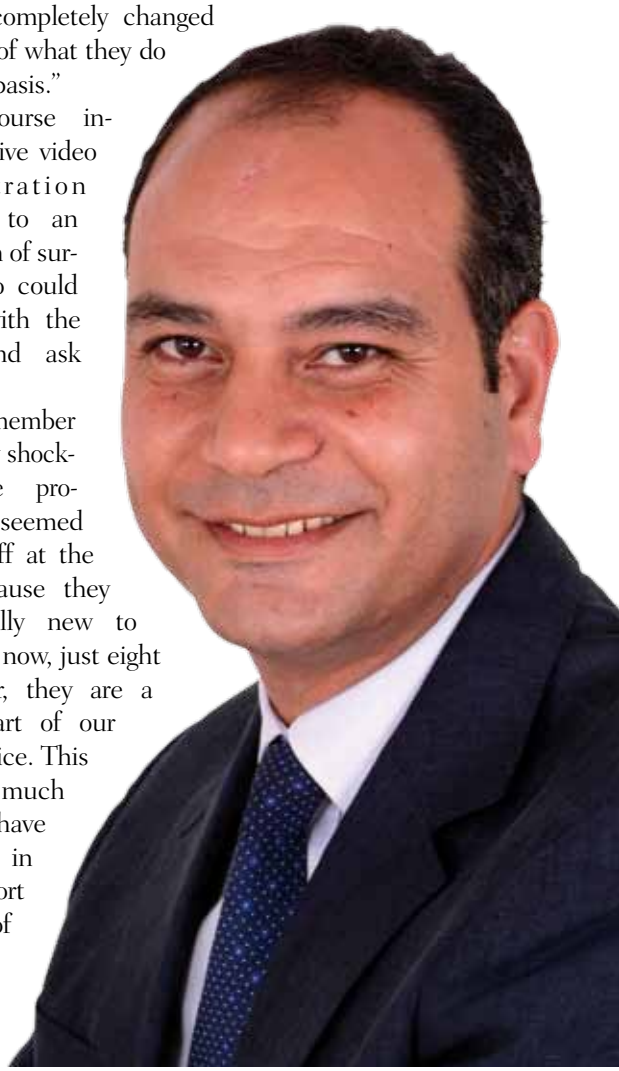
Attitudes are changing however. Today, Youssef's patients specifically request reconstruction. "They no longer fear mutilating surgery, and knowing there will be a visually appealing result at the end actually helps motivate them. We counsel the patient beforehand and explain the various techniques as well as how they might look afterwards, so they can take informed decisions."

Changing how Egypt does breast surgery

A chance to spread oncoplasty techniques among breast surgeons working across Egypt came in 2008, when Youssef met with Alberto Costa, a fellow breast surgeon and head of the European School of Oncology (ESO). Youssef explained the situation and proposed the organisation of an ESO course on oncoplastic surgery in Cairo. "Thanks to Alberto Costa, who gave his full support to this idea, we had a first, highly successful meeting in 2009."

Costa chose a faculty from the UK, led by Dick Rainsbury, Consultant Surgeon at the Royal Hampshire County Hospital and four of his colleagues. "This was an absolutely fantastic faculty, and I can't tell you how this course changed the face of breast surgery in Egypt", enthuses Youssef.

"These professors inspired Egyptian surgeons to consider breast reconstruction as an essential part of their job – it completely changed the scope of what they do on a daily basis."



The course included a live video demonstration projected to an auditorium of surgeons who could interact with the faculty and ask questions.

"I remember vividly how shocking these procedures seemed to our staff at the time, because they were totally new to them. But now, just eight years later, they are a routine part of our daily practice. This is how much things have changed in such a short space of time!"

The oncoplastic

Above: Omar Youssef (centre) with Omar Morsi, surgical oncology resident at the National Cancer Institute (left) and Abdel Hamid Kalawi, lecturer in surgical oncology at Cairo University. *Right:* At work in the operating room with colleague Yasser El Debakey

surgery course now takes place every March. Led by Youssef, it has become an integral part of the NCI's training programme.

In recent years, oncoplastic surgery has seen a surge in popularity, says Youssef, and numerous courses are popping up throughout universities and cancer centres. "Training can consist of cadaveric dissections, or working on real-life models or real patients, drawing lines and planning how to perform the surgery on them. We also now use models made of foam that can be cut and sutured like in real surgery."

Youssef insists that surgeons are sufficiently trained before attempting the techniques on patients. "Even if oncoplastic surgery has become more popular and widespread, I don't want it to be misused. It should be the sole domain of surgeons who have received training and are skilled in the techniques – general surgeons should not be permitted to do it."

He has seen what can go wrong when unqualified surgeons attempt oncoplastic surgery. "The consequences can be cosmetic, with ugly outcomes, or if the tumour is not properly removed there can be a higher chance of recurrence. Each patient is different, and not all patients are suitable for specific types of surgery. Women with larger breasts usually need some type of reduction, but there are several types of reduction, and the surgeon needs to know which one to choose for the best clinical and cosmetic outcome."

In some countries, namely the United States and South America, the breast surgeon removes the tumour then hands over to the plastic surgeon, who finishes the operation. Egypt, however, follows the practice in countries like France and Italy, where it is commonplace for one surgeon to both operate on the tumour and subsequently reconstruct the breast.

"I think breast surgeons should be capable of doing both techniques," says Youssef. "I don't think it is the right approach that someone continues what somebody else has started."

Expertise can be gained step-by-step, he says, by following courses of increasing difficulty and complexity. If at any point a surgeon finds themself needing to do something that is beyond their level, they should immediately refer their patient to a more specialised centre, he insists.

"Body image is very important, and my patients report being able to rapidly resume normal life. This is really fantastic"

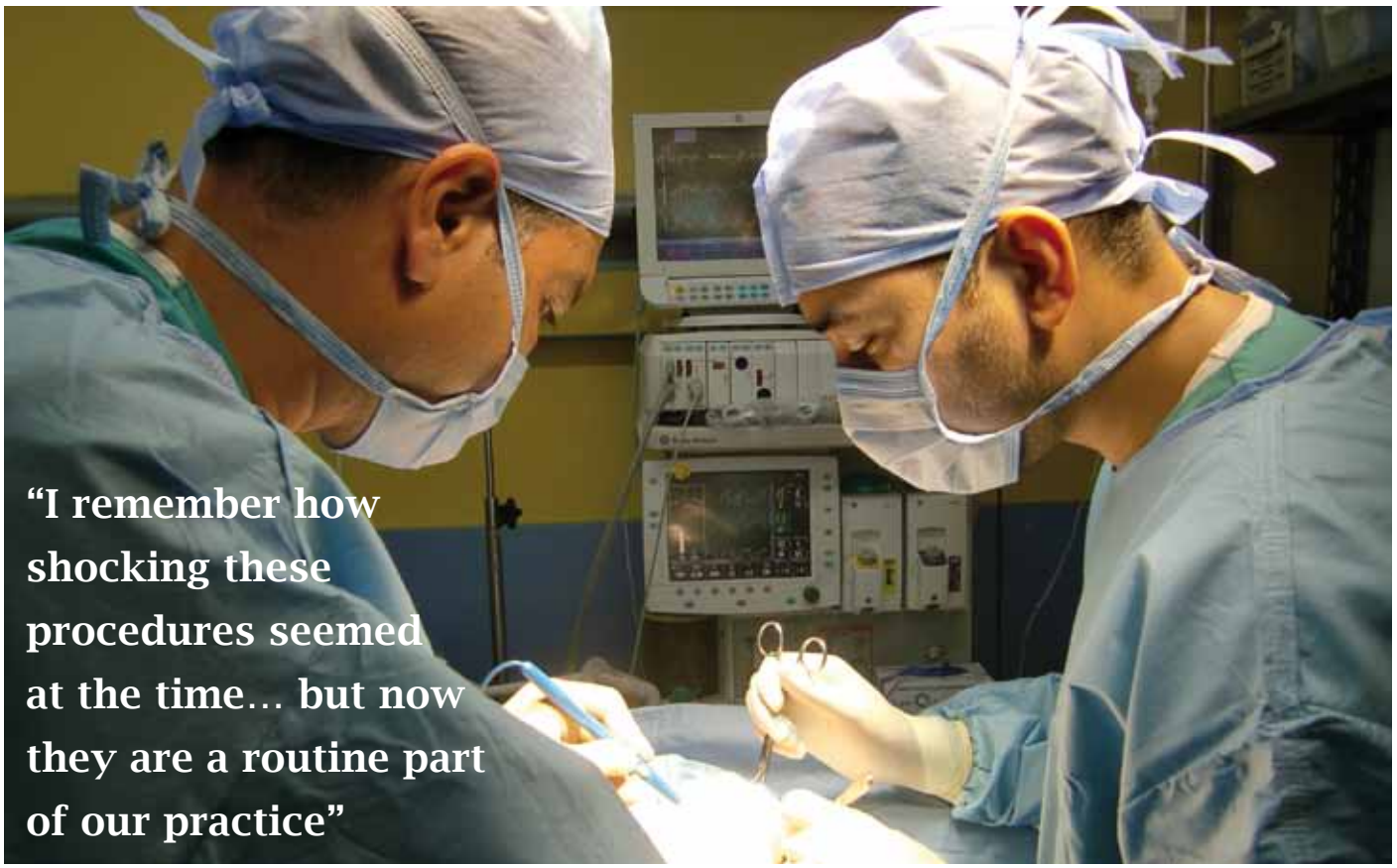
Thanks to the training initiated by Youssef and ESO, today, many of Egypt's cancer centres have surgeons who can perform a wide array of oncoplastic surgical techniques. A recent survey of patient reported outcomes shows that patients who received oncoplastic surgery are highly satisfied with the procedure and with the support and advice given to them by the surgeons and healthcare staff.

"The aesthetic outcomes we can now provide for Egyptian cancer patients no doubt have a strong positive impact on their quality of life. Body image is very important to them and my patients report being able to rapidly resume normal life. This is really fantastic. I feel so happy when I realise how satisfied my patients are with the outcome of their surgery."

Changing attitudes

Marwa Omara, who was diagnosed with early breast cancer in her early forties, is one of them. She agrees that fear of breast cancer, particularly among younger women, is often tied up with fears about the impact it may have on the way they look and their sexuality, and says, "it is important to choose a doctor who you can trust, and you can talk to about your fear and your options, to reach the right choice for you."

"It was important to me to choose the surgery that removed the cancer safely, but at the same time conserved



the breast's shape after the cancer was removed," says Marwa. "Professor Youssef explained to me in detail that, in my case, I could safely undergo breast conserving surgery and he would find out whether the cancer has spread to the lymph nodes under the left arm. In my case, lymph nodes were also removed as part of the surgery."

She believes that the widening access to breast surgeons who are trained in oncoplasty techniques is beginning to reduce some of the fear around being diagnosed with breast cancer, which could possibly help improve early detection. She cites her own case as an example: "I took almost a year to go for mammography after I realised a clear change in the shape of my left breast." Positive experiences of treatment and care are now helping women like her overcome that fear, she says.

Perhaps the best thing of all, argues Youssef, is that this great value to patients comes at a sustainable cost. "You don't need special instruments or set-up, you just need to invest in surgeons so they become skilled in the techniques. Whether a country is rich or poor, every patient has the right to receive the best treatment possible. An aesthetic outcome after breast surgery is not a luxury, but an integral part of the treatment of breast cancer. We have proven that it is within our means, as a developing country, and it has made an enormous difference to patients and cancer management in Egypt," he says.

"The best thing is that this great value to patients comes at a sustainable cost"

In his capacity as the recently-elected President of Breast Surgery International, Youssef now intends to spread this message – and the oncoplasty techniques – to other developing countries. "I have just come back from Myanmar where we organised a two-day course on breast surgery and reconstructive surgery. We are doing the same in different parts of the world. What I want to do during my two-year tenure is take what we have done here in Egypt and use it as an example for other low- and middle-income countries. I have a fantastic Board who share the same ideas, so I really think we will be able to do great things."

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ABBREVIATED Prescribing Information. Rixathon® (Active component: Rituximab). Presentation: 100 mg/ 10 ml and 500 mg/ 50 ml concentrate single-use vials for solution for IV infusion. **Indications:** CD20 positive B-cell non-Hodgkin's lymphoma (NHL); chronic lymphocytic leukaemia (CLL); rheumatoid arthritis (RA); granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). **Dosage and Administration:** For the approved indications, the typical dosage is 375 mg/kg/m² for NHL, GPA/MPA and initial CLL treatment, 500 mg/kg/m² for subsequent doses in CLL treatment, and 1000 mg for RA. Administer as IV infusion under the close supervision of an experienced healthcare professional, and where resuscitation facilities are immediately available. Premedicate with an anti-pyretic, an antihistamine and a glucocorticoid before each infusion. Please see the Rixathon® Summary of Product Characteristics for information. **Contraindications:** Known hypersensitivity to rituximab, any component of the product or murine proteins. Active, severe infections. Patients in a severely immunocompromised state. Severe heart failure (NYHA Class IV) or severe, uncontrolled cardiac disease. **Special warnings and precautions:** Progressive multifocal leukoencephalopathy (PML): All patients treated with Rixathon® for RA, GPA and MPA must be given the patient alert card with important safety information regarding the increased risk for infections, including PML. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. Treatment should be suspended if PML is suspected and permanently discontinued if PML is confirmed. NHL and CLL: Rituximab is associated with infusion-related reactions (IRR), cardiac disorders, haematological toxicities, infections, immunisations, skin reactions; RA and GPA/MPA: methotrexate (MTX)-naive populations with rheumatoid arthritis, IRR, cardiac disorders, infections, hepatitis B infections, late neutropenia, skin reactions, immunisation, concomitant/sequential use of other DMARDs in RA, malignancy. **Interactions:** For detailed information please see the Rixathon® summary of product characteristics. **Pregnancy and lactation:** Women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with Rixathon®. Rixathon® should not be administered to pregnant women unless the possible benefit outweighs the potential risk. Women should not breast feed during and for 12 months following treatment with Rixathon®. **Undesirable effects:** See Rixathon® summary of product characteristics for full list. **Common:** Infections, IRRs, headache, diarrhoea, dyspepsia, dizziness, arthralgia. **Common (NHL):** Infections (esp. bronchitis, sepsis, pneumonia; sinusitis; hepatitis B), haematologic toxicity (neutropenia, leucopenia, febrile neutropenia, thrombocytopenia, anaemia, pancytopenia, granulocytopenia), IRRs, angioedema, hypersensitivity, hyperglycaemia, weight decrease, oedema (peripheral and face), increased LDH, hypocalcaemia, paraesthesia hypoaesthesia, insomnia, vasodilatation, anxiety, lacrimation, conjunctivitis, cardiac disorders (myocardial infarction, arrhythmia, atrial fibrillation, tachycardia), hypertension, orthostatic hypotension, hypotension, bronchospasm, respiratory disease, chest pain, dyspnoea, cough, rhinitis, nausea, vomiting, abdominal pain, dysphagia, stomatitis, constipation, anorexia, throat irritation, pruritus, rash, alopecia; urticaria, sweating, night sweats, skin disorder, hypertonia, myalgia, pain (inc. back, neck and tumour), fever, chills asthenia, headache, flushing, malaise, cold syndrome, fatigue, shivering, multi-organ failure, decreased IgG. **Common (RA):** IRRs, infections (esp URTI and UTI), bronchitis, sinusitis, gastroenteritis, tinea pedis, hypercholesterolaemia, paraesthesia, migraine, sciatica, alopecia, depression, anxiety, GORD, mouth ulceration, abdominal pain, osteoarthritis, bursitis, decreased IgM. **Common (GPA/MPA):** IRRs, thrombocytopenia, constipation, peripheral oedema, infections, decreased haemoglobin, hypokalaemia, muscle spasm/weakness, musculoskeletal pain, back pain/pain in extremities, tremor, cough, dyspnoea, epistaxis, nasal congestion, acne, hypertension, flushing. **Uncommon (serious):** IRRs (including bronchospasm, wheezing, oedema, anaphylaxis and anaphylactoid reactions), cardiac disorders (NHL: left ventricular failure, supraventricular arrhythmias, angina, myocardial ischaemia). **Rare (serious):** infections, including PML and hepatitis B reactivation, severe skin reactions, serum sickness-like reaction, fatal IRRs, PRES. **List of excipients:** sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections. **Excipient with known effect:** Product contains up to 23.06 mmol (or 530.1 mg) sodium per dose. **Incompatibilities:** No incompatibilities between Rixathon® and polyvinyl chloride or polyethylene bags or infusion sets have been observed. **Shelf life:** For detailed information please see the Rixathon® summary of product characteristics. **Special precautions for storage:** Store in a refrigerator (2°C – 8°C). Keep protected from light. **Legal category:** Medicinal product subject to restricted medical prescription. **MA numbers:** Rixathon® 100 mg concentrate for solution for infusion: EU/1/17/1185 /001, EU/1/17/1185 /002; Rixathon® 500 mg concentrate for solution for infusion: EU/1/17/1185 /003, EU/1/17/1185 /004 **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:** July 2017

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*By European Commission (EC)

SANDOZ A Novartis Division

How much is too much?

Will someone please take charge of finding answers?

Precision medicine was meant to see the end of 'maximum tolerated dose' as the standard for introducing new drugs. It hasn't happened, and many patients continue to suffer unnecessary toxicity from overtreatment, with health services picking up the bill. **Peter McIntyre** asks: who should be responsible for optimising our use of cancer drugs?

Developing innovative anti-cancer therapies is science at its most cutting edge. Learning to use these therapies to best effect is perhaps a bigger challenge – one that many clinicians and researchers believe we are failing.

Physicians, patient advocates and cancer leaders are frustrated at a failure to optimise the benefits of new treatments to extend life while minimising harm.

There is a lack of incentive to design and fund trials to optimise doses, combinations, sequences and duration, and a lack of leadership to make it happen.

Writing in this issue of *Cancer World* (p 33), Denis Lacombe, director of the European Organisation for Research and Treatment of Cancer,

says that current models for developing new therapies are not patient-centred, they are drug-centred, "heavily driven by commercial interests, using a chaotic approach, often without proper analytical validation of assays and inappropriate discriminatory cut-offs for biomarkers." As a consequence, he argues, "a plethora of expensive agents [are] arriving on the market based on regulatory trials that fail to provide answers to critical questions asked by treating physicians, patients, and those who evaluate and pay for the therapies."

Lacombe is calling for the system of developing, regulating and evaluating new therapies to be re-engineered in a way that truly places patients at the centre.

He is not the first to raise this issue. At the 2013 Friends-Brookings Conference on Clinical Cancer Research, a group of leading oncologists and regulators in the USA proposed changes to the clinical trials regime, to give greater attention to pharmacokinetics and pharmacodynamics together with better exploration of doses.

Richard Schilsky, ASCO chief medical officer, and Lori Minasian, NCI Deputy Director for Cancer Prevention, co-wrote a briefing paper for the conference with senior members of the US regulatory body, the FDA – 'Optimizing the dosing of oncology drugs' – where they argued that the need to develop drugs quickly often takes precedence over the need to find the 'right' dose.

At the conference, they made the case that the drug development programme does not adequately evaluate long-term cumulative toxicity, especially for patients who remain on the drug for longer because they are living longer. Lack of information about dosage "often leads to a high rate of dose reductions in cancer clinical trials as well as failure to identify patients who may benefit from a higher dose," they argued.

Richard Pazdur, Director of the FDA's Office of Hematology and Oncology Products, told the conference that the cancer research community does an abysmal job of finding the best dose for oncology drugs. "We've had this philosophy that 'more is better'," but the fact that cancer is a life-threatening disease "does not give us license to... accept such a high degree of toxicity," (bit.ly/Friends_Brookings_report).

This problem is not new, but the stakes have been raised by significant rates of toxicities associated with new immunotherapy protocols.

The case of advanced melanoma

The most rapid and dramatic advances in cancer treatment have occurred in advanced melanoma, where survival prospects have been transformed by checkpoint inhibitors – first by the CTLA-4 inhibitor ipilimumab and then by the PD-1 inhibitors nivolumab and pembrolizumab. For many patients life expectancy has been extended for years. But the price paid by patients in terms of side-effects can be very high, particularly when they are used in combination, and question marks remain over whether dosage levels are too high and whether longer term maintenance treatment is necessary.

In May 2015 researchers on the phase III double-blind CheckMate 067 trial concluded that nivolumab alone or in combination resulted in significantly longer progression-free survival than ipilimumab alone (*NEJM* 2015, 373:23–34). Nivolumab was given on permanent (maintenance) doses until disease progression or unacceptable toxicity events, with ipilimumab being given over 12 weeks.

In an update presented at the 2017 American Association for Cancer Research annual meeting (bit.ly/nivo_ipi_update_AACR2017), lead author James Larkin reported that the combination therapy was showing a two-year overall survival rate of 64%, against 59% and 45% respectively for nivolumab and ipilimumab alone.

However serious (grade 3 or 4) treatment-related adverse effects were reported in more than half of patients on the combination arm (58.5%). These included diarrhoea, fatigue, rash, increase in ALT and AST levels, and colitis. Almost one-third of all the patients on the combination arm discontinued treatment (31%), compared with 7.7% and 14.1% in the nivolumab and ipilimumab arms, respectively. However, even in patients who discontinued the combination due to toxicity, Larkin reported that "an impressive survival benefit and responses over 70% were observed."

Another study, the Keynote-029 phase Ib study, led by Georgina Long from the Melanoma Institute Australia, is looking at a lower dose of ipilimumab in a similar combined therapy, but this time using Merck's PD-1 inhibitor pembrolizumab in place of nivolumab, with treatment continued for two years or until disease progression or intolerable toxicity.

In July, Long reported that the trial protocol, which used one-third of the ipilimumab dose used in the CheckMate 067 ipi-nivo trial, showed a "manageable toxicity profile" and "robust anti-tumour activity", and warrants further exploration. Just over a quarter (27%) had adverse events of grade 3 or 4, which was significantly

lower than the 58% in the Check-Mate 067 trial, yet a similar proportion (31%) discontinued the combination or one of the component drugs because of adverse events.

Bristol-Myers Squibb is also sponsoring a post marketing trial of other dose combinations of nivolumab and ipilimumab, but that won't be completed until 2022, while other licence holders are sponsoring combinations of other agents.

"The dosages tested in the original design are not laws of nature"

Bettina Ryll who founded Melanoma Patient Network Europe and chairs the ESMO Patient Advocates Working Group describes how patient priorities have changed over the past five years. "People were very focused on simply having a chance to get out alive. Now we have drugs that work surprisingly well and people who have no evidence of disease and live for years. Of course everyone is still concerned to survive because we still lose too many, but long term perspectives become very relevant."

Among the question patients and their doctors need answered, she says, is whether shorter durations could lead to similar survival benefits without the high levels of serious adverse events. "We should never forget that the dosages tested in the original design are not laws of nature. The first dosage is a mouse model and then we do the first in human and then we go to the maximum tolerated dose. Whether that is the right dose or we could be fine with less, we simply don't know, especially in these new therapies. That is a huge space of uncertainty. There should be a rationale to test this more systematically," she says.

Decisions on stopping treatment, she argues, need to be based on clinical grounds, which will differ from patient to patient, and she says an increasing number of patients are discussing this with their oncologists. "The patients who are willing to stop are either those whose side effects are so bad they say 'I would rather die earlier than suffer this', or people who have had fantastic complete response and the only thing they get are the side effects. People want to step back towards normality."

Denis Lacombe agrees that the lack of scientific basis for deciding how long immunotherapy treatment should continue is a problem. "The duration of immunotherapy in melanoma patients is a shame because, so far, it is impossible to do this trial and we have absolutely no solid evidence, so doctors interrupt treatment on an empirical basis. I think it is a failure of the whole community, including governments."

Solo trial "not feasible"

Doctors are keen to see clinical trials carried out to generate solid evidence on the impact of protocols that could make the treatment more tolerable. However, it seems almost impossible for a single centre to go it alone. At the Pisa University Hospital in Italy, consultant oncologist Antonella Romanini launched a small phase II trial to assess response rate, time to progression and toxicity of nivolumab combined with reduced doses of ipilimumab for patients with advanced melanoma. The trial, approved by the Italian medicines agency AIFA and by the area ethical committee, opened for recruitment in March 2017 supported by the Italian Association Against Melanoma.

Romanini says that the aim was to study a lower dose and less aggressive schedule that could also be offered to BRAF-positive patients who had progressed after being treated with BRAF inhibitors. "If you test a combination that is not so toxic you may be able to use it for patients that have very quick progression and are not in very good shape." The lower dose regime was far cheaper and could, if successful, reduce the costs to the Italian health system.

However, soon after the trial started, the heads of oncology at the hospital told AIFA that they did not think that it was feasible, and the trial stopped.

As company-sponsored trials of combination treatments in Italy are not available in Pisa, Romanini now sends patients to Milan, Genoa or Sienna for treatment, and elderly patients who are too frail to travel have to be treated locally with monotherapy.

She is pressing for the trial to restart, to improve quality of life for patients, but so far without success.

Funding not available

Trials to optimise therapeutic strategies have historically been done by collaborative academic groups, but in the current regulatory and economic environment, and with the high cost of new cancer drugs, that becomes increasingly difficult and the struggle for funding slows progress – and not just for the more rare cancers.

In colorectal cancer, for instance, gastrointestinal cancer specialists have long been concerned at the rate of nerve damage associated with pro-

longed use of oxaliplatin, which since 2004 has been one of the key components of adjuvant chemotherapy regimens such as FOLXOX and CAPOX (also known as XELOX) that are routinely used in patients with stage III (locally advanced) tumours.

This damage can affect sensory and motor function, with symptoms such as numbness and shooting pains in hands and feet. Clinically meaningful nerve damage (grade 2 or greater) is found in well over 40% of patients using either combination.

"For the clinicians, the [disease free survival] difference is very low and the decrease in toxicity is very high – that is very important"

In 2007, Alberto Sobrero and a team in Italy proposed a trial to see whether reducing adjuvant treatment for patients with stage III colorectal cancer from six to three months would be as effective with less damage. The proposal led to the establishment of IDEA (International Duration Evaluation of Adjuvant Chemotherapy) – a collaboration that includes six separate trials involving 16 research groups in 11 countries.

By the end of 2013, more than 12,800 patients had been randomised to receive three or six months of either FOLFOX or CAPOX. The final paper is due later this year, but results presented at 2017 ASCO showed that the overall difference in disease free survival on the shorter regimen was less than one percentage point – 75.5% vs 74.6% (*JCO* 2017; 35S, Late Breaking Abstract 1). For those at low risk of recurrence (defined as cancer spread to 1–3 lymph nodes and not completely through the bowel wall) the difference was even smaller. The rate of serious (grade 3 or 4) nerve damage in patients on the shorter regimen was one-third that reported in patients on the full six months of treatment.

While these results seem intuitively convincing, they did not achieve statistical significance to prove non-inferiority in disease free survival. Despite the statistical near-miss, Thierry André, head of medical oncology at St. Antoine Hospital, Paris, and one of the designers of the IDEA collaboration, says the results have the potential to change clinical practice. "For the clinicians the difference between both arms is very low and the decrease of toxicity is very high and that is very important."

The trial could potentially improve outcomes for large numbers of patients while making savings on healthcare costs. Yet finding the necessary funding proved a lengthy and time-consuming business. The French study, with 2,000 patients, received €1.6 million from the French National Cancer Institute and the Ministry of Health research programme, PHRC. In Italy funding came from the Italian Health Ministry and in the UK from the UK Medical Research Council. "In each country it was the same," says André. "It was very tough to find the money and it was really a fight for everybody."

From planning this trial to reporting results has taken a decade and follow up will continue to assess overall survival.

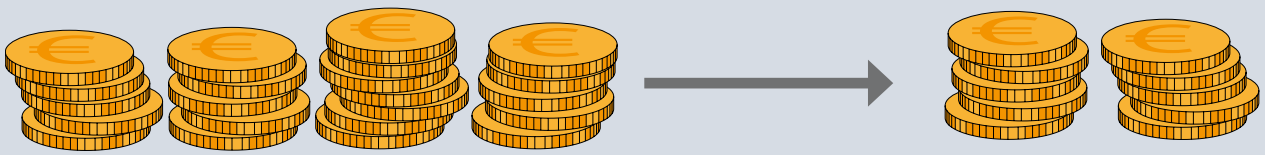
Some doctors feel industry should do more to support efforts to work out how to optimise the use of their drugs. This has been a point of contention in a Swiss study organised across 37 hospitals and canton cancer centres trialling a shorter duration of treatment with the RANK-ligand antibody denosumab. .

This targeted therapy significantly delays the onset of fractures or events that require surgery or radiotherapy in patients with breast or prostate cancer that has metastasised to the bone. However, it increases the risk of hypocalcaemia, while osteonecrosis of the jaw becomes a serious problem after two to three years of

Reducing the risk of neuropathy

Neuropathic damage from oxaliplatin can cause shooting pains, numbness, or even impaired motor function, particularly in hands and feet, which can make everyday tasks difficult. The IDEA trial found that, in patients with stage III colorectal cancer, halving the duration of adjuvant treatment with oxaliplatin–containing regimens, from six to three months, cut the rate of serious (grade 3 or 4) nerve damage by two thirds, with a very minor impact on disease free survival.

Optimisation trials: why payers should get involved



Using nivolumab and ipilimumab in combination rather than in sequence more than doubles the additional cost of gaining an added quality-adjusted year of life, from $90,871 to $198,867

Side effects can reduce the value for money of a therapy in two ways: patients derive less benefit due to reduced quality of life, and there are additional costs associated with any additional care.

In the case of the nivolumab-ipilimumab combination, such is the impact of the side effects that one health economics study estimates that the additional cost per quality-adjusted year of life (QALY) gained with the combination treatment is more than twice the additional cost per QALY gained from using the same treatments sequentially (*JCO* 2017, 35: 1194-202).

The study modelled a hypothetical cohort of patients, mirroring the characteristics of patients in five phase III trials using more than one of ipilimumab, pembrolizumab and nivolumab for BRAF wild-type advanced melanoma.

The researchers obtained data on rates for drug discontinuation, frequency of adverse events, disease progression, and death. Treatment costs related to side effects (drug costs, physician time, and hospital admissions), which were estimated from US Medicare and Medicaid reimbursement rates.

Compared with the first-line dacarbazine treatment strategy, nivolumab followed by ipilimumab produced an incremental cost effectiveness ratio (cost per QALY gained) of $90,871/QALY, while first-line nivolumab + ipilimumab used in first line, followed by carboplatin plus paclitaxel chemotherapy, produced an incremental cost effectiveness ratio of $198,867/QALY.

Using nivolumab or pembrolizumab as a first line treatment was the most cost-effective option. Combining nivolumab+ipilimumab was the least cost-effective strategy. Reserving ipilimumab as a sequential second-line option rather than in combination was associated with improved patient quality of life, fewer serious adverse effects and a lower rate of drop out. The study suggests that lower dosages can produce most of the benefits at lower cost.

The importance of evidence on the risks and benefits of using drugs in different doses, combinations and sequences for getting the best value for money from stretch health budgets is an argument for payers – governments and insurers – to take some responsibility for optimisation trials.

treatment in about 8% of patients, leading to pain, loose teeth and a numb jaw.

The trial aims to recruit 1,380 patients with breast or prostate cancer metastasised to the bone, and will randomise patients to receive either the current maintenance dose of monthly injections or the same dose given every three months.

Roger von Moos, head of medical oncology at Graubünden cantonal hospital and President of the Swiss Group for Clinical Cancer Research (SAKK), says that if the trial is successful, many patients on this long-term therapy will be spared side effects and payers will save millions, given that one dose in Switzerland costs around SF 500 (€ 440).

Recruitment will be completed in 2019, with the outcome known a year later. Progress was slowed because the licence holders Amgen declined to support the trial with finance or to provide denosumab free of charge. Centres in France, Austria, and Greece pulled out because they could not get reimbursement. "We asked Amgen for free drugs for these countries and for some money," said von Moos. "Afterwards we just asked them for free drugs but we did not get it."

The trial has only been possible in Switzerland through financial support from the health insurance companies, which will clearly benefit if the trial is positive.

Researchers were disappointed by

the response of the pharmaceutical company. "They should be interested to test if there is a schedule that is equally effective but potentially less harmful. If we can diminish the price by alternative dosing, these drugs may become affordable in other countries where they don't have approval because they are too expensive."

Who leads and who pays?

The EORTC's Denis Lacombe is calling for a new approach to organising post-approval dosage trials. "The industry community keeps bringing new, clever and very effective drugs forward but comparative effectiveness research is not really being addressed by anyone. There is no room to improve how we give them in sequence, combination and duration, and to which subset of patients. We have to revisit our framework and systems so that this is properly addressed."

He suggests two types of clinical trial – regulatory trials to maintain innovation followed by applied comparative effectiveness trials, taking into account how to optimise a new drug into existing therapeutic strategies. "While I would say the regulatory trials are very well known and done by the commercial sector, there is a grey zone around comparative effectiveness applied clinical trials."

US oncologists and regulators who wrote the briefing note for the 2013 Friends-Brookings Conference proposed something similar – randomised dose comparison studies after the completion of registration trials, prior to marketing approval – a time window when the drug is usually not available to patients – backed with a greater use of patient reported outcomes about tolerable doses.

But while regulators can insist on post-marketing trials, they have limited powers of enforceability – and patients may be reluctant to join trials that vary from accepted dosages. "Post-marketing commitments often cannot be met and are rarely completed within the desired timeframe," the briefing note authors admit.

In one example, the FDA demanded a post-approval dosage trial after a high rate of dose modifications was noted in the phase III trial of cabozantinib for treatment of metastatic medullary thyroid cancer. The US licence holder Exelixis sponsored a trial of 60 mg of cabozantinib versus the label dose of 140 mg, supported by 30 centres in 10 countries. It opened in 2013 but by September 2017 had not yet recruited its target of 188 patients. If the completion date of March 2018 is met, results will arrive more than five years after the higher dose was approved.

In Europe, an opportunity for better addressing some of the optimum use questions may be opening up with the involvement of the European network of health technology assessment bodies (EUnetHTA) in discussing the set up of regulatory trials, as HTA bodies often feed into national processes for assessing the value of new drugs and decisions on reimbursement.

Since July 2017, the EMA and EUnetHTA have been conducting early (pre-registration) consultations with pharmaceutical companies in parallel "to help generate optimal and robust evidence that satisfies the needs of both regulators and HTA bodies". Companies can discuss with regulators and HTA bodies the setup of phase III trials and, in particular, what they will use as a comparator, the endpoints for the trial and which sub groups of the patient population will be included.

The EMA and HTA bodies have been seeking fuller disclosure from companies on evidence generated during drug development in the lab as well as in early trials, saying that this will also give companies a better understanding of what is needed to achieve marketing authorisation and reimbursement.

The director of EUnetHTA, Wim Goettsch, from the National Health Care Institute (ZIN) in the Netherlands believes there has to be a stronger European HTA voice. "It is becoming more and more important that we have much earlier discussion with the manufacturer on which clinical trial we need in terms of data before making reimbursement decisions on a national level."

> **"We need much earlier discussion with manufacturers on the trial data we need before making reimbursement decisions"**

"If you do this at the national level the influence you have on the trial setting will be limited. If we have one European voice to say what we need from the HTA perspective, this influence can be much bigger. That is a crucial starting point, and I think we are going to invest a lot of activity in the coming two years in that perspective."

The EUnetHTA approach is led by the French Haute Autorité de Santé (HAS) France, and the Federal Joint Committee (G-BA) from Germany. EUnetHTA also has an early dialogue

working party with representatives from Italy, the UK, Netherlands, Belgium, and Hungary, soon to be joined by Spain.

EUnetHTA members are piloting three assessments of new cancer drugs and Goettsch says they are insisting on full disclosure. "We have been very specific that they have to provide all the information which they have available and we should be allowed to use those for the assessments."

There are many reasons why data can be blocked. As part of the Get Real project EUnetHTA attempted to obtain data from registries in three European countries on one cancer as a test run to see if these could be used in joint studies across Europe, but were unable to get the information because of procedures in place to protect confidentiality. "There are a lot of process bureaucratic reasons why it is very difficult to obtain data. We are moving, but very slowly."

As well as seeking to speed up joint assessments, EUnetHTA intends to continue to evaluate benefits and risks after a product is on the market. This could lead HTA bodies to ask for additional data from pragmatic trials in a real life setting.

"The challenge then," says Goettsch, "is how are you going to pay for these clinical trials? Who is responsible for that? Sometimes you can still say it is the responsibility of the company. They want to get reimbursement for these drugs and therefore they should also link to what is happening in these countries. This is something we are currently discussing. There is no real answer for that, but I think it is a real issue."

One avenue is to seek support from research funds and other public sources within countries, as the IDEA trial finally managed to do. "If we can show that it will actually lead to savings for the healthcare system there might also be willingness from the healthcare system to invest some money in this."

He hopes that the EU will grasp the nettle after 2020 and support European collaboration on health technology assessments with structural rather than project funding.

Von Moos, of the Swiss Group for Clinical Cancer Research, says that national payers – whether governments or insurance systems – need to be more active in supporting trials that could result in lower dose therapies and huge savings.

"For me it is quite clear. This should be in the interests of payers. In the best cases they can increase the standard of care and they can save money and make modern drugs available for populations who just cannot afford these kinds of treatments."

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Supporting these trials will send a signal to the companies that payers are prepared to challenge label dosage if they think the alternatives have not been properly tested. "The payers have an interest and the power to prove whether the pivotal trial or the design of a trial was really ideal. EMA and HTA should have an influence on the study design before the trial is starting.

"We have to invest much more money in early clinical trials, not only to find the maximum tolerated dose but the optimal dose."

Bettina Ryll, from Melanoma Patients Network Europe, argues it is unrealistic to expect industry to take responsibility for post marketing refinements. "Why should a manufacturer spend money on a clinical study to sell less product in the end?" She also doubts the value of randomising dosage trials when what is needed is smarter data capture and analysis in long-term follow up.

She applauds initiatives such as the Dutch Melanoma Treatment Registry, a nationwide registry that collects data from all melanoma patients to provide insights regarding subsets of patients who benefit from the new drugs.

"Supporting these trials will send a signal that payers are prepared to challenge label dosage"

Ultimately however, the buck stops with national healthcare systems. "In the end it is the state healthcare system that pays for the drugs used in the country, so having access to data showing whether what you are doing works or not makes totally good sense to me. I would not allow national healthcare systems to chicken out of their responsibilities. In the end it is our money – it is tax money or contributions to health insurance that is spent on therapies."

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Let's be honest – our research centres on drugs not patients

Precision oncology is about understanding what is driving an individual's cancer growth, resistance and metastasis, and then targeting those pathways accordingly. Our current research models are good at developing drugs to hit targets. They are bad at learning about which targets need hitting in which patients and how best to do that.

A truly patient-centred approach would not involve just adding the expression of a target of interest as an inclusion criterion to a given trial protocol. That is an inefficient and wasteful way of finding the right therapy for each patient, as it would have to be repeated time and again until the drug–target match is found – if it is eventually found. In addition, scarce biological materials are usually lost in commercially siloed biobanks, and no one addresses treatment questions for those patients who do not express the target.

These are outdated research models, which are heavily driven by commercial interests, using a chaotic approach, often without proper analytical validation of assays and inappropriate discriminatory cut-offs for biomarkers. They are resulting in a plethora of expensive agents arriving on the market based on regulatory trials that fail to provide answers to critical questions asked by treating physicians, patients, and those who evaluate and pay for the therapies, such as: What is the optimal duration of treatment? What are the most effective combinations and sequences?

These unanswered questions add to the uncertainty around biomarker validation and assay validation. In addition, aggressive marketing strategies lead to chaos, inefficiency and waste, with multiple versions of similar agents being developed, because each company wants a full portfolio of its 'own' drug combinations.

Putting the patient at the centre would require replacing the process by which trial protocols seek access to the patients they need, by a process that helps patients get access to the latest science that could help them. Such a process would start with systematic screening of every newly diagnosed patient and the biology of their disease. It would follow the patient through the course of the disease, providing longitudinal clinically annotated bio-collection, addressing tumour heterogeneity and the challenges of recurrence. This process would give patients the best chance to be matched with the best treatment for them, including via access to regulatory trials. Questions about treatment duration, combinations and sequences could be addressed by independent research.

Clinical research and healthcare models are long overdue for transformation. Systems need to be re-engineered to place patients at the centre. This means that new drug/indication trials conducted by the commercial sector and assessed as standalone by the regulatory bodies should be repositioned between two key areas of clinical research activity – they would be underpinned by research documenting the biology of the patients and their evolving disease, and matching patients to treatments, and they would be followed by further clinical research activities that answer questions about how to optimise the treatment strategies.

The starting point must be for all of us involved in developing and optimising treatments to have the intellectual honesty to admit to patients that our current models are not patient centred. We can then work together to re-engineer them.

To comment on or share this Comment, go to bit.ly/cw80-drugs-patients

Denis Lacombe is Director General of the European Organisation for Research and Treatment of Cancer, a major sponsor of academic clinical trials, which also runs a collaborative European platform, SPECTA, that helps deliver high-quality, translational research across tumour types and molecular alterations

OECI

Organisation of European Cancer Institutes

European Economic Interest Grouping

ACCREDITATION AND DESIGNATION PROGRAMME

Designed to improve:

Organisation and Quality of Comprehensive Cancer Care

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Accreditation and Designation Programme
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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

Access to innovation: an ethical concern for all ECCO professions

When did the first debate on access to novel forms of cancer treatment start? Was it with the advent of mastectomy in the 1880s? The development of radiotherapy in the 1890s? Or the burst of new pharmaceutical treatments after World War II?

Perhaps the argument is academic. For each time science takes a step forward in fighting cancer, attention turns to how to ensure uptake of, and access to, the progress. Who wants to be back of the queue when an advance in treatment has been made?

So today's environment, with exciting advances in cancer care still occurring, is in some respects familiar – albeit that, even allowing for inflation, the price tag attached to some emerging personalised treatments would make a healthcare payer's eyes water in any era. As with cancer itself though, the fact that we are familiar with a particular challenge should not mean that we stop searching for new solutions. With this in mind, ECCO recently brought together its 25 member societies to establish key areas of consensus for policy progress on access to innovation. Amongst other central points, our most recent policy position, entitled 'Identifying critical steps towards improved access to innovation in cancer care', explains to health system decision makers that:

- structured pathways are required to systematise the introduction of innovation within health systems;
- patient benefit must be at the heart of evaluating an innovation;
- real world data should help assess innovation benefit beyond the pharmaceutical domain, for example in relation to innovation in surgical techniques, medical devices or new professional services; and,
- a whole-system approach to innovation should be promoted via multidisciplinary leadership (e.g. reviewing current practices and identifying improvement opportunities).

Though the paper delves wider, it does not pretend to offer solutions to all access issues. Instead, it provides a new mandate for ECCO to coordinate its members' views in acting for the patient, and seeking an environment where we can be more confident that scientific advances in treating cancer will benefit the many, not the few.

The debate on access to cancer care has always been vital, in the truest meaning of that word. However, with new treatment costs arguably increasing out of all proportion to the science, our ethics as healthcare professionals precludes us from staying silent on the matter.

The economics of cancer care joins the organisation of cancer care as a fundamental ECCO concern.

The ECCO position paper 'Identifying critical steps towards improved access to innovation in cancer care' is published in the *European Journal of Cancer* (vol 82, pp 193–202), and is freely available online at bit.ly/ECCO_access

Advanced breast cancer advocacy goes global

The advanced breast cancer community has spent many years defining the treatment, care and support patients need to help them live longer and feel and function better. They've now formed an alliance to advocate for those needs to be met across the globe. **Marc Beishon** reports.

A generation ago, stigma surrounding breast cancer – whether early or advanced – was widespread across the globe. It was the advocacy movement that changed this, forcing policy makers and the public to confront an illness that had been largely hidden and that struck mainly women, who are at the heart of family life and caregiving in most countries – and increasingly often the primary breadwinner.

Yet the early advocacy and patient groups by and large failed to challenge the stigma associated with a metastatic breast cancer diagnosis. The later stage of the disease that kills didn't fit with the mood of optimism and hope attached to the pink campaigns and early stage breast cancer groups. Women with advanced cancer found that their needs and concerns were not being addressed either by support groups or, to large extent, by healthcare professionals.

The past 10 years has seen a steady uptick in focus on the unmet needs of people with metastatic breast cancer (mBC), which have grown all the more urgent due to the stalling progress in survival. Milestones include the ABC consensus meeting on advanced breast cancer, launched by the European School of Oncology (ESO) in 2011 (www.abc-lisbon.org); the publication of the 'Global status of advanced/metastatic breast cancer 2005–2015 decade report' (bit.ly/decade_report); and most recently the establishment of the ABC Global Alliance (www.abcglobalalliance.org), another ESO initiative, which draws together organisations with interests in advanced breast cancer, and which will elect its first steering committee members at ABC4 in Lisbon in November 2017.

These efforts have made an impact. The metastatic breast cancer population is now widely recognised as a distinct group with specific needs.

Those needs have been researched and documented (although few countries know how many people are living with the disease, as the information is not collected by cancer registries). A wide range of these issues was publicised in the 'Decade report' and in the Here and Now campaign (www.wearehereandnow.com), and now the ABC Global Alliance has set out a Global Charter of 10 achievable and measurable actions for the next 10 years – which the advanced breast cancer community is united to fight for. They will address public perception and stigma, social and caregiver relationships, healthcare provider communication, advocacy, national policy and more.

Not least is the need to make much greater progress on survival from scientific and clinical research – while there are new agents and approaches in the pipeline, advances are slow and have limited benefits. The aim is to double median survival from the current two to three years, up to four to six years by 2025.

But there is much to gain from raising the quality of treatment and care across the world to current standards by applying the multidisciplinary recommendations issued by the bi-annual ABC consensus conference. As medical oncologist Fatima Cardoso, who is the force behind the ABC 'movement' and initial chair of the Alliance, says: "If all patients had access to everything we already have, we would cut breast cancer mortality by 30%. But the ultimate goal of the charter is to improve both survival and quality of life, and there are more ways to do this than just through science."

What is needed now is to spread the charter's messages to as wide an audience as possible, while being mindful of resource constraints, and to advocate for resources to address the unmet needs that have been so thoroughly researched and defined. That is what the ABC Global Alliance aims to do.

The ABC Global Charter: 10 actions for change

The ABC Global Charter lists 10 actions that are priorities for change, which are listed below. The full wording, which will be available on the Alliance website – www.abcglobalalliance.org – explains and expands on the actions. It also includes a list of key gaps and imperatives that inform the actions for improving ABC (advanced breast cancer) patient care by 2025.

1. Double median overall survival for patients with ABC to at least four years by 2025.
2. Improve quality of life for patients with ABC in clinical practice.
3. Improve availability of robust epidemiology and outcomes data for ABC.
4. Increase availability and access to multidisciplinary care, including palliative, supportive and psychosocial assistance for patients, families and caregivers to ensure patients are receiving the best treatment experience.
5. Strive for all patients with ABC to have financial support for treatment, care and assistance if unable to work.
6. Offer communication skills training to all healthcare providers.
7. Provide accurate and up-to-date ABC-specific information tools to all patients who want them.
8. Increase public understanding of ABC.
9. Improve access to non-clinical supportive services for ABC.
10. Protect workforce rights for patients with ABC.

A global alliance of activists

"The Alliance brings together people and organisations across the world who want to work together to change the lives of people with advanced breast cancer for the better," says Alberto Costa, CEO of the European School of Oncology. "In recent years the ABC consensus meeting has become a magnet for people who want to contribute to defining the best standards of treatment and care for patients with advanced breast cancer. For ESO, launching an alliance aimed at making those standards a reality across the globe seemed an obvious next step."

The Alliance's interim steering committee includes representatives from advocacy groups such as Europa Donna, Breast Cancer Network Australia and the Metastatic Breast Cancer Alliance (which represents groups in the US, where the advocacy movement has the longest history), as well as representatives from industry and from the Union for International Cancer

Harmonising the terminology

Part of the problem about breast cancer communication and awareness is terminology. In cancer generally, it is not uncommon for patients to come away from a consultation having understood the opposite of what their oncologist meant – 'inoperable' does not mean 'untreatable', and 'progression' does not mean that a treatment is working. In some countries, 'secondary' has been used to describe metastatic breast cancer, but the term is confusing, as it can also be used to denote a recurrent, non-metastatic cancer, and not all metastatic breast cancers are relapses, as they can be diagnosed at this stage ('*de novo*' mBC). It also does not convey the same sense of seriousness as the term 'metastatic'.

Danielle Spence says Breast Cancer Network Australia, with the help of the ABC community, has decided to stop using the term 'secondary' to avoid confusion, and also because 'metastatic' is the term used in the great majority of material that people search for on the Internet. "We found it was causing confusion for women with early breast cancer who had experienced a second primary, and was also not resonating with our members who had *de novo* disease," says Spence. The UK, the other notable English-speaking country that still uses 'secondary', may well follow suit, though some research has shown that patients prefer to use 'secondary'.

The term 'advanced', meanwhile, is often taken as interchangeable with 'metastatic', but there is an important distinction. 'Advanced' includes two clinical entities: metastatic disease, which means the cancer has spread to distant sites; and locally inoperable breast cancer, which is characterised by large tumours in the breast and lymph nodes but no distant spread. The Advanced Breast Cancer (ABC) consensus conference covers both stage III (inoperable) and stage IV (metastatic) breast cancer. While with optimal treatment stage III has a much better relative survival rate than stage IV, there are also significant unmet needs and complexity among these patients that warrant inclusion in the consensus.

For most of the world, 'metastatic' is the key term, but confusion about what it means and its implications is widespread.

Control (UICC). Elections at ABC4 will continue this 'multistakeholder' approach, and the new committee will set out priorities for the next two years – certainly advocacy and policy work will be to the fore, as the Alliance aims to give countries support in meeting their biggest concerns.

Danielle Spence, policy and advocacy director at Breast Cancer Network Australia (BCNA), says support for those with metastatic disease had not been emphasised in the past as much as it should have been but, after researching needs, her organisation has begun to remedy this. "We have redesigned our key resource – Hope & Hurdles – to better meet the needs of people with metastatic breast cancer. We were sending this to 1,000 women a year who are newly diagnosed, but we hope to double that. Lack of information and awareness are big barriers, and many find a diagnosis overwhelming, so we have an introductory guide that leads into more detailed information about subtypes, so that people can personalise what they need. We are also raising the profile of mBC issues whenever we can, such as by running dedicated workshops at events."

Awareness of the different facets of the disease needs much promotion, adds Spence. "For example, many people don't realise that there are often long periods of wellness as well as illness during treatment, which itself can be long-term." This has direct impact on other issues such as work and financial concerns, and healthcare organisation. In Australia, says Spence, her group has helped to change government policy to release retirement funds to people with a life expectancy of two years, instead of one, and currently is advocating for specialist nurses, or care coordinators, to help people with metastatic breast cancer to navigate the health and welfare systems.

"Metastatic patients enter the system in a different way to those with early stage breast cancer, and women are telling us that many nurses just don't have an understanding of the metastatic pathways, which often involve more community-based care,"

she says. Having all patients with metastatic disease discussed in a multidisciplinary team meeting is another issue Spence highlights.

A topic that is contentious in many nations is currently being debated in Australia – end-of-life care and right to die legislation. "We surveyed 11,000 BCNA members, including about 500 with metastatic cancer, and about 80% of those with metastatic breast cancer and 75% of those with early disease support assisted dying legislation. It's one of the subjects I'll be talking about at ABC4."

As Spence adds, these issues are typical around the world, and having standards set by the Global Alliance can play a crucial role when writing to ministers about, say, lack of specialist nurses, or reform of welfare conditions. "Having a framework we can quote is great," she says.

In the US, Susan G. Komen, or Komen for short, is one of largest breast cancer advocacy organisations. Kim Sabelko, who heads scientific partnerships and programmes, says while it has been a long journey to overcome the stigma of breast cancer generally, "in the US there has been progress in how we talk about the disease and how it is detected, diagnosed and treated. However, we still have over 40,000 women and men dying of metastatic breast cancer each year, and more than 154,000 people living with metastatic disease in the US," she says. "That's not OK, and so the battlefront is shifting to focus more on metastatic breast cancer."

As in Australia, there is a knowledge gap to address with resources and local meetings, and in the US the financial burden of having advanced disease can be great. "We are fighting this disease on all fronts – providing accurate, evidence-based information about metastatic breast cancer to empower patients and their caregivers; offering support through local meetings, our breast cancer helpline and treatment assistance programme, for example; advocating for policies to ensure mBC patients can afford and have access to timely and quality care; and funding research to discover how to treat and prevent metastasis and bring an end to this disease," says Sabelko. A blog on the extensive Komen website carries patient perspectives, which the organisation aims to weave into everything it does, she says.

"If all patients had access to everything we already have, we would cut breast cancer mortality by 30%"

Komen works at an international level too, as Anna Cabanes, global programmes director, comments. It has a particular focus on low-income countries, where it supports education and cancer control projects to increase capacity to address breast cancer.

It is capacity that is badly needed, she argues: "About 80% of breast cancer in sub-Saharan Africa is diagnosed at advanced stages and even 30–48% in a country such as Brazil. There is perhaps more fear about seeing doctors than stigma against the disease, and we feel there is an opportunity to promote awareness of all stages of breast cancer at once, rather than going through the long 'early to metastatic' route that the US and other developed countries have done."

Cabanes says the issues she sees are women left unprotected by welfare systems and cumbersome bureaucracy, and lack of access to some standard treatments, even in countries with universal healthcare systems. "There's a lot of fragmentation – you could have one treatment, but not the next one, as it's not offered."

Both Cabanes and Sabelko are involved in the Global Alliance. "What I like is that it is truly global – it's inclusive of all economies and settings," says Cabanes. "It could have much impact where there is lot of metastatic cancer, although it will be challenging given that a lot issues are related to healthcare systems." Sabelko adds that it is important to bring organisations together to focus on metastatic breast cancer, to better highlight issues that would not otherwise come in front of policy makers, and also to pool resources – Komen does not want to duplicate work that other agencies are doing, she says. "There is also great power in patient voices to demand access to care and funding for research."

One country where Komen works is neighbouring Mexico. Bertha Aguilar, an advocate in Mexico who was diagnosed with early-stage breast cancer at the age of 30, and is a member of the Global Alliance interim steering committee, says she became involved in 'pink' campaigns in her country, but felt they didn't do enough advocacy to help patients, and particularly women with metastatic breast cancer, some of whom are as young as she was when diagnosed.

Aguilar is a patient advocate and advisor for MILC (milc.org.mx) and

Join the ABC Global Alliance!

The ABC Global Alliance is for people and organisations who are committed to developing, promoting and supporting tangible improvements that will ultimately create awareness and actions that will improve and extend the lives of patients living with ABC worldwide.
To apply for membership go to the Partners and Supporters page of www.abcglobalalliance.org or contact Roberta Ventura at ABCGlobalAlliance@eso.net

Salvati (salvati.org.mx), both non-governmental organisations that are tackling access and treatment issues for mBC, and have representation in several parts of Mexico. "We have big problems with obtaining treatment – there can be waits of months – and in rural communities there can be long distances to travel to see an oncologist, and you won't get an income if you don't work," she says.

There does now seem to be real impetus behind change for the care of people with advanced breast cancer

There is a negative attitude expressed around the world, she adds, with people questioning why women who are going to die should receive costly treatment. "Women are learning that they should be on certain medicines, but they only get what the system has, which is often for early-stage breast cancer," she says. "It means we have to demand better quality of life for women and help them prepare for what's to come, as some will be thrown out of their jobs."

Building public understanding of breast cancer and issues such as workplace rights is crucial and very much the domain of the Global Alliance, Aguilar adds. "Governments that see what other countries are doing are more likely to find the money."

Advocacy must, however, be tailored to local conditions, as Aguilar and colleagues found out at another advocacy group, Cimab Foundation, which won a grant from the UICC and Pfizer to develop Internet resources for the metastatic population, in 2015.

"We thought the Internet would help, but we have found that women in rural communities are often afraid to use it. So we are also working with hospitals to train people as patient navigators, who can help fill information gaps and create care plans."

Online resources do work well in other settings, however. Europa Donna, the coalition of European breast cancer advocacy groups, ran its first metastatic advocacy conference in June 2017, and has launched an mBC website, with resources including an advocacy toolkit and patient videos. These initiatives build on Europa Donna's longstanding support for the Alliance and the ABC conference and its efforts to get governments to address unmet needs, not least by promoting the 2015 European Parliament Declaration on the Fight Against Breast Cancer.

That Declaration made specific demands for patients with mBC, calling on member states to ensure they have access to a specialist breast unit that coordinates care and psychosocial needs.

Marie Pandeloglou, an Australian advocate with metastatic cancer, attended the Europa Donna meeting on behalf of BCNA. "The issues raised by the global advocates are not dissimilar to the challenges Australians living with mBC face – wondering how we are expected to cope with the anxiety, uncertainty, depression, and losing control of our bodies as part of the disease process," she says. "There is a great sense of agreement that people need encouragement, support and empowerment, help in dealing with side-effects of treatment and help with financial stress."

It's been a long time coming, but there does seem now to be a feeling of real impetus behind change for the care of people living with advanced breast cancer.

Not everyone in the breast cancer movement always agrees on the best steps to take next, of course, but as Komen's Cabanes says, it is only by "putting our collaborative hats on" that progress can be made.

To comment on or share this article go to bit.ly/cw80-ABC-advocacy

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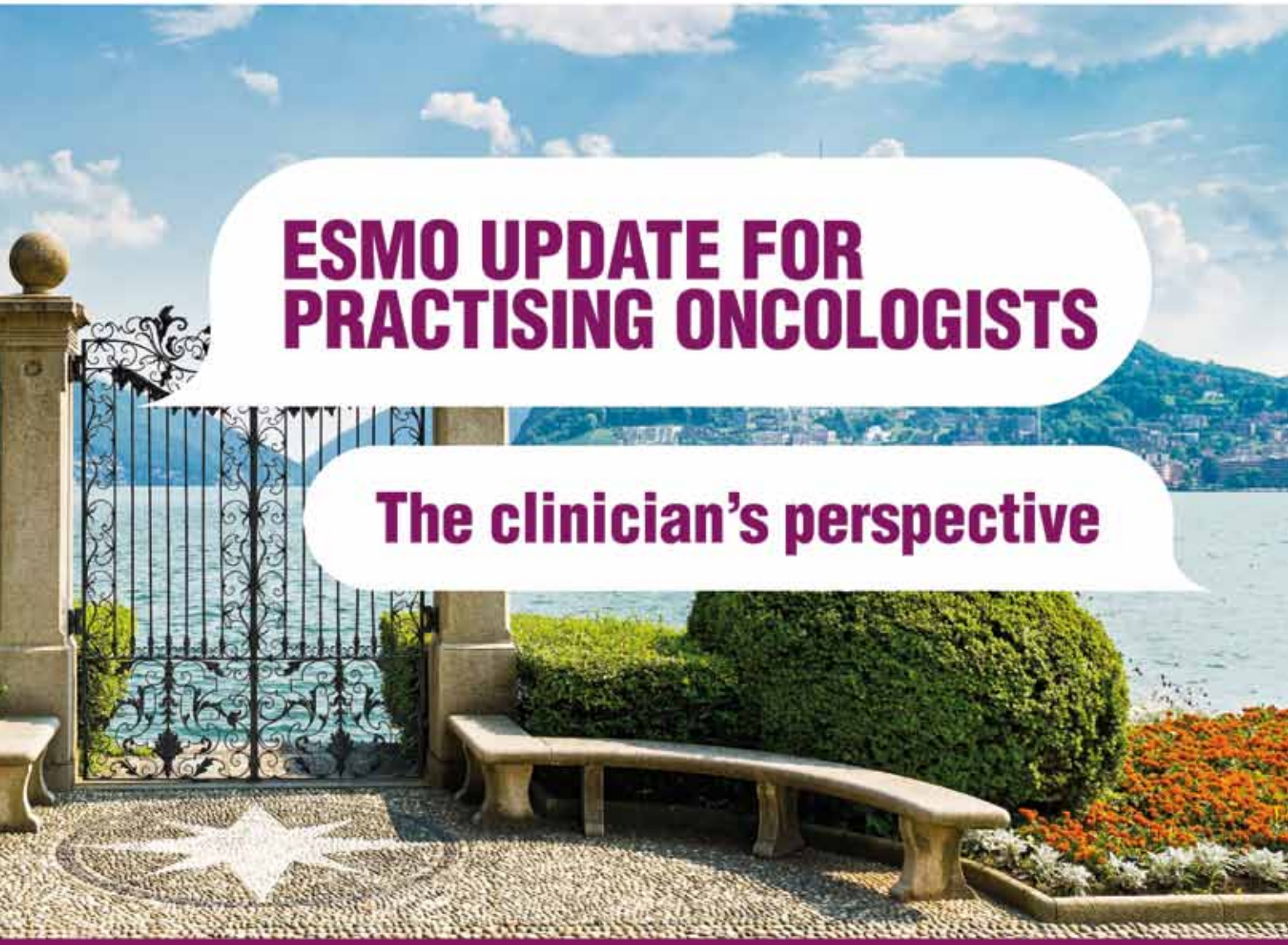

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Immunotherapy in relapsed refractory Hodgkin lymphoma

A chromosomal alteration present in almost all patients with Hodgkin lymphoma makes the disease uniquely vulnerable to PD-1/PD-L1 immune checkpoint blockers. **Astrid Pavlovsky** reviews the trial evidence and clinical experience, and looks to the future possible use of this class of therapy.

This grandround was first presented by Astrid Pavlovsky, from the Department of Haematology, Fundaleu, Buenos Aires, as a live webcast for the European School of Oncology. Emmanuele Zucca, from the Oncology Institute of Southern Switzerland, Bellinzona, posed questions raised during the presentation. It was edited by Susan Mayor. The webcast of this and other e-sessions can be accessed at e-eso.net.

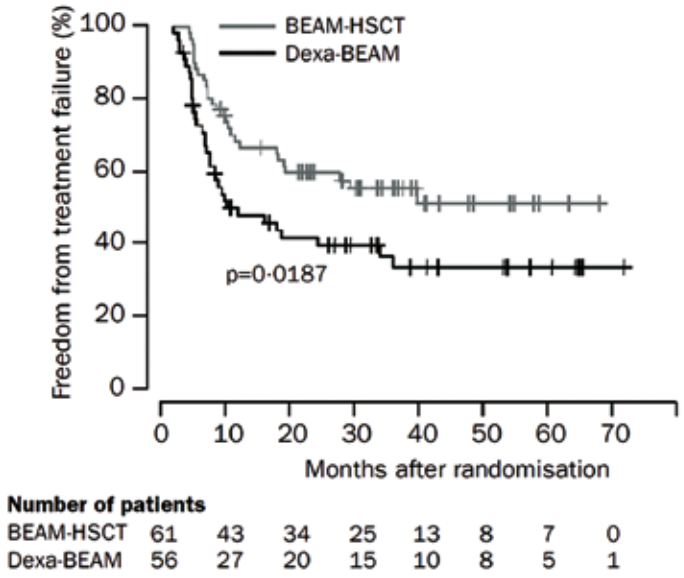
The treatment of Hodgkin lymphoma is a success story in haemato-oncology, with most patients, whether at an early or advanced stage of the disease, being cured with first-line treatment. However, 25–35% of patients have primary refractory or relapsed Hodgkin lymphoma, and a proportion will eventually die of it. We have known for more than a decade that the standard-of-care for patients who relapse after first-line treatment is salvage chemotherapy and autologous stem cell transplantation (ASCT). Two clinical trials have shown that ASCT is associated with significantly greater freedom from treatment failure, which is achieved in around 50% of patients, so this is our first choice of treatment for these patients.

Unfortunately, this means that about 50% of patients relapse after ASCT, and the post-progression survival for this group is poor. Up until 2013, patients who relapsed in the first year after transplant had a median survival of only about one year from the start of disease progression, and for those who relapsed after the first year following transplant, median post-progression survival was only around two years.

Salvage chemotherapy after failure of ASCT has not shown very promising results, and controls disease for only seven to ten months, so this is a subgroup of patients where, until recently, there has been no good standard of care treatment. Different salvage chemotherapy agents, including gemcitabine and vinblastine, have been tried, but with low overall and complete response rates, and with accompanying haematological toxicity.

Recently, we have seen very

ASCT vs chemotherapy for patients with relapsed chemosensitive Hodgkin lymphoma



Autologous stem cell transplantation is the first choice of treatment for patients failing first-line treatment

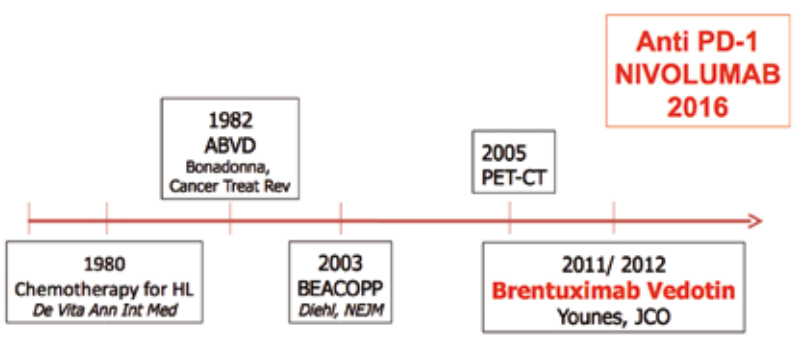
BEAM – carmustine, etoposide, cytarabine, melphalan; HSCT – haematopoietic stem cell transplantation; Dexa – dexamethazone

Source: N Schmitz et al. (2002) *Lancet* 359:2065–71, reprinted with permission from Elsevier

impressive results with monotherapy for the first time, with the use of brentuximab vedotin in patients who have failed after ASCT, with an overall response rate of 75% and a 34% complete response rate (*JCO* 2012, 30:2183–89). However, very few of these patients maintain complete remission, and they eventually relapse.

The figure below traces progress in the management of Hodgkin lymphoma over the last few decades, from the introduction of chemotherapy in 1980, with the MOPP regimen (*Ann Intern Med* 1980, 92:587–95), followed swiftly by the ABVD regimen in 1982 (*Cancer Treat Rev* 1982, 9:21–35). More recently, BEACOPP was introduced in 2003 (*NEJM* 2003, 348:2386–95), followed by the introduction of brentuximab vedotin in 2012 (*JCO* 2012, 30:2183–89). Nivolumab became available in 2016 for use in patients who have relapsed after ASCT.

Progress in Hodgkin lymphoma treatment



Harnessing the power of the immune system

For decades, we have been trying to harness the power of the body's immune system to combat tumour cell growth. Hodgkin lymphoma is a clear example of a disease where there are only a few malignant cells together with a very extensive immune infiltrate.

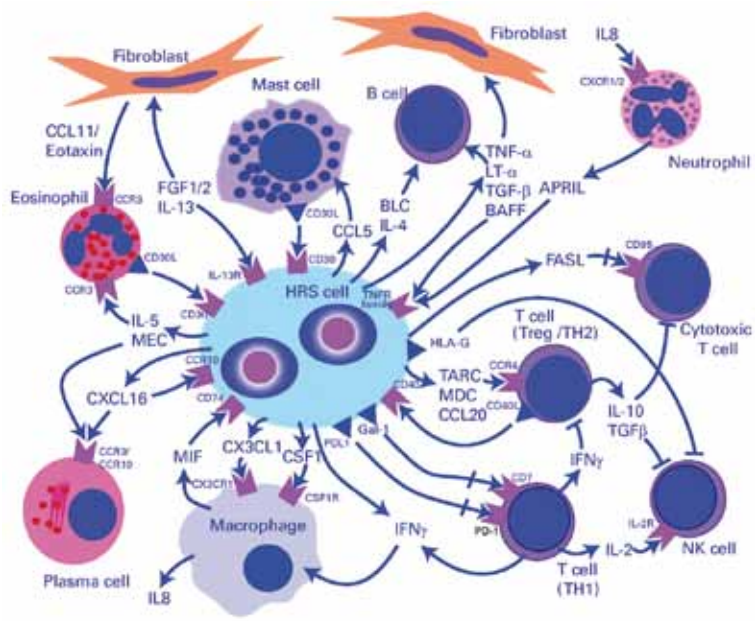
However, this immune infiltrate is ineffective because the tumour cells are still able to grow. So, how can we optimise the power of the immune system to become a line of therapy? Programmed cell death ligand 1 (PD-L1) is an immunomodulatory molecule expressed by antigen-presenting cells as well as by certain tumour cells. It binds to T cell receptors, thereby inhibiting T-cell-mediated immunity.

Almost all patients with Hodgkin lymphoma have an alteration in chromosome 9p24, causing an over-expression of PD-L1 and PD-L2 on the surface of Reed-Sternberg cells, which leads to immune evasion.

This over-expression makes Hodgkin lymphoma uniquely vulnerable to PD-L1 blockade, as it appears that Hodgkin lymphoma cells depend on this mechanism to survive.

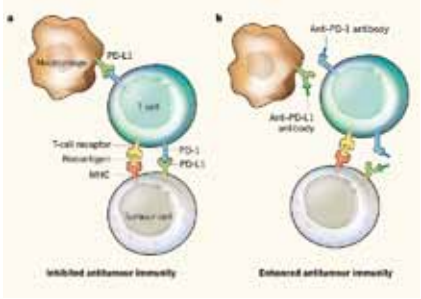
In addition, the 9p24 amplification leads to over-expression of JAK-2, and this mechanism is also being investigated in immuno-oncology.

Optimising the power of the body's immune system in Hodgkin lymphoma



Hodgkin lymphoma has few malignant cells and a very extensive immune infiltrate, but the immune infiltrate does not prevent the cells from growing
HRS – Hodgkin and Reed–Sternberg cells

Inhibited antitumour immunity



Programmed cell death ligand 1 (PD-L1) is an immunomodulatory molecule expressed by antigen-presenting cells as well as by certain tumour cells. It binds to T cell receptors, helping tumour cells evade detection by the immune system

Data on PD-L1 expression in Hodgkin lymphoma

A recent study of diagnostic biopsies in 108 patients treated with ABVD showed that all had 9p24 genetic alterations. These alterations were either disomies, polysomies, amplification, copy gain or translocations. Progression free survival (PFS) of patients was stratified according to stage. Three prognostic groups were seen: early favourable, early unfavourable and advanced stage. In a parallel analysis, PFS of patients was stratified according to type of 9p24 alteration. These resulted in new prognostic groups, showing that the five patients who had polysomy had 100% PFS, and patients with amplification of 9p24 had the worst PFS (*JCO* 2016, 34:2690–97). The prognosis based on clinical stage may be linked to the prevalence of 9p24 alterations. Only 24% of patients with an early stage favourable prognosis had 9p24 amplification, compared to 34% of those with early stage unfavourable prognosis and 50% of those with advanced stage disease. This is the first time we have had a pre-treatment genetic predictor of prognosis in patients with Hodgkin lymphoma (see figure overleaf).

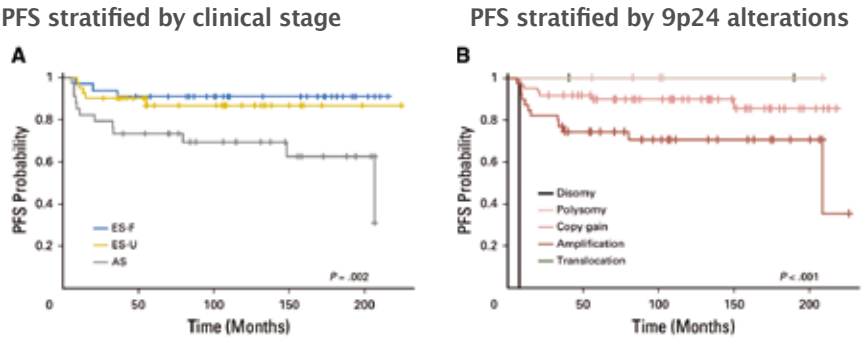
A further study analysed the prognostic impact of PD-1 expression in tumour infiltrating leukocytes in diagnostic Hodgkin lymphoma biopsies in 415 patients treated with ABVD, with or without radiotherapy (*ISHL* 2016, T005). They were divided into either low PD-1 expression (<10% PD-1 positive leukocytes, 85% of patients) or high expression (>10% PD-1 positive leukocytes, 15% of patients). Patients in the high expression group showed an inferior event-free survival compared with the low-expression group. This gives a further possible prognostic tool: patients with high-expression of PD-1 might benefit more from high-intensity chemotherapy or a PD-1 inhibitor as first-line therapy.

These new findings may in the future have implications for planning upfront therapy in Hodgkin lymphoma, recognising that advanced stage disease is associated with inferior outcome and that 9p24 amplification is also associated with an unfavourable outcome. Amplification of 9p24 is more common in advanced stage disease, and Hodgkin lymphoma patients with high PD-1 expression have inferior event-free survival after ABVD compared to patients with low expression.

Studies with immune checkpoint blockade therapy in Hodgkins

We now have two drugs – nivolumab and pembrolizumab – that are fully humanised monoclonal antibodies that block interaction

A genetic predictor of prognosis in Hodgkin lymphoma?



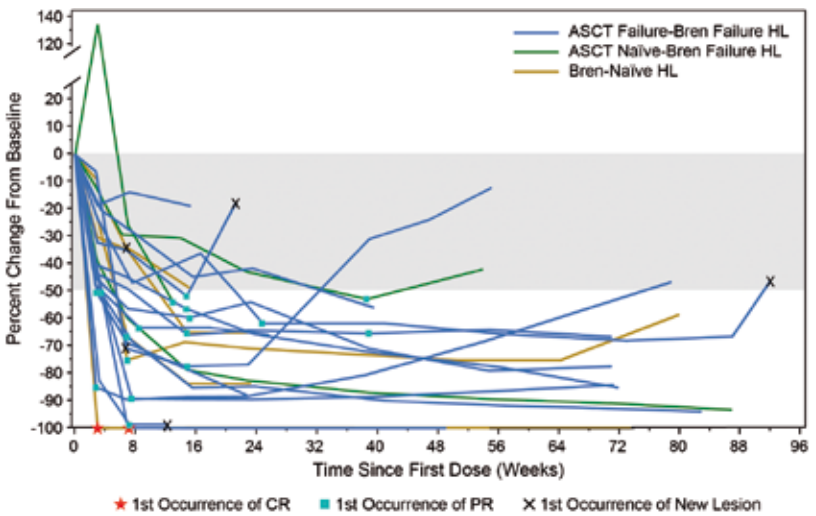
9p24 amplification appears to be a genetic predictor of poor prognosis

A: ES-F – early stage favourable (n=33), ES-U – early stage unfavourable (n=41), AS – advanced stage (n=34); P=0.002 log-rank test. **B:** Disomy (n=1), polysomy (n=5), copy gain (n=61), amplification (n=39), translocation (n=2); P<0.001 log-rank test
Source: MG Roemer et al (2016) *JCO* 34:2690–97, reprinted with permission from the American Society of Clinical Oncology. All rights reserved

between PD1 and PD-L1, which inhibits T cell activity to restore normal immunological function.

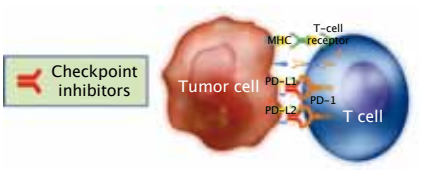
A phase I study (CA209-039) investigated nivolumab in 105 patients with relapsed or refractory lymphoid malignancies and classical Hodgkin lymphoma. Exclusion criteria were: no existing autoimmune disease, no prior organ or stem cell transplant and no prior checkpoint blockade. Of the 23 patients with Hodgkin lymphoma, 78% had undergone prior ASCT and 78% had received prior brentuximab therapy and had failed both, so consequently had poor prognosis.

Responses to nivolumab in relapsed/refractory Hodgkin lymphoma



The phase I CA209-039 study showed that immunological response to nivolumab in heavily pretreated patients with classical Hodgkin lymphoma is quite variable and individual for each patient
ASCT – allogeneic stem cell transplantation, HL – Hodgkin lymphoma, Bren – brentuximab vedotin
Source: J Timmerman et al (2015) 13th International Conference on Malignant Lymphoma, Lugano, Abstract #010

Checkpoint blockade therapy



Nivolumab and pembrolizumab are fully humanised monoclonal antibodies that block the intersection between PD-1 and PD-L1, restoring immunological activity
Source: SL Topalian et al. (2014) *JCO* 32:1020–30, DF McDermott et al. (2015) *JCO* 33:2013–20

Results showed that, of all patients with haematological malignancies, patients with Hodgkin lymphoma had the best response to nivolumab, with an overall response rate of 87%, including 26% with complete response and 50% with ongoing response to treatment on follow-up (median 74 weeks). Nivolumab continued until progression or unacceptable toxicity (Timmerman et al, 2015, 13th International Conference on Malignant Lymphoma, Lugano, Abstract #010).

The figure *left* shows a spider plot of responses to nivolumab, demonstrating the wide variation in response to treatment in Hodgkin lymphoma patients. One patient's lesion grew markedly following treatment before showing a partial response. In contrast, two patients had first complete remissions within four to six weeks. After 76 weeks of treatment, most patients had a sustained partial response. Further analysis showed that two patients maintained a complete response

Defining response to immunotherapy in Hodgkin lymphoma

Until now we have used the Lugano Classification to assess response to treatment, particularly for chemotherapy, incorporating PET to evaluate patients with Hodgkin lymphoma. Chesson and colleagues have published a refinement of the Lugano Classification that takes into account the findings on response to immunotherapy: the Lymphoma Response to Immunomodulatory Therapy Criteria (LyRIC, *Blood* 2016, 128:2489–98).

These criteria include an indeterminate response (IR), which is a provisional term to identify lesions that may be flares or pseudoprogression of disease triggered by an inflammatory response to therapy, in contrast to indicating progressive disease. In the future, we should hopefully be able to distinguish between these two mechanisms but, for now, the definition allows appropriate patients to remain on treatment until reassessment can accurately confirm or refute progressive disease. There are three classifications of indeterminate response (IR):

- IR1 refers to an increase in tumour size of 50% or greater in the first 12 weeks of treatment, but with no clinical progression.
- IR2 indicates the appearance of a new lesion or growth of one or more existing lesions of 50% or greater at any time during treatment, in the absence of overall progression of tumour burden.
- IR3 refers to an increase in PET–FDG uptake (metabolic activity) of one or more lesions with no increase in lesion size or number.

The expert panel recommends repeat scanning after 12 weeks and carrying out a further biopsy to gain a clearer idea of whether a patient has progressive disease or not.

even after stopping treatment, and two patients had late complete responses, with one occurring after stopping therapy.

These findings show that the immunological response to nivolumab is quite variable and individual for each patient. It is very different to that seen with chemotherapy, so we have to evaluate response differently.

It is important to recognise that some individuals have early progression of their lesions followed by subsequent remission, others have durable partial responses with clinical benefit, some patients have late complete responses or improvement in response after stopping treatment, and others have new lesions with or without reduction of pre-existing lesions followed by late response to treatment.

Longer-term follow-up showed that that progression-free survival was 50% after a median follow-up period of 92 weeks, and overall survival was 74%. This is promising and represents a new treatment option for patients with aggressive Hodgkin lymphoma. When the data were reported, most patients had an ongoing response, so further evaluation is ongoing.

Drug-related adverse events were relatively frequent, with 83% of

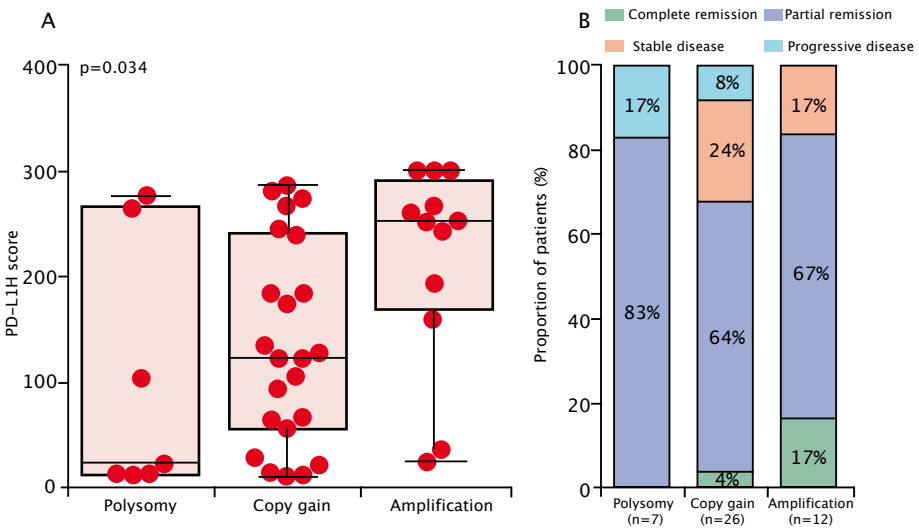
Adverse events with nivolumab in patients with Hodgkin lymphoma

Adverse event	Any Grade, n (%)
Gastrointestinal	4 (17)
Diarrhoea	3 (13)
Colitis	1 (4)
Hepatic	2 (9)
ALT increased	1 (4)
AST increased	1 (4)
Blood alkaline phosphatase increased	1* (4)
Pulmonary	1 (4)
Pneumonitis	1 (4)
Skin	5 (22)
Rash	4 (17)
Pruritus	3 (13)
Pruritic rash	1 (4)
Skin hypopigmentation	1* (4)
Endocrine disorders	
Hyperthyroidism	4 (17)
Hypersensitivity/infusion reaction	2 (9)
Bronchospasm	1 (4)
Infusion-related reaction	1 (4)

In the phase I CA209-039 study, patients with classical Hodgkin lymphoma suffered a wide variety of adverse events. All were grade 1 or 2, except diarrhoea and pneumonitis, which were grade 3. There were no treatment-related deaths. At the time of reporting, all had resolved, except for the two marked * and one case of hyperthyroidism

Source: J Timmerman et al (2015) 13th International Conference on Malignant Lymphoma, Lugano, Abstract #010

PD-L1 expression, 9p24 alterations, and responses in patients treated with nivolumab



Biopsy of 45 patients showed all had 9p24 alterations. Amplification of 9p24 was associated with a higher level of PD-L1expression (A). This was a favourable prognostic indicator for response to treatment with nivolumab (B)
Source: A Younes et al. (2016) *Lancet Oncol* 17:1283–94, reprinted with permission from Elsevier

Hodgkin lymphoma patients having some kind of adverse event, but severe adverse events were quite rare. All adverse events were grade 1 or 2 except diarrhoea and pneumonitis, which were grade 3. There were no grade 4 or 5 events nor deaths related to treatment; 14% of patients discontinued nivolumab treatment due to drug-related adverse events. Most of the adverse events were haematological or skin-related (see table, p 47), and the majority occurred in the first few weeks of treatment, before resolving. However, some patients had severe adverse events later in treatment, so they must be closely monitored using an appropriate algorithm to distinguish between immune-related adverse events and disease progression, to determine subsequent management. Almost all adverse events resolved with management, except for hyperthyroidism, which should be managed by a specialist.

A further phase II study (CheckMate 205) investigated nivolumab in Hodgkin lymphoma patients divided into three cohorts – patients who had failed after ASCT (cohort A), patients who had undergone ASCT followed by brentuximab which then failed (cohort B), and patients who had received ASCT after or before brentuximab (cohort C). Focussing on cohort B, which included patients who had previously failed ASCT and brentuximab therapy, the patients were given 3 mg/kg nivolumab every two weeks until disease progression or unacceptable toxicity. Most patients were treated as outpatients, as nivolumab is a very easy infusion to administer. The objective response rate was 66%, with 9% of patients achieving complete remission. The median time to response was two months, with a median duration of response of eight months. Overall survival at six months was 98% and progression-free survival was 77%, with a median progression-free survival of ten months (Engert et al, oral presentation, European Hematology Association, June 2016).

Forty-five patients were analysed for genetic alterations, and all showed 9p24 alterations, including 85% with either copy gain or amplification. Responses were observed in patients with all types of genetic alteration at 9p24. Patients with amplification of 9p24 had a higher level of PD-L1 expression. This was a favourable prognostic indicator for response to treatment with nivolumab, with 17% showing complete response, which was higher than in the other two groups. In this trial, higher levels of PD-L1 expression associated with 9p24 amplification were associated with greater response to nivolumab with better treatment outcomes.

Combination treatments including nivolumab

Many clinical trials have investigated the safety and efficacy of different combination treatments including nivolumab. A recent phase I/II trial investigated the combination of brentuximab vedotin with nivolumab in 42 patients with refractory or relapsed Hodgkin lymphoma, including 40% with primary refractory disease. Of these, 33% relapsed within one year and 26% relapsed after one year (Herrera et al. 2016, American Society of Hematology Abstract #1105). Treatment involved administration of cycle 1 of brentuximab given on day 1 and nivolumab on day 8, followed by administration of cycle 2 through 4 with brentuximab and nivolumab given in combination on day 1 and then every 21 days. After four cycles

Question and Answer session with Astrid Pavlovsky

Emmanuele Zucca, from the Oncology Institute of Southern Switzerland, Bellinzona, posed the questions.

EZ: I do not agree that brentuximab is chemotherapy-free and I would be more restrictive in the use of the term. I must also highlight that chemo-free does not mean side-effect free. Would you like to comment?

AP: Yes, I must highlight that we are dealing with something different, not necessarily less toxic, and we need more time to see what will happen in patients as they go along. Also, we must see what treatments we can use if immunotherapy were to fail, using information from clinical trials – including whether allogeneic stem cell transplant is an option – because there is limited experience of treatments after checkpoint inhibitors have failed.

EZ: In addition to brentuximab vedotin, do you consider any other agents worth testing in combination with nivolumab? Do you think we will see phase I trials exploring use of these treatments as first-line therapy, or do they have a role only in relapsed or refractory Hodgkin lymphoma?

AP: I think lots of patients do well with ABVD, so I think it's unlikely that all patients will need these treatments as first-line therapy. They are also very expensive compared to traditional therapy. I think further evidence is needed from randomised trials to support the efficacy of these drugs as frontline therapy, and they must show greater clinical benefit than existing treatment [ABVD]. Many patients are cured with ABVD with good overall survival. These are very promising drugs, but we need more time and data to assess economic validity, toxicity and ease of delivery, to decide which patients receive these agents first line. For now, I think the role of these drugs is primarily for refractory and relapsed Hodgkin lymphoma.

With regard to combinations, there are many checkpoint inhibitors that have been combined with chemotherapy in clinical trials, including CTLA-4 inhibitors and PD-L1 inhibitors, and bendamustine has shown good results in refractory disease. Ipilimumab and pembrolizumab have shown promising response in this group of patients. We will soon have good data to support the best combination and to suggest which patients benefit most from particular combinations. However, it will be a challenge to analyse response to these agents in trials.

of treatment, patients' responses were assessed, and those who were eligible could then choose to go on to ASCT.

Preliminary results showed a 90% objective response rate to treatment, with 62% of patients in complete remission (Deauville Score 1–3 on PET scan), 28% in partial remission, and one or two patients with stable or progressive disease. Almost two in five patients (38%) experienced infusion-related reactions to treatment, but the overall safety profile was manageable, with no dose reductions or discontinuations due to adverse events. The incidence of immune-related adverse events was low, and there was no antagonism between brentuximab and nivolumab. The promising activity supports further exploration of this chemotherapy-free regimen for relapsed/refractory Hodgkin lymphoma.

Looking to the future

There are now many clinical trials with different combinations of these new immunotherapy agents, used with other checkpoint inhibitors or other agents, both in first line and in the relapsed refractory setting. Immuno-oncology has changed the scenery for patients with relapsed/refractory Hodgkin lymphoma, with higher overall and complete response rates than traditional chemotherapy.

Nivolumab is currently licensed for patients with refractory or relapsed Hodgkin lymphoma, after ASCT and brentuximab. Toxicity is mostly immune related, but manageable with close monitoring.

Further studies are needed to explore the specific indication for these treatments and to evaluate the best combination and timing of treatment.

We also need to find a different way of assessing clinical response, with many patients showing a long-term partial response.

In conclusion, it is very encouraging to have new options for this subgroup of Hodgkin lymphoma patients, and we are eager to gain further information on how best to use these drugs.

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Why All.Can?
With the growing prevalence of cancer and ongoing pressures on limited healthcare budgets, we need to find new ways to make the most of the resources we have.

Waste must be challenged:

20% of healthcare spending is wasted on ineffective interventions

Waste is not just money, but time, quality of life, and missed opportunities for patients and their families

Efficiency ≠ cutting costs

...it's about continuously ensuring resources are focused on delivering what matters most to patients

Improving efficiency is about re-focusing resources on delivering what matters most to patients, and it requires a long term vision.

We need a longer-term vision which takes a whole system view of cancer care and is focused on four key areas:

1

Patient-relevant outcomes at the heart of cancer planning, delivery and evaluation

2

Investment in data to create a continuous cycle of improvement

3

Concrete mechanisms to create **accountability** across the entire care pathway

4

Political will to focus on better outcomes for patients

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All.Can comprises leading representatives from patient organisations, policymakers, healthcare professionals, research and industry. All members contribute their time for free to the initiative, and all publications from the group reflect consensus of the members, who hold full editorial control. The All.Can initiative is made possible with financial support from Bristol-Myers Squibb (lead sponsor), Amgen and MSD (co-sponsors).

Radiotherapy and immunotherapy – a beneficial liaison?

Ralph Weichselbaum and colleagues explore how enhancing innate and adaptive immunity by combining radiotherapy and immune therapy could tip the balance of the host immune response to promote cure.

This is a summary, by Janet Fricker, of a longer article that was first published in ***Nature Reviews Clinical Oncology****: Ralph R. Weichselbaum, Hua Liang, Liufu Deng & Yang-Xin Fu (2017) Radiotherapy and immunotherapy: a beneficial liaison?* ***Nat Rev Clin Oncol*** *vol. 14, pp 365–379, doi:10.1038/nrclinonc.2016.211, and has been modified with permission.*

nature REVIEWS CLINICAL ONCOLOGY

Radiotherapy is used in around 50–60% of cancer patients, as a curative treatment for those with localised cancer or isolated metastases, and as a palliative treatment for those with widespread disease. Data from many laboratories indicate that local radiation produces systemic, immune-mediated antitumour, and potentially antimetastatic, effects. Additionally, a combination of local radiotherapy and immune-modulation can augment local tumour control and cause distant (abscopal) antitumour effects through increased tumour-antigen release and antigen-presenting cell (APC) cross-presentation, improved dendritic cell (DC) function, and enhanced T cell priming.

Irradiation and host immune responses

Host immune status

A study using a mouse fibrosarcoma model first showed that the host immune status determines radiation-induced antitumour efficacy (*J Natl Cancer Inst* 1979, 63:1229–35). A subsequent study showed a response to high-dose radiation in mouse melanoma tumours implanted into immunocompetent hosts, but not in those tumours implanted in mice lacking immune cells (*Blood* 2009, 114:589–95). Data also showed that radiation promoted antigen-specific T cell priming; however, paclitaxel and dacarbazine can suppress T cell priming and abolish radiation-induced tumour regression, emphasising that chemotherapy timing and composition warrants careful consideration when combined with radiotherapy. Reports from different tumour models highlight the importance of $CD8^+$ T cell infiltration in radiotherapy effects.

Radiation enhances immune responses

Over the past three decades, we have learnt more about how the immune system – T lymphocytes in particular – participates in tumour irradiation response. Localised radiation initiates cell death and release of cytokines and chemokines into the tumour microenvironment, leading to infiltration of DCs, macrophages, and cytotoxic T cells, and suppressor cells such as regulatory T cells (T_{reg}) and myeloid-

derived suppressor cells (MDSCs), as well as the efflux of immune cells, such as DCs, that are important antigen-presenting cells. Radiotherapy can augment innate and adaptive immune responses against tumours, decreasing immunosuppression and potentiating radiation response.

Radiotherapy can induce expression of chemokines, resulting in chemotaxis of T cells into the tumour microenvironment. Preclinical studies showed that radiotherapy-induced liberation of tumour antigens drives migration of antigen-presenting cells to lymph nodes, where T cell priming initiates a systemic response. Furthermore, localised radiotherapy induces antigen release and cross-presentation by DCs in tumour microenvironments, which can orchestrate tumour eradication following radiation, with or without immune modulation.

Research groups report that radiation changes tumour cell phenotype, resulting in upregulation of cell-surface molecules and expansion of the peptide pool, broadening antigens available for presentation, and rendering tumours more susceptible to T-cell antitumour effects. Presence of tumour-infiltrating lymphocytes (especially effector T cells) before therapy correlates with better survival in many cancers.

A study of chemoradiotherapy in rectal cancer showed that the total number of $CD3^+$ T cells and cytotoxic $CD8^+$ T lymphocytes is associated with disease-free and overall survival (*Clin Cancer Res* 2014, 20:1891–99). We speculate that radiotherapy induces release of chemokines, enriching T cell infiltrate, and enhancing T cell priming, providing positive immunological outcomes.

Natural killer (NK) cells are lymphocytes critical to host surveillance against tumours. Irradiation increases expression of NKG2D ligands in human cancer cell lines (*Science* 1999, 285:727–9). NK-cell-based therapies have increasingly been reported, with strategies including immune checkpoint blockade using antibodies to PD-1 or CTLA-4 and adoptive transfer of NK cells engineered to express chimeric antigen receptors (CARs) specific for tumour antigens.

In a mouse 4T1 spontaneous metastasis model, NK T-cell deficiency limited lung metastasis, and enhanced the anti-metastatic effects of radiation and anti-CTLA-4 antibody treatment (*Clin Cancer Res* 2009, 15:597–606).

DCs are myeloid-derived cells that are affected by alterations to tumour microenvironments from irradiation. Chemokines that attract antigen-specific T cells and DCs are released within irradiated tumours. Irradiation increases tumour-associated DCs, enhances mobilisation into draining lymph nodes, augments DC maturation, and increases the ability of DCs to cross-present antigens and prime T cells.

Activating immunosuppressive immune responses

Tumour microenvironments comprise various inhibitory immune cells (including T_{reg} cells) and other stromal cells. T_{reg} cells are a subset of $CD4^+$ T cells critical for regulation of inflammation and autoimmunity, which accumulate in tumour microenvironments and secrete the cytokines TGFβ and IL-10, suppressing effector T cell activation and stimulating suppressive myeloid-derived suppressor cell (MDSC) functions. In response to localised or whole-body irradiation, T_{reg} cell numbers increase in tumours and immune organs, which might reflect cell radioresistance. Radiation-induced increases in T_{reg} cell numbers have been reported within tumours, but not within draining lymph nodes (*Cancer Immunol Res* 2015, 3:345–55). Langerhans cells (radioresistant DC subsets) can stimulate expansion of T_{reg} cells when migrating into draining lymph nodes after whole-body irradiation (*Nat Immunol* 2015, 16:1060–8).

Clinical trials indicate that highly suppressive T_{reg} cells in circulation might represent heightened immune-suppressive environments induced by chemoradiotherapy at least transiently, in patients with different cancers. Thus, targeting T_{reg} cells, and/or the immunosuppressive effector molecule TGFβ, and CTLA-4, might reverse immunosuppression.

MDSCs contribute to tumour progression via stimulation of angiogenesis, tumour-cell invasion of adjacent tissues, and metastasis (*Ann Rev Med* 2015, 66:97–110). Two MDSC subsets are recognised: immature polymorphonuclear and monocytic cells.

Key points

- Radiotherapy not only exerts direct cytotoxic effects on tumour cells, but also reprogrammes the tumour microenvironment to exert a potent antitumour immune response.
- Tumour cell proliferation and cell death due to T cell cytotoxic killing coexist in irradiated tumours, resulting in stable disease that might provide a window of opportunity for immune modulation.
- Radiotherapy enhances antitumour immunity, but also induces immunosuppressive responses.
- The combination of immunotherapy and radiotherapy presents a multimodal treatment approach that involves stimulating and suppressing various pathways.

Interactions of these inhibitory immune cell types can suppress effector T cell function and tumour angiogenesis, and promote tumour progression. MDSCs, tumour-associated macrophages, and other immune cells, are essential for tumour vascularisation.

Evidence suggests MDSCs have a role in chemoresistance and radioresistance. Of note, while MDSC recruitment is an immediate effect of radiation, a drastic reduction in MDSC numbers has been reported 7–14 days after a single high dose of radiation, and this delayed MDSC reduction could be an indirect effect of host adaptive immune response.

Tumour-associated macrophages (TAMs) are classified as immune stimulatory or immune regulatory. A mouse melanoma model showed that depletion of TAMs before irradiation increased radiotherapy antitumour effects (*Cancer Res* 2010, 70:1534–3), but other studies produced conflicting results, emphasising a need for additional studies into how radiotherapy affects TAMs.

Fractionation and immune cell infiltration

With fractionated radiotherapy, fraction size and timing to achieve optimal tumour effects remain to be determined. Studies combining radiotherapy with antibodies targeting a variety of immune checkpoints indicate both ablative and fractionated radiation can be effective in tumour control, depending on the experimental system studied and the approach to T cell modulation used in combination with radiation.

Role of interferon

Type-I IFN signalling in innate immune cells, such as DCs, is essential for their function to prime and activate T cells. In the setting of ablative radiotherapy, type-I IFNs improve antigen cross-presentation and T cell function.

STING signalling pathway

Stimulator of interferon genes (STING) is an endoplasmic-reticulum-associated protein that activates transcription of the type-I IFN gene. In a mouse regressing-tumour model, STING was found to be essential for a radiation-induced anti-tumour response in established tumours (*Immunity* 2014, 41:843–52). *In vitro* and *in vivo* studies have shown STING is required to induce type-I IFN production, and promotes antigen-specific T cell responses following radiotherapy.

When co-cultured with irradiated tumour cells, STING-deficient DCs lose the ability to produce type-I IFN and prime T cells. Ionising radiation is believed not only to kill tumour cells directly, but also to promote innate and adaptive immune responses via STING-mediated DNA-sensing pathways.

Microenvironment and tumour response

In tumour microenvironments, irradiation induces stromal, immunological and vascular changes that are essential for tumour response. Tumours have several fates: elimination, equilibrium, dormancy, and escape. Historically, relapse 5–10 years after chemoradiotherapy has been attributed to tumour dormancy, whereas long-term progression-free survival with palpable tumours after therapy cessation reflects equilibrium. Tumour dormancy involves dampening of immune processes, whereas equilibrium maintains a balanced state. Tumour escape involves evasion of immune-mediated killing mechanisms.

Tumour dormancy and equilibrium

In 1980, it was noted that presence of a palpable tumour and the rate of regression after radiotherapy did not predict cure in preclinical models or patients (*Br J Cancer* 1980, 4S:1–10). In immunogenic experimental models, tumour regression correlates with permanent cure; however, with non-immunogenic animal tumours, no correlation between outcome and tumour resolution at the end of treatment was observed. Hence, investigators suggested that the immune system had a key role suppressing tumours remaining palpable at the end of treatment.

Up to 50% of breast cancers and a subset of prostate cancers relapse more than five years after radiotherapy. Whether differing clinical responses reflect states of equilibrium or dormancy is unclear. One view is that radiotherapy eliminates most tumour cells, but rare radioresistant clones remain, with the extent of initial cell killing proportional to time to relapse. An alternative view is that a state of equilibrium or dormancy exists that may in part be governed by tumour angiogenesis or the host immune system.

Radiation-induced tumour equilibrium

To investigate the roles of intrinsic tumour radio sensitivity and the immune system, we studied radiation-induced tumour equilibrium and dormancy, and the contribution of adaptive and innate immunity to these processes using TUBO (HER2-positive breast cancer) and B16 (melanoma) mouse models (*J Immunol* 2013, 190:5874–81).

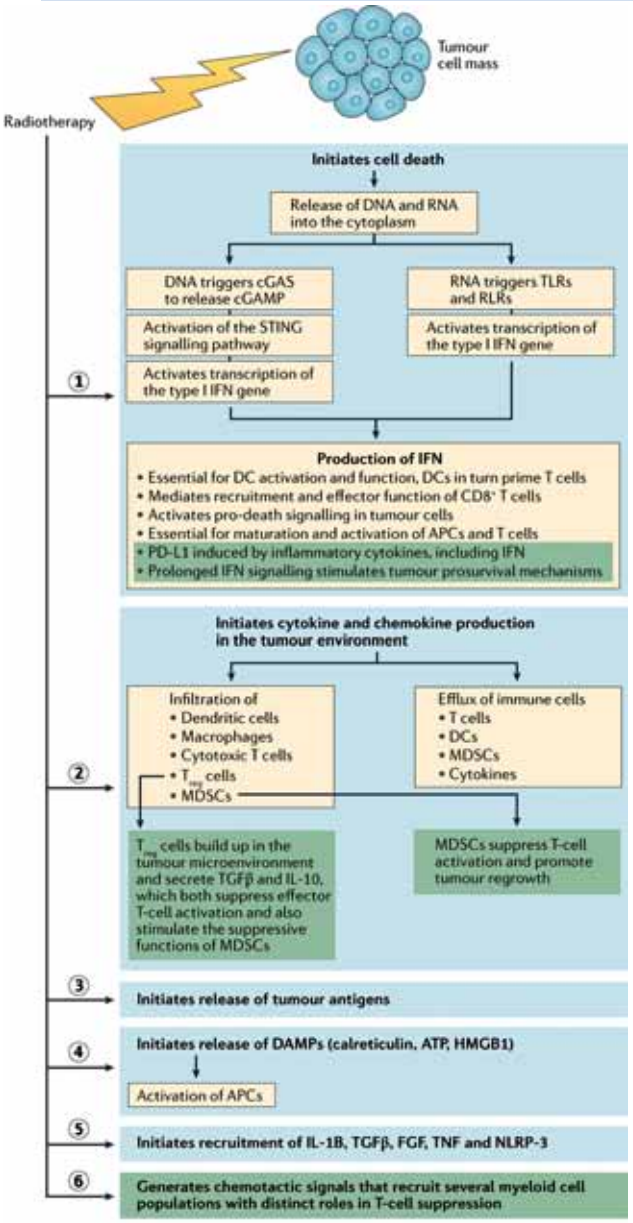
'Early escape' describes tumours with no response to radiotherapy; 'stable tumours' those that regressed and remained stable for 34–60 days; and 'late relapse' when formally 'stable' tumours regrew after 60 days. The spectrum of responses mimicked what has been observed in patients undergoing radiotherapy. The studies indicate that $CD8^+$ T cells might mediate tumour cell death in TUBO tumours, and radiation-induced tumour equilibrium (RITE) might be a balance between cell birth and cell death. $CD8^+$ cells are thought to mediate RITE through IFNϒ ; hence neutralisation of IFNϒ could lead to tumour regrowth. The finding that RITE exists in stable mouse tumours suggests that therapy-induced equilibrium between cancer-cell division and host immune system killing dictates disease status, supporting the feasibility of treating stable disease by tipping the balance (equilibrium) in favour of host antitumour immunity.

Data from tumour models indicates PD-L1 expression is inducible in tumour cells or host immune cells. When PD-L1 was blocked in mice harbouring stable tumours, most tumours regressed, confirming that activation of antitumour immunity can shift the balance towards eradication of non-progressing tumours (*J Immunol* 2013, 190:5874–81).

Notably, in a clinical trial involving 277 patients with a range of cancer types, PD-L1 expression on both tumour and immune cells strongly predicted response to PD-L1 inhibitors (*Nature* 2014, 515:563–7). In a mouse model, radiotherapy and same-day PD-1/PD-L1 inhibition achieved better tumour response than delayed administration (*Cancer Res* 2014, 74:5458–68).

Although clinical confirmation is required, we hypothesise the RITE model is applicable to some patients with radiotherapy-induced stable tumours that do not progress, who might achieve tumour resolution with immune-checkpoint blockade or immune-modulators before relapse. Mouse models are, however, heterogeneous, and not all mice developed PD-L1 expression leading to RITE.

Radiation–induced effects on tumour cells



Radiation enhances antitumour immunity, but also induces immunosuppressive responses, via multiple mechanisms

APCs – antigen-presenting cells; cGAMP – cyclic GMP–AMP; cGAS – cyclic GMP–AMP synthase; DAMPs – damage-associated molecular patterns; DC – dendritic cell; FGF – fibroblast growth factor; HMGB1 – high-mobility group protein B1; IFN – interferon; IL-1β – interleukin 1β; IL-10 – interleukin 10; MDSC – myeloid-derived suppressor cells; NLRP3 – NACHT, LRR and PYD domains-containing protein 3; PDL1 – programmed cell death ligand 1; RLRs – RIG-I-like receptors; STING – stimulator of interferon genes; TGFβ – transforming growth factor-β; TLRs – Toll-like receptors; TNF – tumour necrosis factor; T_{reg} cells, regulatory T cells

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Combining radiation and immunomodulation

The major clinical successes in radio-immunomodulation are the result of the advent of immune checkpoint inhibitors. It has been noted that the PD-1/PD-L1 pathway primarily regulates ongoing inflammatory activ-

ity, whereas the CTLA-4 pathway regulates autoreactive T cell responses. Patients with 'good immune scores' and pre-existing tumour-specific T cells have better outcomes following immune checkpoint therapy (*Nature* 2014, 515:496–8), and in patients who would otherwise not respond to immune checkpoint inhibitors, localised radiotherapy can induce tumour-specific T cells, promoting responses (*Vaccine* 2015, 33:7415–22).

Inhibition of CTLA-4 checkpoint

Inhibitors of the CTLA-4 pathway (e.g. ipilimumab) have shown encouraging results in cancer. CTLA-4 functions as an immune suppressor by increasing the signal intensity required for $CD8^+$ T cells to engage target tumour cells.

Treatment of mouse 4T1 primary mammary carcinomas with irradiation and CTLA-4 blockade inhibited lung metastases, with therapeutic effects requiring $CD8^+$, but not $CD4^+$, T cells (*Clin Cancer Res* 2005, 11:728–34).

Results from a mouse model indicated a hypofractionated regimen plus anti-CTLA-4 therapy was more effective than either alone in inducing immune infiltrate and abscopal effects (*Clin Cancer Res* 2009, 15:5379–88). Results of early clinical studies of anti-CTLA-4 antibodies demonstrate improved overall survival (OS) in a range of cancers. Anti-CTLA-4 therapies have been tested in combination with other treatments, including vaccines, granulocyte-macrophage colony-stimulating factor (GMCSF), other checkpoint inhibitors, radiotherapy and chemotherapy.

A phase III trial to assess radiotherapy plus ipilimumab or placebo in patients with metastatic castration-resistant prostate cancer found no significant difference in OS, but a *post hoc* subgroup analysis revealed a trend towards improved OS, and significance in patients with bone metastasis (*Lancet Oncol* 2014, 15:700–12). In preclinical models, combined radiotherapy and anti-CTLA-4 treatment was efficacious owing to stress-induced NKG2D (natural-killer group 2, member D) expression on tumour cells that survive irradiation, making them susceptible to NK-cell-mediated cytotoxicity (*Oncoimmunology* 2013, 2:e23127).

Inhibition of the PD-1/PD-L1 checkpoint

PD-L1 expression has been observed in solid malignancies, and might be a dominant mechanism of immunosuppression in some tumours.

The presence of PD-L1 in tumours predicts responses to PD-1/PD-L1 blockade, and inhibition of the PD-1/PD-L1 pathway on T cells is associated with antitumour activity in mouse models and clinical trials. A mouse model showed substantial tumour regression with high-dose radiation and an anti-PD-L1 antibody. Dramatic reductions of MDSCs were seen, associated with increased $CD8^+$ T cell infiltration and priming (*J Clin Invest* 2014, 124:687–95). Conversely, when $CD8^+$ cells were depleted, MDSC recovered. MDSC-mediated suppression of T cell function in cancer progression is well-established, and MDSCs are associated with chemoresistance.

In vitro cytotoxicity assays revealed that activated $CD8^+$ T cells kill MDSCs directly, with cytokines produced by activated T cells leading to MDSC apoptosis. By contrast, although IFNϒ production correlates with T cell activity, IFNϒ did not mediate induction of MDSC death in assays.These reports suggest that, in preclinical models, inhibition of the PD-1/PD-L1 checkpoint combined with radiotherapy liberates T cells from immunosuppression, which in turn positively alters the tumour microenvironment.

Several mouse solid tumour models demonstrate synergistic effects of radiotherapy and immunotherapy via checkpoint inhibition, including improved survival using PD-1 inhibitors plus stereotactic radiation in orthotopic brain tumours, compared to either treatment alone, and improved survival adding PD-1 inhibitors to TGFβ blockade plus radiation-induced vaccination, compared with radiation-induced vaccination plus TGFβ blockade alone.

Radiation-induced vaccination involves conversion of tumour into an *in situ* vaccine by inducing immunogenic death of cancer cells, promoting a pro-immunogenic tumour microenvironment and thereby priming tumour-specific T cells (*Int J Radiat Oncol Biol Phys* 2012, 84:879–80).

Data indicate radiation and anti-PD-1 therapy increases memory $CD8^+$ T cell numbers. Although NK cells might contribute to local tumour control, $CD8^+$ T cells have been shown to be required for the antitumour effects produced by combined radiotherapy and anti-PD-L1 antibodies (*Cancer Res* 2014, 74:5458–68).

A preliminary preclinical report indicated that radiotherapy combined with an anti-PD-1 antibody can result in primary tumour control and abscopal effects (*Int J Radiat Biol Phys* 2014, 90:S1), with further studies indicating that the combination induces endogenous antigen-specific immune responses, resulting in improved local control in melanoma and breast carcinoma models (*Oncol* 2015, 29:331–40). Timing of anti-PD-L1 blockade is crucial: concurrent but not sequential radiation results in long-term tumour control (*Oncoimmunology* 2015,

4:e1016709). Currently, over a dozen clinical trials are evaluating anti-PD-1 and anti-PD-L1 antibodies combined with radiation.

The abscopal effect

The abscopal effect (regression or disappearance of lesions outside irradiated fields) is rare with radiotherapy alone, but is increasingly reported when radiation is administered with immune modifiers in preclinical models and patients, leading to suggestions that it is an immune-driven phenomenon, indicating that local radiotherapy produces systemic effects. Studies show localised radiotherapy plus CTLA-4 blockade inhibited development of lung metastases; and radiotherapy plus anti-PD1 antibody treatment produced abscopal effects in a range of carcinoma models, with one study showing almost complete regression of the primary tumours and a 66% reduction in distant tumours.

Several case reports highlight regression of targeted lesions and abscopal effects in melanoma treated with ipilimumab and radiotherapy (*NEJM* 2012, 366:925–31). In the first clinical trial testing abscopal responses with radiotherapy and GMCSF, 27% of patients with metastatic solid tumours experienced the desired effect (*Lancet Oncol* 2015, 16:795–803). Collectively, observations of the molecular and cellular events generating the abscopal effect indicate these are the result of a cellular feedback mechanism involving effector T cells within the irradiated tumour microenvironment, which occurs several days after local radiotherapy and subsequent to APC migration and T cell activation in the draining lymph nodes. Thus, the abscopal effects could be modulated by tipping the balance between positive immune regulators (of T cell function) and negative regulators (of the local and systemic suppressive microenvironment) to elicit strong immune responses.

Conclusions

Current evidence indicates that radiotherapy can invoke both local and systemic immune responses, which can either support tumour cell survival or promote tumour cell death. Enhancing innate and adaptive immunity by combining radiotherapy and immunotherapy is thus crucial to improve patient survival. Current radioimmunotherapy paradigms are based on results from animal models, observations of responses in patients, and preliminary data from trials of combination immunotherapy and radiotherapy. Robust hypothesis-testing clinical trials are required to determine the appropriate approach to integrating these modalities.

For a laugh

"There's no easy way I can tell you this, so I'm sending you to someone who can."

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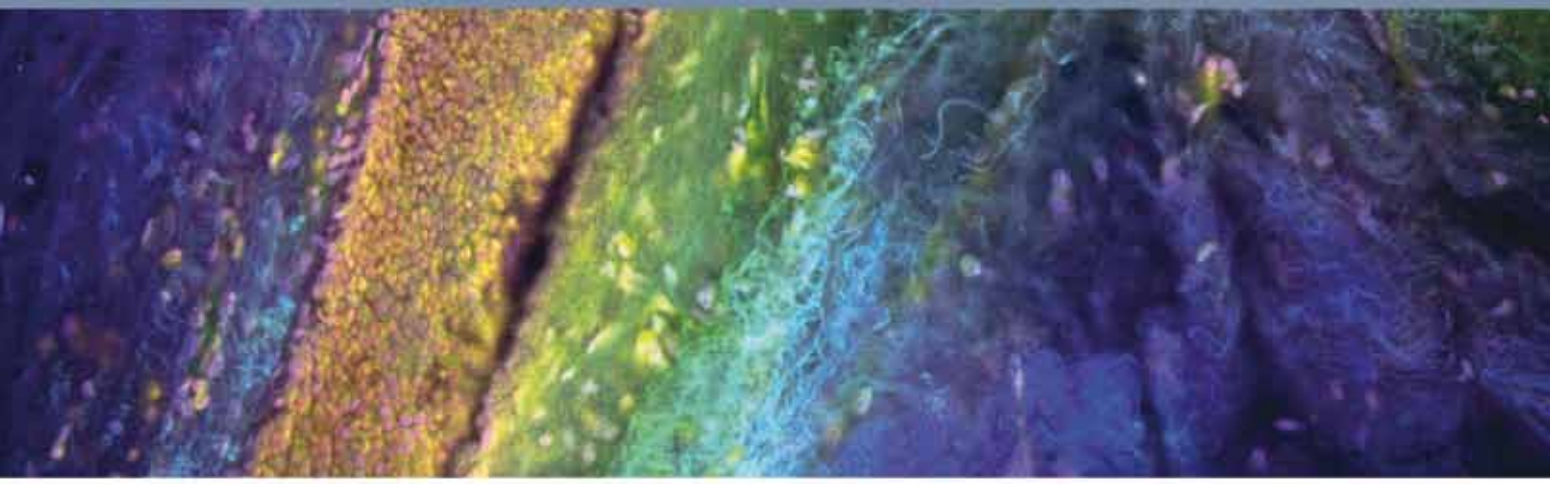

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esso
THE EUROPEAN SOCIETY OF SURGICAL ONCOLOGY

Santiago González-Moreno – President of the European Society of Surgical Oncology (ESSO), and Medical Director and Head of Surgical Oncology at the MD Anderson Cancer Center, Madrid

Better outcomes with innovative surgery

With the knowledge that age is the greatest risk factor for developing cancer, and the recognition that the population is aging, we simply cannot neglect the need to advance European cancer care. We must upgrade our measures in order to improve long-term survival rates and quality of life. The focus on the development of innovative medical techniques is an overlapping priority in both surgery and oncology fields. Innovation is shaping the future of surgical oncology; the pace of change in surgical techniques has increased substantially, and will probably accelerate in the future.

Representing a growing community of more than 16,000 surgical oncologists worldwide, the European Society of Surgical Oncology has a duty not only to support and share the adoption of new ideas, techniques and devices, but also to stimulate and encourage them. Our commitment to the advancement and modernisation of cancer surgery led us to choose "Better Outcomes with Innovative Surgery" as the theme of ESSO 38, organised in collaboration with the Hungarian Surgical Society.

This choice of theme demands an additional dynamic and interactive dimension to our usual format, and we are excited to present a rich and inspiring programme to showcase practice-changing discoveries and advances in surgical research.

The event will bring together top oncology experts for debate sessions, aiming to tackle controversial questions and foster interaction between participants and key opinion leaders. There will be Meet-the-Expert sessions and educational workshops, as well as unique opportunities – including video lectures and mentorship sessions – designed to support our society's professional development. Scientific symposia will dissect existing limitations and explore new trends, patient reported outcomes and state-of-the-art practices. There will also be a heavy emphasis on networking, to take advantage of the delegates' varied educational, professional and cultural perspectives, and to facilitate multidisciplinary collaboration and exchange European best practices.

Together we can bridge the gap on European disparities and contribute to the continuous improvement of cancer treatment quality, accessibility and innovation. We hope you will join us to foster collective progress in surgical oncology.

ESSO 38 will take place on 10-12 October 2018 in Budapest, Hungary.

For more information on registration deadlines or to follow details of the programme as they are announced, visit the congress website: www.essoweb.org/ESSO38
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The do-nothing dilemma

To treat or not to treat? Different people respond in different ways to learning they have lesions that may or may not develop into threatening cancers. **Charlotte Huff** talks to 'patients', doctors and psychologists about reaching a decision on what to do next.

Imagine for a moment that you have a tiny but worrisome lung nodule or, say, a growing bulge in a crucial blood vessel. You have no choice but to continue with normal life: going to work, running errands, paying taxes, negotiating with your kids over screen time. But you're always living, at least to some degree, under the looming shadow of a medical question mark.

Judy Refuerzo ventured further along that uncertain journey this summer, walking the full length of the Camino de Santiago – some 500 miles and 38 days across the Pyrenees into Spain – to commemorate her 60th birthday. It had been a long-planned trek, one that she tackled with a backpack and a close girlfriend for company. She's not in denial, she insists, about the malignant cells that doctors found in her breast nearly two years ago.

She's been getting regular imaging tests to make sure that the cells – collectively called ductal carcinoma in situ (DCIS), or sometimes stage 0 breast cancer – have not migrated beyond the milk ducts. But the California yoga teacher has decided against any kind of treatment, including surgery – at least for now. "I just don't want to be cut open for no reason," she says.

In the process, Judy has joined a growing group of so-called watchful waiters, snared within a modern-day web

of aggressive testing and medical uncertainty.

The concept of watchful waiting (synonymous, for some doctors at least, with 'active surveillance') is nothing new. Through the ages, doctors have sometimes recommended hitting pause on treatment. Increasingly, though, more and more people are caught up in a peculiar medical purgatory, particularly in countries like the USA where an emphasis on screening and high-tech imaging to rule out medical problems can cascade into more testing and other uncertainties.

"I think our technologies are moving faster than our ability to know what to do with the conditions we find," says Shelley Hwang, a breast surgeon at Duke University Medical Center and a prominent DCIS researcher. "And once you know it, you can't un-know it."

"How do doctors counteract that innate human desire to 'do something', not only in their patients, but in themselves?"

Sometimes, as in Judy's situation, people will choose that wait-and-see path. While still quite controversial, some doctors are willing to delay surgery and other treatment for DCIS unless there are signs that the malignant cells are moving into the surrounding breast tissue. In other medical scenarios, patients are told flat out that monitoring is the only immediate option, as it's too risky to operate until circumstances become more life-threatening.

Medicine has reached a crossroads. Shadows, nodules and other changes can be flagged much earlier, in the maybe-or-maybe-not-worrisome stage. Meanwhile, researchers and clinicians are learning that, for some conditions, less medical care might be better, both in the short term and also possibly over the longer haul. Even some cancer cells, it seems, can flare and fade away.

But that shift in medical thinking raises other big questions: Are some people more psychologically able to cope with medical limbo? Can clinicians identify which patients might better weather uncertainty? And how do doctors counteract that innate human desire to 'do something', not only in their patients, but in themselves?

"People don't like this idea of watching," says Rita Redberg, a cardiologist at the University of California, San Francisco. "The whole fact that we've told you to watch… makes you feel like something bad is going to happen." Even though, she says, a lot of things that are watched will never progress, there is a drop in a person's quality of life when they get into a surveillance situation.

If she chose to, Redberg could tout medical credentials that run for pages. She's a long-standing cardiology researcher, a vocal opponent of inappropriate imaging, and the chief editor of *JAMA Internal Medicine*.

In the late 1970s, she and her fellow medical students were learning how to perform a physical exam, which meant practising on each other. One student found a lump in Redberg's neck, which – after more than two decades of monitoring with blood tests – was eventually biopsied in 2000. It was papillary thyroid cancer, the most common form of thyroid cancer. Soon after, she had surgery.

If she had had her biopsy today, Redberg might have had another, albeit controversial, option: to simply monitor her cancer. Surveillance has long been considered an option for low-risk prostate cancer, and now researchers are exploring its use in other cancers, including papillary thyroid, which is, very often, so slow-growing that someone can fare well for years without it spreading.

Another is DCIS, Judy's diagnosis. As mammography and other imaging has become more common and more sensitive, diagnoses of DCIS now make up as many as a quarter of breast cancer diagnoses. Previously, it was virtually unheard of.

The question is: how risky is it to leave those cells alone?

Since few women choose surveillance, research answers are limited. But a recent look back at patients treated in Boston proved encouraging. After ten years, over 98% of women hadn't died from their low-grade DCIS, whether they had had surgery or not.

While the cancer outcomes are crucial, the impact on someone's quality of life shouldn't be ignored. Some women who choose surgery, radiation and other measures for DCIS might struggle with related pain and recovery for some time, Hwang says. But without surgery, she counters, "there's another flavour of misery where you're just worried every day of your life that you're going to get cancer."

Hwang is leading the first large-scale randomised DCIS study in the USA, known as the COMET trial, which will analyse cancer rates as well as the psychological ripple effects. Psychological and quality-of-life aspects also are part of a similarly designed study called LORIS, which was launched in 2014 in the UK.

Prior research shows that women with DCIS harbour similar fears about recurrence and dying as those who have invasive breast cancer, despite DCIS being less serious. "We've got a lot of worry going on and we don't even know if

the treatment that they're receiving actually is of any value to them at all," says Lesley Fallowfield, the principal investigator on the LORIS study's quality-of-life assessment.

During discussions after her 2014 diagnosis, Judy's doctors recommended a myriad of treatment approaches – mastectomy, lumpectomy, radiation and tamoxifen – in various combinations to prevent the malignant cells from spreading. Finally, a surgeon suggested that Judy talk to doctors at the University of California, San Francisco, early proponents of monitoring as an alternative strategy. "He said, 'They have a different view of DCIS than the rest of the world,'" Judy recalls.

As she mulled over her options, Judy worried about the risk of surgery and radiation, including short-term discomfort and possible longer-term side-effects. Plus, no one could guarantee her that the malignant breast cells would be eradicated for good. Do I want to live my life healthy and feeling good, she asked herself, or miserable and not feeling good, with the same outcome?

Judy, who already avoided meat, has made other changes to her diet since her diagnosis, dropping wheat and dairy. She's also taking vitamin D to supplement her low natural levels. She believes that many of us periodically harbour malignancies somewhere in our bodies, cells that can be beaten back with exercise, nutrition and other healthy habits. But she also admits to flickers of doubt: "Occasionally I'll think, 'Why do I think I'm special?'"

Lung cancer CT screening

Theresa Monck, a 63-year-old from Brooklyn, New York, is soaking up her first years of retirement, especially the opportunities to travel. But her next lung scan lurks in the back of her mind. The former smoker started getting annual CT scans in 2013 to look for any early signs of lung cancer. Two small nodules were identified. Over the last several years they have not grown, a reassuring sign.

Still, Theresa has pushed for a biopsy. Doctors, she says, have told her that the nodules are too small to risk the procedure, which involves inserting a needle into her lung. "I don't like having them…" she says. "But what am I going to do?"

Theresa and patients like her are providing some insights into just how much angst men and women living in medical limbo really suffer.

In 2013, the US Preventive Services Task Force recommended CT-scan screening for long-term current and former smokers. (European countries have been slower to

conduct such screening outside of research studies, which are ongoing.) The goal is to find cancers at an earlier and likely more treatable stage.

But there's a significant catch. Anywhere from 20% to 50% of people, depending on the study cited, will have to deal with a false positive, where a nodule is found that, after further testing and scrutiny, doesn't prove to be cancerous. Sometimes patients won't know one way or the other for years, but will continue to undergo imaging to see if the nodule is growing.

For some people monitoring can morph into an endless loop, says Renda Soylemez Wiener, a pulmonologist at Boston University School of Medicine. While the typical guidance is to stop after several years if the nodule hasn't changed, this regular scanning can highlight another nodule, and the clock starts over. "Patients wind up in this prolonged period of uncertainty," she says.

How much distress those scans generate, though, is still not clear. One study tracked just over 2,800 participants in the US-based National Lung Screening Trial. Researchers found that those who had a suspicious nodule detected (and later ruled out) didn't suffer any more anxiety than those whose imaging tests didn't turn up anything.

Joanne Marshall, a former smoker, is among those who might have reason to fuss. Her mother was diagnosed with lung cancer in 2012. Soon after, Joanne got her first scan, which identified three small nodules. But they haven't grown and neither has her concern. "Some people can be nervous nellies – that's just not me," says the 54-year-old, who lives near Los Angeles. "I need to watch it because I would like to have a fighting chance, and I can't take back the smoking history."

But Wiener says her research shows that not everyone is similarly sanguine if a nodule is found. Sometimes patients

act as though they've already been diagnosed with lung cancer, she says. A woman in one of her studies quit her job to find another that would allow more time with her family.

In another study, Wiener assessed the perceptions of 122 veterans whose nodules had been picked up in the course of checking out another potential medical problem. Nearly 40% reported at least mild distress after the nodule was identified; 16% described their distress as moderate to severe.

"We all have personality filters through which we sift medical information, sometimes in surprising ways"

And even when a doctor says that CT scans are no longer necessary, 29% of patients report being 'somewhat nervous' to stop surveillance, and 10% would be 'extremely nervous'.

Theresa, the Brooklyn retiree, had a similar reaction when she learned that clinicians typically don't follow nodules that haven't changed for longer than several years. She'd continue the CT scans, she maintains, even if she had to go to another hospital, and even if her insurance wouldn't cover them and she had to pay herself. How else would she know if one of those nodules ever began to grow?

Theresa and Joanne both carry several small, relatively low-risk nodules in their lungs. Yet their reactions have been notably different. Fallowfield, the principal investigator on the LORIS study's quality-of-life assessment, says research indicates that we all have personality filters through which we sift medical information, sometimes in surprising ways.

Coping strategies

Years back, Fallowfield was involved with a study which looked at the processing styles of 154 women wrestling with the weighty decision of whether or not to have prophylactic surgery to remove both breasts. Just over half of the women – all of whom faced a high risk of breast cancer based on family history or other risk factors – chose surgery. Most of the rest declined, with a small number delaying their decision for various reasons.

Understandably, both groups reported high anxiety at the start. But among those who chose the double mastectomy, those feelings "by and large" eased over the course of 18 months, Fallowfield says. But they didn't among those women who opted for surveillance.

How could that be? Researchers found some indications in a 'ways of coping' questionnaire that they had asked both groups to fill out in order to gauge how they handled life's difficulties. The women who chose surgery tended to have a more proactive, problem-solving approach, and likely that helped ease their anxiety moving forward, says Fallowfield.

The women who declined were prone to using "detachment or distraction as a way of coping with life's traumas," she says. "These were ostrich-head-in-the-sand-type people." But that coping mechanism had a crucial flaw. Imaging tests and check-ups kept reminding them of their cancer vulnerability.

Suzanne Miller, a clinical health psychologist who studies medical decision making, believes that the UK women who turned down the operation fall into a subset known as 'monitors', one of two coping styles that she first described in the late 1970s. The others – 'blunters' – prefer to engage with medical details and discussions on an as-needed basis. "They hear what they're told," she says, but are not inclined to dig further.

Monitors are more likely to do research before an appointment and pepper the doctor with questions. They're also more likely to amplify any medical risks, which can become stressful if they decide on surveillance for a condition such as DCIS, Miller says. They may choose it "on the basis of the rational concrete pros and cons," she says. "But many of them understand going into it that this is going to have an emotional toll."

In recent years, Miller has come to believe that monitors can be divided even further by coping style. 'Non-strategic monitors' likely haven't taken steps to mitigate the emotional toll between scans and check-ups. They might continue to fret and stew, which can snowball into regret that they haven't taken a more 'active' step, Miller says. Hence the pervasive anxiety suffered by the women who turned down prophylactic mastectomy in Fallowfield's study. Another example is men with early-stage prostate cancer who initially commit to surveillance, but eventually go under the knife because they can't stand the uncertainty.

Judy Refuerzo is what Miller describes as a 'strategic monitor', someone who relies on support, self-care and other strategies to dampen their own monitoring tendencies. Along with boosting her nutrition and striving to live life to the max – Judy says she's probably a bit more spontaneous these days – she tries not to think too much about her cancer risk. Yet she still has scans every six months.

"I'm under surveillance," Judy says. "I'm not an idiot –

I'm proactive." In February 2016, Judy's most recent MRI scan showed some DCIS growth, but no signs of invasive cancer.

The desire to act

Miller's tool, the Monitor–Blunter Style Scale, is one way that clinicians can get a snapshot of a patient's coping style. It would also be helpful if a doctor could capture a sense of an individual patient's risk tolerance, says Shelley Hwang, the Duke breast cancer surgeon – something similar, she says, to how financial planners assess whether their client is capable of or interested in taking on additional financial risk.

Patients and doctors caught in this cycle of surveillance are fighting one of the most innate human tendencies: the desire to act, says Paul Han, a physician and researcher who studies medical uncertainty and risk communication. That impulse can infect far more mundane situations than expanding aortic aneurysms or early-stage cancers, Han says, noting that every day doctors must decide whether to prescribe antibiotics to patients with respiratory symptoms.

"Everybody wants something done, when in fact often nothing is really needed except observation and letting things run their course," he says. "But there is this sort of general impatience in our medical culture, and in our culture at large."

Han speculates that this discomfort with watchful waiting might figure more prominently in the USA than in countries in Europe and elsewhere where conversations about healthcare costs and trade-offs are more publicly hashed out. Fallowfield agrees, wondering if the US-based DCIS study (COMET) might struggle more than the UK one she works on (LORIS) to recruit patients willing to have their treatment randomly assigned, as Americans tend to be "less risk-tolerant".

Fallowfield also echoes other clinicians who worry that misleading medical language can unduly alarm patients, ramping up their perception of their own risk status and thus influencing their treatment choices. When talking to LORIS study participants, clinicians use the term 'active monitoring' rather than 'watchful waiting'. "'Watchful waiting' sounds quite passive – you are sitting there waiting for something to happen," she says.

Using the term 'ductal carcinoma in situ' is similarly like waving a red flag in front of patients, Fallowfield says, because it includes the word 'carcinoma'. If keeping DCIS as an acronym is important, she suggests other terminology, such as 'ductal changes in situ' or 'ductal calcifications in situ'.

In the prostate field, there's an analogous diagnosis to DCIS, a pre-cancerous condition called high-grade prostatic intraepithelial neoplasia. It's the word 'neoplasia' that "can set off patient alarm bells," says Ian Thompson, a prostate cancer researcher at the University of Texas Health Science Center in San Antonio.

"Didn't Ralph Nader call the Corvair unsafe at any speed? The terminology does affect behaviour." Thompson and other clinicians have proposed a less malignant-sounding, albeit clunky, alternative: IDLE, short for indolent lesions of epithelial origin.

"It would also be helpful if a doctor could capture a sense of an individual patient's risk tolerance"

To reduce patient fears, clinicians should do a better job at communicating medical risk, says Renda Soylemez Wiener, the Boston pulmonologist. She points out that just one-quarter of 244 patients diagnosed with lung nodules were able to predict with any degree of accuracy the likelihood that their nodules would prove to be cancerous. Overall they pegged their risk at 20%, but their actual risk based on nodule size was 7%. Nearly three-quarters of them didn't realise that some lung nodules grow so slowly that they will never prove to be life-threatening.

A surveillance contract could also help avert patient–doctor misunderstandings, says Brendan Stack, Jr, an Arkansas thyroid cancer specialist. A written agreement for patients considering thyroid monitoring could ensure

an upfront discussion of the risks involved, he says. It could also lay out the circumstances under which the patient's decision would be revisited.

Once a patient has 'self-declared' that surveillance is the best course, it can be difficult to convince them to deviate, even if the malignancy shows signs of becoming more aggressive, says Thompson. "Changing horses from doing nothing to something is sometimes difficult for people, if you will – to push a reboot to the computer and reassess."

Should we stop looking so hard?

From Rita Redberg's perspective, there is one easy way to reduce the expanding pool of watchful waiters: stop searching for medical ills so fiercely in the first place.

She now wishes that she hadn't dug so far, literally, into her own thyroid. After the lump was detected during medical school, a radioactive iodine scan determined that it was a 'hot' nodule – one that produces excess thyroid hormone – but likely benign. Redberg did little more to check it out for some two decades, other than periodic blood tests, until her primary care doctor worried that it might be growing. She agreed to a needle biopsy, which she now regrets. Her surgery in 2000 left Redberg with a scar on her neck. Each day, she takes a thyroid replacement pill.

Strangely enough, Brendan Stack has a similar story. He was teaching medical residents about ultrasound technology and they were practising on his neck when they found a thyroid nodule. It was biopsied twice, but cancer still couldn't be completely ruled out.

Watchful waiting was one possibility. "I couldn't tolerate that," Stack recalls. "I said, 'We're taking it out.'" In 2006, he had surgery to remove the half of his thyroid where the nodule was located. The pathology showed no signs of cancer. Even so, he has no regrets: "I'd do the same thing today."

And Redberg? She's not quite so unequivocal, given how slowly thyroid cancer typically grows. "Probably, on balance," she says, "I would have been happier not to have known about it."

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UPMC is a 14-billion-dollar integrated global health enterprise, closely linked to the University of Pittsburgh. Twenty years ago it opened a transplant hospital in Sicily. Since then, its International arm has expanded to build hospitals and offer consultancy and other services worldwide, with a special focus on cancer care. **Fabio Turone** asked UPMC International President Chuck Bogosta about what they do and why.

Fabio Turone: *UPMCs international operations have developed rapidly in recent decades, but the impression given is of a strategy that was made up on the go...*

Chuck Bogosta: When we first got into this area there was no roadmap. Healthcare is very difficult to globalise. Our strategy from the beginning was the one identified 20 years ago when we opened our first transplant hospital in Sicily. We didn't believe that the concept of medical tourism was sustainable, so instead of focusing on bringing the patients to the US we are more focused on ensuring that patients don't have to leave home.

Our transplant centre in Sicily started with a strong relationship we had with a hepatologist who started to bring patients in need of a liver transplant to Pittsburgh. He proposed approaching the local authorities and the Vatican. Now the hospital has top outcomes one year after transplant, and is working fully with funding from the Italian National Health Service, with around 5% of income derived from international patients. It's a great example of how we were able to export something while learning a great deal from the experience.

FT: *Are you using the experience in Italy to develop similar models in other countries?*

CB: Something that very few other organisations have recognised is that one size does not fit all. It varies by geography, it varies by country. In China for example we provide consulting services, and we would never make an investment.

In Ireland we own 50% of a cancer centre, and in partnership with a private healthcare provider we are opening another cancer centre, of which we will own 50%. In Italy we own one-third of the transplant centre in Sicily and 100% of a cancer centre in Rome. We always have at least a management agreement to provide clinical oversight.

FT: *How much of your activity is focused on cancer, and do you focus on particular treatment approaches?*

CB: At least half of the 12 or so countries and approximately 20 different activities we are involved in are cancer related. We are working with the Union for International Cancer Control (UICC) to develop a model that would be very comprehensive, and include surgical, radiation and medical oncology. In Kazakhstan we are developing a cancer treatment facility and a medical school.

In Sicily the plan is to develop a medical school as well. In Colombia we are in talks to develop a medical school in conjunction with the cancer hospital that we have in Bucaramanga.

In emerging countries, bringing cancer care up to international standards is particularly important. Every country is different, and we also focus on providing opportunities to cancer professionals within the context of the agreements with local partners.

FT: *Some people in Europe worry that the US model might work against the public approach to healthcare*

CB: When we go overseas we view it as an opportunity to understand what the needs are and see if we can fill that gap: we don't necessarily take the approach of bringing the US way of doing things.

For instance the cancer centre in Rome is focused on high-end radiotherapy and radiosurgery, for which patients had to go to Milan. We were the first to bring this technology to that part of Italy; that was our main motivation.

All of the reimbursement issues, the licensing and regulatory issues, the needs were in place to bring an investment. We see private patients, we see public patients and the Italian Government didn't have to come up with at least $10 million. I look at it as a great example of a win–win for the Italian Government, since it's much cheaper to keep patients in Rome.

FT: *How do you balance the incentive to make the activity profitable with a commitment to achieve the best outcomes?*

CB: There are three reasons why we do what we do. We would never go anywhere where we didn't believe we can improve the quality of healthcare and – this goes hand in hand – UPMC's reputation globally. It also has to make good business sense: we have to be able to sustain a financially viable operation. All three of them have to exist.

We are a $14 billion organisation, but we essentially are a community asset, guided by community principles: there are no shareholders. We have a bit of a schizophrenic mission: for our organisation in the United States we have to improve the Pittsburgh reputation and support the academic and clinical missions of UPMC.

That's a different perspective from the one we discuss with our partners overseas, in which our number one priority is to improve the quality of healthcare. Pittsburgh evolved from being a heavy industry region to what now we call Meds&Eds, medical and education are the driving economic force today.

Each project is unique, but we don't partner with real estate developers nor with private equity firms, because their focus is completely financial. It's much more important for us to partner with governments, with health ministries, with healthcare organisations.

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Chuck Bogosta is Executive Vice President of UPMC and President of UPMC International. He also leads the UPMC Hillman Cancer Center, which uses a 'hub and spoke' network model to allow patients to access high-quality treatment in their local community. Before joining UPMC he was a founder member of Corporate Health Dimensions, which specialised in direct contracting of pharmacies and outpatient clinics for major companies.

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Image guided radiotherapy in clinical practice
11-15 February 2018 | Budapest, Hungary

Comprehensive and practical brachytherapy
4-8 March 2018 | Ljubljana, Slovenia

Particle therapy
5-9 March 2018 | Vienna, Austria

Multidisciplinary management of lung cancer
10-12 March 2018 | Brussels, Belgium

Foundation of leadership in radiation oncology NEW
20 April 2018 | Barcelona, Spain

Advanced skills in modern radiotherapy
6-10 May 2018 | Rome, Italy

Target volume determination - From imaging to margins
13-16 May 2018 | Prague, Czech Republic

Evidence based radiation oncology
27 May - 1 June 2018 | Athens, Greece

IMRT and other conformal techniques in practice
3-7 June 2018 | Talinn, Estonia

Dose modelling verification for external beam radiotherapy
10-14 June 2018 | Dublin, Ireland

Brachytherapy for prostate cancer
14-16 June 2018 | Avignon, France

Basic clinical communication in oncology NEW
15-17 June 2018 | Brussels, Belgium

Clinical practice and implementation of image-guided stereotactic body radiotherapy
2-6 September 2018 | Porto, Portugal

Image-guided radiotherapy and chemotherapy in gynaecological cancer: focus on adaptive brachytherapy
2-6 September 2018 | Madrid, Spain

Hematological malignancies
5-8 September 2018 | Utrecht, The Netherlands

Physics for modern radiotherapy (joint course for clinicians and physicists)
9-13 Spetember 2018 | Budapest, Hungary

Basic clinical radiobiology
15-19 September 2018 | Dublin, Ireland

Target volume determination - From imaging to margins
23-26 September 2018 | Moscow, Russia

Imaging for physicists
23-27 September 2018 | Vienna, Austria

Advanced treatment planning
23-27 September 2018 | Athens, Greece

Multidisciplinary management of head and neck oncology
30 September - 3 October 2018 | Lisbon, Portugal

Multidisciplinary management of non-melanoma skin cancer NEW
4-6 October 2018 | Brussels,Belgium

Advanced brachytherapy for physicists
7-10 October 2018 | Valencia, Spain

Best practice in radiation oncology - Train the RTT (Radiation Therapists) trainers - part I
22-26 October 2018 | Vienna, Austria

Positioning and immobilisation for radiation therapy NEW
3-4 November 2018 | Vienna, Austria

Comprehensive quality management in radiotherapy - risk management and patient safety
4-7 November 2018 | Athens, Greece

ESTRO/ESOR multidisciplinary approach of cancer imaging
5-6 November 2018 | Rome, Italy

Accelerated partial breast irradiation
11-14 November 2018 | Brussels, Belgium

Research course in translational radiation biology and oncology
11-14 November 2018 | Florence, Italy

POSTGRADUATE COURSES OUTSIDE EUROPE

ESTRO/AROI 3D radiotherapy with a special emphasis on implementation of MRI/CT based brachytherapy in cervical cancer
8-11 March 2018 | Lucknow, India

Basic clinical radiobiology
10-13 May 2018 | Melbourne, Australia

Multidisciplinary management of head and neck oncology
11-13 May 2018 | Osaka, Japan

Advanced technologies
20-23 May 2018 | Petaling Jaya, Malaysia

Palliative care and radiotherapy
5-7 June 2018 | Mexico City, Mexico

Combined drug radiation treatment: biologic basis, current applications and perspectives
13-16 June 2018 | Chengdu, China

AROI Course in Collaboration with ESTRO on Advanced Technologies
Endorsed by ESTRO
2018 | India

PRE-MEETING COURSES

Six pre-meeting courses at ESTRO 37
20 April 2018 | Barcelona, Spain

UNDERGRADUATE COURSES

Medical Science Summer School Oncology for Medical Students (Vienna/ Groningen)
2-11 July 2018 | Groningen, The Netherlands

ESO-ESSO-ESTRO Multidisciplinary Course in Oncology for Medical Students
27 August - 7 September 2018 | Poznan, Poland

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