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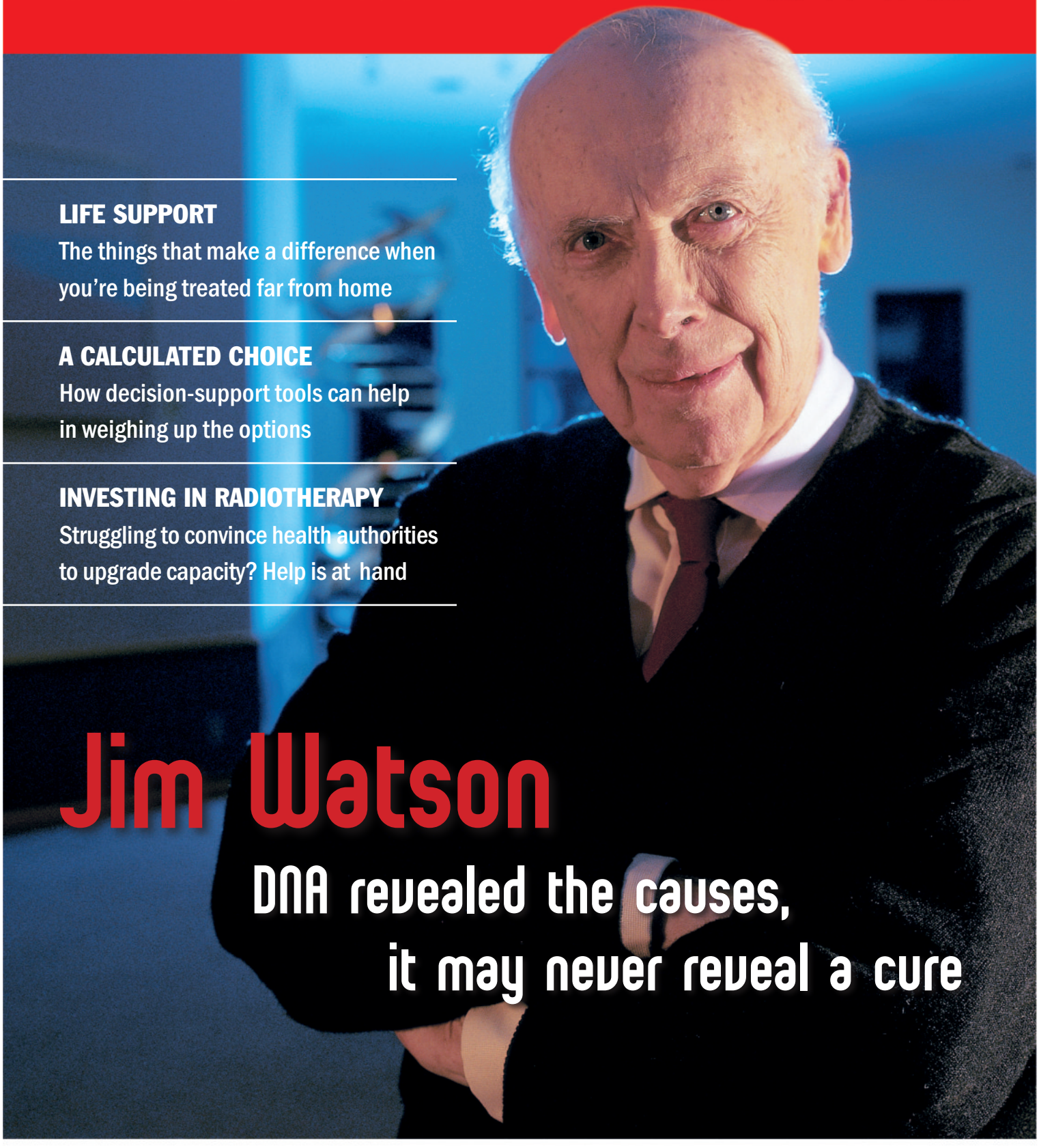

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Cancerworld

Shaping the future of cancer care

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European School of Oncology
Learning to care

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

Supporting patients in distress

KATHY REDMOND EDITOR

Distress – the range of unpleasant emotions associated with a cancer experience – is common in patients and their loved ones. With appropriate support most people can cope and adapt to their new reality. However, there are many who do experience clinically relevant mental health problems, such as anxiety and depression, which need to be identified and dealt with in a timely manner.

Unfortunately, emotional distress often goes undetected, and some patients are left to struggle with mental health conditions that are hard to bear, even though there are a range of evidence-based interventions that could help them. This matters, because mental health disorders can lead to worse cancer outcomes, in addition to the impact they have on the patient's wellbeing and ability to function.

There are a number of factors that contribute to this unsatisfactory situation. Patients are sometimes reluctant to seek help or admit to feeling distressed, because of taboos surrounding mental health disorders. These taboos can also influence clinicians, who may be reluctant to label a patient as having a mental health condition. Lack of experience, lack of time, low index of suspicion and failing to enquire about relevant symptoms can all play a role. Lack of specialist support once mental health problems are picked up is also an issue.

In an effort to tackle this problem, the International Psycho-social Oncology Society (IPOS) is campaigning to have emotional distress measured as the 'sixth vital sign' in cancer patients, and psychosocial care integrated as a core domain of quality cancer care. Progress will depend on overcoming the many social, organisational and economic obstacles that prevent cancer patients from being routinely screened and treated for distress. Incorporating regular screening for distress into routine cancer care would be an important first step towards addressing gaps in the provision of mental health services in the oncology setting.

Easy-to-use, short assessment tools, such as the distress thermometer, are already available. However, it is unlikely that busy cancer clinicians will start to routinely screen patients unless this is introduced within the context of a proper programme aimed at improving psychological care in oncology. This would need to include elements such as training, guidelines and resources for aftercare, should patients require specialist mental health support. Including psychosocial care in audit and certification protocols would also help ensure its proper integration into routine patient care.

Cancer takes a huge emotional toll on patients – not just those with advanced disease or undergoing treatment, but also long-term survivors. It is unacceptable that high levels of emotional distress are not detected and treated appropriately, and we cannot allow this to persist.

The cancer community needs to get behind the IPOS campaign (http://tiny.cc/6th_vital_sign) and show that we're not just interested in treating the disease but we also care about patients' mental wellbeing. ■

Jim Watson:

DNA revealed the causes, it may never reveal a cure

ANNA WAGSTAFF

Nobel laureate Jim Watson is calling on the cancer community to take a long hard look at what has been achieved by blocking the molecular signals that drive individual cancers, and to consider whether it is wise to bet so heavily on the potential of targeted therapies.

Sixty years after Jim Watson and Francis Crick famously resolved the double helix structure of DNA, which opened the door to understanding the nature of cancer, there is still no cure in sight for advanced disease. Now Watson, the surviving member of the duo, who went on to pioneer and write the book on molecular biology, and led the Human Genome Project as its first director, is questioning whether genetic approaches to treating cancer can ever lead to the breakthroughs we need.

At 85 years old, Watson has spent recent years applying his vast knowledge and impressive intellect to the problem of incurable cancers, and has reached the following conclusions: To cure cancer you need to kill cancer cells. Targeted biological therapies don't kill cancer cells, they are not curing cancer and it is unlikely that they can be made to do so in a practical or comprehensive way in the near future. It's time for a change in strategy.

"We know the current approach is not working, because on the whole it has made no dent in cancer mortality," he says.

Watson is speaking in his study at the Cold Spring Harbor Laboratory, New York, the research and education institution he directed and led from 1968 until 1994, and where he now holds the salaried position of chancellor emeritus. "They call me emeritus because they don't always like what I say," he remarks with

RAPHAEL GAILLARDE/GAMMA

the irreverent humour that has characterised his long career at the cutting edge of science.

But his point about targeted therapies is completely serious. He offers the example of the EGFR inhibitors Iressa (gefitinib) and Tarceva (erlotinib). "There's no doubt EGFR inhibitors work best against cancers that contain activating mutations in their tyrosine kinase EGFRs, which is the case in about 10% of lung cancers. But even in the people they really work in, they work for about a year, tops. Then resistance. So if you look at their effect on lung cancer mortality, it really isn't measurable, because it's 10% of cancers, and one extra year… The cancer world has ignored resistance saying we'll just get another drug. The problem is that once we get resistance the cancer is usually resistant to other drugs. Other drugs are not so effective, and the cancer becomes incurable."

Watson still takes an impish delight in having a go at 'the cancer research establishment' – but he doesn't want people to use that as a reason to dismiss what he is saying. He too had high hopes about the potential of targeted drugs in the early days – indeed Tarceva was co-developed (with Genentech) by a company Watson helped found at Cold Spring Harbor back in 1983, under the name Oncogene Science, later renamed OSI Pharmaceuticals. "I'm not blaming anyone," he insists.

"We didn't really appreciate how important it was to kill the cell – just kill it… All the good chemotherapy drugs were isolated because they caused apoptosis. Poof! The cells die. But these targeted therapies don't kill. They stop the growth of the cell. But they don't necessarily kill them. They can sometimes lead to apoptosis, but not in a simple clean fashion. That wasn't appreciated."

BETTMANN/CORBIS

At the Nobel Prize Award Ceremony, in Stockholm, December 1962. The award for determining the structure of DNA was given jointly to Jim Watson (second from the right), his collaborator Francis Crick (third from left) and Maurice Wilkins (far left)

For years, Watson recalls, "we were all looking for the [VEGF] inhibitor that would block angiogenesis. I was part of it, and I became quite enamoured of this stuff, really because it seemed that we could get away from chemotherapy. But the irony of it is that Avastin [approved in the US in 2004] only works in conjunction with chemotherapy." And as he points out, chemotherapy, being strongly mutagenic, tends to sow the seeds of resistance in the cancer it aims to destroy.

For the past few years, Watson has been turning his attention to things that all cancer cells have in common, however advanced the stage, no matter how chaotic and mutated the cancer cell, with a particular focus on the cancers that are the most resistant to treatment. So rather than looking for ways to inhibit the 'always on' signals that typically trigger particular cancers (HER2, RAS, RAF, MEK, ERK PI3K, AKT, mTOR and the rest), he is searching for weaknesses in the key regulatory and metabolic features that are common to all 'always on' cancer cells. He argues that we should focus far more on the wide range of metabolic and oxidative vulnerabilities that arise as a consequence of the uncontrolled growth and proliferation capacities of cancer cells.

Metformin, the type 2 diabetes treatment, offers some vital clues, he says. Known to protect against a wide variety of cancers, and to selectively kill cancer stem cells (which are normally highly resistant), it is now in trials to see whether it can augment response to cancer treatment. Watson is not confident the results will be positive, but is convinced something significant is going on which needs to be better understood.

Metformin is Watson's kind of drug – it seems to work better in cancers that are hardest to treat. "A really intriguing thing about metformin is that it kills triple receptor-negative breast cancer much better than say lobular breast cancer. So it kills the nastiest cancers, it doesn't kill the others."

It turns out, he says, that metformin kills cancer cells that have lost both copies of the powerful p53 tumour suppressor gene much better than those with both p53 genes in tact. "Even though normally p53 promotes

"What we need to find out is if there are any drugs that will essentially inhibit our stress-handling systems"

apoptosis and that ability has been taken away, it still kills tumour cells." This gives Watson reason to believe that the drug may prove to be more active against late-stage cancers where cells are so mutated that most will have lost both their p53 genes. He also cites research by Michael Pollak, head of cancer prevention at the Department of Oncology at McGill University in Montreal (*Cancer Discov* 2012, 2:778–790) indicating that metformin kills cells that can't handle stress. "This means that if the cell can't handle stress then you can kill it. So what we need to find out is if there are any drugs that will essentially inhibit our stress-handling systems. I want a pre-existing one because I don't want to have 10 years to wait to develop one."

In January this year, Watson published an article in the Royal Society journal *Open Biology* (vol 3, p120144), that draws together diverse evidence on something else that he believes to be a common factor playing a role across late-stage cancers. Under the title *Oxidants, antioxidants and the current incurability of metastatic cancers*, Watson sets out the hypothesis that, while high levels of oxidants are known to be mutagenic and dangerous, low levels of reactive oxygen species (ROS) may be essential for the proper functioning of cellular apoptosis.

This theory has obvious implications for the potential harm being done by the huge industry in anti-oxidant foods, drinks and supplements. As Watson remarks in his paper, "Blueberries best be eaten because they taste good, not because their consumption will lead to less cancer." But it is the implications for overcoming the resistance to cancer therapy that Watson believes merit far more attention than they are currently receiving.

The hypothesis is intriguing because it has the potential to throw light on many seemingly unrelated observations, which are set out in Watson's paper.

- The importance of ROS in the processes that induce cell death – both in the body's normal regulatory function and in many chemotherapies
- Absence of ROS – hypoxia – as a characteristic of resistant cancer cells, including cancer stem cells
- The failure of anti-angiogenesis therapies to kill cancer cells without concomitant chemotherapy (the cells become hypoxic as their blood supply is choked off)
- The negative results of trials of vitamins A, C and E to prevent cancer, with vitamin E actually being associated with a small increased risk of many types of cancer
- The observation that cancer cells resistant to chemotherapy tend also to be resistant to radiotherapy, which implies a common mechanism of resistance.

Missing from the evidence presented in the *Open Biology* article is another interesting part of the jigsaw puzzle that Watson received from a reader in response to its publication, and which has convinced him more than ever that he is onto something very important. It shows that, when it comes to preventing type 2 diabetes, "exercise-induced oxidative stress ameliorates insulin resistance", and taking anti-oxidant 'health' supplements can preclude the health benefits of exercise in humans (*PNAS* 2009, 106:8665–70).

So a picture is emerging that somehow links the metabolic condition of type 2 diabetes with cancer (and Watson suspects some degenerative diseases as well). Metformin seems to have an effect in both. We know metabolic syndromes and obesity are risk factors for cancer, we know exercise is preventive against cancer and diabetes, and now, at a biological level, this role of ROS and anti-oxidants seems to be emerging. And all of this, says Watson, has probable connections to the 'Warburg effect', an observation

"I'm feeling slightly frustrated that I can't do something, but I stopped doing science when I was 33"

known about since the 1920s that cancer cells tend to produce energy in a way that differs from normal cells, the chief disparity being that they do not require oxygen, but use a high rate of glycolysis (up to 200 times higher than in normal cells), followed by lactic acid fermentation.

Watson is the first to concede he doesn't have the answers, but he's convinced he's asking the right questions and refers to his *Open Biology* paper as "my most important work in years."

"I'm feeling slightly frustrated that I can't do something. But I stopped doing science when I was 33," he says. While he was still boss at Cold Spring Harbor he could at least have directed some of the institution's limited resources in this direction. But now, he concedes, "all I can do is write papers and hope that readers are open to unorthodox ideas."

Cold Spring Harbor Laboratory does in fact convene occasional meetings bringing together people working on metformin, for instance, but that is a far cry from the concerted research effort that Watson argues is needed. Hence his plea to those who control the bulk of cancer research funding to take an honest look at the prospects that targeted cancer therapies will ever deliver a cure for cancer, and consider whether it may not be time to change tack.

"We can carry on and sequence every piece of DNA that ever existed, but I don't think we will find any Achilles heels. We've had about 10 years. It's not the story I wanted to hear.

I would have hoped for a lot more success."

So what would Watson do if he were in charge? "My own solution is to identify people who have ideas about drugs that will attack the uniqueness of the biochemistry of cancer cells. We still don't know the reason for the Warburg effect…. If I had two billion dollars I would give it to 20 biochemists, give them $100 million each and tell them – go to it. You have to unleash biochemistry, and there is essentially no biochemistry left because everyone moved into DNA."

Not surprisingly, perhaps, Watson puts enormous faith in the power of unfettered intelligence, while he rarely misses an opportunity to needle the movers and shakers in cancer research who control where the big money is spent, and sit on grant committees and peer review boards. In his *Open Biology* article he identifies the "inherently conservative nature" of the cancer research establishment as "the biggest obstacle today to moving forward effectively towards a true war against cancer," because they are "still too closely wedded to moving forward with cocktails of drugs targeted against the growth-promoting molecules."

Watson himself has never sat on a peer review board, and is proud that he has never been an insider. "I generally find it does not pay to argue with the establishment or hope that they will change their mind," he says. "Crick and I didn't try to change the protein-oriented world. We just did our own thing and it worked." (Many leading scientists had been expecting the secret to inheritance to be found in proteins – not least because of their diversity and potential complexity – so the discovery that it is based on sequences of only four nucleic acids was breathtaking.)

Watson's formula for success is: "Read a lot, go to meetings, travel, try to have a job in a place where you are surrounded by bright people. You need people to talk to, but you have to get new ideas, which you only will get from reading something from another field that doesn't seem related but is."

Being bright doesn't make you successful, he says. "Most geniuses are precocious because they have phenomenal memories. You can remember a lot which helps you solve problems. A chess grandmaster will have in his head 5000 games – every move. So it takes a good memory to start with. Though that won't make you

a world champion because you have to, in some sense, be wise."

For Watson, Cold Spring Harbor Laboratory represents the sort of place he is talking about, where people can spend time surrounded by bright people and have time to talk and generate new ideas. That is what it was for him, back in 1948 and 1949, when he spent two hugely formative summers there in the company of some of the world's best scientific brains, including Salvador Luria, who had taken Watson on as a PhD student in his lab in Indiana University, and was immersed in pioneering work on genetics in microbes that would later win him a Nobel Prize.

"In those days you didn't spend the summer in Indiana. There was no air conditioning. People came here to the coast so they had someone to talk to. Then there was a tradition that doesn't exist now. Summer was good for talking. And then you would do the experiments. Now people think that the summer is a time to do experiments. So the summer isn't a relaxed period any more."

ANDREAS FEININGER/GETTY

Simple. Watson posing in 1957 with a model of his great discovery: the elegant double helix structure that makes us who we are

But important though all this is to achieving scientific success, more important still, says Watson, is being in the right field at the right time. "You have to be in a field that is going to move. And that is a very hard thing sometimes to guess."

Watson's own track record on this score shows he's done better than most, which is one reason why, having first become interested in curing cancer before even enrolling in his first course on tumour viruses back in 1947 – on account of a 40-year-old uncle who was dying of melanoma – he has remained a key player in propelling cancer research forward for more than 65 years.

Having started at the tender age of 15 majoring in zoology at Chicago University, with ambitions to becoming an ornithologist, Watson came across Erwin Schrödinger's *What is Life?* – a book that inspired and influenced many important brains of his generation. It prompted him to switch focus to the work being done by the Indiana-based microbiologist Luria and others looking at the genetics of bacterial viruses. Picking up on the achievement of the Caltech-based chemist Linus Pauling in using X-ray crystallography to determine the physical structure of amino acid, Watson then made the correct call to learn related techniques to determine the structure of DNA, which he famously did with Francis Crick as a post doc research project at Cambridge University. Returning to the US following this epochal discovery, he took up a post at Harvard teaching tumour viruses, then switched focus to RNA, "because we had to find out how the information in DNA got into proteins."

"I had just learnt that bacterial viruses carry enzymes involved in helping their replication,

"I want to see if we can cure cancer in five years, I'm not interested in curing it in 20 years"

so I thought maybe the essence of cancer was a virus coded for an enzyme involved in DNA replication. And this enzyme, when incorrectly integrated in a host cell, could just be the signal to start the cell cycle."

In 1959 Watson attended a session of the American Association for Cancer Research (AACR) on the polyoma virus – a DNA virus known to cause all sorts of tumours in immunocompromised mice. "I realised it was very small. It might be so small it would only have a few genes… This was before recombinant DNA, before we even knew about messenger RNA. It was just the idea that you could get mutants and so on. Not very precise. The idea that the true essence of tumour viruses was turning on the cell cycle. And to within limits that was right."

Watson carried on with his work, "doing the fundamentals of molecular biology," but kept an eye out for where the action was happening in other areas. One of these areas involved three people who were looking at the polyoma virus from a DNA perspective: Renato Dulbecco in the Salk Institute (a close collaborator with Luria, who Watson knew from his Cold Spring Harbor summers), Leo Sachs in Israel, and Michael Stoker, also known to Watson, from his Cambridge days, who was then at the Institute of Virology in Glasgow.

"So I followed what they did. In *The Molecular Biology of the Gene* [still a standard textbook, now in its 7th edition], I write a chapter on cancer. It's the first time you have ever exposed the world of molecular biology to the cancer problem." (It was nice to write because there were no referees, he adds. "I could write whatever I liked.")

In 1968, a young biologist named Joseph Sambrook, working in Dulbecco's lab, found evidence that the SV40 genome was integrated into transformed cells. "The basic idea was right. That's what got Dulbecco his Nobel Prize."

Meanwhile, a financial crisis at Cold Spring Harbor Laboratory had prompted Watson to move in to save it, and in 1968 he took over running the place full time. He made another good call, to set up the Tumor Virus Group, and hire Sambrook to head up a cancer virus group. What followed was a tremendously productive period. "The idea was to find the genes – mutants and so on," Watson explains. "That seemed really hard. And suddenly recombinant DNA came along."

Recombinant DNA was a game-changing genetic engineering technology invented in California, at Stanford and UCSF, which, in addition to providing a basis for the biotechnology industry, opened the way for exploring the genes of cancer cells – though in the face of strong opposition from people concerned about the implications of this new technology. "I spent four years fighting the environmentalists, who didn't want us to do recombinant DNA," says Watson.

It wasn't long before the first oncogene was isolated – *Ras*, discovered simultaneously by Michael Wigler at the Cold Spring Harbor Laboratory, Robert Weinberg at the Massachusetts Institute of Technology (who'd previously worked in Dulbecco's lab) and Mariano Barbacid, a Spanish molecular biologist working at the US National Cancer Institute. "And the moment you found the genes, you wanted to find the protein product and then you wanted to find the inhibitor."

Then came the first tumour suppressor, *Rb*, the gene responsible for retinoblastoma, which had been known about since the 1970s, and was isolated in 1986 by Stephen Friend working in Weinberg's MIT lab. The work showing "in a clean way" that *Rb* was in a tumour was done by the adenoma virus group working at Cold Spring Harbor Laboratory. Watson also successfully argued for, and then served as first director of, the Human Genome Project that first identified

and mapped the entire set of 20,000–25,000 human genes.

"And now we know there are at least 10 tumour suppressors for every real driver. Most of the control is inhibitory," says Watson, summing up what he considers to be a job well done.

Sadly, despite the high hopes, this incredible journey of discovery, which identified the genetic mutations that cause cancer, has not resulted in finding cures. Watson sees no reason to believe that carrying on endlessly sequencing tumour DNA will deliver breakthrough new treatments.

Right now, he believes that finding out more about the metabolic weakness in cancer cells is a far more productive way to proceed.

JEFF ALBERTSON/CORBIS

A practical man. If the right resources are given to the right people, Watson believes a cure for cancer could be in sight by the time he reaches 90

If this sounds like a recipe for spending another 20 years elucidating every dot and comma of the metabolic process of normal and cancerous cells, that is certainly not how Watson sees it. "The question of curing cancer is a practical question that is somewhat separate from the pure research of how does cancer work," he says, and he argues that it is the people who want to carry on with the DNA sequencing who are looking to gather knowledge for its own sake.

"Propelling me 40 years ago to turn the Cold Spring Harbor Laboratory into a major site for unravelling the genetic underpinnings of cancer was the belief that once the gene-induced molecular pathways to cancer became known, medicinal chemists would go on to develop much more effective gene-targeted drugs," Watson writes in the introduction to his *Open Biology* article.

He never believed in the 10- to 20-year timetable proposed by the proponents of the War on Cancer back in 1970. But he does feel we are there now. We finally know enough to turn the knowledge gained, not only about genes but also about cellular metabolism, into much more effective treatments.

"I didn't think I had any chance when I was 25. Now I think there is a chance. Now I've reached 85 I think I want to reach 90. The reason is, I want to see if we can cure cancer in five years. I'm not interested in curing it in 20 years."

He believes that this timetable can be met if the right people have enough resources.to get the job done. "Whether we cure cancer or not is likely to depend on whether some private very rich people give money to non-traditional sources. I'd just like some rich person to give me $200 million. But who is going to give money to an 85-year-old? So going back to what I said before: two billion dollars could provide $100 million each for 20 of the best biochemists in the world.

"Some things you can do with your wits alone. You can write a text book. But you can't produce a drug. It doesn't matter how bright you are, you need the money. Even though it sounds like I'm criticising everyone, and it sounds like sour grapes, I just hope someone realises that what I'm proposing is actually very practical." ■

A calculated choice

The role of decision-making tools in personalising treatment

MARC BEISHON

Computers are better than doctors at processing the large amounts of information involved in personalising treatments. But which decision-making tools can be relied on, and how can they best be used to help inform shared clinical decision making?

'The computer will see you now.' This was a recent headline on a British newspaper story about how a lung cancer prediction model outperformed oncologists' predictions of survival and the chances of certain complications. This may have been a surprise to some, but for many years doctors in most branches of medicine have been using decision support tools of various types to help decide on treatments. What's changing is the need for much more sophisticated decision tools, because diseases such as cancer now have so many more variables to consider that even experts cannot process them all without help, as the newspaper story reported.

Such is the power of these prediction tools that the developers of the lung cancer model, based at the Maastro clinic in Maastricht, Netherlands, consider that it is now unethical not to use such models for certain diseases as part of cancer care. That's partly because the stakes can be very high in making healthcare decisions, as the correct course of action can be a matter of life or death in many situations – not least in cancer, where it is often said that there is only one chance to give the best treatment for people with disease that may progress. But decisions also affect all parts of the cancer journey, even before any diagnosis, from stopping risky behaviour such as smoking and deciding whether to attend a screening programme, to cosmetic considerations about surgery, to the particular challenges in planning care at the end of life.

But these decision support tools in cancer are still in their early stages, and while there are already many of them, they vary greatly in quality and usefulness. Given that their use is on the increase as decision making in cancer becomes more complex, it is becoming important to evaluate how they can best be integrated into everyday clinical practice.

Today, anyone can go to the Internet and find many risk and survival

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

prediction calculators, especially for breast and prostate cancer. These tools have mushroomed in recent years as researchers have realised they can exploit increasingly rich data sets from cancer registries and other sources to calculate scores that are tailored to the characteristics of an individual. The calculators are an additional weapon in the armoury of oncologist and patient, who already have much information to weigh up, from guidelines and consensus groups, from second opinions and patient groups, and of course from the staging, imaging and genomic data from tumours. All a patient wants is the best decision about the future that suits them as an individual – and not a population group.

As Andrew Vickers, a research methodologist at Memorial Sloan-Kettering Cancer Center in New York argues, prediction is everything in cancer. "As a cancer researcher I see the disease predominately as a problem of prediction. For example, most early cancers do not cause symptoms and the reason we take out a lump is that we predict it will spread and cause problems if we don't. And prediction is also the main problem for the spectrum of care from screening and detection to end of life decisions."

Prediction modelling started in the coronary field, says Vickers, with the Framingham Heart Study of 1948, which tested people in a town in Massachusetts and followed them for many years to see if they developed heart disease. Today there are more than ten risk calculators for cardiovascular disease, diabetes, hypertension and more on the Framingham website, and they have been the basis of much worldwide primary care decision making about say taking statins. Other heart models have been developed that give a more accurate prediction for certain populations, and have been validated in databases of millions of patients.

Cancer prediction tools have a much more recent history and, thus

"As a cancer researcher I see the disease predominately as a problem of prediction"

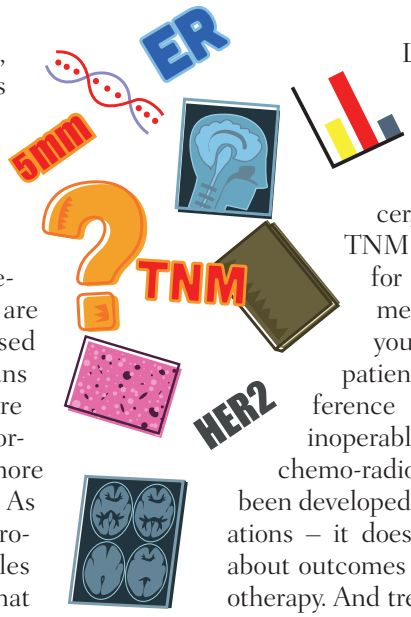
"The risk is that without decision tools a patient will be subject to lottery medicine"

far, smaller datasets. As Vickers notes: "In the early 1990s it was common for a woman with breast cancer just to be handed a leaflet with a simple five-year survival risk based on only one crude variable – the stage of the tumour. It was only later in the 1990s, with the rise of the Internet and more use of computers, that it became possible to make predictions based on multiple variables as a routine part of cancer care."

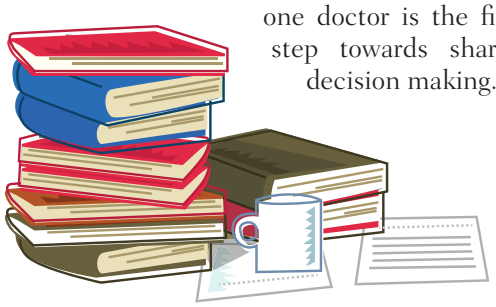
He makes the point that decisions about whether to give treatments such as adjuvant chemotherapy, based on one or two factors such as stage or lymph node involvement, "make no sense". "Take gastric cancer and the staging about how far it has spread through the muscle wall – you can't make the case that if it has spread you need chemotherapy and if it hasn't you don't – because the assumption is that no one recurs if it hasn't spread. I'm not saying that the way we have been giving such treatments is necessarily bad, but that it makes no sense in terms of risk prediction."

Risk prediction, he says, addresses the problem of using risk classifications with cut-off points such as stage or certain PSA levels in assessing risk of prostate cancer, where for example a high-risk classification can mask a big variation in actual risk in that group.

Philippe Lambin, head of radiation oncology at Maastricht University Medical Centre, and medical director of the Maastro Clinic, adds: "Oncology has made a lot of progress using guidelines, which are sort of recipes for treating large groups of patients, but everyone recognises we are moving to individualised medicine, which means we have to input more and more variable information and output more treatment options. As humans can only process about five variables at most, the risk is that without decision tools a patient will be subject to lottery medicine.



"Furthermore, there is now a push for shared decision making, which makes sense as with many options the preferences of the patient are also very important. Without decision support tools we just can't say what all the likely outcomes and complications are of a series of different treatments, because doctors are just very bad at predicting the future. Making better decisions in a reproducible way independent of any one doctor is the first step towards shared decision making."

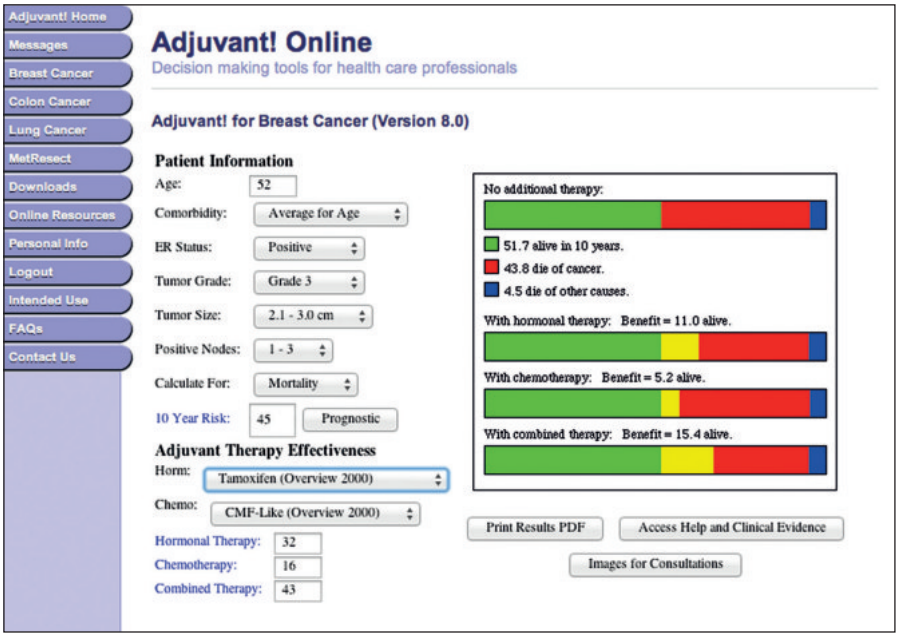


Lambin also takes issue with the traditional international TNM staging system. "In lung cancer, which I know best, TNM doesn't work at all for non-surgical treatments, especially when you have inoperable patients – there is no difference in survival between inoperable stage I and III after chemo-radiotherapy. TNM has been developed by surgeons for operations – it doesn't tell you anything about outcomes after radio- or chemotherapy. And treatment decisions are not only based on survival but on complications and quality of life – even if TNM worked it is not enough."

One of the first prediction tools that addressed more factors is the Adjuvant! program for early invasive breast cancer, developed by Peter Ravdin and colleagues in the late 1990s in the US, and since put on the Internet as the Adjuvant! Online website (which also now covers lung and colon cancers). For breast cancer, it allows oncologists to assess the risks of recurrence and dying within 10 years according to factors such as age, menopausal status, oestrogen receptor (ER) status, number of positive lymph nodes, and according to adjuvant therapy (hormonal or chemo-therapy, or both). The results are presented in colour-coded bar charts that show how far different therapy options lower the risk of death for any given set of risk factors.

Adjuvant! is not just a pioneering program, it has been widely used as a clinical tool that helps patients reach decisions on the option best for them, according to their own preferences and priorities, when it comes to balancing reduced risk against the drawbacks of a given treatment. An important randomised study showed that its use translates into women making different judgements about adjuvant therapy, because their risk is more clear; for example, those with little to gain used less therapy than the care-as-usual group. (The risk information would be even clearer, another study has found (*Cancer* 113:12), if Adjuvant! Online were to change the way it presents its results from bar charts to pictograms.)

Adjuvant! has also been a subject of validation work in other populations and, as with the Framingham heart model, it has been found to underestimate risk in some groups. For example, in 2011 French and Dutch researchers found that "Adjuvant! Online needs to be updated to adjust overoptimistic results in young and high-grade patients, and should consider new predictors such as Ki-67, HER2 and mitotic index" – the latter point indicating that such tools should incorporate new biological knowledge. (A nice site that has decision-making data about cancer mutations for oncologists and patients is My Cancer Genome, a "one-stop tool that matches tumor mutations to therapies," run by Vanderbilt-Ingram Cancer Center in the US.)



Adjuvant! was one of the first computer programs designed to help doctors and patients understand the implications of different treatment options tailored to individual risk factors. Originally developed for patients with early invasive breast cancer, it is intended as an aid to discussion and shared decision making; unlike many other tools, it is not designed to be accessed by patients directly

Developers of other prediction tools, such as CancerMath (cancermath.net), developed at Massachusetts General Hospital, also say the algorithms they use are better than Adjuvant!, while there is also the major ongoing work on gene expression profiles (principally MammaPrint and Oncotype DX in breast cancer), which are being compared with Adjuvant! Recently, a prospective trial of Mammaprint showed good results for women avoiding chemotherapy after five years, but one expert commented that it is "hazardous" to rely only on a five-year follow up, and Vickers considers that deaths that do occur in women who forgo chemotherapy need to be carefully quantified alongside the decrease in treatment.

Another well-known set of prediction tools, for prostate cancer, was developed by Michael Katten and colleagues, and are known as the Katten nomograms – nomograms being the term for calculators that predict the probability of survival, recurrence and so on from multiple variables. But in the past few years, says Vickers, there has been an explosion in online nomograms. "It's all too easy to set one up because all you need

Adjuvant! has been widely used to help patients reach decisions on the option best for them

"It's all too easy to set one up, but the question is whether they can really help patients"

is a data set and statistics software – but the question is whether they can really help patients," he says.

Sloan-Kettering has a comprehensive set of cancer nomograms (at nomograms.mskcc.org), and is a leading developer of prediction tools, but as Vickers says, if you now Google 'cancer nomogram' you will be deluged with sites all purporting to offer calculators, and he is concerned that relying on many of them could result in more harm than good. For prostate cancer alone there are dozens of nomograms for virtually all clinical situations. In several papers, he warns that despite their "enormous promise", most prediction models have not been validated on different datasets – which should be a fundamental principle – and that the actual clinical consequences of using models is also rarely evaluated.

For the latter point, he cites a paper that has evaluated two calculators used to help decide whether to carry out a biopsy to detect prostate cancer, which is a frequent question. It found that when an approach called decision analytics is applied, one tool would do more harm than good with most men with typical acceptance of risk. "Practical assessments of the real-world effects of prediction modeling on medical decision making and patient outcomes are all but unknown in oncology," he writes in one paper.

Vickers is working on his own model for prostate cancer biopsy. "We have looked at more than 10,000 men so far and that's not good enough for us to gauge how well it works. We need the same statistical rigour as when we trial drugs for good versus harm, although we may not need randomised trials in most cases." The fact that most of the major nomogram sites also reference academic papers on which the models are based is reassuring, but the papers' discussions inevitably also say there is much more work to be done.

So it seems that much caution is needed in interpreting the results, and this raises issues about the direct access patients and families have to many of these proliferating prediction tools, although most have strong disclaimers and some, such as Adjuvant! Online, have a registration form designed to restrict access to medics, to ensure patients review the results together with their doctor.

As Vickers says, "Before [the Internet] we were worried about oncologists making decisions without telling the patients; now we are worried about patients making decisions without telling the oncologist."

In the case of the Maastro Predict models – currently for lung, rectal, and head and neck cancers (see predictcancer.org) – Lambin says the policy is that they should be externally validated with large datasets, and should be continually updated. To this end, Maastro and other clinics in the Meuse-Rhine region (Netherlands, Belgium and Germany) have set up the Euregional Computer Assisted Theragnostics project (EuroCAT) to develop a federated database of medical characteristics to feed into systems such as prediction programmes. While developing software products from this work is problematic as it requires costly European CE mark regulation, says Lambin, "the nomogram approach is a way of avoiding this and getting the data into the clinic."

Although based on multidisciplinary practice, the Predict models have a focus on radiotherapy, which is Lambin's field and the specialism at Maastro. As he explains, in recent years radiotherapy has become so complicated that old manual methods have long been set aside in favour of electronic treatment planning systems. The precision of administering radiation, he adds, is much more than can be applied for a drug in terms of how it works in the body, although progress is being made with labelled agents.

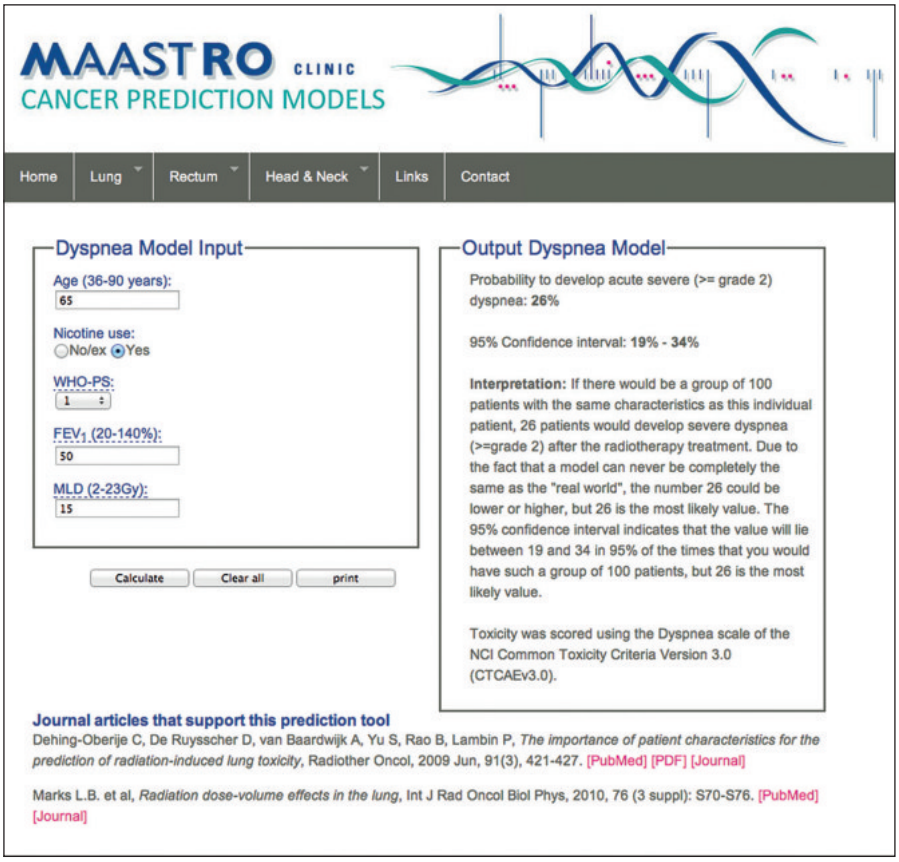
"Our rectal cancer prediction model is proving to be very useful as we can tell two weeks after the start of radio-chemotherapy treatment

whether a patient will need surgery – and in this cancer, avoidance of surgery can have a massive impact on the quality of life," says Lambin.

The lung cancer story that made the news is about a study conducted by Lambin's colleague, Cary Oberjie, who asked radiation oncologists not only to predict the chances of patients surviving for two years, based on data from more than 100 people, but also whether they would suffer from dyspnoea (shortness of breath) or dysphagia (difficulty in swallowing) after undergoing radiochemotherapy. There are Predict tools for each of these factors. The oncologists were asked for their predictions at the time of first seeing a patient, and then again after a treatment plan had been decided. The results show that the Predict models at both points considerably outperformed the oncologists, whose own predictions were not much better than 50%, or chance.

"Our models have also been validated prospectively – they are much better than doctors and the TNM classifications," says Lambin. He recognises though that randomised trials, comparing decision support-based treatment with guideline-based treatment, may be necessary to convince the oncology community, and that could be a next step. It is also a challenge to know how to integrate more variables, in particular genomic assays. "But I'm more a believer in non-invasive, 3D data from advanced imaging, as tumours are always heterogeneous and molecular assays are based on a random biopsy from part of a tumour. Sometimes that works, as in breast cancer, but often it doesn't if the tumour microenvironment has to be involved."

Further, Lambin stresses that these prediction tools should eventually be holistic in nature by integrating data on quality of life and side-effects, not least because this can improve shared decision making with patients. At present, an oncologist may need to use a range of tools to gauge treatment and complications such as acute or delayed side-effects, but he adds that at Maastro there is a prototype that brings these models into one interface. ■



The Predict tools developed at the Maastro clinic in the Netherlands focus largely on radiotherapy procedures, processing individual risk factors to give probabilities not just in relation to survival but also to the risk of serious side-effects associated with different treatment options, such as suffering dyspnoea as a result of different doses of radiotherapy in lung cancer

"Our rectal cancer prediction model tells us two weeks after the start of treatment whether a patient will need surgery"

Easing the cancer journey

SIMON CROMPTON

Having to travel long distances or stay away from home while being treated for cancer takes its toll in anxiety, stress and isolation. Could more be done to ensure policies that centralise services don't make some patients' lives unbearable?

DECLAN DOHERTY

A life saver. Without this charity-run bus, driven by a volunteer who is himself a survivor, many cancer patients living in the north west of Ireland would have to make the long journey to Galway and back by public transport – a round trip of up to 600km. Some of these passengers get to stay at the Inis Aoibhinn facility, attached to the cancer centre

Since his diagnosis in 2009, Dearn McClintock has been undergoing tests and treatment for prostate cancer at a hospital 250 km from his home.

"I realise that centralisation and medical economies require cancer patients to travel to large centres for highly skilled procedures," says Dearn, who lives in Donegal, Ireland. "But for the patient travelling long distances for treatment it's grim stuff."

Just how grim, and just how much travelling long distances for cancer treatment affects quality of life, treatment decisions and even outcome, might not be fully appreciated by policy makers and funders of cancer services.

According to Richard Flaherty, of Cancer Care West in Ireland, it is all too easy to underestimate the effects of travel. "Around 40% of people who have been through cancer say it has affected them psychologically," he says. "Put yourself in the shoes of someone of who is 70, lives in a rural area, is coming to the city for the first time, and finds themselves in a long line for treatment in a busy hospital. They have to find accommodation if they're receiving a course of radiotherapy. They're experiencing the stigma and fear of cancer, often away from their family. They'll be feeling tired, and maybe sick, and maybe they'll have to spend five days a week for two months staying in a Bed & Breakfast on their own."

For some, the solution is a new kind of cancer facility: accommodation centres specifically created – normally by voluntary bodies – to support patients who live a long way from their cancer centre. One of them is the Cancer Care West Lodge in Galway, Ireland. Named Inis Aoibhinn, it provides a place to stay for patients undergoing radiotherapy treatment at University Hospital Galway – recently designated one of Ireland's eight national cancer centres. And it provided Dearn McClintock with a lifeline.

Dearn lives a good four hours away from the Galway hospital travelling by car; there are no trains and the roads are not fast. "It's quite a journey even when you're on good form," he says. "I thought it was grim when I had to travel after biopsies, until my wife drove me home when I had a catheter. I remember every bump of that road."

Most of the time, Dearn drove himself to hospital and back. When he started a seven-week radiotherapy course in September last year, his best option was to drive down to Galway on Monday morning, stay in a Bed & Breakfast (B&B) for the five days of treatment, then drive home on Friday.

"By the second week it was getting hard," says Dearn, who is 54. "I was quite sick from the radiotherapy, and it wasn't great being stuck in that B&B room 22 hours a day. I was homesick and feeling quite lethargic, and really didn't have the energy to get out. By the time I got home at the weekends I was totally drained."

Then he was offered a place at Inis Aoibhinn for the remainder of his treatment – a room with its own

Patients with metastatic colorectal cancer received fewer systemic regimens if they lived far from a cancer centre

bathroom, the company of other people going through similar experiences, and 24-hour nursing support to help him with increasing treatment side-effects. "Spending time with other patients with prostate cancer made a lot of difference: there was a feeling that we were comrades in arms." He is all too aware that many others travelling to national centres in Ireland for treatment are not so lucky.

Impact on treatment outcomes

There is currently a dearth of research on the impact of travel on cancer patients. A literature review published in the *European Journal of Cancer Care* in December 2000 commented on the paucity of valid research to draw on. But there are some studies which take patient experiences like Dearn's beyond the anecdotal. An American study in the journal *Cancer Causes and Control* in August 2006 showed that women with early breast cancer were less likely to choose optimal treatment including breast conservation surgery and radiotherapy if they lived a long way from the treatment facility.

A Canadian study, published in *Oncology Exchange* in August 2011, indicated that patients with metastatic colorectal cancer received fewer systemic regimens and were less likely to enter a clinical trial if they lived a long distance from a cancer centre.

The Oxford Cancer Intelligence Network in the UK has also provided some evidence that the travel distance may be a crucial influence on treatment decisions. In its report on travel times to radiotherapy centres for head and neck cancer patients in England between 2006 and 2008, it concluded that, for patients requiring courses of radiotherapy longer than six weeks, "travel times may be a discouraging factor when considering the choice of radiotherapy over surgery". It noted that providers have been looking at ways of minimising the impact of travel times on patients, such as organising hostel/hotel accommodation near to the radiotherapy centre.

Renée Otter, former director of the Northern Comprehensive Cancer Centre in Groningen, the Netherlands, has made the case for keeping services more local when cancer services are being reorganised – partly because of quality of life issues for patients (see Cross Talk, *Cancer World* March–April 2013). She points out that more than 65% of cancer patients in Europe are aged over 60 when diagnosed, and many have mobility problems. For the 30%–45% of patients in Europe who are diagnosed when their cancer is too advanced to be curable, being able to spend as much time as possible at home, or at least with family, becomes even more important.

A good place to stay

Facilities that try to address some of these issues are springing up across Europe in towns and cities whose cancer centres serve large and often rural regions.

At home in CLAN Haven. Avoiding the stress of long daily journeys or the loneliness of a hospital ward or Bed & Breakfast makes all the difference to patients and families

In Aberdeen, Scotland, the CLAN Haven accommodation centre offers patients and their relatives and carers a home from home for up to seven weeks while they attend Aberdeen Royal Infirmary for treatment. Relatives can also stay there while the patient is in hospital. It accommodates radiotherapy patients for up to seven weeks in 27 bedrooms with their own bathrooms. The infirmary serves the whole of the North East of Scotland and the islands of Orkney and Shetland.

It was set up by the charity Cancer Link Aberdeen and North (CLAN)

11 years ago. "Aberdeen is the oil capital of Europe and accommodation is in short supply and is also very expensive," says Debbie Thomson, CLAN chief executive. "Options for radiotherapy patients travelling any distance were limited – hospital bed, hotel or B&B, or if they were lucky a relative living close to the hospital."

The health authority, NHS Grampian, refers radiotherapy patients to the centre and pays for their stay, although the centre receives no statutory funding and is reliant on donations and fundraising. There are kitchen and lounge areas, support personnel, and a range of support services on offer – complementary therapies, relaxation sessions, counselling, social events and even a minibus to ferry patients to hospital and back.

"Without us, people would be very isolated – maybe in a hospital ward," says Debbie Thomson. "Some would have shattering daily trips. Cancer is stressful enough, and you don't want the additional burden of travel. We have thousands of letters from people saying how their stay with us made their situation bearable. I think it's the peace and the freedom to do what they want that people appreciate most."

CLAN CANCER SUPPORT

Al Richards, 77, lives on the island of Orkney, and eight years ago was prescribed radiotherapy for prostate cancer at the Aberdeen Royal Infirmary. He knew he would have to fly down for treatment, but otherwise had no idea how he would manage. "I know some people from the island regularly flew down for treatment, but that was completely impractical."

When a place at CLAN Haven was offered, "it was as if the sun had come out again, and everything became a little easier". This year, Al has had to return to CLAN Haven to receive further treatment and a course of hyperbaric oxygen therapy at the hospital. His wife Margaret has been able to stay with him throughout the five-week course – without any need to return to Orkney.

"When you've got cancer, having your mind put at ease is extremely important, and I've spoken to many people with cancer who feel the same," he says. "I know many people who come from Orkney for treatment, and they haven't been off the island before and they feel very scared – not just because of the cancer, but about how they are going to manage, and what their family are going to do."

"It can be quite hard travelling by air, and then it can be confusing getting around in the town, especially for older people who haven't been here before. Travelling can also be very costly, and when you get to our age, you have to watch your outgoings."

It's a similar story for patients in

"When you've got cancer, having your mind put at ease is extremely important"

"Centralisation of cancer services is making the need for such centres more urgent"

other European cancer centres that serve dispersed and rural populations. In Norway, the Varde Centre in Tromsø supports patients attending the university hospital, and is one of four national support centres for patients having to travel long distances. Opened in 2012 and run by the Norwegian Cancer Society in partnership with health authorities, it is a meeting place for patients and their families, providing a relaxation room, kitchen, information, support, activities and toys for children.

Centre co-ordinator Hilde Nordhus says that patients who have to travel long distances for treatment – sometimes many hundreds of kilometres – have an additional challenge. "Many have to be away from their families for many weeks. Those who have radiation treatment over several weeks miss their families and feel lonely and anxious. They say it is good to have the Varde Centre, where they can meet others in the same situation and facing similar challenges."

Centralisation of cancer services, she says, is making the need for such centres more urgent. "I think that more cancer treatments should be given in rural areas, so that patients can be with their families and avoid travelling so far."

The problems associated with travel to treatment are by no means limited to areas of very dispersed populations, or only to adults. The impact of travel on the whole family becomes especially apparent in child cancer.

A policy issue

In 2010, the UK charity CLIC Sargent for Children with Cancer published the findings of an analysis of 10,000 records from its database of children who the charity has supported. It found that, while the development of specialist treatment centres has undoubtedly improved survival rates for children, travel to and from treatment centres can create significant challenges for young cancer patients and their families.

It found that 77% of childhood cancer patients do not live in a city with a principal treatment centre and that the average round trip travelled for treatment by children and their families is 60 miles, taking on average one hour 50 minutes. But some children and their families reported a round-trip of 902 miles, taking 16 hours.

CLIC Sargent for Children with Cancer concluded that this travel greatly increased pressure on families, causing "massive disruption to their work and family lives and their ability as a family to lead a 'normal life'".

Most cancer patients undergoing treatment know that 'normality' is an idea that changes substantially after diagnosis. But sometimes it is the little, indefinable things which researchers and policy makers find hard to measure that make life bearable in the face of stress, exhaustion and separation: Dearn McClintock remembers that a conversation with a nurse at Inis Aoibhinn helped him overcome the diarrhoea that was making any form of journey virtually impossible.

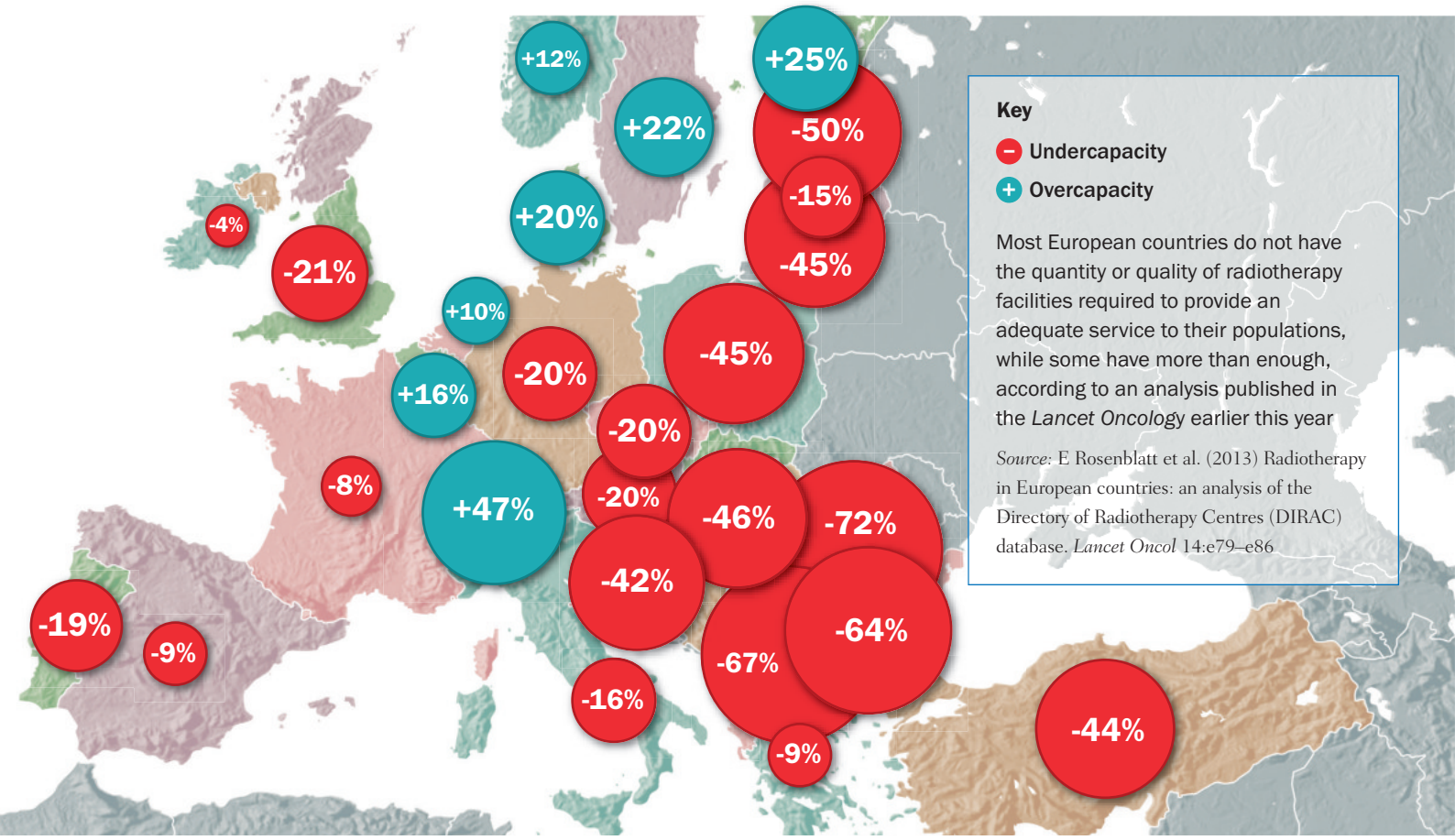
What value do you put on such support? Many of the centres that provide it receive no state funding and are dependent on voluntary contributions – even though it is state policies driving the centralisation process that makes them so indispensible for patients.

Dearn McClintock wonders whether this is right. "I understand centralisation and the need for economies of scale," he says. "But these centres rely on charitable donations and I think perhaps governments should be providing support."

"You can only admire what organisations like Cancer Care West do to raise voluntary contributions to run such services. Inis Aoibhinn is the most positive place to be. The guests are cheerful because the staff are marvellous and it is all provided free of charge."

"My strongest emotion experienced over the last three years has been gratitude to those that cared for me and my admiration for their skill and kindness to those of us in need." ■

"I understand centralisation, but these centres rely on charity; I think governments should provide support"



Radiotherapy capacity across Europe: what it should be, and what it is

MARC BEISHON

Winning the argument for expanding and upgrading radiotherapy facilities is not easy in the present economic climate. Comparative data and cost-effectiveness models can help build a convincing case.

How many radiotherapy machines are there in each country in Europe? It might seem an easy question to answer given that it is hard to overlook a large radiotherapy suite complete with several linear accelerators (linacs), and ancillary equipment such as CT, MRI and PET scanners, and treatment planning workstations. Earlier this year, *Lancet Oncology* (vol.14, pp 79–86) carried a lengthy paper that looks to have these numbers well documented in terms of actual installations and estimated need, from a group reporting on the European portion of the Directory of Radiotherapy Centres (DIRAC) database, which is managed by the International Atomic Energy Authority (IAEA). The authors conclude that there is "a substantial disparity in the availability and organisation of radiotherapy services between countries".

The inventory attracted a lot of attention around Europe. It was commented on by a number of professional societies and cancer organisations, and also featured in *Nature Reviews Clinical Oncology,* because it has been some years since a similar survey was published, and the headline finding is a call for modernisation of facilities, particularly in East and South-East Europe.

But there was also some criticism about the accuracy of figures from various countries. Further, the paper, and a detailed reply from colleagues at Europe's radiotherapy and oncology society, ESTRO, raise important questions about whether these data alone are good enough to inform policymakers, or whether new value and cost-effectiveness indicators are needed to make investment decisions in what tend to be very expensive facilities, both in terms of equipment and personnel.

Previous data came from the QUARTS (quantification of radiotherapy infrastructure and staffing needs) project, published in 2005, and carried out by ESTRO. Both projects have uncovered unmet needs in radiotherapy, mainly on the basis of counting centres and machines and then estimating from cancer incidence and population in each country whether there is sufficient capacity to deliver required treatments, given that a proportion of patients should have radiotherapy as part of their treatment (the DIRAC paper says "roughly 45–55% at some point").

The analysis of the DIRAC database was carried out by the European Network for Information on Cancer (EUNICE) over several years. EUNICE covers 33 countries, including all members of the European Union plus others such as Iceland and Turkey. DIRAC itself has a long history as a global listing of radiotherapy facilities, dating back to 1959, and now lists 137 countries and more than 7600 radiotherapy centres. In Europe the authors found 1286 active radiotherapy centres as of July 2012.

The authors calculated indicators by counting the number of 'teletherapy' machines per centre (with linacs being by far the most common type of equipment), as well as brachytherapy units. The picture that emerges is one of varying levels of concentration of services, with some countries such as the UK and the Netherlands having facilities centralised in fewer, large units. They also looked at the adequacy of radiotherapy capacity in each country. Using benchmarks from the earlier QUARTS project, and total population figures for each country, they calculated the number of machines that would be required to provide 'average' and 'minimum' levels of service, and compared that with the actual number of machines, to show the level of unmet need. Figures range from 72% in Romania (i.e. Romania has around one-quarter [28%] of the radiotherapy machines needed to serve its population), to –47% in Switzerland (meaning Switzerland has almost 50% more machines than it requires).

There are a number of limitations with this study, as the authors acknowledge. The benchmarks they used are crude and the QUARTS benchmarks are old, and don't take into account possible new national guidelines. The report also does not take into account the epidemiological cancer profiles of each country. The authors note, in particular, that demand for radiotherapy depends heavily on breast and prostate cancer incidence, which could be affected by screening programmes. The study also doesn't address quality issues – it is mainly a counting exercise – and it was not able to include data on personnel, because of the difficulties in defining just who is a radiation oncologist and other roles such as physicists and technicians in a manner that was applicable across countries.

Cost-effectiveness models

In a detailed comment on the *Lancet Oncology* article, colleagues from ESTRO query the accuracy of the data in DIRAC, finding some discrepancies when checked against figures from national radiation oncology societies. But the more substantial issues they raise is that more reliable data now exist on how radiotherapy is used, and that many of the acknowledged shortcomings of the DIRAC analysis – such as epidemiology, staffing and economics – are being addressed in ESTRO's Health Economics in Radiation Oncology (HERO) project.

"We want to show what would be the cost of installing new technology such as IMRT to an optimal level"

Among the team running HERO is Yolande Lievens, head of radiation oncology at Ghent University Hospital, Belgium, who has a background in health economics, and did her PhD on costing and value for money in radiotherapy. That study focused on her own (previous) hospital, comparing it with another in the Netherlands to see whether the methodology she had developed was translatable to other centres.

Lievens says that a first step in Belgium, as in other countries, has been defining what the real costs of providing radiotherapy are, so that the appropriate reimbursement can be made and planned for. "But now, as with the drugs side, authorities are also asking what the cost-effectiveness is – with radiotherapy evolving very quickly we have to provide information on the value for money of novel treatments compared with standard ones," she says.

A paper by Lievens and colleagues at University Hospitals Gasthuisberg in Leuven, Belgium, entitled 'The cost of radiotherapy in a decade of technology evolution' (*Radiother Oncol* 2012, 102:148–153), shows how a costing model can be implemented in a centre as technology advances. In the decade under discussion, costs roughly doubled, with contributing factors being complex treatments and new techniques, such as intensity-modulated and image-guided radiotherapy (IMRT/IGRT).

As Lievens explains, while the aim of the QUARTS study had been to provide a blueprint of equipment and personnel at a national level across Europe, and estimate the need and unmet need for radiotherapy, it had also aimed to carry out an economic analysis along similar lines to the one in her study. However, the project funding ran out. Now, in line with ESTRO's mission to provide more support for national societies, the HERO project has taken on that task. "And there are many countries that still face difficulties in arriving at a correct reimbursement for radiotherapy, hence the importance of providing evidence on the cost-effectiveness of our treatments," she says.

HERO is now revisiting the baseline data on radiotherapy units, this time in more countries, but there is also a formal arrangement with the Collaboration for Cancer Outcomes Research (CCORE), an Australian project that has come up with a more robust gauge of how many patients should be given radiotherapy (the basic figure is 52%, which is at the higher end of the DIRAC estimate). "This will allow us to evaluate needs for radiotherapy based on the incidence of cancer in European countries," says Lievens. "What we want to show first is how much it costs to deliver radiotherapy based on resources as they are now, and in countries where there is under-resourcing what would be the cost of installing new technology such as IMRT to an optimal level. Moreover, we want to present a methodology for cost-effectiveness of radiotherapy at the national level to support the implementation of novel technologies and improve treatments in certain cancers."

The HERO project

There are four main steps in HERO:

- Mapping resources
- Estimating optimal resources to meet needs
- Cost accounting at national level – so far this has mainly been done only at departmental level, as with the paper in Leuven, and
- Building cost-effectiveness or economic evaluation models, again at national level.

"We want to compare countries, and our aim is to develop the costing and cost-effectiveness models in core countries before rolling it out across the whole of Europe," says Lievens. The project also aims to benchmark radiotherapy against other oncology treatments from an economic standpoint.

Some countries, such as the UK, have detailed programmes on radiotherapy needs and costing, derived from data specific to their healthcare systems, says Lievens, but these are not readily translatable to a European model. '*Radiotherapy services in England 2012*', a good report that shows how Britain's NHS is approaching radiotherapy, notes that substantial new capacity is still needed. In addition to setting out national targets, there is a model called Malthus for simulating radiotherapy demand at local level, which also uses CCORE. "But most countries are not as far advanced," says Lievens, "and we want a methodology that is applicable to all, and especially to those that cannot at present go into such detail on their own."

HERO, she adds, is nearing the end of the information gathering stage, surveying not only the number and type of equipment and personnel, but also cancer incidence and the proportion of patients treated with radiotherapy, and details of existing national planning guidelines and reimbursement systems, in each country.

The data collection is a challenge – even in a small country such as Belgium, national data on equipment and personnel were not available. "If we did not have these data in Belgium, you can imagine that in countries such as Germany and Italy, where there are many small private centres, it is even harder to collect the details. In each country our first task has been to find contacts who can and are willing to collect the data – and that is not easy. Take Belgium: at the time of the first data collection there were three radiotherapy societies. Two societies have merged since and all have changed presidents – so who is the right contact?"

ESTRO is employing a data analyst to check information, which should be finished in 2013. The needs analysis and cost calculations are also underway, while the work on cost-effectiveness will not start until 2014. The models, she says, aim to cover the changing complexity of treatments and do 'what if?' analysis of, for example, the cost and cost-effectiveness of introducing IMRT across a country, or the impact of starting a screening programme for breast cancer on the uptake of radiotherapy. "We hope that once the national radiotherapy societies see the advantages of HERO, we will be able to collaborate and collect data on a continuous basis," she adds.

Countries need support to make the case not only for more facilities, but also training programmes. "And although lobbying is not part of the project we hope that by making the case for radiotherapy we will help bring it to wider attention in the public mind, as it is often not presented in a positive way – just when things go wrong or it is deemed unaffordable."

Julian Malicki, director of the Greater Poland Cancer Centre in Poznan, has been involved with both QUARTS and HERO, and says benchmarks are particularly needed in countries such as his, where there is a shortfall of radiotherapy (the DIRAC study estimates 45% of the needs in Poland are unmet). "We did have a national cancer plan in 2005, under which the government allocated more resources to radiotherapy, but it is a 10-year programme that is nearing its end, and some say enough has been given to radiotherapy and cancer, and that other disciplines need more money now. Yes, the gap is narrower now than it was, which is why we need better data that projects like HERO will provide to convince the government to continue with investments in cancer."

The province of Greater Poland has 3.5 million people served by two cancer institutes – one public, which is Malicki's centre with eight machines, and also a private facility. Malicki says his centre is building two satellite units in cities up to 100 km from Poznan. "It has been very important to use data to justify these needs to our regional government," he says. Cancer incidence does differ among countries, he adds, but not significantly, "and the best way to convince decision makers is to show them what a European optimal level of provision looks like. We need more investment not just to speed up infrastructure but also the number of specialists – in my medical university we have problems recruiting students who want to specialise in radiotherapy. HERO will also help to show what personnel we will need in the future."

In Poland, he says, the national head of radiotherapy collects data on resources, but other data, such as on distribution of new cases of breast and prostate cancers, are less available at present. "We have made our submission to HERO, but the data do vary in accuracy. The cost-effectiveness model will be the most important for us, because we need to come to conclusions about how much we need for radiotherapy care."

This practical assistance in gauging the adequacy of national radiotherapy capacity and building a strong cost-effectiveness case for investment where appropriate will doubtless be welcome throughout Europe's radiotherapy community. Greater coordination between the IAEA, which produces the DIRAC directory of radiotherapy at a global level, and ESTRO's HERO project could lead to less duplication of effort in Europe, and potentially open the way for other parts of the world to benefit from the HERO methodology and experience. ■

"The best way to convince decision makers is to show them what a European optimal level of provision looks like"

New paradigms to explain metastasis

Understanding what drives cancer cells to break loose, travel around the body and seed new tumours – and how to inhibit this process – will be key to developing effective new therapies. A leading researcher presents an overview of what is known and what remains to be discovered.

Metastasis – the spread of cancer cells to distant organs – is one of the conditions that I primarily take care of as a clinician caring for women with breast cancer. Despite recent developments and new treatments, metastasis remains the leading cause of death from breast cancer, and five-year relative survival rates are significantly lower in patients with distant metastasis. As for other solid cancers, metastasis continues to drive mortality, motivating clinicians to figure out new ways to think about metastasis and improve survival for our patients.

Traditional views of metastasis

Historically, one of the ways we have thought about metastasis, certainly in breast cancer, is that a primary tumour develops and metastasis happens in a linear fashion. It is rather like stops on a train track that are going in one direction, whereby a woman develops a primary breast tumour and cells are shed from the tumour and spread in an anatomical fashion to

European School of Oncology e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the chance to discuss a range of cutting-edge issues with leading European experts. One of these is selected for publication in each issue of *Cancer World*.

In this issue Elizabeth Comen, of the Memorial Sloan-Kettering Cancer Center in New York, describes pioneering research and new paradigms that are improving understanding of the biological mechanisms of metastasis.

Daniel Helbling, from the Gastrointestinal Tumour Center in Zurich, Switzerland, poses questions arising during the e-grandround live presentation.

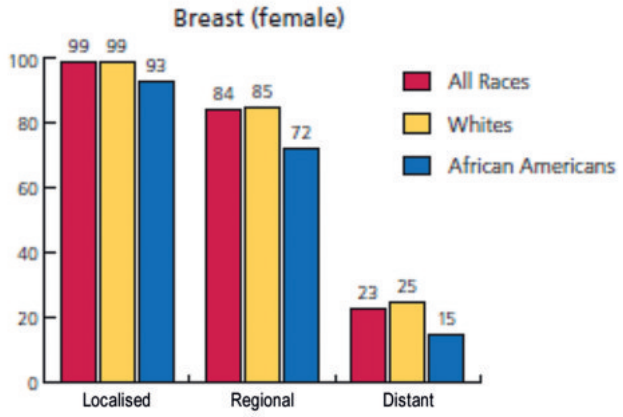
Edited by Susan Mayor.

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

adjacent lymph nodes. After that point, if a woman's disease goes unchecked, she may develop disease that spreads to distant sites such as the brain, the lung or the bone. And once disease has spread to distant sites, we know that although it is potentially treatable it is certainly not curable.

This idea of the anatomical spread of the cancer, where it moves in a unidirectional fashion from the primary site to distant sites, drove our thinking about breast cancer for almost a century. It was the rationale behind radical mastectomy that for almost a hundred years was the only surgical way to manage breast cancer. The idea was to remove the primary tumour and, in order to cure the woman, to remove any of the adjacent structures that the cancer would naturally progress to – the breast in its entirety, the underlying tissue, the muscle and bone in some instances, and the axillary lymph nodes. This was the rationale behind extensive axillary node dissections, with the accompanying morbidity and upper extremity lymphoedema that many women experienced.

FIVE-YEAR SURVIVAL RATES IN BREAST CANCER (%)

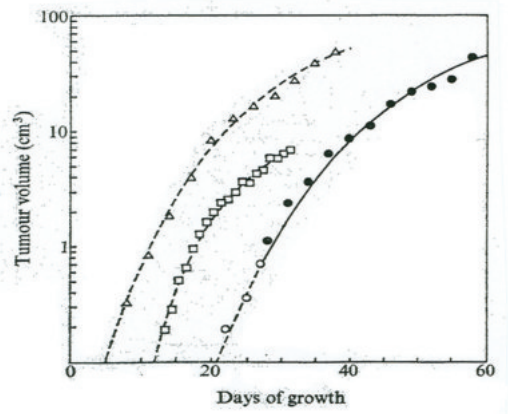


Distant metastatic spread is the leading cause of death

Source: American Cancer Society (2012) www.cancer.org

The conundrum is that, even with radical mastectomies, not all women are cured. Similarly, some women develop metastatic disease even with no lymph node involvement or after having an incredibly small primary tumour. And some women have extensive metastatic disease but no lymph node involvement and we can't even find the breast primary in some patients, although biopsies of distant sites confirm they have breast cancer.

GOMPERTZIAN GROWTH



All solid tumours start with a fast growth rate but, over time, larger tumours grow more slowly

Source: L Norton et al. (1976) *Nature* 264:542–545
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Seed soil hypothesis

This led to the thought that perhaps breast cancer spreads in a multidirectional fashion rather than unidirectionally. This 'seed soil' hypothesis envisages cancer as a seed that travels throughout the whole body, with the environment (or 'soil') as important to the spread of the seed as the properties of the seed itself. Examining breast cancer within this context is critical to understanding how breast cancer cells can spread from their primary site, where they have everything they need, go into the circulation and somehow find themselves in distant metastatic sites and thrive in some women but die in others.

Gompertzian growth

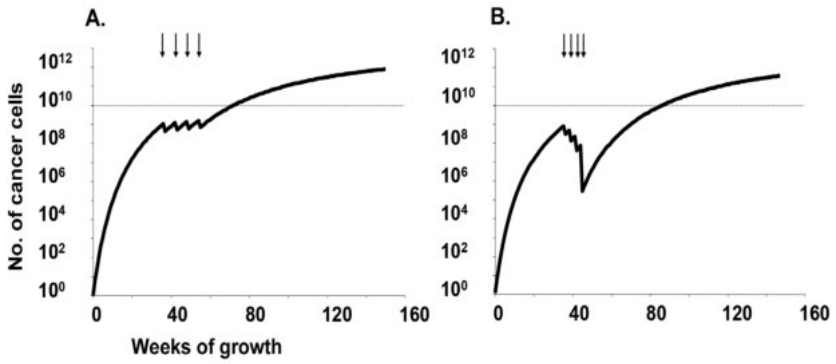
Early in his career Larry Norton showed, using very simple and elegant experiments, that cancers grow in what is called a Gompertzian fashion.

Benjamin Gompertz was an 18th century mathematician best known for his laws of mortality showing that populations grow very quickly during early stages of development and then plateau over time.

Cancers grow in a similar fashion. Each of the lines in the figure *left* traces the growth of different cancers. This growth pattern applies to all solid tumours – they start with a fast growth rate when they are small but, over time, larger tumours grow more slowly.

Gompertzian growth curves helped us understand tumour growth and revolutionised how we treat women with breast cancer in the adjuvant

THE NORTON–SIMON HYPOTHESIS



The hypothesis that the rate of regression is proportional to the rate of growth provided the rationale for dose-dense regimens that use shorter time intervals between chemotherapy doses

Source: L Norton et al. (2005) *The Oncologist* 10:370–381

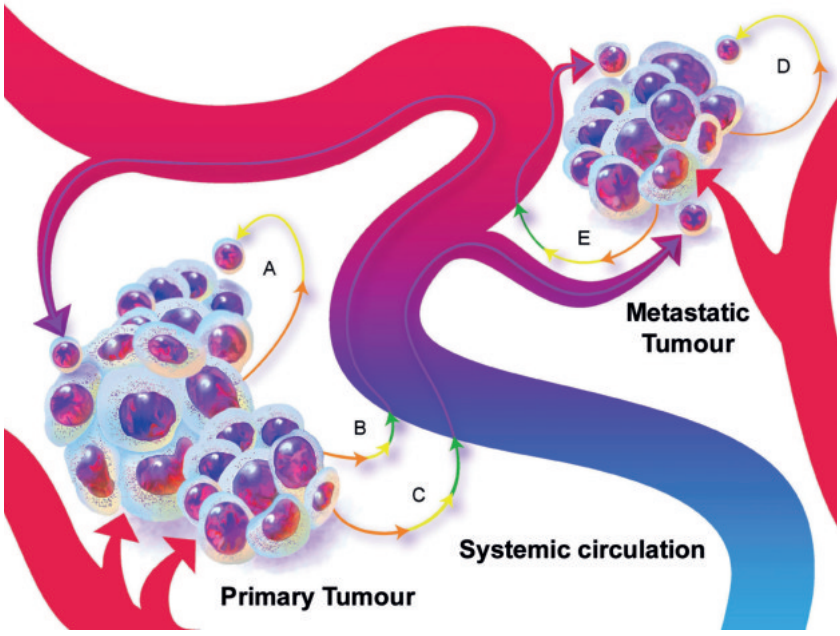
Gompertzian growth curves in primary cancer growth

Work by Norton and Massagué at Sloan-Kettering Memorial Cancer Center, distinguishing between primary tumour growth and metastasis, led to the hypothesis of self-seeding. Mathematical models, observations in patients and laboratory models showed that cancer cells are peripatetic, moving in a multidirectional fashion, seeding not only regional sites but also distant sites and, most importantly, the original site – the primary tumour (see below). Cancers do not grow just by cell division. If they were growing by cell division alone then they would grow in an exponential fashion, but we

setting – that is after they've had surgery to remove their primary breast tumour, and when we have a window to try to cure them of their disease.

Norton and colleagues showed with the Norton–Simon hypothesis that the rate of regression of tumours is proportional to the rate of growth. So, ideally, you want to catch cancers at a shorter interval, hitting them with chemotherapy at shorter intervals so as to decrease the interval in which they can regrow. The impact of treating at shorter intervals is demonstrated in the figure above, showing chemotherapy given every three weeks in the left graph and every two weeks on the right, in what's called a dose-dense fashion. Cancer has less chance to regrow in a shorter time interval, and continuing to give chemo in this fashion over time decreases the growth rate of the cancer and the overall tumour burden. In breast cancer this rationale led to dose-dense chemotherapy, which, in turn, significantly improved overall survival.

THE SELF-SEEDING MODEL OF EPITHELIAL CANCER



Cancer cells move in many directions, seeding multiple sites and even re-seeding the primary

Source: L Norton, J Massagué. (2006) *Nature Medicine* 12: 875–878. Reprinted with permission from Macmillan Publishers Ltd

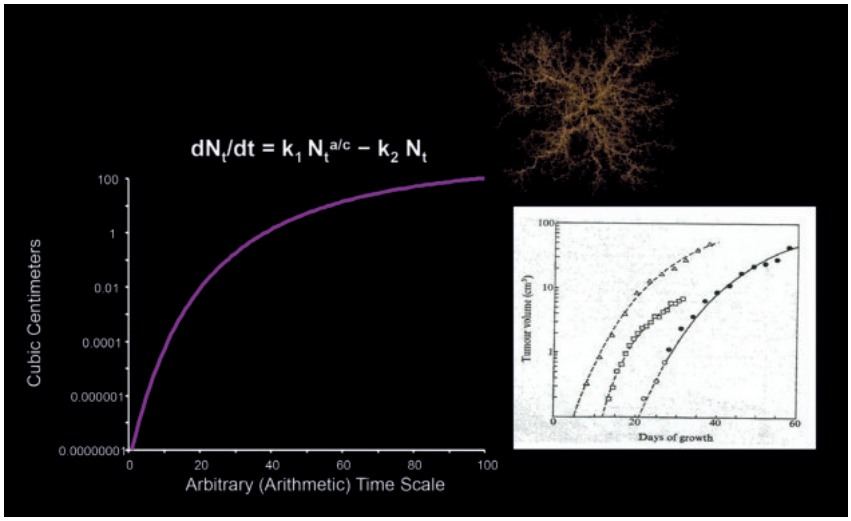
know from the Gompertzian growth curves that the growth of the cancers eventually plateaus, at least at the primary tumour site.

Self-seeding can take place along multidirectional paths. In pathway A, shown in the figure on p39, a cancer cell leaves the primary site and may travel only a short distant before returning to the primary site. The cell returns back home because that's where its resources are and the soil where it started to grow. The cancer cell could also take pathway B, where the cell dislodges and travels into the blood system before coming back to the primary tumour. Alternatively, a cancer cell leaves the primary tumour and goes to a distant site. A cancer cell can also self-seed among distant metastatic sites. These multiple different processes remind us that the cancer spread is not simply a linear process and that the body is a dynamic system in which cancer cells can move and travel.

The self-seeding model essentially explains the Gompertzian growth of a primary tumour and growth at different sites (*Nature Rev Clin Oncol* 2011, 8:369–377; see below). The equation explains that the growth rate of a primary cancer is a function of the ratio between the cancer's surface area and its volume. The growth rate decreases as the cancer gets larger because the surface area is not growing as fast as the volume. A larger tumour has a lower surface-to-volume ratio and a slower growth rate. This is the next step in the hypothesis, thinking about cancer not simply as one mass that is growing from the inside out but rather a mass that is growing from the inside out but also from the outside in. So the concept of the surface changes – it's not simply one solid mass but a conglomerate of masses. If we begin to think about cancer and self-seeding as a topographical process where the concepts of inside and outside are different, this really changes the way we perceive primary cancer growth.

Proof of self-seeding by circulating cancer cells has been demonstrated in a mouse model, injecting donor cancer cells labelled with red fluorescent dye at one site in the mammary fat pad and recipient tumour labelled with green dye at another site. Over time, the fluorescence is an amalgam of red and green, proving self-seeding by circulating cancer cells (*Cell* 2009, 139:1315–26).

SELF-SEEDING EXPLAINS GOMPERTZIAN GROWTH



Thirty-five years after *Nature* published Norton's finding that solid primary tumours grow in a Gompertzian fashion, Comen, Norton and Massagué showed that this growth rate can be explained as a function of the ratio between the cancer's surface area and its volume. The growth rate decreases as the cancer gets larger because the surface area, which provides the bed for self-seeding, is not growing as fast as the volume

Source: E Comen, L Norton and J Massagué. (2011) *Nature Rev Clin Oncol* 8:369–377

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Question: *Coming back to Gompertzian growth, this is probably well proven by experimental models, also by observation. However, in clinical situations I sometimes see patients who have a slow growing tumour at the beginning but then growth suddenly explodes. So is the model sometimes not true?*

Answer: *I think the model refers to patients who have not had any treatment. There are certainly instances where cancer cells can acquire new mutations that make the disease explosive, where they're not only self-seeding going back to the tumour but they're exploding in metastatic sites. But at some point even explosive growth plateaus or, as often happens in these cases, the disease is no longer compatible with life.*

Question: *Regarding the phenomenon that cancer cells travel all the time, constantly coming and going: is this really a common phenomenon? Does it happen all the time or does it just affect a small number of patients? When you imagine cancer, do you think of it as a hive of bees, always moving about?*

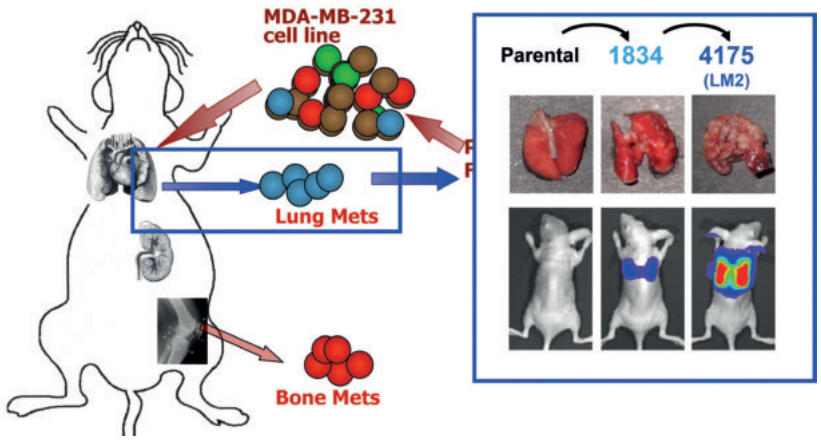
Answer: *No. I think that there are some cancers that just stay where they are, but there are other cancers that have a tremendous ability – whether by the stem cells they have or other mutations they acquire – to move in a multidirectional fashion. What makes them able to do this is not the genes associated with mitosis and cell division but those that are associated with escaping the blood stream or migration.*

Differentiating between primary tumour growth and metastasis

A series of elegant experiments took the pleural fluid from a breast cancer patient containing an amalgam of cells and introduced the cell line (MDA-MB-231) into mouse models, which were then grown into subsequent lines of mice. Results showed you could breed mice to have particular sub-clones of metastatic colonies that were either lung specific or bone specific. The figure above shows the parental cell line does not really do much when injected into another mouse. But you can sequentially breed these mice to have either 1834 cell lines or 4175 (otherwise known as LM2) cell lines, which are highly specific for lung metastasis. Similarly, shown in the red circles, you can have cell lines that have an affinity for spreading to the bone.

This tells us that a primary tumour is quite heterogeneous, as are metastatic colonies. What allows cells to grow in different sites is not simply a process of cell division but sub-colonies can have unique gene signatures that are associated with particular metastatic sites, so the seeding that occurs can be a function of specific characteristics of sub-colonies of cells that are in one primary tumour. Different seeds can have different affinities for different sites in the body.

IN VIVO SELECTION TO IDENTIFY METASTASIS MEDIATORS



Different seeds can have different affinities for different sites in the body, as has been shown by studies that bred mice to have particular sub-clones of metastatic colonies that are either lung specific or bone specific

Source: IJ Fidler. (1973) *Nature* 242:148–149, reprinted with permission from Macmillan Publishers Ltd; Y Kang et al. (2003) *Cancer Cell* 3:537–549, reprinted with permission from Elsevier; AJ Minn et al (2005) *Nature* 436, 518–524, reprinted with permission from Macmillan Publishers Ltd

Question: *During an operation can cancer cells go on the loose, and can each of them then self-seed wherever they land?*

Answer: *I wish my surgical colleagues were here to answer that question. This has been debated in the literature. I think some people worry that when you do different biopsies you may be shedding some cancer cells. To my understanding this has not been borne out in the literature; however, there are probably instances when there is some shearing of the cancer cells, and these may go into the bloodstream. One of the things that some of my colleagues are trying to do is to cryoablate cancer cells before they operate on them, not only to introduce some sort of necrotic process, but also to release some of the antigens associated with the cancer and in turn, perhaps, motivate the immune system to act as a surveillance against some of those cancer cells. There are a number of studies trying to figure out how we best deal with the primary tumour to improve survival rate.*

The figure overleaf summarises the different patterns of breast cancer growth and spread. Pathway A shows a primary cancer with some dysplasia or potentially rapid growth where the cancer is growing from the inside out but also seeding itself. Some of the cancer cells may progress to the lymph nodes (B) or out into the bloodstream and then come back

to the point of origin (C), forming organ-of-origin metastases. D shows how cancer cells can spread to distant metastases from the primary. And E shows that distant metastases can go from organ to organ.

F illustrates the idea that cancer cells can spread very early at the time of diagnosis and remain latent for years. In breast cancer there are patients (often oestrogen-receptor positive) who were diagnosed 20 years ago and they think they've been cured, but 25 years on they come in with back pain and have developed explosive bone metastases. I'm really interested in the markers of this latency. How is it that cancer can spread at the time of diagnosis and remain dormant for so many years before reawakening? Some of my colleagues have looked at Src signalling as an important marker for bone metastatic latency and other colleagues are looking at what makes it explosive and also what protects the body from developing metastatic disease.

G shows spread from metastases to metastases. In patients with simultaneous neoplasms of different types, metastases from one type to the other have long been documented (*J Neurosurg* 1983, 774–777; *Urology* 1987, 30:35–38).

Finding new solutions to cancer

How does the self-seeding hypothesis help us find new solutions to cancer? Showing that a drug can shrink a primary tumour doesn't necessarily tell you whether the drug has the capacity to reduce seeding. We need to separate treatments that are anti-mitotic, which focus only on preventing cell division, and those that are more focused on anti-seeding properties, with anti-metastatic activity – looking at what gives a tumour its mobility as well as what makes it grow. This will reframe how we think about cancer and, in turn, offer new therapeutic strategies. And it's not just the seed, but also the soil or the microenvironment around cancers that is incredibly important. What is it about that microenvironment that allows the cancer cells to grow?

Question: *What parameter do you have to measure for anti-seeding therapies? Is there any clue about what you measure to see if a therapy is really anti-seeding?*

Answer: *The problem is trying to develop models we can use in the lab. The obvious answer would be to see if an agent works in patients, but we don't do that right away. We always start with models in the laboratory in which we can study seeding properties and not just shrinking the primary tumour.*

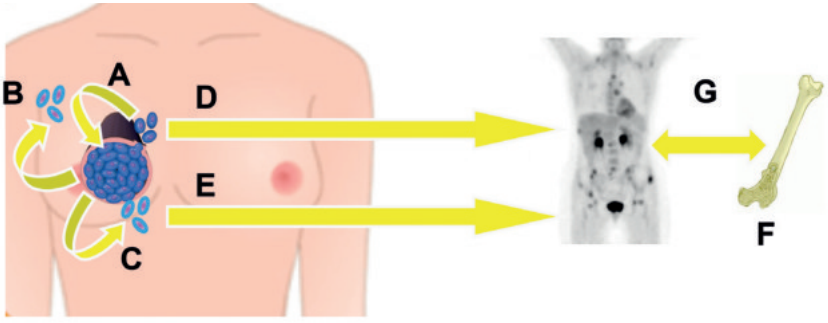
There are a number of different molecules that we believe are associated with seeding, and we are trying to study these in the laboratory to see if we can develop models that are able to show seeding tendencies. Massagué's laboratory has developed mouse models with cell lines that are lung metastatic or bone metastatic that we can use to develop drugs to decrease bone metastasis or lung metastasis.

Interplay between oncology and immunology

There is an interplay where the seed interacts with the soil, and I am interested in how the immune system plays a role in either promoting or inhibiting metastasis. In particular, I am looking at how neutrophils can help promote primary tumour growth in some cases, while in others they can decrease metastatic seeding.

An example in a mouse model, also shown in patients, of how the microenvironment can play a key role in seeding is the finding that a subset of neutrophils decreases lung metastasis. Control mice injected with breast cancer cells through the

GROWTH AND SPREAD OF BREAST CANCER



Breast cancers grow and spread in many different ways.
A – Dysplasia and rapid growth; B – Nodal metastases; C – Organ-of-origin metastases;
D – Distant metastases from primary; E – Distant metastases from organ;
F – Latency (bone=Src signalling); G – Metastases from metastases

Source: E Comen, L Norton, J Massagué. (2011) *Nature Rev Clin Oncol* 8:369–377

tail vein developed lung metastases. We took out circulating neutrophils from a similar population of mice, with lung metastases and primary tumours, and found these circulating neutrophils have cytotoxic properties to cancer cells. We gave these neutrophils to mice injected with cancer cells that we would expect to develop lung metastasis and found a reduction in the burden of lung metastases (*Cancer Cell* 2011, 20:300–314).

Was this just a function of the neutrophils, so the neutrophils don't need to be in contact with a cancer in order to reduce seeding? We did the same experiment with G-CSF-stimulated neutrophils that had had not been primed by having previous contact with cancer cells, and found they had no effect in reducing metastatic burden.

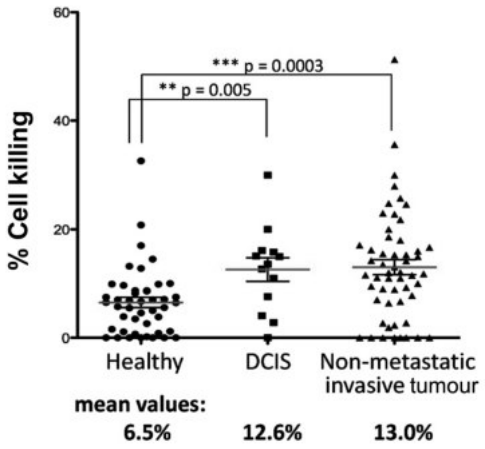
But what about patients? We took blood from healthy women who were accompanying breast cancer patients to clinic visits and compared it with blood from women with ductal carcinoma *in situ* – preinvasive lesions. We also took blood from women newly diagnosed with breast cancer with an intact primary tumour and no evidence of metastatic disease. We spun out their neutrophils and found the neutrophils from breast cancer patients were able to kill twice as many breast cancer cells in a petri dish compared with neutrophils from healthy volunteers.

This tells us that some breast cancer patients have neutrophils able to kill cancer cells, which triggers an incredibly exciting thought process. It tells us that it is not just about the cancer itself, but the immune system is crucial in helping to fight breast cancer and potentially breast cancer seeding. I am interested in the neutrophils themselves and also what may be in the serum to help promote neutrophils to either kill cancer cells or alternatively to promote tumour growth. We are studying what these serum factors are and which factors activate neutrophils to kill breast cancer cells as opposed to helping them grow.

Summing up

Redefining the problem of cancer spread requires understanding the flow of metastasis as not simply a result of linear anatomy, but also as a dynamic, multidirectional process. Primary growth may be not only a process of cell division but potentially also self-seeding. Laboratory and clinical evidence suggests that metastasis happens not only in a linear fashion but also by distant and self-seeding of both the primary and metastatic sites. Metastasis may be a function of specific signatures within the heterogeneous cell population of a primary tumour. Prognosis is a consequence of the inherent biology of a cancer, which may not always be reflected in the number of lymph nodes involved or the size of the tumour.

NEUTROPHIL CYTOTOXICITY IN BREAST CANCER PATIENTS



In vitro **studies show that neutrophils from breast cancer patients can kill around twice as many breast cancer cells in a petri dish compared to neutrophils from healthy volunteers**

Source: E Comen (2013), unpublished data

We need to continue to understand the biology of the cancer cells that we're studying, not just as a conglomerate mass, but whether they have aggressive or non-aggressive properties.

To develop new therapies we need to remodel the way we think about treating breast cancer and focus not just on cell division but also understanding the seeding processes and the microenvironment. ■

Take home points

- Cancer spread is a dynamic multidirectional process.
- Decrease in primary tumour growth has limitations as a clinical trial endpoint.
- Drug development needs to differentiate between anti-mitotic and anti-seeding.
- Manipulating the tumour microenvironment, including the immune system and blood vessel growth, has a role to play in anti-cancer therapies.

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nature REVIEWS CLINICAL ONCOLOGY

Secobarbital in Seattle – why lose sleep?

HARVEY MAX CHOCHINOV

The Seattle Cancer Care Alliance has added physician-assisted suicide to its host of services for patients within the final six months of life. According to a recent report published in the *New England Journal of Medicine*, the programme has been well received by patients and clinicians alike. So, why lose sleep?

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About two years ago, the Seattle Cancer Care Alliance (SCCA) added physician-assisted suicide to their list of offerings for terminally ill patients thought to be within six months of death. A recent publication in the *New England Journal of Medicine*[1] describes how this service, sanctioned under the Washington Death with Dignity Act, has turned out. Although the report includes all the expected metrics – how many people inquired into the Death with Dignity Program, how many received a lethal prescription of secobarbital, how many died as a result of said prescription – the authors' take-home message is that the programme has been well accepted by patients and clinicians, and that the business of medicine at SCCA goes on as usual. So, why lose sleep?

According to Greek mythology, a Chimera was a monstrous fire-breathing creature, usually depicted as a lion, with the head of a goat arising from its back and a tail that ended in a snake's head. Describing such a creature depends completely on where one stands; based on their vantage point, observers might conceivably recount accurate and yet entirely contradictory images. Clearly, the issue of physician-assisted suicide and euthanasia is a modern day Chimera, and it remains amongst the most polarising and contentious issues in all of medicine. Legions of opponents and proponents have waged battle, armed with powerful and seemingly convincing arguments: autonomy, the sanctity of life, the right to die, the slippery slope, the imperative of palliative care, the integrity of medicine as we know it and, lest we forget, dignity. And yet, we seem no closer to resolving how to tame this beast; as my daughter, who studies medieval literature, tells me: "slaying dragons is a tricky business" (LJ Chochinov, personal communication).

It seems futile to rehash all the same arguments, and hubris to think that one more voice, on either side of the political/legal/ethical/clinical fence, could make any real difference. Although the report[1] suggests that there is no need to lose sleep, I find myself unable to rest easy. For instance, we are told that of 200 surveyed SCCA physicians, 29 respondents identified themselves as willing to consult and prescribe for the Death with Dignity Program. Aside from their willingness to be involved with the programme, nothing is said about their expertise in attending to the needs of dying patients. Given that a desire for

death and requests for assisted dying are usually driven by psychosocial and existential considerations,[2,3] it is important to know what level of expertise these physicians have in those matters. Prior studies on healthcare provider willingness to offer assisted suicide demonstrate an association with various personal factors, including concerns about analgesic toxicity, diminished empathy and lesser knowledge of symptom management; in fact, it would seem that doctors who have least contact with patients with a terminal disease are most likely to support legalisation of assisted suicide, while those with the most experience are oppositely inclined.[4–6]

The Death with Dignity Program describes a prominent role for designated social worker patient advocates.[1] Advocacy consists of confirming that a terminal prognosis has been documented, arranging for a prescribing physician, documentation of the patient's wish for physician-assisted dying, verifying that the patient is a Washington resident and, most critical, the completion of a psychosocial assessment – that is, evaluating patients for depression and decision-making capacity. Although the report is silent on the characteristics of these social workers,[1] prior studies examining the role of mental health professionals in hastened death decisions are telling. A study of psychiatrists in Oregon found that those opposed to assisted suicide were more likely to work with the patient to prevent the suicide, whereas those who supported it were more likely to either take no further action or support the patient in obtaining a lethal prescription.[7] The authors conclude that, "[psychiatrists'] moral beliefs influence how they might evaluate a patient requesting assisted suicide". Only 6% of psychiatrists were very confident that they could adequately assess whether a psychiatric disorder was impairing the judgement of a patient requesting assisted suicide within a single session; just over half felt very confident that they could do so within the context of a long-term relationship.[7] What implications does this have for healthcare providers and consultants who are neither mental health experts, nor necessarily know patients for any extended period of time?

Loggers et al.[1] indicate that no one given a lethal prescription required a mental health evaluation for depression or decisional incapacity; in fact, Death with Dignity participants were infrequently referred to the pain or palliative care services. Why might that be? The authors report that it was because of an absence of symptoms at the time of the request to be part of the programme. It would seem then, that symptoms indicative of suffering, such as losing autonomy, loss of dignity, feeling a burden to others (all prominent amongst the beneficiaries of the Death with Dignity Program), are not on the therapeutic radar, or perhaps deemed beyond the purview or reach of medicine.

'Death with dignity' has become a global euphemism for physician-assisted suicide and euthanasia. That these measures are so universally affiliated with the language of dignity is surely an indictment of the culture of medicine, which largely ignores death and tends to abandon patients when cure is no longer viable. This culture of medicine often fails to deliver adequate relief from pain and distress associated with terminal illness, despite there being effective means to do so (it is worse for dying children than adults; worse for the frail elderly and cognitively impaired; worse for people who are poor, members of ethnic minorities or the disabled; worse for people with non-cancer-related fatal illnesses; and worse for people living in rural or remote regions).[8] When lethal prescriptions and fatal injections are hailed as 'death with dignity', it underscores how few expectations patients have of medicine, and its ability to offer effective, humane alternatives.

Dignity-conserving palliative care requires thoughtful attention to patients' physical, psychological, existential and spiritual dimensions of suffering.[9] It requires that personhood not be overshadowed by patienthood. When our research group published a dignity-conserving approach to end-of-life care,[10] Faye Girth, the executive director of the Hemlock Society USA (which was a national right-to-die organisation) conceded "if most individuals with terminal illness were treated this way, the incentive to end their lives would be greatly reduced".[10] To be clear, palliative care should no more be seen as the perfect foil to suffering, than medicine should be pitched as the perfect foil to death. There will always be a tiny minority of patients who, in spite of the best care possible, will want to control the timing and circumstances of their death; and will want the law of the land changed so as to entitle them to have their physicians help them do so. One thing is for certain – this Chimera will not be easily slain. ■

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

newsround

Selected reports edited by Janet Fricker

Study evaluates specificity and sensitivity of lung cancer screening

■ New England Journal of Medicine

The latest data to be published from the US National Lung Screening Trial (NLST) documents exact differences between screening with low-dose computed tomography (LDCT) and chest X-ray (CXR), providing the first thorough evaluation of risks and outcomes associated with each method.

Lung cancer represents the largest contributor to cancer mortality, with experts trying for many years to determine optimal ways to decrease death rates through more accurate and effective screening. NLST is a large-scale, longitudinal clinical trial that, between August 2002 and April 2004, randomised more than 53,400 study participants from 33 centres equally to annual screening for three years with either LDCT (n=26,722) or standard CXR (n=26,732) to evaluate whether lung cancer screening saves lives. To be eligible for the study, funded by the US National Cancer Institute, subjects needed to be asymptomatic, aged between 55 and 74 years, to have a history of at least '30 pack years' of smoking, and either to be a current smoker or to have smoked within the previous 15 years. An earlier publication from the group found that LDCT in comparison to CXR produced a relative reduction in mortality from lung cancer of 20% (95%CI 6.8–26.7, P=0.004). The current publication, describing the results of the first round of screening (first of three) and diagnostic evaluations initiated on the basis of positive findings at the screening visit, was intended to evaluate whether the reduction in mortality achieved through LDCT is worth the potential increase in morbidity.

Results show that a total of 7191 participants (27.3%) in the LDCT group and 2387 (9.2%) in the CXR group had positive screening results. In the LDCT group, 6369 participants (90.4%) had at least one follow-up diagnostic procedure compared to 2176 participants (92.7%) in the CXR group. The diagnostic procedures included imaging in 81.1% of LDCT positive patients compared to 85.6% of CXR patients and surgery in 4.2% of LDCT patients compared to 5.2% of CXR group patients.

Further results showed that stage 1 lung cancer was diagnosed in 158 LDCT participants versus 70 CXR participants and stage IIB to IV lung cancer in 120 LDCT participants versus 112 CXR participants. The sensitivity (proportions of positives correctly identified) was 93.8% for the LDCT group versus 73.4% for the CXR group; while the specificity (proportion of negatives correctly identified) was 73.5% for LDCT group versus 91.3% for the CRX group.

"As expected, more positive screening results, more diagnostic procedures, more biopsies and other invasive procedures, and more lung cancers were seen in the low-dose CT group than in the radiography group during the first screening round. In addition, more early-stage lung cancers, but similar numbers of late-stage cancers, were diagnosed in the low-dose CT group," write the authors.

In a separate press release the lead investigator Timothy Church, from the University of Minnesota School of Public Health, commented that the analysis provides clinicians with additional facts to discuss with patients who share similar characteristics as the NLST participants (current or former heavy smokers over the age of 55). "The results also caution against making blanket lung cancer screening recommendations, because each person's trade-off between the risk of having an unnecessary procedure and the fear of dying of lung cancer is uniquely individual," he adds.

■ The National Lung Screening Trial Research Team. Results of initial low dose computed tomographic screening for lung cancer. *NEJM* 23 May 2013, 368: 1980–91

Molecular tumour profiling diagnoses cancer of unknown primary

■ Journal of the National Cancer Institute

Three different approaches for evaluating molecular tumour profiling (MTP) in patients with cancer of unknown primary (CUP) find that the diagnostic accuracy ranges between 74% and 77%, reports a US study.

Approximately 20% of patients present with a tumour identified in metastatic sites. While for the majority of cases, a clinical history, physical examination, laboratory tests and histologic assessments disclose the primary site, enabling site-directed chemotherapy, in around 4% of cancer diagnoses, primary sites elude determination.

MTP offers the potential to provide a powerful diagnostic tool for identifying the

tissue of origin in patients with CUP. The clinical value of MTP, however, has been difficult to determine, because in most patients the anatomic primary site is never identified. Verification of assay results at autopsy have not proved feasible.

In the current study, Anthony Greco and colleagues, from the Sarah Cannon Cancer Center, in Nashville, Tennessee, set out to estimate the accuracy of the MTP assay in determining the tissue of origin diagnosis. Between March 2008 and January 2010, the investigators undertook a retrospective review of 171 CUP patients on whom they performed MTP using a 92-gene reverse transcription polymerase chain reaction assay capable of identifying 26 different tumour types. Two separate patient groups were considered, one consisting of 151 patients followed prospectively and a second prospective cohort of 24 patients, whose primary sites were identified during clinical follow-up.

Methods used to assess the accuracy of MTP diagnoses in CUP included evaluation of CUP patients who subsequently developed clinically detectable primary sites (latent primary sites); the comparison of specific MTP diagnoses made by immunohistochemistry (IHC) staining methods; and the combination of directed clinical/histological findings and IHC staining obtained after MTP diagnosis was available.

Results show that a single MTP diagnosis could be made in 144 of 149 patients who had adequate tumour specimens to perform the assay. Of the 24 patients who had latent primaries discovered months to years later, 18 were found to have the correct diagnosis by MTP (75%). Diagnoses made by single IHC matched MTP diagnoses in 40 out of 52 patients (77%). The concordance here was particularly noteworthy in colorectal (93%) and breast cancer (100%).

The data, conclude the authors, support the accuracy of MTP assays in CUP diagnosis. "Accurate diagnosis of the tissue of origin will provide important information to better manage all these patients and to guide appropriate therapy in the future as therapy for these tumor types improves," they add.

In an accompanying commentary, Arnold Schwartz and Noam Harpaz, from George Washington University, Washington DC, write that CUPs may be biologically different from their cognate primary tumours. "Consequently identification of primary site of CUPS may only be one component of optimal cancer management," they conclude.

■ FA Greco, W Lennington, D Spigel et al. Molecular profiling diagnosis in unknown primary cancer: accuracy and ability to complement standard pathology. *JNCI* 5 June 2013, 105:782–790

■ A Schwartz and N Harpaz. A primary approach to cancers of unknown primary. *ibid* pp 759–761

Hepatitis B virus reaction only occurs with anthracyclines

■ British Journal of Cancer

Anthracyclines are the only chemotherapy agents that result in reactivation of hepatitis B (HBV), reports a study of 1149 cancer patients from Singapore. Routine screening for hepatitis B, the authors conclude, may not be warranted for low- or moderate-risk chemotherapy regimens.

In 2008 the US Centers for Disease Control and Prevention recommended HBV screening before any form of immunosuppressive therapy including cytotoxics. While HBV reactivation is a recognised complication for patients with solid tumours undergoing cytotoxic therapy, little is known about the exact frequency of HBV reactivation and its associated risk factors. Apart from anthracyclines, the HBV reactivation risks of other commonly used chemotherapy regimens in solid tumours have not been well described.

In the current study, Soo Chin Lee and colleagues, from the National University Cancer Institute, Singapore, set out to compare HBV screening rates as well as reactivation risks in patients receiving several common chemotherapy regimens for solid tumours at a tertiary cancer centre in Singapore. Singapore is a country where HBV is known to be endemic, with a carrier rate of 6% compared to the US carrier rate of 0.3–0.5%.

The medical records of eligible patients who, between January 2007 and December 2010, had received one of six commonly used chemotherapy regimens for solid tumours were reviewed. A total of 1149 patients were identified, including 434 (38%) who received doxorubicin-based regimens, 196 (17%), who received oxaliplatin- or irinotecan-based regimens, 245 (21%) who received carboplatin/gemcitabine and 274 (24%) who received capecitabine chemotherapy. Overall the HBV screening rate was 39%.

Results showed that of the 448 patients who were screened for HBV, 30 (7%) were found to be positive for HBsAg (the hepatitis B surface antigen), and that 28 out of 30 received prophylactic antiviral therapy with no reactivation.

Out of the 1149 patients, three (0.3%) developed HBV reactivation, all of whom were breast cancer patients who originated in the unscreened doxorubicin group (3 out of 214, 1.4%). This was in comparison to 0 out of 487 (0%) of unscreened patients in the other three groups ($P<0.001$). All three patients were admitted for acute hepatitis and had HBV DNA levels $>10^8$ IU/ml at the time of admission.

"Our study showed that the overall clinically apparent HBV reactivation risk in patients with solid tumours treated with chemotherapy is low, even in an endemic region. In particular, none of the 487 unscreened patients who were treated with oxaliplatin- or irinotecan-based chemotherapy, gemcitabine/carboplatin, or single-agent capecitabine developed clinically evident HBV reactivation," write the authors.

While routine HBV screening for patients with solid tumours on high-dose glucocorticoids or high-risk anthracycline-containing regimens is supported, it may not be

necessary for the other lower-risk chemotherapy regimens, even in endemic regions like Singapore. Ideally, they add, these findings should be further evaluated and confirmed by prospective studies.

■ W Ling, P Soe, A Pang et al. Hepatitis B virus reactivation risk varies with different chemotherapy regimens commonly used in solid tumours. *Br J Cancer* 28 May 2013, 108:1931–35

Study defines most effective antibiotic for cancer patients with *Clostridium difficile*

■ Journal of Clinical Oncology

Treatment of *Clostridium difficile* associated diarrhoea (CDAD) is more effective for cancer patients with the antibiotic fidaxomicin than vancomycin.

CDAD, also known as *C difficile* infection (CDI), is an opportunistic infection that occurs mainly in hospitalised patients. A recent study showed that the incidence of CDAD among cancer patients was six-fold higher than in other hospitalised patients, and nine-fold higher for haematopoietic stem cell transplant patients. Depressed immune responses, prolonged hospitalisation, exposure to chemotherapy and repeated antibiotic treatments all contribute to their increased risk.

Over the past three decades the antibiotic treatment choices for CDAD have been metronidazole and vancomycin, but recently fidaxomicin has been approved in the US and Europe for treatment of CDAD. Little is known, however, about the treatment response of cancer patients to these drugs.

In the current *post hoc* analysis Oliver Cornely and colleagues, from University Hospital of Cologne, Germany, explored pooled data from two independent controlled trials that between them had randomly assigned 1105 patients with CDAD to 10 days of oral treatment with fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily). The first study, NCT00314951, was conducted between April 2006 and July 2008 in Canada and the US, and the second study, NCT00468728, between April 2007 and November 2009 in Canada, the US, and Europe.

The investigators defined two subgroups: 183 patients who had cancer (87 in the fidaxomicin arm and 96 in the vancomycin arm) and 922 who did not (452 in the fidaxomicin arm and 470 in the vancomycin arm).

Results showed that the clinical cure rate was 79.2% for patients with cancer compared to 88.6% for patients without cancer ($P<0.001$). The median time to resolution of diarrhoea (TTROD) was 100 hours for patients with cancer versus 55 hours for patients without cancer ($P<0.001$), and furthermore patients with cancer had a 62.3% sustained response rate at 28 days versus 70.9% for patients without cancer ($P=0.020$). Cure rates were similar for patients without cancer treated with fidaxomicin (88.5%) or vancomycin (88.7%, $P=0.913$).

But for cancer patients, fidaxomicin had an 85.1% cure rate compared to a 74% cure rate for vancomycin (OR 2.0, 95%CI 0.95–4.22, $P=0.065$). Furthermore, the median TTROD was 74 hours with fidaxomicin for cancer patients versus 123 hours with vancomycin ($P=0.045$).

"In summary, patients with cancer had significantly lower clinical cure and 28-day post-therapy sustained response rates than patients without cancer, and the differences were greater for patients treated with vancomycin than fidaxomicin," conclude the authors.

"Rapid and sustained resolution of CDAD is particularly important for patients with cancer," they add, "because diarrhea often results in dose reductions or delays of chemotherapy or radiotherapy."

■ O Cornely, M Miller, B Fantin et al. Resolution of *Clostridium difficile*-associated diarrhea in patients with cancer treated with fidaxomicin or vancomycin. *JCO* 1 July 2013, 31:2493–99

Palliative care intervention programmes enable home deaths

■ Lancet Oncology

Introducing a regional intervention programme of palliative care services significantly increased cancer-related home deaths and patient and family assessments of quality of life, a Japanese study has found. The OPTIM (Outreach Palliative Care Trial of Integrated Regional Model) study also found improved communications between healthcare professionals treating terminal patients.

While improvement of palliative care is considered an important public health issue, knowledge around how to best deliver palliative care services remains inadequate.

In the OPTIM study, between April 2008 and March 2011, Tatsuya Morita and colleagues, from Seirei Mikatahara General Hospital, Shizuoka, Japan, implemented a comprehensive programme of interventions for regional palliative care in four regions of Japan. Interventions consisted of four elements: improvement of knowledge and skills, increasing availability of specialised palliative-care services, coordination of community palliative-care resources, and provision of appropriate information about palliative care. The programme did not require any structural or financial changes for implementation. Investigators surveyed patients, bereaved family members, physicians and nurses, both before and after interventions had been introduced. Eligible patients were adults with metastatic or recurrent cancer of the lung, oesophagus, stomach, colon, rectum, pancreas, liver, biliary system, kidney, prostate, bladder, breast, ovary or uterus.

Responses from 859 patients, 1110 bereaved family members, 911 physicians, and 2378 nurses were analysed in the pre-intervention survey, and from 857 patients, 1137 bereaved family members, 706 physicians, and 2236

nurses for the survey after the interventions had been introduced.

The proportion of home deaths increased from 348 out of 5147 (6.76%) before the intervention programme to 581 of 5546 (10.48%) after the intervention programme ($P<0.0001$). Family members of patients who had died at home confirmed that they had wanted to die at home in 194 of 221 cases (87.78%).

Quality of life surveys comparing post-interventions scores with pre-interventions scores showed improvements for both patient-reported quality of life ($P=0.0027$) and family-reported quality of life ($P<0.001$).

After the introduction of interventions, physician-reported and nurse-reported difficulties decreased significantly ($P<0.0001$), with qualitative interviews showing improved communication and cooperation between healthcare professionals because of greater opportunities for interaction at various levels.

"Our study adds important insights about the comprehensive effect of regional palliative care programmes and the crucial value of communication between health-care professionals to improve palliative care at a regional level," write the authors.

The absolute number of home deaths, they add, was still low after the interventions, suggesting that some structural or financial changes are needed in the healthcare system before a further increase in the proportion of home deaths can occur.

In an accompanying commentary, Stein Kaasa, from the Norwegian University of Science and Technology, in Trondheim, Norway, writes, "Recognition of palliative care as an intrinsic part of overall cancer care is as important as improvement of symptom classification and management."

■ T Morita, M Miyashita, A Yamagishi et al. Effects of a programme of interventions on regional comprehensive palliative care for patients with cancer: a mixed methods study. *Lancet Oncol* June 2013, 14:638–646

■ S Kaasa. Integration of general oncology and palliative care. *ibid*, pp 571–572

Pregnancy does not adversely influence breast cancer survival

■ Journal of Clinical Oncology

Women with breast cancer diagnosed during pregnancy showed a similar overall survival to non-pregnant breast cancer patients, a rapid communication abstract has found.

During pregnancy breast cancer is one of the most commonly encountered malignancies, with approximately 0.2–2.6% of all breast cancers occurring in pregnant women. In the first half of the 20th century there was a general belief that breast cancer under the stimulus of pregnancy was especially aggressive and that surgical treatment was pointless and contraindicated. Since then, surgical treatment of breast cancer during pregnancy has become commonplace, and in the last decade, chemotherapeutic treatment during the second and third trimesters has been introduced and deemed not to harm the foetus. However, whether pregnancy itself negatively influences prognosis has remained a subject of debate, and there is still no comprehensive understanding of the interaction between pregnancy and breast cancer carcinogenesis.

In the current study Frédéric Amant and colleagues, from University Hospitals Leuven, Belgium, set out to determine the prognostic impact of pregnancy when breast cancer is diagnosed, and to compare survival between women with breast cancer during pregnancy and patients who were not pregnant. The study combined two international multicentre cohort studies: the German Breast Group and the International Cancer in Pregnancy study. The main analysis was performed using Cox proportional hazards regression of disease-free survival (DFS) and overall survival (OS) on exposure (pregnant or not), adjusting for age, stage, grade, hormone receptor status, human epidermal growth factor 2 status, histology, type of chemotherapy, use of trastuzumab, radiotherapy and hormone therapy. It is the largest cohort study to explore the influence on pregnancy in breast cancer to date, say the authors.

Altogether 447 women with breast cancer in pregnancy were registered, of whom 311 (69.3%) were eligible for the analysis. They were compared with 865 women with breast cancer who were not pregnant. The hazard ratio of pregnancy was 1.34 (95%CI 0.93–1.91; $P=0.14$) for DFS and 1.19 (95%CI, 0.73–1.93; $P=0.51$) for OS. The main Cox model resulted in an average predicted five-year disease-free survival probability of 65% for pregnant patients. According to the model, this would have increased to 71% if these patients had not been pregnant (but all other characteristics were identical). For OS, the average predicted five-year survival probability would have increased from 78% to 81%.

"The observation that patients with BCP [breast cancer in pregnancy] experience survival rates comparable to those of non pregnant patients is important when they are counselled. Breast cancer treatment during pregnancy does not jeopardize maternal prognosis," write the authors.

In an accompanying commentary, Richard Theriault and Jennifer Litton from the University of Texas MD Anderson Cancer Center, Houston, write, "This study provides additional comfort for women and physicians who must care for the pregnant patient with breast cancer. The cancer can be treated, the pregnancy can be maintained, labor and delivery can be successful, and the outcome for mother and neonate can be expected to be favorable."

■ F Amant, G von Minckwitz, S Han et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. *JCO* doi:10.1200/JCO.2012.45.6335

■ R Theriault and J Litton. Pregnancy during or after breast cancer diagnosis: what do we know and what do we need to know? *ibid* doi:10.1200/JCO.2013.49.7347

Refusing treatment

People take treatment decisions on the basis of their personal perspectives as much as the medical pros and cons. Doctors need to be able to deal with this.

MOSHE FRENKEL

In the late 1990s, I was working as a family physician. During that time, I was integrating complementary therapies into routine practice in family medicine, as well as being involved in academic work and teaching family physicians and residents. Even with a very open mind toward complementary therapies, when it came to patients affected by cancer, I strongly advocated that these therapies should not be used as an alternative to conventional treatment, but rather as complementary approaches with a single goal of improving patients' well-being and quality of life.

During my years of consulting cancer patients and families, I noticed an increasing number of patients who declined conventional cancer treatment, a phenomenon that piqued my curiosity but somehow was not acknowledged by my colleagues, other than to mention that they had another "difficult patient". One of these patients was Suzanna. Suzanna, who was born in England and emigrated to Israel in her late teens, was an attractive divorcee in her mid-40s. She had been working as a complementary practitioner for many years. When she entered the room, you could not ignore her presence: she is tall with dark long hair, piercing green eyes, and a smile that warms your heart. But one day in 1997, she found a 3-cm lump in her left breast that extended to the skin. From that moment, her life turned upside down. A quick process of evaluation including mammography, ultrasonography and biopsy confirmed the diagnosis to be infiltrating ductal carcinoma. At that time, assessments of hormone receptor status or other prognostic factors were not available.

At first, like most people, Suzanna was shocked and devastated by the diagnosis. She underwent surgical excision, which confirmed advanced disease (stage IIIB) with six of eight affected axillary glands, and she was advised to begin chemotherapy as soon as possible. She came to me distressed

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TROELS GRAUGAARD/GETTY IMAGES

and ambivalent about undergoing chemotherapy. During our prolonged and charged discussion, she suddenly asked me a question I had never heard from any of my patients. She asked me to look through the medical literature and determine her chances for recovery if she received chemotherapy. With my limited knowledge of oncology at the time, I assumed that the survival rate would be around 80%.

After consulting the literature, however, I was surprised to find that, given her advanced disease stage and the chemotherapeutic agents available at that time, her chances for survival would be only 32%.

When I shared this bad news with her, she didn't seem too upset. In fact, she asked me to do her another favour: to search the medical literature again and see what her chances for survival would be without chemotherapy. With both sadness and conviction, I told her, "You will die." Still, she urged me not to jump to conclusions, but to take a second look.

So, I dove into the research once more. To my surprise, during that time, when the Internet and PubMed were relatively new, finding the answer to her question in the current medical literature was not easy.

Finally, after spending a few hours in the local medical library, I unearthed a relevant article that estimated the survival rate of women with diseases at the same stage who did not receive chemotherapy. It was 26%.

At that point, Suzanna firmly said: "Look, chemotherapy would add only 6% to my survival rate. But I would lose my hair, which is so precious to me, it would affect my social interactions, and I

We must integrate the medical balancing of pros and cons with the patient's personal perspective

would suffer nausea and vomiting. In fact, the oncologist gave me a list of side-effects two pages long! I've decided that I am willing to risk losing the theoretical 6% advantage chemotherapy would give me. Chemo would destroy my quality of life. I am not doing it."

I was taken aback by her cold calculations. I told her she was making a great mistake, and I tried to change her mind. Not even the persistence of her oncologist and repeated calls from various clinic staff convinced Suzanna that she should change her mind. Her oncologist, an experienced physician, was puzzled by her decision and informed her that she had six months to live if she did not follow his treatment recommendations, and if that was her decision, there was no reason for her to continue to see him. Nonetheless, she decided against chemotherapy and began trying a wide variety of alternative and complementary therapies that she heard about from other cancer patients.

Close to 15 years have passed, and this issue of patients refusing conventional therapy still concerns me deeply. What is the actual extent and incidence of this experience? What is the best approach to address this issue? How should we confront the issue of a patient who makes an informed decision to decline therapy that we feel might be beneficial? Should we close the door on the continued care and follow-up of these patients?

Although the refusal of cancer treatment is a serious concern and has been shown to reduce the effectiveness of treatment and decrease survival duration after diagnosis[1,2], the phenomenon itself has been scarcely studied. The number of patients who make this decision is not very well known, but the number appears substantial enough to warrant close attention[3]. Studies have reported rates of less than 1% for patients who refused all conventional treatment[4] and 3–19% for patients who refused chemotherapy partially or completely[5–9].

We tend to think that refusing therapy leads to a poorer quality of life as the disease progresses without treatment. Interestingly, that might not be the case.

A study that evaluated the quality of life of 140 cancer patients who had refused, discontinued, or completed chemotherapy revealed that the quality of life of patients who refused or discontinued chemotherapy was no different than that of patients who completed treatment[10].

In my interactions with patients who seek advice about complementary therapy options, I occasionally meet patients who have actually decided to decline treatment. Some have shared their decision process to refuse treatment, partially or completely, but most have not shared this decision with their treating physician. More commonly, during their search for second or third opinions, patients do not return to any of their original physicians for treatment and are lost to follow-up. Patients are looking for a physician to share their decision with a trusted professional who is willing to listen to their account of their painful journey. When they share their rationale for refusing conventional treatment, they mention multiple reasons, such as fear of adverse side-effects of cancer treatment (particularly chemotherapy), uncertainty about treatment effectiveness, hopelessness, helplessness, loss of control, denial (about their illness), psychiatric disorders, dysfunction in the health care system, and, above all, issues surrounding communication and the patient–physician relationship[4,11–18].

Patients are often aware of the serious side-effects and complications that are likely to accompany conventional therapies, and some have witnessed the ultimate futility of such interventions. They weigh the evidence and often make choices that reflect their underlying values and beliefs rather than rely on medical evidence or advice as the determining factor. Nonetheless, these patients keep their medical appointments and seek reassurance that they will not be

abandoned, that when needed, palliative care services would be available to them, and that they would not die in pain, but with dignity and have some control over the end of their life. In the meantime, they focus on living in the present, keeping to their usual schedules and routines, working, presiding over family gatherings, and seeking support and affirmation from close family and friends[16].

The unique patients who refuse conventional treatment are at times self-directed, confident, and active, and have thought deeply about the meaning of life and cancer and about their cancer treatment options.

It may not always be easy for clinicians to deal with these types of patients as they deviate from the norm and challenge current evidence[3]. Physician response is not always supportive of these decisions that patients make. Although physicians understand that patients have the right to decide about their treatment and recognise the possibility of an in-between phase when treatment effects and outcomes are far less predictable, physicians nevertheless tend to categorise their patients dichotomously: those who can be cured and those for whom a cure is no longer possible[18]. Patients who fall into the former category and refuse conventional treatment are considered "difficult patients" or "noncompliant."

Current evidence suggests that healthcare professionals often feel uncomfortable, troubled, and even distressed when dealing with patients who make decisions that go against medical advice. In such situations, communication between patients and the healthcare team can become strained, impacting on future contact and quality of therapeutic interaction[16]. In a recent qualitative study on women who refuse conventional treatment, and reflect back to their experience, they mention that a better first experience with their physicians might have made a difference in the treatment path they ultimately chose. They said that they would have been more likely to accept conventional treatment earlier had they felt that they had caring physicians who acknowledged their fears, communicated hope, educated them about treatment possibilities, and allowed them time to adjust to their diagnosis and assimilate information before starting treatment[17].

This experience with Suzanna made me aware that the communication between the patient and the physician must integrate the medical balancing of pros and cons of treatment effectiveness with the patient's personal perspective. It seems with the current trend of 'patient-centred care' that there is a need to get a better insight into the role that the patient's view of life, their values, and personal judgements play in the decision-making process. In addition, an approach that uses effective communication with these patients and integrates their values with current medical evidence is needed.

Communication is crucial in establishing trust with patients, gathering information, addressing patient emotions, and assisting patients in decisions about care[19–21]. The quality of communication in cancer care has been shown to affect patient satisfaction, decision making, patient distress and well-being, compliance, and even malpractice litigation[22,23]. Treatment decision making is an ongoing process; thus, patients who initially refuse treatment may later choose to undergo conventional cancer treatment if given the adequate support, information and time necessary to make the decision. Even if patients have declined oncologic care, they may continue to see their primary care providers and family physicians. Patients need to feel that they have not been permanently excluded from the healthcare system even if they make choices that are contrary to the recommendations of their medical team[24].

As to Suzanna, to my initial astonishment, she thrived. In 2007, she published a book with an inspiring title: *Six Months to Live, Ten Years Later*[25]. She became a daily reminder for me that there are exceptional patients, and refusing treatment is only the tip of the iceberg and presents a major challenge that needs to be addressed. ■

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

My World

Clodagh McHugh works as an oncology nurse specialist with patients at every stage of their disease and with all types of cancer. Based at a leading teaching hospital in Dublin, she lectures on oncology nursing and is involved in drawing up safety guidelines relating to oral chemotherapy. She scored the top mark in the learning assessment test at the end of this year's ESO-EONS Masterclass for advanced oncology nurses.

Why I chose to work in cancer

My final placement in a year-long rotation programme after qualifying as a nurse was spent at a haematology/oncology unit. I loved the ethos there, which wholeheartedly embraced the care of the patient and family.

What I love most about my job

It's a privilege to work with people and families who are going through a very difficult, frightening and sometimes vulnerable time in their life. I love the autonomy I have as a clinical nurse specialist, and the diversity of my role, from supporting patients, lecturing, keeping updated on developments and working as part of a very dynamic multidisciplinary team.

The hardest thing about my job

As health professionals, there is so much that is out of our control. We can't make everything better, but we can try to make things easier and more manageable.

What I've learned about myself

Life is for living, and I try to make good use of my time off. I've learned not to take things or people around me for granted.

I'll never forget...

Four weeks spent in Malawi teaching nurses working in cancer. Essentials are in very short supply, which makes it hard for them to do their jobs effectively. But they are very enthusiastic about developing their service, and four nurses have enrolled in an online oncology programme. It was very challenging and overwhelming at times, but an amazing experience.

A high point in my career

Being selected to participate in a six-week clinical trials training programme for cancer nurses at the American NCI and being chosen to participate in the 6th ESO–EONS Masterclass for advanced oncology nurses.

I wish I were better at...

Time management. I find it hard to prioritise non-clinical duties over direct patient care.

What I value most in a colleague

I enjoy working with someone who is dynamic, patient-focused, respectful of colleagues and who can work well in a team but can also use their own initiative. I value people who take pride in their role and aim to improve the service, and importantly people who can share a laugh.

The most significant advance in my specialism in recent years

In nursing, the establishment of the role of clinical nurse specialist in Ireland in 2001, focused on providing specialised care, and contributing to assessing needs and planning, delivering and evaluating care.

My advice to someone entering cancer nursing today would be...

Always focus on the patient and treat them as you would like to be treated. As you develop your career, focus on both your clinical knowledge and clinical experience, as each complements the other. Most importantly, make sure you have a good life/work balance.

What I wish I'd learned at nursing school

I wish more emphasis had been placed on interpersonal skills. Each patient has their own unique background, personality, life experience and coping mechanisms. Communication and interpersonal skills are vital in helping each patient to successfully navigate their individual cancer journey. ■