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The compelling case for integrated palliative care

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Enriqueta Felip
breaking boundaries in lung cancer

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Cancerworld
Shaping the future of cancer care

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Cancer control is (still) a vote winner

KATHY REDMOND EDITOR

EU member states have just kicked off the second 'joint action' on cancer, which is set to run until 2017. The Comprehensive Cancer Control Joint Action (CANCON) will pick up where the recently ended European Partnership for Action Against Cancer (EPAAC) left off. It will cover many of the same areas, but with a greater focus on integrating cancer services at a regional level and on the role of primary and community care – areas traditionally considered to be beyond the scope of European collaboration.

The benefits of working at an EU level to improve cancer control were first convincingly demonstrated by Europe Against Cancer, which ran from 1987 to 2000, with a primary focus on raising awareness as well as screening, data collection and tobacco control. Whether this added value can also be realised in the organisation and delivery of cancer services is a question we address in an article (page 36) that looks at what we have learned from the experience of EPAAC.

The unparalleled level of public health investment in cancer made by the EU over the past 30 years was recently showcased at the EU Summit on Chronic Diseases. Initially this investment arose from a combination of opportunism and serendipity. Europe Against Cancer was the brainchild of Presidents Craxi and Mitterand, of Italy and France, who were looking for ways to show that Europe was more than just a free market, and could deliver on things that mattered to the citizens of Europe – and Mitterand, as we now know, had by chance just been diagnosed with prostate cancer. That early investment was crucial in raising awareness about the social and economic burden of cancer, which then opened the way to several further European initiatives.

EU laws have a significant yet often unacknowledged impact on cancer control and, while member states continue to resist European interference in decisions on healthcare spending, there is a growing recognition of the potential for learning from each other and adopting common strategies that can be adapted as needed, as most recently demonstrated by EPAAC. What's really positive about its successor, CANCON, is the increasing focus on quality improvement. This spans the entire spectrum of cancer control, from prevention through to palliative care, with cancer services – including community care, survivorship and rehabilitation – on the agenda for the first time.

This programme has the potential to address the ongoing and unacceptable disparities in cancer outcomes that still exist between different European countries, and the European cancer community needs to get behind it. European Parliamentary elections will take place in late May, and this gives us all the chance to argue for candidates to continue to give cancer the attention it deserves at an EU level, and to show their electorates that Europe can still deliver on things that matter.

Enriqueta Felip: breaking boundaries in lung cancer

SIMON CROMPTON

Building a lung cancer team that works seamlessly to do the best for each patient was the biggest challenge in Enriqueta Felip's career. Her focus today is on increasing collaboration across Europe, which she sees as key if patients are to benefit quickly from the new opportunities offered by personalised therapies.

It's a clear and crisp morning, but the air outside Vall d'Hebron Hospital overlooking Barcelona is far from fresh. There's the pervasive smell of tobacco smoke outside the red-marbled hospital reception as patients stand around getting their nicotine fix. Around the corner, in less conspicuous places, there are people in white coats doing the same thing.

It's a sight that deeply disturbs Enriqueta Felip, head of the hospital's lung cancer unit. Felip, who has established her unit as one of Europe's most important centres for researching innovative lung cancer therapies, is not a woman given to making statements based on anything but the clearest evidence. And when it comes to smoking, she is unequivocal.

"Around 85% of lung cancer would not exist if it were not for smoking," says Felip, who is Associate Professor of Medicine at Barcelona's Universidad Autónoma. "So yes, it deeply worries me when I see people smoking, especially outside the hospital. As professionals, we have to give out messages to stop tobacco use every day... but it is not easy. It is an addiction."

Those working in lung cancer must, perhaps, have special qualities. Their conviction that things could – should – be different is countered by a deep pragmatism about making the best of things as they are, and a non-judgemental

compassion for their patients. Felip, who is in charge of both management of lung cancer and trials at the hospital, is full of both qualities: there's a job to be done to help people. "I always tell my patients it's not their fault. Give up smoking now, yes, but don't feel guilty."

The last thing her patients need is a guilt-trip. Although advances in the management of non-small-cell lung cancer, which makes up more than eight out of every ten lung cancers, have led to small increases in five-year survival rates across Europe over the past 30 years, the prognosis for most people diagnosed with lung cancer is still poor. Averaged across Europe, only 13% of people survive for five years after diagnosis, according to the EUROCARE-5 study published this year. In most cases the disease is already advanced by the time it is diagnosed. Fully 50% of Felip's patients are diagnosed with stage 4 disease, 30% at stage 3 and only 20% at stages 1 and 2 – so palliative therapy has long been the mainstay of treatment.

But things are beginning to change. Specialist care in Barcelona has taken a major upturn since Felip established the thoracic unit from scratch 20 years ago – a time when there was still debate over whether patients with stage 4 disease should be treated at all.

And thanks to increasing understanding of the molecular biology of the disease, the landscape of lung cancer treatments is changing radically, giving future patients – and those currently included in clinical trials – the prospect of new life-extending options. One of the main reasons that Enriqueta Felip has remained at Vall d'Hebron is that phase I facilities are available that have allowed her to work on the development of the next generation of drugs for lung cancer.

New approaches are desperately needed to improve not only patients' prospects but also the perception of lung cancer within oncology

JORGE NOGUEIRA

"They are having mammographies for breast cancer and that is good, but they are still smoking"

as a specialism where the success rate is pitifully poor and progress depressingly slow. Lung cancer is the commonest form of cancer globally (13% of all cases, according to the International Agency for Research on Cancer), and the main cause of death from cancer (accounting for 1.59 million deaths a year). Even though lung cancer causes more cancer deaths than prostate, breast and colon cancer put together, it struggles in most countries for the attention of politicians, funders and the public, compared to gender-specific cancers. As Felip points out, the economic crisis in countries such as Spain has recently made the fight for funding for translational research even more difficult. "We currently have support, but we need to be sure that this will be maintained, or increased, in the future."

The struggle for profile isn't helped by persisting attitudes that those with lung cancer have only brought the disease on themselves – conveniently overlooking the role of industry in turning them into addicts in the first place.

The alarming fact is that lung cancer is on the rise among women. In the early 1900s, Felip points out, lung cancer was virtually unheard of in women. "But since the 1960s it has progressively reached epidemic proportions, becoming the leading cause of cancer deaths among women in the United States, and the third most common cause of cancer death in women in Europe."

The increase may well be solely because women are smoking more, or it may also be because they are more susceptible to the carcinogens in tobacco smoke – several case control studies have indicated this, though the association is still far from established.

"Women tend to be much more aware of other cancers, such as breast cancer," she says. "They are having mammographies for breast cancer and that is good, but they are still smoking, even though lung cancer is the main reason for cancer-related death in some countries. Around a quarter of the patients I see in my office are women, and this was not the case ten years ago. In 2007, we started a national collaboration to capture the clinical characteristics of women with lung cancer, and we thought it would take eight to nine years to collect enough women, but we did it within five."

Felip has noted another alarming trend: people with lung cancer are getting younger. The average age people receive a lung cancer diagnosis is 65, but Felip is today treating her youngest patient ever, a 25 year old. "I don't have clear data on this, but it is certainly true that nowadays I see younger patients with stage 4 disease – 33, 35, 37 years old is not unusual."

Despite this, and despite her perplexity that smoking is still blithely pursued by so many, Felip refuses to be gloomy.

"I think the scenario is changing," she says. "We have some patients who are living a long time, and clinical trials with very impressive results."

The big game changer in the past decade was the discovery, in 2004, that up to 20% of non-small-cell lung cancers cases harbour mutations in the epidermal growth factor receptor (EGFR) proto-oncogene. Studies have indicated that treating this subgroup of patients with oral tyrosine kinase inhibitors (TKIs) that inhibit EGFR extends their progression-free survival and improves their quality of life – and is more effective than chemotherapy as a first-line treatment. Testing for the mutation makes it possible to identify which patients will particularly benefit from this treatment.

"This has significantly changed treatment," says Felip. But things have moved on further. Research by Felip has revealed the molecular mechanisms by which many people acquire resistance to this treatment, after an initially dramatic response. The presence of an EGFR mutation, designated T790M, is linked with resistance, and Felip is now involved in ongoing clinical trials evaluating T790M-specific inhibitors. "We are seeing very good responses to this."

The other big story in lung cancer was the discovery in 2007 that around 5% of patients with

non-small-cell lung cancer – often never smokers – have a gene inversion on chromosome 2 which results in an oncogene called EML4-ALK or the ALK translocation oncogene. Recent preclinical and first-in-human studies have demonstrated that an oral ALK-inhibiting TKI achieves a response in almost six out of ten patients. A randomised trial in patients with advanced ALK-positive tumours has shown that treatment with an ALK inhibitor significantly extends progression-free survival and improves quality of life when compared to chemotherapy. New ALK inhibitors are now in the pipeline, and new molecular markers are continually being identified, providing potential for more targeted therapies. "It's a very exciting area," says Felip.

GETTY/ULRICH BAUMGARTEN

A disturbing trend. Felip has seen a steady rise in the proportion of women treated at her clinic, and patients are getting younger

That is the present. The future will present more treatment options. Immunotherapy is about to change treatment algorithms for patients with non-small-cell lung cancer, says Felip. Until now, the big idea of using the body's own immune system to attack cancer cells has yielded little of practical value for people with lung cancer. But advances in the understanding of the immune response to tumours – particularly the programmed death (PD) pathways – have led to the development of several new antibody-based treatments.

Recent phase I trials in lung cancer have shown a response in more than two in ten patients who had already undergone previous treatment. What is especially exciting is that the patients who benefit most from immunotherapy are those for whom ALK- or EGFR-inhibiting drugs are unlikely to bring benefits. "Importantly, these drugs are well tolerated and we have seen long-lasting responses," says Felip.

With treatment horizons moving towards individualised molecular approaches, the availability of biomarker testing is now becoming an important priority for people with lung cancer.

"Lung cancer is becoming a paradigm for personalised therapy, and we need to ensure that all lung cancer patients in Europe are tested for EGFR and ALK alterations, and treated accordingly. There are also other biomarkers that we are beginning to understand are important, such as BRAF, HER2, and ROS1."

It's with a view to making the most of these developments in a coordinated way across Europe that Felip has this year accepted the role of programme co-ordinator for lung cancer with the European School of Oncology. She organised the first ever ESO 'Lung Cancer Observatory' at the European Lung Cancer Conference in Geneva this March. Drawing together medical oncologists, surgeons, pathologists, biologists,

"Nowadays I see younger patients with stage 4 disease – 33, 35, 37 years old is not unusual"

"Oncology offered the opportunity not just for research, but to have a relationship with people living with disease"

other health professionals and patients, it effectively set an agenda for the ESO lung cancer programme for the next 12 months.

"We need to push forward with a European programme for lung cancer, so I'm very excited that in forums like this we have the opportunity to share, discuss and work together on the priorities at a European level."

European collaboration is, Felip believes, one of the biggest challenges facing lung cancer. It is already happening to some extent through ESO and the European Thoracic Oncology Platform, but if surgeons, oncologists, pathologists and all those specialising in lung cancer could do more to break their national boundaries, collaborate on trials and share information, important questions would be answered more quickly.

For Felip, there are clear priorities for action. One is finding ways to involve increasing numbers of patients in clinical trials of "these exciting new molecules" in early-phase development. Another is to find ways of integrating the molecular profiling of patients into clinical practice throughout Europe. "In the next decade, lung cancer treatment should change to be the paradigm of personalised therapy; to my mind it is now essential to know whether the patient has EGFR or ALK mutations."

Implementing screening programmes to increase detection of non-small-cell lung cancer at a much earlier stage, when it can still potentially be cured by surgery, is also a priority, Felip believes. Although ESMO advised, in 2010, that trials of low-dose CT scanning of high-risk people had not yet produced enough evidence of overall benefit, the ESMO Guidelines Working Group is currently looking at newer data with a view to updating the guidelines.

"To me it is clear," says Felip, who serves on the Guidelines Working Group editorial board. "The study from the National Cancer Institute in America showed a 20% reduction in lung cancer deaths among current or former heavy smokers who were screened with low-dose CT scans. It's true that there are a number of aspects that should be resolved before this becomes a standard of care. We need to know it is cost efficient, we need specialised centres, and we need skilled radiologists, because interpreting these images is not easy. But there is currently a lack of awareness of the issue among clinical oncologists, and no clear guidance on screening strategies. So for me this is a clear area to discuss at the European level."

Felip, a subject editor of minimum clinical recommendations for diagnosis, treatment and follow-up in lung cancer for ESMO, is today one of Europe's most respected names in lung cancer. She has achieved her reputation by quiet diligence, not by blowing her own trumpet.

She was born in Barcelona, and has always lived there. She says she went into medicine simply because she liked people and liked science – and the subject combined both. After completing her medical degree at the Universidad Autónoma in 1987, she decided to take a residency in medical oncology at the associated Vall d'Hebron Hospital: "I knew surgery wasn't for me; with oncology there was the opportunity not just for research, but to have a relationship with people living with disease. This is important: it's our objective, it's the most important thing." And she was immediately drawn into lung cancer. During her residency, she spent three months working at the thoracic unit of the Memorial Sloan Kettering Cancer Center in New York, and on her return and completion of her PhD her then boss, José Baselga (now at Memorial himself), encouraged her to set up a thoracic unit with specialised staff.

"Up until then, nobody was doing lung cancer in my institution," she says. "There were people treating breast cancer and colon cancer, but not lung cancer. So when I finished my residency in 1992 there was this opportunity to build something.

"For years I was the only medical oncologist

JORGE NOGUEIRA

in my hospital seeing people with lung cancer. But today I have a department with four specialist medical oncologists seeing more than 400–500 new patients a year. The situation has changed hugely, and I have had great support from my bosses, but it has not been easy. You have to fight for excellence in lung cancer, and I think specialised professionals are essential if you want to achieve the best results."

There have been opportunities for Felip to move on, but what has kept her in Barcelona has been the prospect of building the thoracic unit even further, the opportunities available for trial collaborations, and the good facilities for early-phase clinical trials: "I have the opportunity here to work on immunotherapy, T790M inhibitors and ALK second-generation inhibitors, because we have the facilities."

For the past ten years, tumour boards and multidisciplinary collaboration have been fundamental to the Vall d'Hebron approach – and Felip continually emphasises their fundamental importance in lung cancer. This is growing as treatments become more advanced, and there is the need for input from the patient and palliative care teams from the earliest stages.

"The biggest challenge I have had in my career has been building a good team. It is important

"Working closely with pathologists and biologists has become so important in lung cancer"

"I believe it's very important to interact with people and share information – it's part of my job"

for so many reasons. It means we can give the best possible attention to the patient. It means we have support and can share with colleagues in sad situations.

"Today, we have tumour committee meetings twice a week. We discuss a tailored approach for each patient, how to get a good picture of the extent of disease. We know that for a group of patients, combined chemotherapy and radiotherapy achieves good results. We have also learned how to select patients for individualised therapy, so we discuss the best ways to get tissue samples for molecular marker testing. Working closely with pathologists and biologists has become so important in lung cancer – tumour sampling is vital, and the number of markers you are looking for is growing all the time. It means we are working with thoracic surgeons in a different way. Even with stage 4 disease, where surgery wouldn't otherwise be indicated, we sometimes need their involvement to provide samples."

I raise the subject of women in oncology. Felip is, after all, a high-flyer in a male-dominated world. She was also a panellist at the ESMO Women for Oncology (W4O) Forum at the 2013 European Cancer Congress. W4O aims to help female oncologists access leadership positions, in the light of a recent ESMO survey which indicated that less than 15% of women oncologists have a leadership position.

So does she think that women face problems in reaching the top in oncology? Her answer is guarded. Both men and women face the challenge of having enough time, especially time for a family, says Felip. She agrees that some women definitely have problems with childcare and taking a break in their career, but argues that it is families that need support, not necessarily women.

"We have a lot of women oncologists in Spain and in Europe, and many in very senior positions, and I don't think we are under-represented," she says. "I think W4O is a good initiative, because it is good that women physicians can share the range of their experience with men, and that is important if we are working together. But personally, I don't see any problems with being a woman in oncology."

She is reluctant to be drawn on the subject because (being a stickler for evidence) "I don't have a clear picture of the situation," and acknowledges that her view is dictated by her own experience. She has a seven-year-old son, and has been lucky to have the constant help of her retired parents, who looked after him when he was a baby, and get him to school and back today.

"Our lives are very busy. I do a lot of travelling to conferences because I believe it's very important to interact with people and share information – it's part of my job. It's not a problem – I can do it. And it shouldn't be a problem for men either."

So what advice would she offer to a young woman wanting a career in oncology? "I think they should work hard, apply for grants, talk to oncologists in key positions, go to congresses, be involved. They should compromise." I'm intrigued she feels that compromise should be important to the work of oncologists, and then become puzzled when she uses the word again, as I ask her about the greatest influence on her career.

"Compromise," she says. "Getting involved. Improving our patients' profile. Learning every day." I ask her to explain what she means by compromise, and then we work out that we are experiencing one those linguistic misunderstandings that can cause complications at international level. The Spanish word "compromiso" means commitment in English.

Far from saying that it is important to adjust your own views according to those of others, she is asserting the opposite – the need to pledge oneself to a cause. And if there is a cause that needs the commitment of people like Felip – bringing profile, knowledge and hope – it is lung cancer. ■

Protecting patients' nervous systems

Are we getting the care-cure balance right?

MARC BEISHON

The debilitating impact neurotoxic drugs can have on patients' long-term quality of life has been systematically underestimated. Can oncologists do more to pick up potential symptoms before they become irreversible?

Cancer patients about to start chemotherapy are often faced with a long list of possible side-effects, depending on the type of cancer and the drug or drug combination involved. They may also be facing side-effects from surgery and radiotherapy, so there is a lot to take in. Some side-effects, such as neutropenia, pose a serious risk, but only during treatment. Others, such as heart damage, may be irreversible, and have a lifelong impact on the quality of a patient's life. Chemotherapy-induced peripheral neuropathy (CIPN) is one of these. Not only can it cause a range of mild to severe problems during treatment, but it can manifest itself strongly just after treatment, and can impact very heavily on a patient's life for a long time, if not indefinitely.

CIPN is a condition that mainly damages the long nerves that extend to the feet and hands – a 'stocking and gloves' distribution – and can affect sensory or motor function, most often the former, with symptoms such as numbness and shooting pains. Some people are so severely affected that they may regret having the curative cancer treatment that caused it. Its mechanisms are not well understood, with little indication of who will suffer most, and there is no current treatment that can prevent it or do much to alleviate it. It affects 30–40% of patients across all neurotoxic drugs, but with some agents up to 70–90% of patients may be affected.

This presents a serious obstacle to successful treatment and, like all long-term effects, the problem is becoming more widespread as the population of cancer patients expands. While it only occurs in certain classes of chemotherapies used in some cancers, the treatments are among the more common, such as taxanes for breast cancer, and platinum agents for colorectal tumours

SHUTTERSTOCK

(see table, page 14).

Oncologists are often faced with a difficult decision about whether to stop or alter potentially life-saving treatment, and problems with neuropathy are a common reason for patients themselves deciding to stop therapy. Where severe problems arising from nerve damage do develop, health professionals also face the challenge of how to help patients to manage the symptoms.

CIPN has moved up the side-effects agenda in recent years, says Guido Cavaletti, a neurologist at Milan-Bicocca University, Italy, who has been treating and researching this condition for more than 20 years. "That's because patients have been asking for a better quality of life as oncologists have been able to improve survival, and there has been a particular push for more attention to CIPN in the US, where patients tend to be more demanding, and as other side-effects can now be better managed," he says. "But we still have virtually nothing for CIPN."

Common symptoms

Cavaletti explains that the incidence of CIPN is much more frequent with the older chemotherapy drugs, although some of the newer biological therapies can also be neurotoxic. Numbness is the typical sensory symptom – being unable to feel heat or cold, or a pin prick. Motor symptoms include unsteadiness on one's feet, or even being unable to walk far at all, in more severe cases. There are also pain symptoms: neuropathic pain is one of the most complicated pain types managed by neurologists or pain specialists, says Cavaletti.

What is a puzzle with CIPN is that, while it is known that nerve endings start to be damaged and can get progressively worse with chemotherapy, currently there is no way to tell what an individual's risk is for developing neuropathy. "If I have ten patients, maybe two will develop severe neuropathy, four will have nothing and the rest some degree of symptoms – but we haven't been able to identify the risk factors for who will get severe problems," says Cavaletti.

Also unexplained is when CIPN will take hold, or what the symptoms will be. Dawn Storey, a consultant medical oncologist at the Beatson West of Scotland Cancer Centre in Glasgow, who has researched CIPN as part of her strong interest in supportive oncology, says: "The onset of acute neuropathy varies from patient to patient. Some get symptoms early on and have to stop treatment prematurely, whereas some get through treatment without many symptoms, but then may develop severe pain and disability after treatment stops – that's what we call 'coasting', and it is often seen with platinum drugs."

Although things do get better for the majority of people over several

"If someone cannot feel the pedals in a car, they can't drive, or they may be too unbalanced to walk far"

months, she adds, there are those who are left with long-term life-limiting symptoms, and little is understood about why patients develop different symptoms at different times, and why some and not others are left with long-term problems.

What is clear is the harm that can be done to patients, who can suffer a range of debilitating conditions. They may be relatively minor – Cavaletti mentions women who have had taxanes, who report they can no longer wear elegant shoes to the theatre as they feel too tight. "But imagine you are wearing boots and gloves permanently, or if you feel you have to wear gloves but it's quite warm outside."

If someone cannot feel the pedals in a car, they can't drive, or they may be too unbalanced to walk far.

Storey says that oxaliplatin is a drug that tends to have different symptoms during the acute, treatment phase and post-treatment. In the acute stage, people can become hypersensitive to cold and experience difficulty swallowing – these usually go away in a few days, she notes. "Long term chronic symptoms tend to be the typical neuropathy, like numbness, shooting pains, pins and needles and problems with actions such as fastening buttons, writing and even toileting, as patients can't feel the toilet paper." Other drugs such as taxanes tend to have similar symptoms in both phases, although paclitaxel can cause a specific acute pain syndrome during treatment that affects the hips and trunk.

One group of cancer patients who have a particularly high incidence of CIPN are those with multiple myeloma. In this group, the nerve condition is not just a side-effect of the biological therapies, bortezomib (Velcade) and thalidomide, but can also develop as a complication to the myeloma itself. About 30% of patients are affected and it is a common topic of discussion at support groups. People report some awful symptoms of being unable to walk, pain and sleeplessness at night, and feelings of hopelessness.

Pain can be extreme to the extent that some patients can't bear to have bedclothes over them, Storey adds. "I got interested in CIPN because I was disheartened that people were being cured of their colorectal cancer, but I was seeing them in their 50s or early 60s being unable to dress themselves, walk, write or drive safely, and losing their jobs because of their disability – that's not success to me."

As Cavaletti also says: "What we have now are cancer survivors living with severe damage. It's a small group but we need to eliminate it. For example, there is a young psychologist colleague here who had testicular cancer two years ago and was cured with cisplatin – but now he cannot work as he can't hold a pen. And he's only 32 years old."

An underestimated problem

Knowledge about CIPN's incidence also appears to be lacking, although it is almost certain that long-term effects are underreported both in clinics and in trials. "Estimates of the proportion of patients affected by functional impairment due to neuropathy two years after the completion of treatment for colorectal cancer are about 4%, but it's probably much higher than that," says Storey. "In audit work I have done it seems that about 20–30% have some sort of impairment – and the disparity arises because published studies focused more on the anti-cancer effect of the chemotherapy rather than reporting long-term side-effects, which some oncologists rate as less important."

NEUROTOXIC DRUGS

A variety of anti-cancer drugs operating via different mechanisms have the capacity to damage patients' nerves, including:

Platinum analogues
Cisplatin
Carboplatin
Oxaliplatin

Antitubulins
Paclitaxel
Docetaxel
Ixabepilone
Vincristine

Proteasome inhibitor
Bortezomib

Other
Thalidomide

Source: Adapted from Guido Cavaletti and Paola Marmiroli (2010) *Nature Rev Neurol* 6:657–666

GRADING OF NEUROPATHY: NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) v4.03

ADVERSE EVENT	DESCRIPTION	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Peripheral motor neuropathy	Inflammation or degeneration of the peripheral motor nerves	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy	Inflammation or degeneration of the peripheral sensory nerves	Asymptomatic; loss of deep tendon reflexes or paresthesias	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Dysesthesia	Distortion of sensory perception, resulting in an abnormal and unpleasant sensation	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self-care ADL	–	–
Neuralgia	Intense painful sensation along a nerve or a group of nerves	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	–	–
Paresthesia	Functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold and warmth that are experienced in the absence of a stimulus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	–	–

The earlier version of this grading scale (CTCAE v3) was the one used in most clinical trials and was strongly criticised as not reflecting patients' experiences. This version (v4.03) contains many amendments, but the continued reliance on how patients interpret the terms "mild", "moderate" and "severe" remains controversial

Instrumental ADL – preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc
Self-care ADL – bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
Source: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

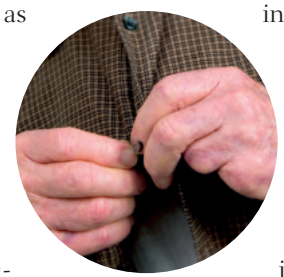
Another contributing factor is partly a result of the way that CIPN is assessed, she adds. Long-term studies used in guidelines have adopted the US NCI's Common Terminology Criteria for Adverse Events (CTCAEv3) – one of several tools that can be used for CIPN – and most often significant neurotoxicities have been reported only at grade 3, which is 'severe interference with daily living'. But distinguishing this from grade 2 – 'moderate' limits on daily living – can be an artificial judgement, says Storey, so "CTCAEv3 is now recognised as unfit for purpose in assessing CIPN. CTCAE v4 is a slight improvement, but I would still encourage investigators to report grade 2 and 3 because functional impairment of any degree matters hugely to patients."

In practice, this has probably resulted in considerable harm. "From the point of view of most oncologists, if it's grade 3 the drug is stopped, but if grade 2 it tends to continue to be given – so oncologists have probably been giving far too much oxaliplatin and

caused more nerve damage than was realised. There is no official guidance on applying the criteria and oncologists tend to be biased in favour of giving a drug rather than stopping it, because of course they want to prolong life or prevent a cancer from coming back."

A recent indication of the extent of long-term CIPN in people given oxaliplatin for colorectal cancer was reported at the EORTC survivorship summit (see also page 42), by Lonneke van de Poll-Franse, from Tilburg University in the Netherlands. A quality of life questionnaire was sent to more than 1600 patients, on average six years after diagnosis, 500 of whom had received chemotherapy. About one in three of those who had been treated with oxaliplatin reported tingling, painful hands or feet up to ten years after diagnosis, and indicated that this CIPN "tremendously impacted on quality of life" across scores for social and physical functioning, and overall health.

Oncologists who specialise in cancers such as colorectal and multiple myeloma will tend to be more experienced with CIPN, as they see it most often, and they may therefore stop or reduce doses and switch to alternatives earlier. But there needs to be both a refinement of the assessment tools and greater interest in neuropathy among oncologists, according to Cavaletti.



While there are the usual centres of excellence in cancer – Storey for example did her work on CIPN at the Edinburgh Cancer Research Centre, where there are palliative and supportive care specialisms – Cavaletti says that up until the last few years it was common in some countries for neurologists to carry out much of the research on CIPN, and indeed to see patients, when oncologists should really have been doing more.

"Oncologists should be prepared to properly recognise and score the severity of CIPN and not just send patients to us once they are sure there is neuropathy – that's not very useful for the patient." Cavaletti makes a comparison with neuropathy caused by diabetes. "I don't see these patients unless they are very different from usual – they are well managed by diabetes specialists, and we need to achieve the same with oncologists, some of whom are wary of a neurological exam – they think it is complicated and difficult but that's not true."

The critical point in managing CIPN during treatment is not to wait until it's too late: the treatment should be changed before symptoms become so severe that they are irreversible. In the absence of effective treatment for CIPN itself, this is about the only primary strategy of value, says Cavaletti. He agrees that the NCI's CTC scale is inadequate and a more robust method is needed to give oncologists the confidence that, for example, mild symptoms are not progressing so there is no need to move to a lower or less frequent dose, or another agent, or discontinue chemotherapy.

"It's about managing the patient and not the side-effect that emerges," he says, noting that when thalidomide first became available for trials in multiple myeloma, there were concerns that it would need specialist neurologic monitoring. "Now, in work on producing an improved assessment tool, it is clear that in 99% of cases a clinical evaluation is sufficient – you don't need instrumental evaluation."

But that clinical evaluation must comprise two elements, he adds – both the doctor's assessment of nerve changes and the patient's own report, although initially it can seem that the different viewpoints can be hard to reconcile. "But it is the same problem from two perspectives, and is particularly important as we have no objective tools to say measure pain in a patient. We don't have an operational patient-reported outcome measure in CIPN yet, but we are working on it and combining it with clinical evaluation is a goal for our research."

Asking patients about symptoms, and ensuring they understand the potential long-term implications, is particularly important, as studies have shown that patients often don't like to mention side-effects for fear that their treatment might be stopped.

"These patients are well managed by diabetes specialists – we need to achieve the same with oncologists"

"Part of the answer lies in improved communication with patients, including at the start of treatment"

As Storey adds: "We also know from research that patients are more likely to disclose their symptoms to a nurse than to a doctor, who patients often assume is more focused on cancer management than on issues such as fatigue, anxiety, depression and CIPN. And, patients who are cured often don't want to sound ungrateful, saying they can put up with CIPN – but I know some who have said they would not have taken the chemotherapy if they had known it was going to make them feel that bad. But most won't tell you and they certainly won't if you don't ask."

Improving evaluation

Cavaletti is principal investigator for the CI-PeriNomS group, which is testing existing scales for assessing CIPN together with quality of life tools, including the EORTC's QLQ (quality of life questionnaire), with the aim of producing a standardised outcome measure, and a new cohort of patients is being assessed this year. "We had our first meeting in 2007 and while we have expanded the study group to 20 centres, most in Europe and some in the US, we have been unable to get any support for our work," he says. Most of the researchers are neurologists, but more oncologists have come on board, he adds.

Storey, who has been involved with the group, feels part of the answer lies in better communication with patients, including at the start of treatment. "I discuss drug options at length with patients, asking about hobbies, such as knitting or playing an instrument, that CIPN could adversely affect." The point is echoed by van de Poll-Franse, who was involved in the study of patients treated for colorectal cancer. She agrees that quality of life should be part of the discussion when considering oxaliplatin as an adjuvant therapy.

There are various treatments that can alleviate symptoms in some people, and an increasing number of trials are investigating which work best for CIPN. Antioxidants, antidepressants, anticonvulsants (such as pregabalin), opioids and analgesics, including topical substances such as menthol, and acupuncture, are all in the frame. Storey has trialled menthol cream and found a good response to pain, although she says it may worsen it in some cases.

Newly published guidelines from ASCO recommend treatment with the antidepressant duloxetine, and suggest that gabapentin, and a compounded topical gel containing baclofen, amitriptyline HCL, and ketamine may also be used, as their utility has been shown in other neuropathic pain conditions.

Finding biomarkers and genomic information that can predict who will suffer most is also a research avenue, and of course more personalised treatment will cut the number of patients receiving neurotoxic drugs in the first place.

Genetic information may indeed be the best path, as Charles Loprinzi, a medical oncologist at the Mayo Clinic in Rochester, US, and an expert in CIPN, has recently noted. There were hopes for a prevention approach for oxaliplatin by infusing calcium and magnesium, but a recent trial he led has proved negative (*JCO* doi:10.1200/JCO.2013.52.0536).

The NCI guidelines are unable to offer any recommendation on prevention, due to the lack of high-quality consistent evidence.

As Cavaletti laments, there is much more interest in funding work on CIPN in the US, where he says that the National Institutes of Health (NIH) has launched a programme to discover the mechanisms that cause it, and there have also been meetings on improving outcome measures in clinical trials, which have had strong participation from patient associations. "To my knowledge there is nothing like this in Europe and it's a gap we need to fill," he says.

Storey agrees, saying that research funding in palliative and supportive care has been curtailed in the UK, and that not all cancer centres have the multidisciplinary resources of Edinburgh, where there is access to neurologists, anaesthetists and palliative care colleagues for problematic cases. In fact she says that some of the most useful help that her patients receive is from colleagues in occupational health. In a pilot in Glasgow they are helping with adaptations in the home, such as foam handles for kettles, elastic shoelaces, temperature checks for bathwater. "We must talk to patients about CIPN because they are often battling on their own," she says. ■

The patient touts

Christiane Hawranek and Marco Maurer, freelance print and radio journalists, won a Best Cancer Reporter Award for their exposé of the agencies that exploit foreign patients seeking treatment for cancer and other serious conditions. They published this piece in *Die Zeit*, and the story was also broadcast on radio by Bayerischer Rundfunk.

Ruslana Fadiwa is dancing, watched by her grandparents. Klavdia Petrowa, 65, and her husband Leonti Fadiw, 62, are in a gymnasium in the city of Yoshkar-Ola, 700 kilometres east of Moscow. While their eight-year-old granddaughter competes in her first major gymnastics event, they are talking about a place that they have never been to: Düsseldorf. "Do you remember how I walked round the Kremlin in Kazan three times in the hope that Ruslana would get well again in Düsseldorf?" Klavdia says to her husband. Ruslana had cancer and was treated in the University Hospital in Düsseldorf when she was four years old.

"Yes, of course," replies Leonti, and the couple go on to describe their dealings with a medical travel agent from the German town of Lüdenscheid: he certainly helped save their granddaughter's life, but the family are now embroiled in a long-running lawsuit because they believe he vastly overcharged for his services. The amount involved is some €45,000.

BR/ALEXANDER STAHL

Award winners. Christiane Hawranek and Marco Maurer

Medical travel agents arrange for

patients from other countries to be treated in German hospitals; they trade on the outstanding reputation of German healthcare. Most agents have roots in their patients' home country; their work includes finding the patient a suitable hospital in Germany, agreeing costs and dates, translating medical reports into German and providing an interpreter during the patient's stay in Germany.

A noble occupation, it might seem. But examples from German hospitals show that agents do not always deal fairly with their customers. One doctor tells of an agent who allegedly charged the patient twice the actual cost of the hospital treatment. The head of the Coordinating Office for International Patients at Düsseldorf University Hospital says she has had "distasteful experiences" with the agencies. Bavaria's Secretary of State for the Environment and Health says she knows of "only one or two agencies that are perhaps reputable". A member of the board of a state chamber of physicians refers not to "medical travel agents" but to "patient touts". Frank Ulrich Montgomery, President of the German Medical Association, asserts that there are "dubious agents" who 'import' patients into Germany. A nurse at a German university hospital goes so far as to say that some agents "stop at nothing".

Jens Juszczak is sitting in his office – room E108 on the first floor of the Bonn-Rhein-Sieg University in Sankt Augustin, where he is a researcher in the Department of Economics. Juszczak has been studying medical tourism for the last ten years. On his desk are the latest research figures, which show that some 200,000 international patients came to Germany in 2012. They contribute about a billion dollars a year to the tight budgets of German hospitals, which is why talk of medical tourism usually paints a positive picture, and points to the clinics' attempts to attract sheikhs and oligarchs. No mention is made of the fact that less-well-heeled patients, such as Ruslana Fadiwa, are also being persuaded to come to Germany. And virtually no one speaks of the agents who have interposed themselves between hospitals and patients. Juszczak says that about two-thirds of all hospitals that treat international patients make use of such agents.

BR DIE ZEIT

Exposed. This well-researched piece of investigative journalism is adding to pressures to regulate the agencies that make money from patients seeking to travel to Germany for medical treatment

22 WIRTSCHAFT

11. APRIL 2013 DIE ZEIT N°16

Die Krankenschlepper

Dubiose Agenturen vermitteln ausländische Patienten nach Deutschland. Hiesige Kliniken zahlen dafür VON CHRISTIANE HAWRANEK UND MARCO MAURER

Krankenhäuser zahlen »Fangprämien«, wenn ihnen Patienten vermittelt werden

"If you pay the money today, you can be in Germany tomorrow"

Medical travel agents, like estate agents, work on a commission basis – they receive payment for each patient that they introduce. The market is not transparent. Juszczak states that up to 1,000 agents work with German hospitals; to do their job they need nothing but a mobile phone, contacts abroad and knowledge of the relevant language. Anyone can call themselves an agent. Doctors and nurses are usually unaware of what agents have agreed with their clients. This is confirmed by Marlies von Borries, head of the Coordinating Office for International Patients at Düsseldorf University Hospital: "No, we don't know that," she says.

The day after Ruslana's competition, her father, Roman Fadiw, is sitting at the kitchen table in the bright two-bedroom flat on the fourth floor of the five-storey building in Yoshkar-Ola where he lives with his wife Nadezhda and their two children, Ruslana and Serafin. In front of him is a calculation of costs amounting to €100,000, drawn up by the medical travel agency in Lüdenscheid. He has sent his daughter to play in her bedroom – he doesn't want her to listen to the story of her illness. In February 2008 Ruslana was constantly complaining of stomach ache. The children's hospital in Yoshkar-Ola attributed the pain to a gastric cyst – the first misdiagnosis, as the Fadiws now know.

Ruslana's father insists on taking the reporters to the hospital at 104 Volkova – a red and grey building erected in the heyday of the Eastern Bloc. Brown-stained mattresses are stacked high, out-of-date drugs lie about in battered boxes, and in one corner stands a plant with a note attached to the pot: "This plant is sick – please don't touch." Roman Fadiw pauses in front of the plant and says: "living in Russia is alright if you are in good health and don't get ill."

SERGEY KOZMIN/AGENTUR FOCUS FÜR DIE ZEIT

Ruslana Fadiwa, who was treated in Germany for Burkitt's lymphoma, with her parents Roman and Nadezhda

Just four months after the initial investigation in Yoshkar-Ola, and after several misdiagnoses in Moscow hospitals ("oncological disease ruled out"), the Fadiws discovered what was wrong with their daughter: Burkitt's lymphoma, a cancer of the lymph glands with good prospects of a cure if treated promptly. Because the Russian doctors had taken four months simply to arrive at a diagnosis, the family had by now lost trust in Russian hospitals. They searched on the internet for one in Germany. According to Juszczak, this is what most people do; in the former USSR people usually use the Russian search engine Yandex. Typing "treatment in Germany" into Yandex brings up virtually nothing but names of medical travel agents – the hospitals themselves are not mentioned. The Fadiws decided on the agency in Lüdenscheid because its website looked professional – there were pictures of the owner with confidence-inspiring men in white overalls. Towards the end of July 2008 they telephoned the agency and were told: "If you send me the money today, you can be in Germany tomorrow." "I can get the money together," replied Fadiw. By western European standards the Fadiws are an ordinary middle-class family, neither oligarchs nor desperately poor –

The hospitals looked about for extra sources of income and discovered patients from abroad

four of them in a two-bedroom flat, bunk beds for the children, washing machine; the father, Roman, owns four fashion boutiques in the city. The bank gave them a loan of €80,000. They also borrowed money from friends. To meet their debts and pay off the first loan, they later had to take out a second one, which they have still not paid off.

When they arrived in Düsseldorf, the family say they felt "helpless and speechless". The interpreter provided by the agency was unable to cope with medical terminology; in meetings that the Fadiws had with a senior doctor at the university hospital, he frequently said: "I can't translate that – I don't understand it." Roman Fadiw tried to complain to the agency, but whenever he phoned he was told that the deposit of €100,000 was not enough and he needed to send more money. Fadiw became suspicious. He asked the agency whether he could see the hospital's invoices. On being told that this was not possible, he made further enquiries at the hospital's International Office.

He discovered that the hospital's bill had amounted to about €40,000 – far less than the initial payment Fadiw had made. In addition, the Fadiws had viewed the €100,000 as a security deposit – if any money were left over, they thought they would get it back, less the commission. This was confirmed by the district court of Hagen in a partial judgment pronounced in 2010. The judge declared, "No lump-sum payment was made (…) but a deposit, a lodgement."

The agency responded to questions from *Die Zeit* through its lawyer, who stated that the company had also paid the family's accommodation costs and that this was the reason for the large bill. The Fadiws dispute this. They say they stayed with acquaintances in Düsseldorf and they produced photos of a student flat near the hospital which they say they paid for themselves. Even when reminded, the lawyer sent no proof of additional costs, but only the invoices from the hospital and the interpreter, amounting to some €45,000. In his letter, the lawyer proposed that the parties "await the judicial verdict".

Every German hospital receives a fixed sum for a particular treatment – €1,500 for a birth without complications, around €100,000 for a liver transplant. Part of the purpose of these flat-rate payments, which have been in place for ten years, is to reduce the length of hospital stays and cut costs. Previously a hospital could boost its profits by keeping patients for as long as possible; charges were based on the number of days spent in hospital. Under the flat-rate system, by contrast, hospital staff need to ensure that patients do not exceed the "maximum length of stay" – if they do, the health insurer reduces the amount it pays. This has resulted in empty beds and forced the closure of some hospitals, especially in rural areas.

The hospitals looked about for extra sources of income and discovered patients from abroad, whom they seek to attract at medical fairs in Dubai or Moscow. These patients are self-payers; their money goes direct to the hospital and can be used, for example, to buy new medical equipment, from which German patients funded by health insurers also benefit. The law acknowledges that the prices paid by self-payers are freely negotiable. But profiteering – which is defined as occurring when the payment is twice the market value of the service provided – is frowned on. Judges assume that the profiteer is exploiting the weak situation of his customer, which in the case of Ruslana Fadiwa was probably true – her parents feared for their daughter's life.

The Coordinating Office for International Patients at Düsseldorf University Hospital is prepared for clients from abroad; on the way to the office we pass a large blue sign in Cyrillic and Arabic script. Marlies von Borries, who is in charge of the department, admits that her hospital works with agencies, but says that it has become more circumspect – and it no longer does business with the particular agency in Lüdenscheid. Moreover, a year and a half ago the hospital started sending out its invoices in duplicate: one copy to the agency, the other to the patient. Von Borries repeatedly emphasises that her hospital has adopted a "special approach", since it pays no commissions.

Experts such as the economist Jens Juszczak maintain, however, that many hospitals pay "the commissions

The doctor wondered what the agent had promised his patient to persuade her to come to Germany

that are usual in the sector". This means that agencies receive "bounty payments" if they send foreign patients to these hospitals. Many also charge the patient a fee – usually 15% of the treatment costs. So the agencies cash in twice – they get paid by the patients and by the hospitals.

Towards the end of 2011 the Kiel district court ruled that the commission agreement between hospital and agent was itself unethical. A medical travel agent had sued a university hospital in north Germany that had promised the agent a 22% commission for each patient, which it had not paid. "The court found that the agreement was invalid, because it damaged the relationship of mutual trust between doctor and patient through inappropriate commercialisation," explains Norman Langhoff, a Berlin lawyer who specialises in medical law. *Die Zeit* is in possession of letters from a number of German hospitals that contain promises of such commissions. For Ulrich Montgomery, President of the German Medical Association, these represent "clear cases of referral for payment, which is prohibited under the medical profession's rules".

Julia Laube [name has been changed] is no longer prepared to keep quiet. She is a young assistant doctor at a university hospital and understands the importance of international patients to her employer. But when she speaks of the Russian woman whose treatment in her clinic was arranged by an agency, she uses the same phrase repeatedly: she died "totally alone", says Laube, looking over her shoulder as if to reassure herself that she is not being overheard. If her boss got to hear that she had been talking about internal hospital affairs, she could be fired. "Totally alone".

Nevertheless, Laube wants to talk. She no longer wishes to be part of a system in which patients from other countries are at the mercy of medical travel agents, hospital administrators and the pressure to cut costs. "Seeing how my patient died thousands of kilometres away from her family was devastating," says Laube. The woman had pancreatic cancer. "At least a month before her death it was clear that we were never going to cure her." But her family had no money to come and visit her. The doctor wondered what the agent had promised his patient to persuade her to come to Germany in the first place. She asked the senior consultant whether there were any rules for medical travel agents and their patients. "No", was the concise answer.

There are no rules governing what medical travel agents do, and no quality control either. The Green Party's spokeswoman for prevention and patient rights, Maria Klein-Schmeink, wants to change that, and is calling for a certification scheme for agencies, on the grounds that foreign patients are "too easily exploitable".

Melanie Huml, Secretary of State in the Bavarian Ministry of Health and a member of the Christian Social Union (CSU), believes it is inappropriate for the "grey area" of the medical travel agencies to be included in the glossy white and blue brochures used all over the world to publicise Bavaria as a centre of medical excellence, and attract patients such as the Fadiws to Germany. The Secretary of State, who is herself a doctor, therefore plans to set up a special government office that will provide reliable information to international patients seeking treatment in Germany – thereby bypassing the agencies. The office is set to open this year; the Bavarian government has funded the project to the tune of €5 million.

Bavaria's Minister President Horst Seehofer (CSU) has himself spoken out in favour of the scheme. Roman Fadiw, too, sees it as a good way of getting patients to come to Germany. If this option had been available when Ruslana was diagnosed, he might not be having to go to Hagen in April for the next court hearing*. When asked whether he had not perhaps acted somewhat naively and overhastily back in 2008, he replies that he would have grasped at any straw to save his daughter. "Wouldn't you do the same?" ■

*The court ruled in favour of the family last September, and they received a refund of around €50,000.

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Cooperative research by BR-Hörfunk and ARD-'Report München'

Living with cancer or dying of cancer? The case for earlier palliative care

PETER MCINTYRE

People do better throughout their cancer journey when their physical, psychological and spiritual care needs are attended to. But how do we overcome entrenched mind sets that still resist integrating palliative and oncologic care?

Philip Larkin, associate professor in clinical nursing at University College, Dublin, began working as a palliative care specialist 25 years ago in rural West of Ireland. "What was called palliative care then was very much terminal care. We were called at the end of life, literally hours and in some cases minutes before death. It was not unknown to arrive at the house and find that the patient had already died."

Larkin contrasts his clinical work today at Our Lady's Hospice and Care Services in Dublin with the marginal role that palliative care was afforded in a general hospital setting when he began. "We used to go into hospital predominantly to visit cancer patients. If the oncologist was on his ward round we were not allowed on the ward. He did not want to see us; he did not want to know. That has all changed."

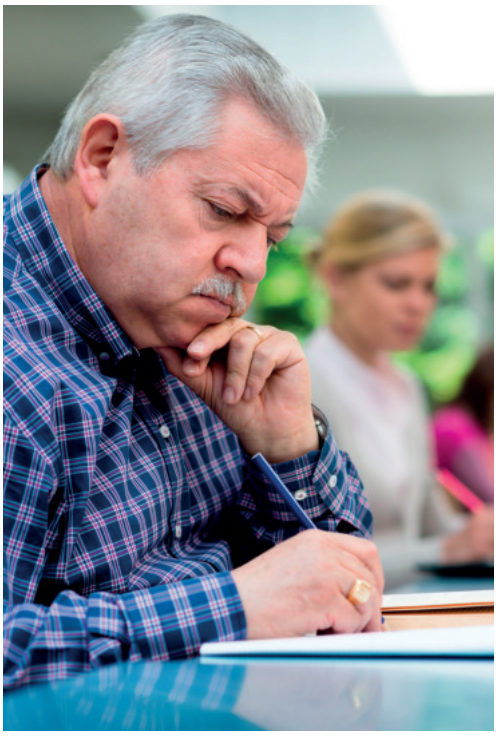
The value of palliative care early in the progression of cancer is becoming increasingly clear. The World Health Organization, and the European and US oncology societies ESMO and ASCO, all advocate its early introduction alongside treatments designed to increase survival.

In 2002, the WHO changed the definition of palliative care to "[care that] improves the quality of life of patients and families who face life-threatening illness, by providing pain and symptom relief, spiritual and psychosocial support, from diagnosis to the end of life". The definition specifies that palliative care "is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy…"

Larkin strongly supported the change. "We started to see that the earlier involvement of palliative care in the overall care of certain groups of patients meant they would have a better outcome in terms of quality of life and the quality of their death. End of life care was still part of the spectrum, but we started to see much earlier referrals, seeing people not within hours of their death but probably within weeks or months."

Research supports early intervention

The most cited research comes from Jennifer Temel and colleagues at Massachusetts General Hospital in Boston, where 151 patients with metastatic non-small-cell lung cancer were randomised to receive early palliative or standard oncological care (*NEJM* 2010, 363:733–742). Those who received early palliative care reported better quality of life,



ALAMY/ DARTMOUTH-HITCHCOCK MEDICAL CENTER

while fewer had depressive symptoms. The most startling finding was that the patients who received early palliative care survived more than two months longer on average than those on standard care (11.6 months vs 8.9 months), despite receiving less aggressive treatment.

Quality of life in the palliative care group actually improved over the trial period, comparable to improvements seen in patients who respond to cisplatin-based chemotherapy – "a formidable challenge," Temel observed, "given the progressive nature of the illness."

Temel speculated that poor quality of life and depression may themselves be factors leading to earlier death. It was also possible that integrating palliative and oncologic care ensured the best possible anticancer therapy, especially during the final months of life.

A larger study, conducted at Princess Margaret Cancer Centre, Ontario, was reported by Camilla Zimmermann and colleagues in the *Lancet* in February 2014. Oncology units were randomised to deliver early specialised palliative care or standard oncological care to 461 patients with advanced cancer. Specialist intervention included a multidisciplinary assessment, telephone contact from a palliative care nurse, a monthly outpatient clinic and a 24-hour on-call service. The trial measured change in quality of life, symptom control and satisfaction with care.

After three months, the change in scores from the baseline were significantly different between the two groups for Quality of Life at the End

"We need to adopt a grey scale of curative therapy, supportive care and end of life care"

of Life (QUAL-E), and satisfaction with care (FAMCARE-P16), though not for symptom control (Edmonton Symptom Assessment System, ESAS) or for communication with healthcare providers (CARES-MIS). The change in the score for the Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being (FACIT-Sp) scale – which was the primary endpoint – was also better in patients receiving palliative care than the control group (an improvement of 1.60 compared to a deterioration of -2.00), but the result was not statistically significant. At four months, however, the improvements in the intervention group were significant on all scales except for communication with healthcare providers.

Both sets of researchers called for further studies to address these issues.

Helping people to live

Larkin points out that helping people live until they die has been a key principle of palliative care since it was expounded by Cicely Saunders, the founder of the palliative care movement. "We are there to help people to live as fully as they can within the confines of their illness, until natural death occurs."

However, changing public and clinical perceptions is not so easy. "We as practitioners can say, 'This is who we are and this is what we do,' but it is a bigger struggle to get people to understand that it is not just about the dying."

Irene Higginson, director of the Cicely Saunders Institute and professor of palliative care at King's College London, agrees that palliative care is about helping people to live. "I find the term 'end of life care' a bit misleading for people, and frightening. A lot of what we do is helping people live well despite a chronic or deteriorating illness or knowing they are dying. If you manage the symptoms, and help people to live as well as possible, when it comes to the end of life they have done the things they wanted to and spoken to the people they wanted to speak to."

The question of whether someone is living with cancer or dying from it becomes less clear-cut as treatments extend life.

Roger Wilson, president of Sarcoma UK, was diagnosed with a soft tissue sarcoma in 1999 and with regional metastases in the following year. After surgery and chemotherapy, his surgeon told him that the cancer was not curable. "I suppose I have been in palliative care ever since," he said. "I am now in year 15 and I still have periods with active disease, although none is actually detectable at the moment."

Wilson, who was an independent producer and writer for the BBC before becoming ill, prefers the term 'supportive care' as descriptive of his own experience of episodes of acute treatment, followed by rehabilitation, physiotherapy, prosthetics care and psychological support.

After seven years of remission, a recurrence led to the amputation of the lower part of his left leg in 2007. Further recurrence was treated with surgery and radiotherapy in 2012. In 2013 his doctors discovered lung metastases. After two rounds of specialised surgery, using a laser knife, Wilson has since been tumour free – although not cured.

"The black and white line between curative and palliative care has got to go. We need to adopt a grey scale of curative therapy, supportive care and end of life care. We need to get the medical community on board. Being able to cross these grey boundaries is very important.

"Many patients who are not curable are receiving tyrosine kinase inhibitors and antibodies which can extend life and alleviate disease symptoms and side-effects. Their cancer is not terminal and may never become terminal. In this context, supportive care seems a very practical and sensible term."

Alongside medical care for symptoms and side-effects and measures to prevent recurrence, Wilson lists psychological care, spiritual support and rehabilitation as key parts of supportive care. "Each patient has a set of needs which have to be connected to some form of service delivery attached to a menu. Patients need to be guided through the menu."

Higginson agrees that the line between living with cancer and dying from cancer is ever more blurred. "For a lot of people who get cancer, the decision of whether it is curable or not curable is not so much one or the other. There is a grey area where you might be having life extension. Most advances in cancer treatment

are not new cures, rather they discover life extension or put someone back into remission."

Sometimes palliative care is given to resolve symptoms so patients can continue with potentially curative therapy. Severe mucositis, for instance, may need treating in patients with a haematological cancer. Even after a cure, palliative care may be appropriate. Higginson gives as an example someone who was successfully operated on for lung cancer but had a pre-existing chronic obstructive pulmonary disease. "They suddenly got very breathless. The problem was that surgery removed a big part of their lung, and because they had been sitting still they became debilitated. We are able to make them feel a lot better by treating their pre-existing lung disease and strengthening their muscles."

Nathan Cherny, director of Cancer Pain and Palliative Medicine Services at Shaare Zedek Medical Center, Jerusalem, chaired the ESMO palliative care working group from 2008 until 2013 and has led efforts to integrate palliative care into oncology. He wishes change would happen more quickly. "Oncologists in general are very quick on the uptake of disease-modifying new innovations, but palliative care is one of those innovations where the oncology world in general has been fairly slow. There is a mind-set problem."

Cherny argues that the treatment of patients with early-stage disease and a high possibility of cure is the easy part of cancer treatment. "The care of patients where there is no prospect of cure, integrating the best anti-cancer treatments with the best supportive and palliative care strategies, is much more difficult," he says. "It requires personal and infrastructural resources, and is much more reliant on interdisciplinary cooperation. There is a need for a higher level of specialisation and expertise to assist in management and optimising the outcomes for these patients."

Integrated care or separate specialty?

In Cherny's Shaare Zedek Center, oncologists have palliative care training and the two services share a team of social workers, psychologists and spiritual care providers. They also share space in the day hospital, allowing patients to be screened by palliative care nurses with members of the multidisciplinary team on site to provide care in real time. "The patients who have got physical and psychological symptoms are the same patients who are presenting for chemotherapy or other treatments in the oncology day hospital," says Cherny.

Most specialists agree on the need for a close working relationship, but believe that palliative care should remain as a distinct specialty. Philip Larkin says: "Palliative care has something unique to offer to the care of patients. In the same way as you have a gerontology team or an oncology team, you should have a palliative care team."

Higginson says this is especially important as palliative care expands its role for patients with stroke or heart diseases or other conditions. "Increasingly, people who have cancer are also elderly and have arthritis or respiratory conditions or heart disease, because people who get cancer are living longer." This older age group often misses out on palliative care, and extending provision is essential to avoid discrimination, she says.

However, Higginson also sees the benefits for patients of inviting palliative care specialists into the multidisciplinary team. "I bring something that a lot of other people in the room cannot bring: a wider view of the person's other medical and health problems. Palliative care doctors are very good at looking at the whole person.

"Oncology is becoming more specialised as oncologists learn more and more about the specific management of groups of tumour cells. You expect the oncologist to have a certain level of core skills in palliative care, but it is not enough to say oncologists can do it themselves – that would imply

"Palliative care is an innovation where the oncology world has been fairly slow. There is a mind-set problem"

"I bring something that a lot of other people in the room cannot – a wider view of the person's other health problems"

that what we do in 10 years' time will be the same as what we do now. Without a specialty, that is what you would get."

Palliative care is increasingly seen as cost-effective. Xavier Gomez, who developed the Catalonia Project – a WHO demonstration project that provides inpatient, outpatient and community-based services for more than 23,000 patients across a region of 7.3 million people – says that the €52 million spent on delivering this type of care results in a net saving of €16.7 million by reducing use of acute and emergency beds.

Despite this growing consensus, there are huge gaps in care across Europe, and a need for further research. In 2010 the EU provided a grant worth €4 million to create a EURO IMPACT network in palliative care research, aimed at monitoring and improving palliative care. However, in 2011 Irene Higginson reported that just 0.2% of cancer research funding in the UK was being spent on researching palliative and end of life care.

Personalised care

For the palliative care specialist, 'personalised care' means much more than targeted drugs. In his work for ESMO, Cherny promotes a human approach to cancer care, where personalised medicine is about the person, not just about the science, and where people who cannot be cured are just as important as those who can. "There is a clear tendency to focus on the hope for a cure or of avoiding disease or early detection. The patients who are not going to be cured are in a sense like the ugly step-sister of cancer care.

"The term personalised medicine has essentially been hijacked to reflect the bio-science model of medical care, and I think we need to vigorously reclaim the social model. Targeted approaches are potentially important, but biological targeted therapeutics is only a part of personalised medicine.

Cherny argues that patients want to be seen and treated as more than the biology of their diseases. They want a commitment of care that is sensitive to their complex and often changing needs, and they want physicians who are confident, empathetic, humane, personal, forthright, respectful, and thorough.

"When patient needs are well tended and the patient is well cared for, the surviving family will never forget the experience. When they are neglected, it results in harm to the patient and long-term harm to the surviving families – it is never forgiven."

Irene Higginson uses similar language: "I would really like to recapture person-centred and individualised care being about what the individual needs, with all their diseases, rather than it just being about their genetic make-up," she says.

Higginson devised the Palliative Care Outcomes Scale (POS) to capture patient priorities and concerns, beyond what can be seen in blood tests and scans. "POS tells you what problems someone has, their symptoms, and what matters to them. It is a bit like having a scan for how the person is. We are finding for some diseases that POS is a better marker of deterioration than biological tests. How the person is feeling goes off first, before their blood tests reveal it."

This suggests that patients should be given a greater role in assessing their own conditions. However, some clinicians are reluctant to let go of their high-tech security blanket. "That's interesting," observed one colleague, looking at her data. "It shows we need a better biomarker."

Higginson sighs: "Why don't we just get better at asking people what their symptoms are? We do all these fancy tests to look inside the body, when simply asking someone how they are tells you a lot."

ECONOMIC BENEFITS

The Catalonia palliative care project led to overall savings of €16.7 million due to reduced use of acute and emergency care

She feels that open-ended questions, such as "What is your main problem at the moment?", give patients permission to raise issues they did not think the clinical team would want to know. "The job of the clinician is to read those things and try to respond," she says. "We medics tend too much to go on knowing the answer rather than finding out where the person is."

POS has identified neglected physical issues, including breathlessness, fatigue and weakness, as well as psychological issues, ranging from the need for information to depression, anxiety and fear, and family issues.

Supportive care or palliative care?

The language used to describe care and therapy reflects nuances and differences of approach. ESMO distinguishes between 'supportive care', to optimise comfort, function and social support at all stages of illness; 'palliative care', when cure is not possible; and 'end of life care', when death is imminent.

Roger Wilson would expand the definition of 'supportive care' to cover everything between a cure and end of life care, and drop the term 'palliative care' altogether. But Philip Larkin, while supportive of many of Wilson's aims, is concerned that language should not confuse patients. "When people speak about the 50% of people they cannot cure as having supportive care, it is not entirely clear who delivers it and where palliative fits within that. We as professionals have a responsibility to be very clear about who we are and what we represent, so that patients don't get misleading messages."

He cites the case of a man with prostate cancer having radiotherapy to prevent spinal cord compression and reduce the risk of paralysis. "We know that the radiotherapy is simply to manage the condition. My concern is, does the patient understand that it is not curative? Is there something within them that is hoping that it is?"

Larkin teaches his students that honesty is the best policy, but says that does not mean it has to be brutal honesty. "The first few meetings can be quite gentle as you feel your way to figure out where people are at," he suggests. "On a first visit a patient may say: 'The doctor says you are a pain specialist'. I would say, 'Yes, I am here to deal with your pain and I come from the palliative care team and we look after the symptoms.' I am constantly checking in with people. Do they have a concept of what the palliative care team means?"

It's not a question of having to talk about death and dying, he adds, but of being honest with patients about who you are and what your role is. "There may come a time when I need the patient to trust me; that won't happen if he feels that I misled him at the beginning," says Larkin.

End of life care

The fact that palliative care has a role to play in many stages of treatment should not disguise the fact that it still has a critical role when a patient is indeed dying.

Larkin challenges his palliative care students to think about what they can do for people who are dying that is different to any other practitioner. "What is your added value, because all nurses care for dying people?" They came to the conclusion that they have particular expertise in managing the transition between living and dying. "If a patient is given bad news about their illness, one of their questions they have in their head is 'How long have I got?' That is something that palliative care is very good at being able to manage in a sensitive way. They are able to lead patients and families very gently along a path of realisation."

Larkin was amazed, when working in the West of Ireland, at how rural communities could read indicators. "There was myself and four women in the community team, and they used

"The term personalised medicine has been hijacked to reflect the bio-science model of medical care"

"We do all these fancy tests to look inside the body, when simply asking someone how they are tells you a lot"

to say that if the women came you were doing fine, but if the man came you were on your way."

They would watch who came to the door and what they brought with them, especially looking out for the syringe driver that allows a combination of drugs to be delivered subcutaneously (and is today used in the active management of symptoms). Larkin recalls: "The lay perception was that if the syringe driver came to someone's house, it meant they would be going to a funeral in two or three days."

Roger Wilson believes patients need support to address issues of life and death and their spiritual needs from an early stage. "It comes down, at the end of the day, to being able to answer for yourself some of the difficult questions like, 'Why did I get this and what happens to me now? If I am going to die – what happens?'

"I am definitely not talking about religion. For people who have a religion, their minister can be a tremendous support and guide, but for those who do not have a religion or reject religion, there is still something needed – some form of existential counselling. 'I am going to die – what happens?'"

At a critical moment, Wilson found his own guide. "I went through a very bad time psychologically when I had the first recurrence – the regional metastasis in 2000. I found a counsellor who was a Buddhist. I got a lot of very practical approaches to living and to dying.

"I have a very, very supportive partner. I could not imagine surviving without her. Your partner probably has a rougher journey in many respects. I go into hospital and lie on a couch and they stick needles in me or chop a bit out. There is a predetermined course and you get on with it. For her, there are all kinds of uncertainties during that 12 or 24 hours."

He has had a long time to think about his own illness and his own mortality. "I feel very committed to talking as openly as I can. I want others to open up and to get their views in the whole context of supportive care. As far as I am concerned, I am not fighting cancer. I am not going to be a loser as and when I die. I am someone who hopefully will be remembered for having done his best to come through it, face it, and help other people through the challenges it presents." ■

SURVIVAL BENEFITS

8.9 months

11.6 months

Integrating palliative care with anti-cancer treatment not only improves quality of life, but can even extend life, as was shown by the Temel study of patients with metastatic non-small-cell lung cancer (*NEJM* 2010, 363:733–742)

What did we learn from the European Partnership for Action Against Cancer?

ANNA WAGSTAFF

The recently concluded Partnership programme marked the first time that EU member states have taken a joint approach to improving cancer plans and the organisation of services. Was it a worthwhile exercise? And where do we go from here?

Can countries improve the way they organise and deliver cancer care by working together at a European level? It's hard to know until it's been tried. As member states consider healthcare to be a purely national policy area, EU involvement has not been welcome and the option has not been on the table.

Not, that is, until five years ago when a limited opportunity opened up with the establishment of the European Partnership for Action Against Cancer (EPAAC), "to more effectively coordinate activities and actions that are taken within different policy areas by Member States and other stakeholders, with the aim of reducing the increasing and unequal European burden of cancer." (Communication from the European Commission COM/2009/0291).

The Partnership was set up by the European Commission in June 2009 to run for five years. The move was in response to sustained pressure from some member states, from the European Parliament and from many European advocacy groups, who wanted the EU to continue the efforts started with Europe Against Cancer, a programme that ran from 1987 to 2000.

However, this new initiative differed from its predecessor in three important ways.

- Its work was to be carried out through a 'Joint Action', led by representatives from participating member states, rather than through the Commission.
- Its budget was around 80% smaller, shared equally between the participating member states and the Commission.
- Along with health promotion, quality screening, statistics and indicators, its remit included healthcare policy and organisation – areas that had been out of bounds for previous European work on cancer.

Shared solutions to a common problem

European countries are struggling to cope with common problems of ageing populations, rising rates of cancer, more people living longer with cancer, and escalating costs

of treatment, at a time of tight constraints on health spending, so working together to find solutions should make perfect sense.

Yet major differences in the organisation of healthcare across countries raise questions about how feasible or desirable it is to coordinate the search for solutions. National histories, cultures, and priorities are reflected in which healthcare professionals deliver what services in what settings, as well as in who is responsible for commissioning healthcare and how it is funded, governed and evaluated. These differences are jealously guarded under the principle of 'subsidiarity', which defines healthcare policy, among other areas, as the sole prerogative of each member state.

The great advantage of working together through a Joint Action was that this is a voluntary activity led and organised by member states that wish to be involved, and it was therefore free from any sense of 'Europe' telling countries how to run their health services. The potential downside, however, was the challenge of organising work across the full spectrum of cancer control, entirely through co-operation and compromise. Participants – not just member states, but also all interested partners, from professional groups, institutes, advocacy and industry, working at international, European, national or even regional levels – brought to the table their own agendas and were invited to a 'horse trading' session to agree the full programme of action. It took a little more than a year to get the whole thing up and running.

The Joint Action came to an end in March of this year, having run for its allocated three years. Tit Albreht, who served on the steering committee and led work on cancer plans, is positive about the interaction between representatives from member states and the results achieved, given the limited resources and timescale. He admits, however, to a certain early scepticism about whether the Joint Action format could be made to work. His country, Slovenia, had played a major role in getting the project off the ground – it was at the conclusion of their presidency in 2008 that the European Council called on the Commission to present an EU Action Plan that would expressly include consideration of "the appropriate framework for effective cancer control policies and sharing best practices in cancer prevention and care". However, the idea that the programme would be patched together from the various agendas of interested parties, was not necessarily what they had had in mind.

Of the 10 'work packages' that emerged from the horse trading, Albreht mentions, in particular, the one on healthcare. "The care issue finally worked out very well. But at that particular workshop, there were so many issues put forward that I thought it would be pretty amazing if they really could be managed within a single work package. It almost seemed like a separate project in itself."

The work package in question had no fewer than 12 'deliverables', including the "identification and assessment of best practices on organisational approaches to cancer

Differences in how healthcare is organised raise questions about the feasibility of finding common solutions

"The networks issue has been very local or regional and there are few forums to discuss experiences"

care" – which might be seen as a field of study in its own right rather than merely one of 12 topics in one of 10 work packages of a three-year project. Other healthcare topics included the feasibility of harmonising clinical guidelines at an EU level, developing common standards in care for children with cancer, assessing palliative care needs, and implementing clinical guidelines.

The man in charge of delivering on these deliverables, together with 15 collaborative partners and 14 associated partners, was Josep Borràs, a professor of public health at the University of Barcelona, director of the Catalan cancer strategy, and scientific coordinator of the Spanish cancer strategy. Happily, this latter role, which involves reaching agreement between Spain's highly autonomous regional health systems and the ministry of health, had given him plenty of experience in consensus building, and he welcomed the diversity of both the participants and goals.

Reports of the work done by the healthcare and other work packages can be found on the epaac.eu website and in a book, *Boosting Innovation and Cooperation in European Cancer Control*, which presents key findings, and is downloadable from the site. They document the successful completion of the overwhelming majority of the planned projects. For Borràs, however, while the outcomes are clearly important and will have an impact, the big achievement of the healthcare work package was that it demonstrated that, despite differences between healthcare systems, it is possible for European countries to work together to improve standards of cancer care. "We showed it is feasible, and probably useful, and raised the interest of all the stakeholders," he says.

Cancer networks

Borràs singles out the discussions about networks as a model for organising cancer care as one of the more significant in terms of showing the European added value.

Conducting the analysis of different models of cancer networks was quite a challenge, he says, because there are very different models. Some are strongly supported by health administrations, while others are more informal, "more of an agreement between organisations or between professionals that works quite fluidly, with nothing very strong from the organisational point of view."

There was, however, no lack of enthusiasm, he says. "People were really interested in learning from other experiences, because the networks issue has been very local or regional and there are few forums to discuss experiences. Most of them don't even have a proper evaluation to be published and discussed. There are a couple of assessments of networks in France, Spain or Italy, but there is not a body of knowledge. In that way the interest of the partners involved was very high and they were very happy with the experience."

Three networks were analysed in detail: one in the Lombardy region of Italy, another in Belgium and the third in Spain. Participants from four further networks, in England, France, the Netherlands and Denmark, also

BEST PRACTICE FOR CANCER NETWORKS

The consensus conclusions on best practice for cancer networks reached by the EPAAC healthcare work package include:

Organisation: Some level of structure and leadership is essential to give stability and continuity. This may require some adjustment to regulation and funding mechanisms, which often do not facilitate inter-organisational coordination.

Patient input: Many networks were struggling with this, often because of lack of organisation – patients can't have a voice when there are no structures they can participate in.

Primary care: GPs and other primary healthcare professionals will have an increasingly important role, particularly in the care of patients living with cancer, so networks need to find effective ways to relate to this sector.

Evaluation: This was recognised as a key element of good practice, even though currently it is carried out only by a small minority of networks. Linking outcomes data to cancer registries was suggested as a way of monitoring quality and driving quality improvement.

contributed at a workshop on the topic, which developed a consensus over best practice that was felt to be valid across all health systems.

With the EPAAC work now over, Borràs is looking forward to carrying on Europe-level work on networks and the organisation of cancer care through a new Joint Action, which will run for a further three years, under the title CANCON. This will be the final funding for joint actions on cancer and Borràs wonders how the opportunity to work together on these issues, which has engaged and enthused so many participants from so many countries, will be able to continue.

Cancer plans

Albreht, who heads up the Centre for Health Care at Slovenia's Institute for Public Health, reports a similar level of engagement and enthusiasm among people from the different member states working with him on mapping and analysing cancer plans in Europe, with a view to drawing up guidelines of best practice.

He points out that giving government representatives the chance to exchange information and experiences directly is much more productive than exchanges confined to academic discourse or conducted at ministerial level: "you didn't have this political style of plenary discussion of what are basically professional issues, but it operated more as a sort of 'back office'". Representatives from Slovenia, the Netherlands, Belgium, Ireland, Malta and Italy formed a 'core group', with other countries, including Finland, Germany, Spain and France, also contributing a great deal. But it was the level of engagement and interest right across the 27 countries of the EU, plus Norway and Iceland, that was the most pleasant surprise. Albreht had anticipated having to spend time and effort getting countries to respond to the survey sent out to establish whether they had a cancer plan, and if so how it was organised and what it covered. In the event, few needed prompting, and the real problem became analysing the large amounts of detailed information that came back. Most countries also took great interest in the results of the survey, "which helped engage national and regional health authorities in the analysis of the plans," says Albreht "and prompted them to take a more critical look at their own."

Participating in the work was harder for smaller member states, particularly those without their own cancer strategy; in some cases a single person in a ministry is responsible for all non-communicable diseases. But there are ways around this, says Albreht, such as appointing an expert to be the point of contact on cancer policy issues, "something I feel actually developed during the course of EPAAC in quite a few member states."

There were also some warning shots fired by countries worried about being pressured into doing things against their will, he adds: "For instance, there were some member states who said: 'If you are going to present a list of new indicators then you can forget about us ever discussing this'– though this was in fact never our intention."

Their work was made easier, says Albreht, by the wide diversity of countries involved: small like Malta, large like Germany, highly centralised like France, and highly regionalised like Spain. Some had a strong emphasis on primary healthcare, community care, and nursing involvement, others were more geared to high-end care in a hospital setting. Each had a different funding mechanism and service delivery model. Albreht believes that this diversity made compromise easier. "If you are seeking solutions on the basis of what will work, for instance, in a decentralised system, then the centralised systems may feel that is not something they will want to pursue. I'm not saying that in the EU you have to go for the minimum common denominator at any cost, but you have to take note of important differences in health systems – and not just in health systems but simply in the way that a country operates."

A consensus was reached about the key elements of a well-structured national cancer plan, which is shown overleaf. A guide on how to develop cancer plans, with sections addressing each aspect, is currently being finalised and will be published on the epaac.eu website very shortly. The

Interest in the results of the survey of cancer plans prompted countries to take a more critical look at their own

"We are always showing something is feasible, and then we stop and have to begin again"

guide will also define a set of indicators by which countries can monitor progress on each aspect of the plan – which will be the bare minimum needed to do the job, Albreht hastens to add.

Like Borràs, who led the work on models of cancer care organisation, Albreht believes that the experience and outcomes of the EPAAC Joint Action show that it is feasible and highly worthwhile to work together to find common solutions in healthcare. He is hopeful that a way will be found to continue the work started by the Partnership after CANCON finishes in 2017, though quite how this could be done remains an open question.

"We don't have a European Cancer Institute or any supranational institute that would take this over, and I'm not authorised to say one should be established, though we feel that a European Union body should be responsible for the future steps after 2017." He sees the agreement to re-establish an EU committee of experts nominated by member states as a welcome start, "but of course an experts' committee is not a structure that can deal with day to day challenges."

One possible solution would be to extend the remit of an existing structure, such as the European Centre for Disease Control, in Stockholm, which currently only deals with communicable diseases. "There are people who ask: why do we invest this effort of having a 300-strong staff worrying about a problem that is clearly a known and important challenge for health systems, but is not comparable from the point of view of the burden of disease, cost, and cost in the burden of life. So there are voices that say there should also be a department for non-communicable diseases, and such a department could have an analytical and monitoring role, as opposed, for instance, to just being a data collection centre."

His sentiments are shared by Josep Borràs. "Now we have shown that this is feasible and probably useful through many experiences within EPAAC, I think something more permanent should be provided by the EU, to promote these kinds of changes in a more permanent way. We are always demonstrating something – showing that it is feasible – and then we stop and have to begin again, but in a slightly different way, because continuing in the same way is not considered appropriate. So one of the issues here is to guarantee some kind of continuity."

Neither Borràs nor Albreht is a 'eurocrat', and both have taken high-level responsibility for improving cancer care in their own countries. Their verdict is that EPAAC did indeed demonstrate that countries can improve the way they organise and deliver cancer care by working together at a European level. The question now is whether these countries can agree a long-term way to allow this to go forward in a smooth and continuous fashion. ■

BEST PRACTICE FOR CANCER PLANS

This EPAAC work package involved representatives from all member states, EUREGHA (which represents regional and local health authorities), WHO Europe, the European Observatory on Health Systems and Policies, and others.

A survey revealed that, by the end of 2011, 23 out of 27 member states already had some kind of a cancer plan. While some were truly comprehensive, others exclude key areas of care, particularly in relation to survivorship issues, while a few focused exclusively on rolling out new areas such as screening.

A consensus was reached on the elements that should be present in a truly comprehensive cancer plan, which formed the basis for drawing up a guide countries can refer to in developing their own.

These include:

- Governance
- Cancer data and information
- Psychosocial care
- Palliative and end of life care
- Resources, infrastructure, technology, drugs and cancer-specific expenditure
- Survivorship and rehabilitation
- Early detection and screening
- Cancer prevention and health promotion

Top trials group turns its attention to survivors

MARC BEISHON

EORTC boosts efforts to address the long-term problems faced by people who have been treated for cancer.

The number of people who are living long lives after cancer treatment has been rising year on year, leading to a quadrupling of this population between 1975 and 2005, with an estimated 35 million survivors now living in the developed world. Yet interest in their needs has developed only recently.

One reason is that the issues faced by survivors vary greatly owing to differences in ages and cultures, and also different cancers and treatments. There is a wide spectrum of needs and priorities. Even the word 'survivor' carries different connotations for different people – some do see themselves as having battled through and are happy to have survived long after diagnosis and treatment, but others don't want to be 'labelled' in a way that ties them to such a major event once they are told they are cured. Many people living with metastatic disease also reject the word as not reflecting their day-to-day lives.

Yet 'survivorship' is a term that has become widely adopted for a field of research on care and support for the phase of life that follows primary treatment to the end of life, or recurrence (different definitions are used), covering a wide spectrum of issues – health, psychosocial and economic – that are common to people who have been treated for cancer.

Most of these issues are still poorly recognised and, all too often, survivors are being left to try to organise the care they need on their own.

This is an area of research where the US took the lead and remains well ahead of Europe. But Europe is now beginning to catch up, with a number of important initiatives launched

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

in recent years (see box overleaf), including the establishment of a collaborative group on survivorship, a network for survivors of child and adolescent cancers and the UK launch of the first national integrated programme to ensure every patient has their needs assessed and a care plan developed as their anti-cancer treatment comes to an end.

Most recently, the EORTC, which organises and coordinates clinical and translational research across Europe, stepped into the arena, launching its own cancer survivorship task force, and organising a two-day survivorship summit in Brussels this January.

Elizabeth Moser, chair of the task force, and head of radiation oncology at the breast unit of the Champalimaud Cancer Centre in Lisbon, outlined to the summit participants the nature of the challenge they are trying to address. "We have to spread information to clinicians, social workers and care givers. But do we have the information on the size of the problem – how many survivors there are and how many are at risk, and what we can do to avoid worse outcomes?" Much more data are needed to inform guidelines, said Moser, and although much has been done to reduce toxicities in cancer treatments, there is

"There have been five decades of large-scale clinical trials, and data can now be collected from those patients"

"Little is known about combination of treatments, modern radiotherapy techniques, targeted agents..."

a big knowledge gap in long-term follow-up.

The good news, she added, is that there have been five decades of large-scale clinical trials, and data can now be collected from patients who underwent them. This, however, requires much greater organisation and communication across countries, and will be the biggest part of the survivorship research effort.

The task force is calling for collection of patient data from around Europe to provide the basis for developing prediction risk scores for late physical and mental effects. It also wants to collect information on current management of late-effects at national level, and promote broad networking among not only primary care professionals and patient advocates but also politicians, the insurance industry and economists.

As a research organisation and a pioneer of quality of life measures, the EORTC is well-placed to coordinate research into late treatment effects from its clinical trials work, and it recognises the urgency of this work, as current information on late-effects is often hopelessly out of date. As Moser and colleagues point out in setting out the rationale for the survivorship task force, while there are well-documented serious late-effects from chemo- and radiotherapy, "the literature is focused on treatments dating from the 1960s to the 1980s" – and many of these are obsolete (*Eur Oncol Haematol* 2013; 9:74–76). "Little is known about combination of treatments, modern radiotherapy techniques, targeted agents, and hormonal treatments. Few studies have obtained data directly from patients and/or have considered preexisting co-morbidity, lifestyle, and obesity of survivors. There are few guidelines for the management of adult cancer survivors, and little is known about management and barriers in healthcare within different European countries."

Initially, the task force intends to look at the main physical late-effects such as heart problems and secondary cancers following certain common and rare primary tumours (in adults, not children) – lymphoma, breast, colorectal, prostate, gynaecological and testicular. However its remit will also cover a broader range of issues encountered by cancer survivors, including infertility and sexuality, cognitive dysfunction, and social impact, such as difficulties in obtaining work or insurance.

Early results

Moser reported on the initial survivorship research, in lymphoma trials. Questionnaires were sent to thousands of patients across Europe, which has so far resulted in published studies on semen preservation, premature ovarian failure, and parenthood. Analysis of factors such as radiotherapy dosing and impact on overall health, work, finance and more is yet to come. It's a lot of work, she said, and needs to take into account sources of bias

CATCHING UP WITH THE US

Europe has been slower than the US to focus on the problems faced by survivors, but a number of initiatives have been launched in recent years

1986 US National Coalition for Cancer Survivors is launched.

1996 US National Cancer Institute sets up the Office of Cancer Survivorship.

2000 American Society of Clinical Oncology launches the Study of Cancer Survivors.

2008 The Pan-European Network for Care of Survivors after Child and Adolescent Cancer, PanCare (pancare.eu), is launched (see also *Cancer World* 2014).

2008 National Cancer Survivor Initiative starts in England (ncsi.org.uk), and produces a model for planning care that is ahead of the US in terms of health care organisation, particularly with respect to primary care.

2012 The European Collaborative Group on Cancer Survivorship (ecgcs.eu) is established.

2013 CANWON, a cancer and work network, is launched to address workforce-related issues for cancer survivors.

Survivorship now also features as part of the activities and conferences of organisations such as the European Cancer Patient Coalition (ECPC) and Europe's medical and radiation oncology societies ESMO and ESTRO.

such as people who have died.

This work on lymphoma and also leukaemia survivorship is now informing solid tumour research. Moser mentioned a survivorship project on early breast cancer, which aims to update the results from six trials that took place between 1986 and 2011. Barriers must come down between tumour-specific groups, she said, because late-effects such as second malignancies and cardiovascular problems are often related to specific treatments rather than specific cancers.

A multidisciplinary effort will also be crucial in addressing issues such as fertility, cognitive dysfunction, and psychosocial functioning – the latter being the most complicated because of the variety of factors.

Can we also intervene in the lifestyles of survivors? Moser pointed out that it is particularly hard to influence younger people, who often drink and smoke, increasing their risk of developing problems later on. Other speakers emphasised that taking exercise, changing diet and making other lifestyle changes can greatly improve outcomes and/or quality of life, but noted that peers rather than health professionals are probably the best influencers. The American Cancer Society has drawn up nutrition and physical activity guidelines for cancer survivors, reported Catherine Alfano, deputy director of the US National Cancer Institute's cancer survivorship research programme. She added, however, that while exercise and maintaining a healthy body weight are the best ways to tackle survivorship health problems, convincing someone with fatigue to take a walk can be hard.

Long-term data

The need for long-term data, especially on toxicity, was addressed by Connie Vrieling, a radiation oncologist from Switzerland. Looking at breast cancer, she noted how more patients are living with the consequences of treatment – "and if we stop at ten years in the follow-up of our trials we simply do not get the data." As an example, she gave data from long-term outcomes from treating DCIS breast cancer with either excision or excision plus radiotherapy – and noted that a higher rate of secondary cancers in the radiotherapy group could call into question applying radiotherapy to all women. She also asked whether it is possible to get at data on risk factors such as smoking – in some places this is possible – and she mentioned the potential for gene expression and proteomic profiling from studies where tissue is stored.

Researchers, health policy makers and advocates are not the only ones with an interest in long-term data on cancer survivors, however. Delegates at the summit may have been surprised to hear no fewer than three presentations from insurance and banking executives in the opening session. As the executives made clear, their companies need the data too so they can accurately reflect the risk they undertake in offering cancer survivors products such as life and travel insurance, and loans.

Insurers are major number-crunchers in their own right, as they collect information to inform their risk assessments. John Turner, of reinsurer Swiss Re, said that cancer is the cause of two-thirds of private critical illnesses payouts in the UK, and few claims are denied. But what about insuring people who have had cancer? "The problem is how we make it insurable – it is a serious threat to life. But we have to reflect the improvements in survival." He charted how insurers model insurance applicants with a history of cancer, and how things have changed – the current recommendation for stage 1 breast cancer is to offer a standard premium after two to three years – whereas in 1995 that wouldn't have been offered until after ten years.

Krish Shastri, chief executive of InsureCancer, a travel insurance firm that only insures people who have a diagnosis of cancer, said: "For us, survivorship starts from the minute of diagnosis to the end of life," noting that for his business, it is hospitalisations that carry the most risk – and there are very few data on this. Travel for all sorts of reasons is crucial to quality of life, he added, and he appealed for more knowledge from aggregating European data that would enable better insurance underwriting to address the frustration voiced by many survivors about the lack of affordable insurance options.

"Use of radiotherapy to treat all DCIS could be called into question if data show it leads to more secondaries"

Cancer registries can be used to send out questionnaires to collect data on quality of life

Patient-reported outcomes

Lonneke van de Poll-Franse, professor of cancer epidemiology and survivorship at Tilburg University in the Netherlands, described how data can be collected on quality of life, with reference to the Eindhoven region where the cancer registry is used to send out questionnaires in an open access project called PROFILES – Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship. Patients are being asked about quality of life after a range of cancers and for specific conditions such as chemotherapy-induced peripheral neuropathy (see also Protecting Patients' Nervous Systems, on page 12). About 60% of patients aged under 50 in one sample reported problems in obtaining life insurance, for example.

As she added, by continuously monitoring the long-term impact of cancer and new therapies, registries become focused on patients, not just cancer. "By collecting data on patient reported outcomes, we can contribute to discussion on the added value of new therapies in daily clinical practice, and also socio-economic implications." Other registries are doing the same, she said, citing a systematic review that looked at how this is a work in progress as a resource for survivorship studies (*Cancer* 2013, 119:2109–23).

Kathy Oliver, from the International Brain Tumour Alliance, spoke on the input that advocacy can provide for the clinical trial community, affirming the need to build patient-reported outcomes into research, and mentioning biobanking as another area for collaboration with patient groups. She also added yet more items to an already long list of survivorship issues, such as the guilt often experienced by survivors, and she emphasised how important care plans are once main treatments ends.

An integrated national survivor plan

It was fitting that the UK's approach to survivorship care plans was presented at the summit, given the lead

PREVALENCE OF LONG-TERM EFFECTS

At least **1 in 4** (500,000) people in the UK are facing poor health or disability after treatment for cancer

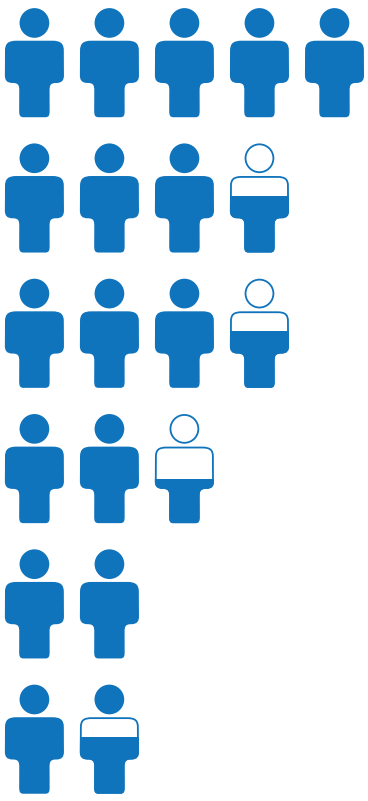
At least **1 in 6** (350,000) people living with and beyond cancer are experiencing chronic fatigue

At least **1 in 6** (350,000) are having sexual difficulties

Around **1 in 8** (240,000) are living with mental health problems, which can include moderate to severe anxiety

At least **1 in 10** (200,000) are living with moderate to severe pain after curative treatment

Around **1 in 13** (150,000) are affected by urinary problems such as incontinence



These estimates relate to the UK's population of around 2 million cancer survivors. The picture is likely to be broadly similar across Europe.

Source: Throwing Light on the Consequences of Cancer and its Treatment (2013) Macmillan Cancer Support

the country is taking. Jane Maher, National Health Service improvement lead for cancer, said that by 2009 it was recognised that one in three patients had unmet needs by the end of their treatment, from a population of two million survivors. She outlined the stages between treatment and end of life – recovery, early and late monitoring, and progressive illness – and pointed out that differences between cancers means the timeframes for these stages can vary widely.

Central to the strategy, she said, is a recovery package surrounded by reviews, care planning, wellbeing events, financial support, and managing treatment consequences. These have been shown to help the majority of breast cancer survivors, and about half of survivors of colorectal and prostate cancer, into 'self-management' away from hospitals. To enable this, a holistic needs assessment is used to 'shape a conversation' at the end of treatment, from which a care plan is sent to the person's GP. The GP then writes a treatment summary, which is a tool to improve communication between cancer services and primary care. Testing of both paper and electronic needs assessment has been underway for some time in about 200 hospitals.

Maher said it is a big challenge to change the perception of cancer from only being managed in acute settings to one where the outside community shares its perspective with specialists, and there are clearly major cultural and organisational differences among countries. One approach to care planning may not work elsewhere.

The message from the summit is that cancer survivorship is on a steep learning curve and there is a long journey ahead, given the many issues and the rising numbers of survivors. But there are steps that can and should be taken now, such as combining current data and making it widely available, starting to plan for care, support and prevention, and collaborating both at European level and worldwide. ■

A call for global collaboration

International collaboration, not just in Europe but across the world, was called for by several speakers at the summit, notably Catherine Alfano, deputy director of the US National Cancer Institute's cancer survivorship research programme. She presented five themes that she said can best be answered through global collaboration:

1. Identifying ideal care models. One way to do this is to test diverse models, such as provision from multiple agencies. Alfano noted that it is hard for countries to do this alone. In Germany, for example, it is impossible to test rehabilitation because it is mandated and cannot be randomised.

2. Learning from each other's cultural influences on care – for example people in the UK seem to be receptive to the model of 'self-management', which Alfano commented is "great", but is the opposite of what Americans demand from their providers (though she suggested it might perhaps be carefully marketed to them).

3. Technology, such as using registries to drive personalised care, telemedicine for remote areas, managing survivorship plans, empowering survivors to engage in care, and rapid learning for improvement.

4. Optimal collaboration among health providers – oncology, primary care, cardiology, physiotherapy, psychology and so on. Alfano illustrated this with a slide showing each specialist is talking to the survivor but not to each other. "Who should be responsible for survivorship care?" she asked, given challenges such as a projected shortage of oncologists and primary care professionals, and obtaining reimbursement.

5. Prevention. "We have to focus survivorship care on prevention," said Alfano. The paradigm should be to focus on health behaviours as well as late-effects, as many people with early-stage cancer will not die of the disease. It is about creating 'well survivors'. Prevention, she noted, is one of four pillars of survivorship care identified by the US Institute of Medicine, along with surveillance, intervention and collaboration. As part of the answers, Alfano considered that much could be learnt from how large businesses focus on certain projects with measurable goals, and choose partners strategically to maximise individual strengths and productivity. "If you want to go fast, go alone. If you want to go far, go together," she concluded, quoting an African proverb.

"It is a big challenge to change the perception that cancer can only be managed in acute settings"

How Europe can develop better, cheaper cancer drugs

Modern tools of biological investigation give us opportunities to develop drugs much more efficiently. The president of Europe's most important trials organisation explains how these opportunities can – and must – be exploited to start delivering drugs that are more effective and more affordable.

The road to developing a new medicine – translating a new idea into a drug licensed to treat patients – is long, often too long. Traditional drug development moves through preclinical studies to phase I, II and III trials, with increasing resources needed for each stage, from 25–30% of costs for preclinical work to the bulk of 40% for phase III late-stage development. The attrition rate is enormous. For every 10,000 compounds screened, only one will make it successfully to the clinic. But are we really sure that the remaining 9,999 others are really not useful in any way? The current approach means we don't know how many potentially useful compounds we may have missed.

The figure overleaf shows the attrition rates for therapies in recent phase III trials, with nearly 60% failing due to lack of efficacy (*Nat Rev Drug Discovery* 2013; 12:569). Oncology is the leading therapeutic area for late-stage failures. We're doing something wrong when we fail so late, and particularly in oncology if we fail more often than in other areas.

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, Roger Stupp, head of the Cancer Centre at the Zurich University Hospital and president of the EORTC, explores the challenges and opportunities associated with clinical research to develop new therapies for cancer in Europe today, and suggests key measures to optimise academic participation in future research. Denis Lacombe, scientific director at the EORTC in Brussels, poses questions raised by participants during the live online presentation.

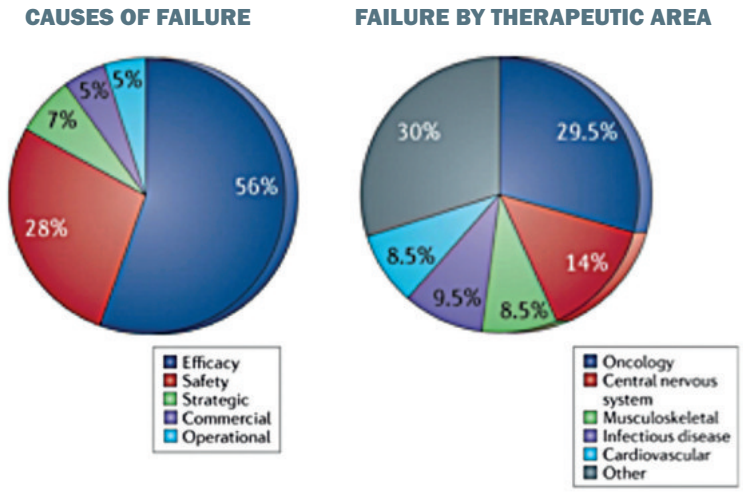
Edited by Susan Mayor.

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

Academia is currently involved rather late in the traditional drug development model (see below), usually at phase III for larger trials or at phase IV for investigator-driven optimisation or extension of indication after approval, with perhaps some work in target and drug discovery. Everything in between is largely led and organised by pharmaceutical companies, but I think there are opportunities for academics to contribute more in the earlier stages of clinical development.

Research and development costs for a novel oncology compound are more than $1 billion, and the costs are increasing. Despite this high cost, 75% of cancer drugs have no meaningful effect on the patient. The number of clinical trials has declined over the past decade, but costs and failure rates remain high. Why do so many trials fail? Up to 30% of trial sites never recruit a single patient, expending costs and effort for nothing. This could improve with better selection, knowing which centres can really deliver. Over half of the trials do not meet their enrolment targets, so will never give us an answer, which is worse than a negative trial in terms of failure to provide useful information.

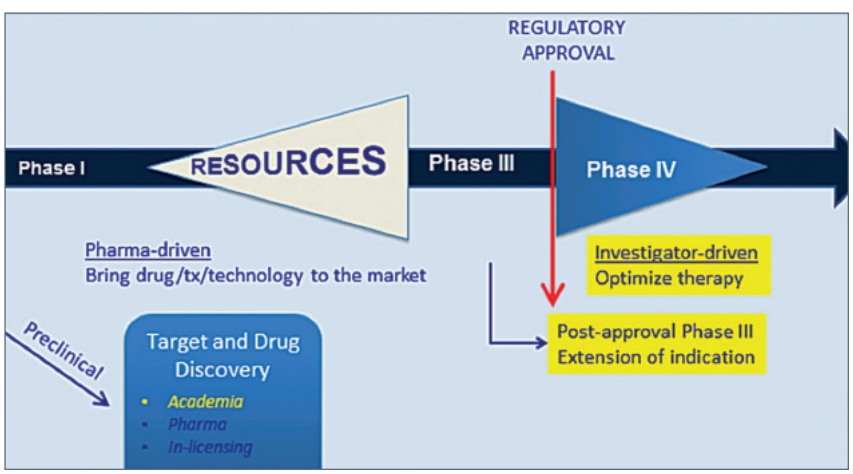
ATTRITION RATES IN PHASE III TRIALS 2011/12



Better testing at early trial stages could avoid wasting time and resources on phase III trials that are destined to fail

Source: J Arrowsmith and P Miller (2013) *Nat Rev Drug Discovery* 12:569 Reprinted with permission from Macmillan publishers Ltd

POSITION OF ACADEMIA IN TREATMENT DEVELOPMENT



Better drug development requires input from academia at a much earlier stage

The current model of drug development is not sustainable. It has a high failure rate, the high cost of new drugs results in some people being denied access and, most importantly, large numbers of patients continue to being treated with ineffective or insufficient regimens as a consequence. Drug development needs to change in a way that recognises the far-reaching changes to the landscape of how we conduct trials: with more modern and efficient tools, we can do more, and we can do it more efficiently. The landscape is also changing in how we practise medicine, moving from working in separate medical specialties to interdisciplinary disease management teams using a problem-centred rather than discipline-based

approach. Non-specific chemotherapy is being replaced by rational and targeted treatments; organ- and histology-based classifications are moving to an approach that is driven by signalling pathways, which can be used to detect patients at risk and develop more effective drugs with less toxicity. We are also moving from treating disease symptoms and loss of normal function to prevention, intervening before symptoms appear, with the aim of preserving normal function.

Towards personalised medicine

The future for more efficient treatment development is to move towards personalised medicine, resulting in the right treatment for each individual patient so they can receive the optimal treatment according to their personal profile, the host profile, and the tumour profile. The move from histology to molecular disease classification results in disease fragmentation from relatively common cancers into many different, rarer subtypes, as illustrated below for lung and breast cancer.

It is important to recognise that expression profiles of thousands of patients are needed to generate a robust gene list that accurately predicts outcomes in cancer, and some current predictors are not as reproducible as we would like to think. Only by bringing a lot of data together can we analyse molecular subtypes accurately and understand what is happening. Analysing thousands of variables in hundreds of samples poses a major challenge, requiring expert support from biostatisticians.

The idea that a targeted treatment blocking a single signalling pathway will be effective is too simplistic because there are multiple redundant signalling pathways, so blocking one means an alternative is then used. We also need to recognise that not every target identified is druggable. In order to identify druggable targets we need companion diagnostics and also standardisation of testing.

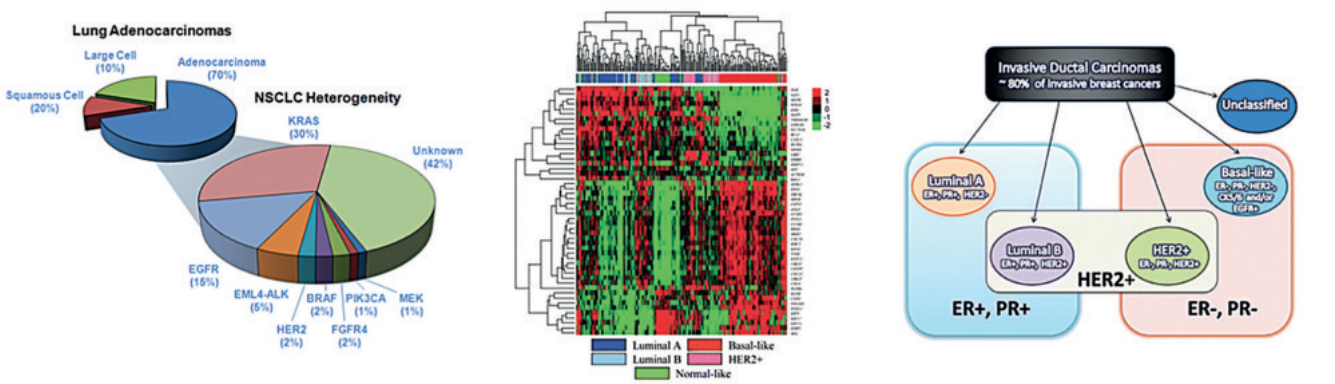
We need help from regulators to facilitate new drug development using a personalised medicine approach. Many current regulations that are designed to protect patient safety, stifle patients' access to innovation. It is important to focus on measurable parameters and define what constitutes a meaningful endpoint, including quality of survival. How low or how high do we want to set the bar for new treatments? Is a median survival prolongation of six weeks worth it? Does the median mean anything? These are all questions that we have to ask and for which answers have to be found individually for each tumour type and treatment we investigate. We need to ensure that trials are representative of the 'real world'.

Collaboration versus competition

Disease fragmentation is a challenge, but it can be overcome with effective collaboration and sharing of data, including finding a way for competing groups and industries to collaborate where there are synergies. National healthcare systems need to find ways to work together, and different medical disciplines need to collaborate.

Two examples of precompetitive collaboration are the Structural

MOLECULAR DISEASE CLASSIFICATIONS



As the disease becomes increasingly fragmented into smaller molecular subgroups, access to vast quantities of data becomes essential to accurately predict outcomes

Genomics Consortium (SGC) at the Universities of Oxford and Toronto, supported by private funders and charities, and the Innovative Medicines Initiative (IMI), which brings together the European Commission and the European Federation of Pharmaceutical Industries and Associations. They work in a precompetitive way by carrying out the basic science relevant to drug discovery. This is now done largely in the preclinical field – in imaging and in new technology – but I think we can also find ways for more collaboration, rather than competition, on the clinical side.

The issue of intellectual property (IP) is often a concern in consortium agreements, and can lead to undue delays or good ideas may not be pursued at all, even though it may be more rewarding to have a small share of a successful operation than 100% of a failure.

The changing approach to drug development requires more focus in the early phases to ensure we expose fewer patients to pivotal trials that fail (see figure). We need to ask the right questions upfront in early clinical trials: is the target present and is the target relevant for the tumour being investigated? What is the interaction between the tumour and the stroma? What redundancy of pathways is there? We also need to learn more about the pharmacology and assessing whether the drug reaches the target and if there are any off-target effects. Can we image the drug effect with modern technology?

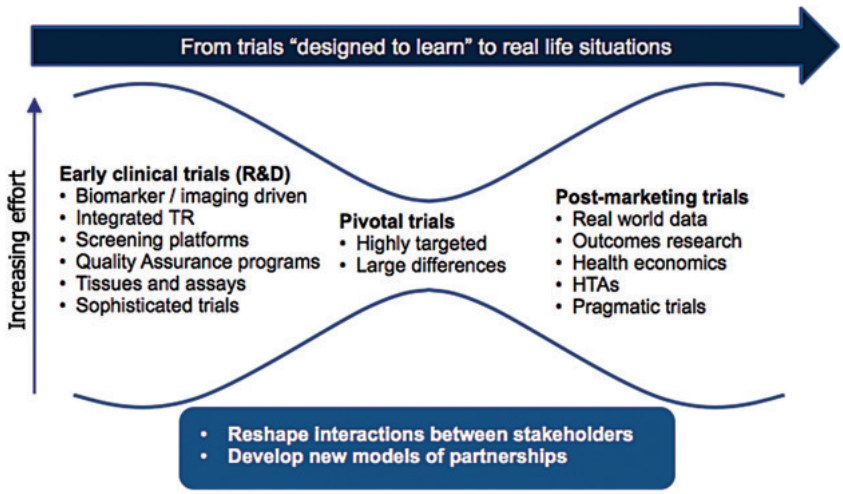
Greater investment in early clinical trials requires that we learn more from every single patient we treat, mandating translational research rather than seeing it as optional. This will ensure we expose the least number of patients to potentially ineffective and toxic agents. Then we will be able to carry out pivotal trials in enriched populations, which will require fewer patients to demonstrate efficacy, because there will be a much greater signal. We can then move on to test a new drug again on a larger scale in the real world, which requires learning how to collect data in a simplified manner. We need to reshape the interaction between the different stakeholders and develop new models of partnerships. Data collection and data sharing is in the interests of each and every patient, and it should be mandatory – overemphasising data protection obstructs progress.

Everybody talks about translational research, however not much is done in practice. One way the EORTC is addressing this is with a molecular screening platform – the Screening Patients for Efficient Clinical Trials Access (SPECTA) platform. This 'takes the trial to the patient' by ensuring tumours are subtyped and categorised at a molecular level early on, and then if their cancer recurs after standard treatment upfront they can enter a trial for second- or third-line treatment that fits their characteristics. This requires collaboration between industry and academia to ensure new treatments can be used in appropriate patients. Having an independent molecular screening platform ensures that patients can be directed to appropriate trials.

In this approach the patient's tumour tissue goes to a biobank upfront where it is analysed in a quality controlled manner, and the information is stored in a clinical database. If the patient progresses, information is exchanged to assess suitability for trials of novel treatments that would be appropriate. The trial may sometimes go to the patient or sometimes the patient will travel to the trial.

The EORTC SPECTA programme tries to categorise different types

RESHAPING DRUG DEVELOPMENT



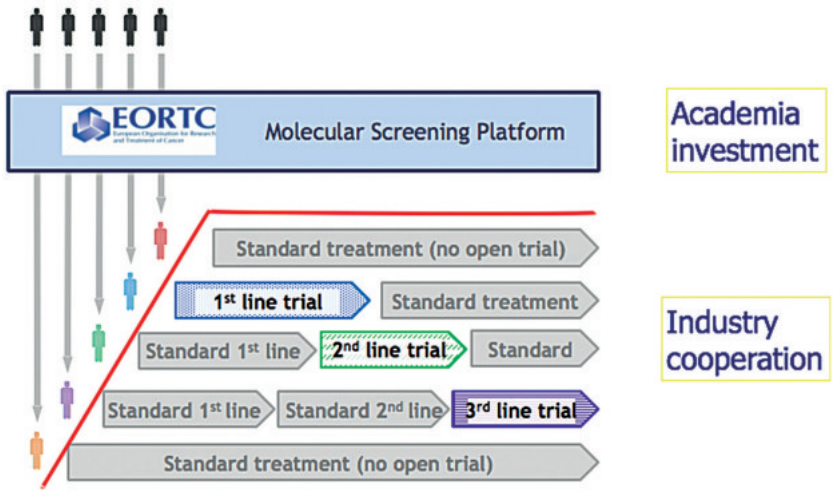
Greater effort made at an earlier stage will increase the chances of successful pivotal trials

of cancers. A platform is already up and running in colorectal cancer, with others in advanced development for lung, prostate, brain and melanoma. We are working closely with pathologists, experts in biobanking, biostatisticians, industry, patient representatives and regulators to ensure procedures meet regulatory standards.

Standards and quality assurance are essential to ensure that pathology and molecular testing are done in the same way in different laboratories. Individual academic laboratories alone may not have sufficient numbers of samples to fulfil accreditation and standardisation procedures; however, collaboration with a certified platform may allow them to develop the expertise in a specific area. A centralised platform offers a service that can be much cheaper and more efficient.

The EORTC infrastructure supports new-generation clinical trials. We have quality assurance platforms in radiotherapy, and we have a platform for imaging so that we can analyse and compare images in a unified way.

ACCESS TO CLINICAL TRIALS



Screening patients for their molecular subtype at the time they are diagnosed can help ensure they are quickly enrolled into relevant trials if their disease progresses

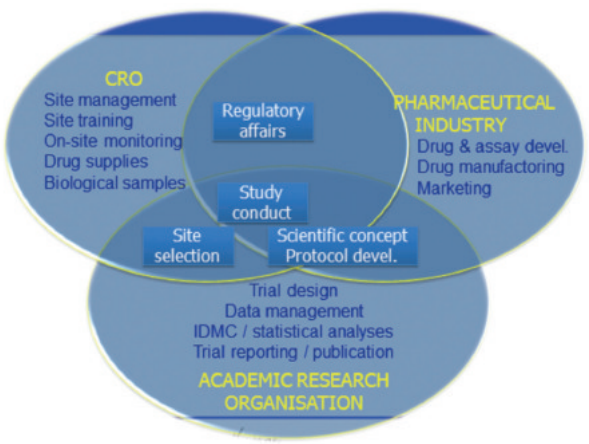
Where do we have opportunities as academics?

I think there are plenty of opportunities for academics to work, for example, on combination radiotherapy plus drugs and/or radiosensitisers. Progress in the treatment of numerous solid tumours, including brain tumours, head and neck cancer, lung cancer and cervical cancer, over the last twenty years has always been made when we combined drugs and radiation. There are plenty of opportunities to explore new approaches of combined treatments with radiation, but this can only be done when we work in close collaboration among academics and together with industry partners.

When you consider collaboration – and EORTC is an example of an academic cooperative group – every one of the stakeholders has something to bring to the table. But there is a lot of overlap and things we can do better together. There are variable models of collaboration depending on the project, and depending on the new treatment and approach (see figure *left*). I think we need to bring academia to the table early on when it comes to the scientific concept, protocol development, site selection, how to carry out trials, and how to do it in the most efficient way.

What can an academic consortium

VARIABLE MODELS OF COLLABORATION



Getting the model of collaboration right between academia, the pharmaceutical industry and contract research organisations is key to developing better cancer treatments more efficiently

such as EORTC offer? We offer expertise in clinical development and in specific disease areas that is only available in a highly sophisticated and well-run group with appropriate experience, with members who know each other and who have worked on several previous protocols. This expertise spans decades, not just a few years. Previous experience means academia has expertise in disease benchmarking. Only academia has a long-term horizon: with EORTC, trials have been followed up for up to 50 years. How else would you determine long-term toxicity complications or secondary malignancies?

Effective collaborative research needs a network of people who trust each other and who are highly motivated. They need to feel part of something, which ensures they are highly motivated and so perform better than just being 'hired for service' in trials run solely by industry. I think independence is important and a platform of academics can be helpful for trials that test several competitors' compounds and strategies. We can achieve synergies including use of one molecular testing platform, testing for a series of aberrations and then directing patients to the most promising protocol. Trials may even share a common control arm.

Academic consortia such as the EORTC can provide the experience and expertise to get a trial done efficiently, from the initial concept to protocol development and trial enrolment. We are often asked the time to first patient enrolment, but the more important question is the time to enrol the last patient – that's what matters – and we ensure we get the last patient in efficiently. Time to the first patient is confounded by regulatory issues, delays in contracts, remarks and diverging recommendations by ethics committees. Here inclusion of patient advocates may be helpful. ■

Denis Lacombe, headquarters director of the European Organisation for Treatment and Research in Cancer (EORTC), Brussels, hosted a live question and answer session

Q: *Do you think the 'pick the winner' model proposed by acute myeloid leukaemia researcher Alan Burnett [head of the Experimental Cancer Medicine Centre in Cardiff, Wales] is a good platform to develop and assess new drugs for clinical trials?*

A: It's one among many models, and there is not going to be one single approach. It depends on how many compounds and approaches you have to test in parallel and what disease is being studied, but it goes in the right direction. It also depends at what stage of the development we use it. Using the 'pick the winner' model with some controlled randomised designs early on and trying to discard the losers very early on would help a lot. We currently have too many losers that we take along too far in the drug development process.

Q: *How can we better collaborate to ensure rational combinations of different anticancer agents are used together earlier in the development process, despite competition between different companies?*

A: We need to hit several targets at several levels so we need to combine treatments. Doing this in a non-competitive way using a somewhat neutral platform will help. Pharma is used to collaborating in joint ventures and co-developments, so this could be applied to early development perhaps, with two compounds in combination. Currently 56% of trials fail because of lack of efficacy, so we need to overcome this.

Q: *We need more international access to patients because of disease fragmentation. How do you see the future of this in Europe, because we do not necessarily operate in an optimal regulatory environment?*

A: We need to stand together in Europe otherwise pharmaceutical industry drug development is going to move elsewhere. Our healthcare systems are too fragmented, with a national rather than international focus. Other regions of the world are bringing resources together, picking up in innovation. I would call on the EU and regulators to partner with us in order to develop better treatments to achieve improved health and quality of life for the European population.

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nature REVIEWS CLINICAL ONCOLOGY

Smart therapeutic strategies in immuno-oncology

ALEXANDER EGGERMONT AND CAROLINE ROBERT

For cancer therapies to succeed, induction of an anticancer immune response is required. Immuno-oncology approaches are shaping the treatment landscape for patients with advanced-stage melanoma and other solid tumours. These new approaches may enhance immune system activity to improve outcomes, including the potential to achieve long-term survival benefits in many patients.

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The knowledge that tumour cells can use complex and overlapping mechanisms to avoid immune detection laid the foundations for immuno-oncology to become an anticancer treatment. Current strategies are based on agents that can break immune tolerance. The most recognised class of immuno-oncology agents – checkpoint inhibitors – modulate pathways that either switch off T-cell activity (reducing tumour-induced immune suppression), or stimulate T-cell activity, thus potentiating antitumour responses.[1] These agents are recognised as breakthrough treatments for advanced-stage melanoma; they also show considerable promise in other tumour types, particularly renal cell carcinoma and lung cancer.[1]

Unlike other therapies approved for advanced-stage melanoma that target tumour cells directly, checkpoint inhibitors modulate T-cell activity to enhance antitumour immune responses. The most striking benefit of this approach is durable tumour control and survival.[2] Mature data in thousands of patients have shown that around one in five patients treated with ipilimumab, an antibody that blocks cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), has the potential to survive for at least three years – and up to ten years – from treatment initiation, which more than doubles results with conventional drugs.[2] Similarly, treating patients with antibodies that block the programmed death-1 (PD1) receptor, or its ligand, PD-L1, has proved highly promising.[3,4] Results of extended phase I trials evaluating two anti-PD1 antibodies (nivolumab and MK-3475) showed objective response rates (ORRs) of 30–50% in patients with advanced-stage melanoma, with most responders having durable benefit.[1] Results with nivolumab showed an unprecedented 44% of patients surviving for at least two years.[1] Additional trials could inform the optimal sequencing of anti-PD1 and anti-CTLA-4 therapies: although anti-PD1 therapy is effective following prior treatment with ipilimumab, does the same hold true for the reverse sequence? Anti-CTLA-4 antibodies centrally target the interaction between antigen-presenting cells and T-cells in the lymph-node compartment, whereas anti-PD1 antibodies act mainly peripherally on the interaction between tumour cells and T-cells at the tumour site. Thus, various opportunities for synergy or

optimal sequencing of the drugs are to be explored. Current studies are addressing these questions.

There is little doubt that impressive results have been obtained by inhibiting a single immune checkpoint, but could antitumour immunity be enhanced through dual or triple blockade? Early results seem promising. Among 53 patients with a response to the ipilimumab–nivolumab combination regimen, blocking CTLA-4 and PD1 resulted in an ORR of 40%, and clinical activity was observed in 65% of patients; at the maximum doses associated with an acceptable level of adverse events, most patients had a reduction in tumour volume of at least 80%, according to WHO criteria of response. Responses were deep but also rapid, occurring within 12 weeks.[5] These results, however, might not differ significantly from those results obtained with MK-3475 alone in 135 patients, in whom response rates of 41% were observed using RECIST criteria.[4] However, direct cross-study comparisons of these trials are not scientifically valid owing to differences in patient populations, the number of patients, number and timing of prior therapies and prognostic factors. In contrast to treatment with anti-PD1 alone, the rate of grade 3–4 adverse effects related to the ipilimumab–nivolumab combination regimen was high (53%).[5] Data from phase II and III randomised studies including the ipilimumab–nivolumab regimen are eagerly anticipated to determine if this regimen is superior to anti-PD1 monotherapy and, if so, at what price in terms of toxicity.

Monoclonal antibodies against other immune checkpoint proteins, such as TIM3, LAG3, OX40, and KIRs (killer immunoglobulin-like receptors) are all being investigated in clinical trials and serve as potential components of a combination strategy.[6] It is possible that once the 'brakes' elicited by the immune system have been released with one antibody, the inclusion of an agonistic antibody such as anti-OX40 could augment antitumour immune activity further. In other words, breaking tolerance at the central (anti-CTLA-4) and peripheral (anti-PD1) levels, opens the door for efficacy of agonists, whereas the use of T-cell activators (monoclonal antibodies or cytokines) alone does not lead to appreciable success, as T-cells are neutralised at both the central level as well as the tumour site. Of course, the potential for overlapping and/or additive toxic effects of the individual agents, particularly those resulting from over stimulation of the immune system, would need to be carefully monitored.

"In other words, breaking tolerance at the central and peripheral levels, opens the door for efficacy of agonists"

Potential combination strategies are not limited to the different immune checkpoint ligands and receptors. A rationale also exists for combining checkpoint inhibitors with other immunotherapeutic approaches, such as cytokines that increase the number of activated T-cells in the circulation, or conventional cancer therapies, such as targeted kinase inhibitors, chemotherapy or radiotherapy.

Patients with BRAF-mutated advanced-stage melanoma have the option of receiving treatment with ipilimumab or a BRAF inhibitor (such as vemurafenib or dabrafenib). Possibly, in the near future, a combination of a BRAF inhibitor and a MEK inhibitor (dabrafenib plus trametinib), will become the next standard of care, based on the efficacy of this combination to significantly prolong progression-free survival (PFS) compared with dabrafenib alone.[7] Compared with a PFS of approximately two months with dacarbazine, and around six months with a BRAF inhibitor, a PFS of more than nine months was observed with the combination of a BRAF inhibitor and MEK inhibitor.[7] The distinct activity profiles of the two classes of agents, together with recent evidence that BRAF inhibition has immune-enhancing properties, suggest combination therapy might prove beneficial. A phase I study to investigate the combination of ipilimumab and vemurafenib, however, was associated with four to five times higher-than-expected rates of hepatotoxicity, suggesting that concurrent treatment may not be possible.[8] However, the timing of administration of the various agents in this dual approach (immunotherapy and cytotoxic agents of any nature, including tyrosine kinase inhibitors) will be of great interest. In this approach, the administration of agents that induce a quick transient response (such as seen with BRAF and MEK inhibitors) can create the time and space to administer immuno-oncologic agents. Being able to deliver immunotherapy by smart sequencing of different treatments will become an increasingly important strategic goal. Treatment with some chemotherapies can result in tumour cell stress and death that stimulate a tumour-specific immune response, or increase levels of tumour surface molecules that facilitate recognition by the immune system. Immuno-

genic cell-death-inducing agents can thus be successfully combined with an immuno-oncologic agent, resulting in an enhanced anticancer immune response.[9] Another interesting concept is the possibility of inducing immune-mediated abscopal effects, as seen with radiotherapy. Here, significant tumour regression both at the site of irradiation and outside areas support the notion of an enhanced systemic immune response and suggest localised radiotherapy in combination with immuno-oncology is worth pursuing.[10]

"Being able to deliver immuno-therapy by smart sequencing ... will become an increasingly important strategic goal"

Durable tumour control and long-term survival depend on harnessing the power of the immune system. Data with agents that block CTLA-4, PD1 and other checkpoint proteins are not only providing a benchmark against which future therapies will be compared, but are stimulating interest in alternative sequencing or smart combination approaches that could improve outcomes even further. In changing the treatment landscape, immuno-oncology advances currently offer renewed hope to patients with advanced melanoma and to patients with other solid tumours in the near future. ■

References for this article can be found at www.cancerworld.org

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newsround

Selected reports edited by Janet Fricker

Optimal time for initiation of adjuvant chemotherapy according to subtype

■ Journal of Clinical Oncology

Time delays in initiation of adjuvant chemotherapy have an adverse effect on outcomes for breast cancer patients with stage II and III disease, triple-negative tumours and HER2-positive tumours treated with trastuzumab, a single-institution retrospective cohort study has found.

Randomised clinical trials have shown survival benefits associated with use of adjuvant chemotherapy in early-stage breast cancer. The optimal time to initiation of adjuvant chemotherapy and impact according to breast cancer subtype, however, are less clear.

In the current study, Mariana Chavez-MacGregor and colleagues, from MD Anderson Cancer Center, retrospectively reviewed the medical records of 6,827 women with stage I to III invasive primary breast cancer who received adjuvant chemotherapy between 1997 and 2011. Patients were categorised according to time from definitive surgery to adjuvant chemotherapy into one of three groups: <30 days, 31 to 60 days and >60 days.

Results show that for patients with HER2-positive tumours who received trastuzumab, the five-year overall survival (OS) estimate was 88% for those starting chemotherapy within 30 days, versus 87% for those starting chemotherapy within 31 to 60 days, and 75% for those starting chemotherapy after 60 days (P=0.01).

Patients with triple-negative breast cancer had a 74% decrease in overall survival if they started chemotherapy between 31 and 60 days of surgery compared with starting within 30 days (HR 1.74, 95% CI 1.32–2.29, P<0.001).

The subgroup of patients with stage III disease had a 76% decrease in overall survival if they started chemotherapy more than 60 days after surgery versus 30 days or less (HR 1.76, 95%CI 1.26–2.46, P<0.001). Among patients with stage II disease, the distant-relapse-free survival (DRFS) decreased by 20% if they started chemotherapy more than 60 days after surgery versus 30 days or less (HR 1.20, 95% CI 1.02–1.43, P=0.03).

The timing of chemotherapy showed no effect on outcomes (OS, RFS, or DRFS) in patients with stage I disease, HER2-positive tumours not treated with trastuzumab, and hormone-receptor-positive tumours.

"Among patients with stage II and III BC [breast cancer], TNBC [triple-negative BC], and HER2-positive tumors, every effort should be made to avoid postponing the initiation of adjuvant chemotherapy," write the authors. Since adverse outcomes occurred when chemotherapy was delayed by more than 60 days, they add, medical oncologists should have sufficient time to initiate treatment.

In an accompanying commentary, Marco Colleoni, from the European Institute of Oncology, Milan, and Richard Gelber, from the Dana-Farber Cancer Institute, Boston, write: "A review of the cause of death for these patients may reveal that co morbidities (e.g., cardiac) delaying initiation of anthracycline-containing chemotherapy may be exacerbated by trastuzumab, and that the results shown... are not entirely related to delayed administration of chemotherapy." Since two-thirds of the patients had hormone-receptor-positive disease, they add, there is no indication that time to initiation of chemotherapy makes much difference for the majority of patients.

■ D de Melo Gagliato, A Gonxalex-Angulo, X Lei et al. Clinical impact of delaying initiation of adjuvant chemotherapy in patients with breast cancer. *JCO* 10 March 2014, 32:735–744

■ M Colleoni, R Gelber. Time to initiation of adjuvant chemotherapy for early breast cancer and outcome: the earlier, the better? [editorial] *ibid* pp 717–719

Young families a barrier to radiotherapy for breast cancer

■ JNCI

Competing demands of childcare create barriers for women completing radiation therapy after breast cancer surgery. A US study has found that having at least one child aged less than seven years old resulted in statistically significant lower odds of receiving radiotherapy than having no children or older children.

Evidence-based literature has confirmed the effectiveness of radiotherapy after breast-conserving surgery, especially among young patients. While several population-based studies have investigated factors associated

with radiotherapy compliance, the majority have focused on elderly populations. Estimates suggest that approximately 60% of breast cancer patients diagnosed between 2005 and 2009 were aged less than 65 years.

The current study by Ya-Chen Tina Shih and colleagues, from the University of Chicago, explored factors associated with non-compliance with radiotherapy among insured young patients (aged 20–64 years). The investigators used a nationwide database to review medical and prescription records of 21,008 patients with insurance coverage who received breast cancer surgery between January 2004 and December 2009.

Results showed that 892 women (4.25%) had at least one child under seven years old; 1,584 (7.54%) had all children older than six years and at least one aged 7–12 years; 2,016 (9.6%) had all children older than 12 and at least one child aged 13–17 years; and 16,516 (78.62%) had no children or all children aged older than 18.

In comparison with women with one child under 7, those with at least one child aged 7– 12 were 32% more likely to receive radiotherapy (OR 1.32, 95%CI 1.05–1.66, *P*=0.02); those with one child aged 13–17 were 41% more likely to receive radiotherapy (OR 1.41, 95%CI 1.13–1.75, *P*=0.002); and those with no children or children older than 18 were 38 % more likely to receive radiotherapy (OR=1.38, 95%CI 1.13–1.68, *P*=0.001).

Statistically significant lower odds of receiving radiotherapy were observed among patients enrolled in a Health Maintenance Organization (HMO) or Preferred Provider Organization (PPO) with capitation versus other plan types (OR 0.70, 95% CI 0.63–0.77), and for patients who travelled long distances for radiotherapy treatment, determined by evaluating whether the patient's geographical area differed from her healthcare provider (OR = 0.72; 95%CI 0.60–0.86). In addition, results show that patients who are the primary holders of insurance policies are more likely to have radiotherapy (OR = 1.20; 95%CI 1.10–1.31).

"Our finding that a young child in the home is a barrier to completion of appropriate breast cancer therapy underscores the unique challenges confronted by younger (aged 20–50 years) cancer patients," write the authors. Additional work, they add, is needed to understand the impact of family structure on other aspects of cancer care and to develop robust interventions tailored to the unique needs of younger cancer patients.

■ I-W Pan, BD Smith, Y-CT Shih. Factors contributing to underuse of radiation among younger women with breast cancer. *JNCI*, published online 7 December 2013, doi:10.1093/jnci/djt340

Survey finds hours of care related to burnout

■ Journal of Clinical Oncology

Hours per week devoted to patient care is the dominant professional factor associated with oncologist 'burnout', a survey by the American Society of Clinical Oncology (ASCO) has found. The survey, which is the first national study to evaluate burnout and career satisfaction among US oncologists since 2003, reports that 45% of oncologists have at least one symptom of burnout and that oncologists in academic practice display greater job satisfaction than those in private practice.

The very fact that oncologists work long hours, and are continually exposed to death and suffering, places them at risk of burnout, a syndrome characterised by emotional exhaustion, treating people as if they are objects, and loss of meaning or purpose in work. Studies suggest that physicians experiencing burnout are more likely to reduce their work hours and/or pursue early retirement.

Between October 2012 and March 2013, Tait Shanafelt and colleagues, supported by ASCO, undertook a survey evaluating the personal and professional characteristics associated with career satisfaction and burnout among US oncologists. Altogether 2,998 US oncologists were contacted, of whom 1,117 (37.3% of overall sample) completed full-length surveys. Of these, 377 (33.8%) worked in academic practice, and 482 (43.2%) in private practice, with the remainder working in other settings. The full-length survey included 60 questions exploring a variety of personal and professional characteristics, with burnout measured using the Maslach Burnout Inventory (MBI) – a 22-item questionnaire.

Overall results showed that 484 oncologists (44.7%) were burned out on the emotional exhaustion and/or depersonalisation domain of the Maslach Burnout Inventory, with 45.9% of oncologists in academic practice displaying burnout versus 50.5% of those in private practice (*P*=0.18). In a multivariable analysis, younger age and greater number of hours spent seeing patients each week were independently associated with burnout for oncologists in both practice settings. Each additional year of age reduced the risk of burnout by approximately 4–5%, and each additional hour spent seeing patients increased the risk of burnout by 2–4%.

Differences between oncologists working in the different settings included that oncologists in academic practice were more likely to focus on treating patients with one particular type of cancer, spent a greater proportion of their time supervising physicians in training, and saw nearly half as many patients in outpatients per week as those in private practice (37. 4 vs 74.2; *P*<0.001).

Overall a higher percentage of respondents working in academic practice than private practice said they would become a physician again (87.5% vs 79.2%, *P*=0.0016) and the same was true about becoming an oncologist again (85.1% vs 77.5%, *P*=0.0053).

"The strong, incremental relationship between time devoted to patient care and burnout is concerning, especially given the projected shortage in the supply of oncologists during the coming decades," write the authors. Given the prevalence of burnout and evidence that it erodes physician personal

health and quality of care, they add, future studies need to focus on how to address this problem.

■ TD Shanafelt, WJ Gradishar, M Kosty et al. Burnout and career satisfaction among US oncologists. *JCO* 1 March 2014, 32:678–686

Head and neck cancer: nurse-led interventions improve quality of life

■ British Journal of Cancer

Nurse counselling and after therapy intervention (NUCAI) improved health-related quality of life and depressive symptoms among patients with head and neck cancer, a Dutch longitudinal randomised controlled trial has found.

Patients with head and neck cancers are prone to have poor health-related quality of life (HRQoL) following treatment, with people known to experience deterioration of HRQoL directly after starting treatment and up to 11 years after completion. The multidimensional problems observed include issues with emotional and physical function, general cancer symptoms (e.g. fatigue and pain) and symptoms specific to head and neck cancers (e.g. swallowing and dry mouth). Nurses, who are already involved with patient care, and have skills and knowledge around medical and practical aspects of head and neck cancer, are considered to be in a key position to deliver interventions.

Between January 2005 and September 2007, Ingeborg van der Meulen and colleagues, from the University Medical Centre Utrecht, the Netherlands, randomly allocated 205 patients with head and neck cancer from outpatient oral maxillofacial and otorhinolaryngology clinics to NUCAI (n=103) or usual care (n=102). The NUCAI intervention, provided by trained nurses, aimed to help patients manage the physical, psychological and social consequences of their disease and its treatment with advice, emotional support, education and behavioural training.

Nurses opened sessions with discussions of current physical problems and explored life domains including home situations, (resuming) work, household and leisure activities, mood and emotional distress, partner relations and intimacy and family and social life. Patients could be referred to psychiatrists or health professionals specialising in psychosocial problems.

Patients received a maximum of six counselling sessions lasting 45 to 60 minutes every two months, over a period of one year, starting six weeks after completion of cancer treatment. Health-related quality of life was evaluated with the EORTC QLQ-C30 and QLQ H&N35, while depressive symptoms were evaluated with the CES-D.

Results show that at 12 months the intervention group showed a significant improvement in emotional and physical functioning, including pain, swallowing, social contact, mouth opening and depressive symptoms (P<0.05). At 18 months, global quality of life, role and emotional functioning, pain, swallowing, mouth opening and depressive symptoms were significantly better among patients in the intervention group than in the control group, and at 24 months emotional functioning and fatigue were significantly better in the intervention group.

The programme, believe the authors, appears a promising intervention for implementation in daily clinical practice. "Compared with other, more intensive, interventions... we consider the NUCAI to be a relatively low-cost intervention, given its nurse-led approach and the relatively few sessions involved. Moreover, findings suggest that it can be implemented in the follow-up care for HNC [head and neck cancer] patients, although the overall costs and feasibility of the intervention remain to be investigated," write the authors.

It is important, they add, that nurses who offer the intervention have extensive experience in the care of patients with head and neck cancer and good communication skills, and are self-reliant and able to work closely with other professionals.

■ IC van der Meulen, AM May, JRJ de Leeuw et al. Long-term effect of a nurse-led psychosocial intervention on health-related quality of life in patients with head and neck cancer: a randomised controlled trial. *BJC* 4 February 2014, 110:593–601

Complications of prostate cancer treatment defined

■ Lancet Oncology

Patients with prostate cancer undergoing primary radiotherapy have higher incidences of hospital admissions, rectal or anal procedures, open surgical procedures and secondary malignancies than patients undergoing surgery, a population-based retrospective cohort study has found. Conversely, the Canadian investigators showed that patients who had primary surgery were more likely to undergo subsequent urological procedures.

Studies of complications resulting from surgery or radiotherapy for prostate cancer have focused largely on symptoms of incontinence and erectile dysfunction. In the current study, Robert Nam and colleagues, from Sunnybrook Health Sciences Centre, Toronto, set out to assess other complications associated with prostate cancer treatments.

The team used administrative hospital data, physician billing codes, and cancer registry data to analyse a cohort of 32,465 men in Ontario who underwent either radical prostatectomy (n=15,870) or radiotherapy alone (n=16,595) to treat prostate cancer, between 2002 and 2009. They measured the five-year cumulative incidence of key treatment-related complication endpoints: hospital admissions, urological, rectal, or anal procedures, open surgical procedures and secondary malignan-

cies. To assess the baseline incidence of these outcomes in the general population, the team randomly identified 32,465 age-matched controls with no history of prostate cancer.

Results showed that patients given radiotherapy had a higher incidence of complications for hospital admissions, rectal or anal procedures, open surgical procedures, and secondary malignancies at five years than did those who underwent surgery (adjusted hazard ratios ranged from 2.08 to 10.8, *P*<0.0001). The cumulative incidence in years 5 to 9 of developing a second malignancy was 4.5% (95%CI 3.8–5.5) in the radiotherapy group versus 1.8% (95%CI 1.3–2.4) in the surgery group.

The most common site of second malignancies was the gastrointestinal tract (87 per 100,000 person-years in the radiotherapy group and 28 per 100,000 person-years in the surgery group; *P*<0·0001).

The number of urological procedures, however, was lower in the radiotherapy group than in the surgical group (adjusted HR 0.66, 95%CI 0·63–0·69; *P*<0·0001). All risks were significantly higher for prostate cancer patients than the 32,465 matched controls with no history of prostate cancer.

"Clinicians should discuss these complications, in addition to the well-known adverse effects of incontinence and erectile dysfunction, with their patients when talking about treatment options for clinically localised prostate cancer," write the authors.

In an accompanying commentary, Michael J Eble from RWTH Aachen University, Germany, writes that, while population-based studies have the advantage of delivering sufficient patient numbers to identify small increases in the risk of secondary malignancies, the effects can be "negated by the presence of unbalanced confounders".

■ R Nam, P Cheung, S Herschom et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. *Lancet Oncol* February 2014, 15:223–231

■ MT Eble. Complications from treatment of localised prostate cancer. *ibid* pp134–135

Sentinel node biopsy: patients with intermediate thickness melanomas benefit most

■ New England Journal of Medicine

Sentinel node biopsy prolongs distant disease-free survival and melanoma-specific survival in patients with lymph node metastasis from primary tumours of intermediate thickness, the final ten-year analysis of the Multicenter Selective Lymphadenectomy Trial (MSLT-I) has concluded.

The MSLT-I trial, initiated in 1994, set out to investigate whether sentinel-node biopsy with immediate lymphadenectomy of involved nodes yielded better outcomes in melanoma than 'watchful waiting' with delayed lymphadenectomy, performed only when nodal recurrence becomes evident during observation. Sentinel-node biopsy was developed by Donald Morton, the first author of the current study, who died just before publication. The five-year results of the third interim analysis, published in 2006, focused on patients with intermediate thickness primary tumours, while the current ten-year follow-up data also includes patients with thick primary melanomas.

The final report involved 1,560 patients with localised cutaneous primary melanomas who were randomly assigned to undergo sentinel-node biopsy plus immediate lymphadenectomy if metastases were detected in sentinel nodes (*n*=943) or close observation with delayed lymphadenectomy if nodal metastases developed during observation (*n*=617). Altogether 1,270 patients had intermediate thickness lesions (1.20–3.50 mm) and 290 patients had thick lesions (>3.50 mm).

Among subjects with intermediate thickness melanomas, ten-year disease-free survival was 71.3% for patients in the biopsy group versus 64.7% for those in the observation group (HR for recurrence or metastasis = 0.76; *P*=0.01). For subjects with thick melanomas, ten-year disease-free survival was 50.7% for patients in the biopsy group versus 40.5% for those in the observation group (HR 0.70; *P*=0.03).

For patients with intermediate-thickness melanomas and nodal metastases, biopsy-based management improved ten-year distant-disease-free survival (HR distant metastasis 0.62; *P*=0.02) and ten-year melanoma-specific survival (HR for death from melanoma = 0.56; *P*=0.006). This was not seen in patients with thick melanomas. For the overall study population (where only one in five subjects had nodal metastases) treatment-related differences were not found for ten-year melanoma-specific survival.

"Although some patients with nodal metastases from thick melanomas may benefit from lymphadenectomy, our findings suggest that the timing of that intervention is not as critical as it is for patients with intermediate-thickness melanomas," write the authors, adding that the number of patients in the trial with thin melanomas was too small to draw conclusions.

In an accompanying commentary, Charles Balch from the University of Texas Southwestern Medical Center, Dallas, and Jeffrey Gershenwald from MD Anderson Cancer Center, Houston, write: "This practice changing trial shows the important role of early identification and surgical removal of regional metastases, both in obtaining staging information and in improving survival in defined cohorts of patients with melanoma."

■ DL Morton, JF Thompson, AJ Cochran. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *NEJM* 13 February 2014, 370:599–609

■ CM Balch, JE Gershenwald. Clinical value of the sentinel-node biopsy in primary cutaneous melanoma. *ibid* pp663–664