European School of Oncology
Learning to care

Cancerworld

www.eso.net

n° 78 May / July 2017

Efficacy in three indications

Metastatic pancreatic cancer
in combination with gemcitabine for first-line treatment of adult patients

Metastatic breast cancer
as monotherapy when first-line treatment fails and anthracycline containing therapy is not indicated

Non-small cell lung cancer
in combination with carboplatin for first-line treatment when surgery and/or radiotherapy are not indicated

Abraxane®
nanoparticle albumin bound paclitaxel

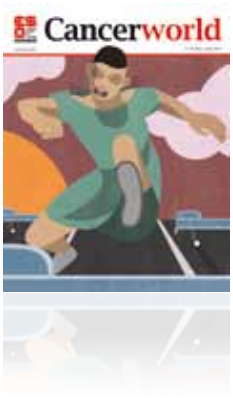
Prescribing Information: Abraxane® 5 mg/ml powder for suspension for infusion.
Refer to the Summary of Product Characteristics (SmPC) before prescribing.
Name of medicine: Abraxane 5 mg/ml powder for suspension for infusion **Active ingredients:** paclitaxel formulated as albumin bound nanoparticles. **List of excipients:** Human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate). **Available dosage form:** Powder for suspension for infusion. The reconstituted suspension has a pH of 6-7.5 and an osmolality of 300-360 mOsm/kg. The powder is white to yellow. **Authorised indication(s):** Abraxane monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated. Abraxane in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. Abraxane in combination with carboplatin is indicated for the first line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. **Dosage regimens and routes of administration:** Breast Cancer - The recommended dose of Abraxane is 260 mg/m² administered intravenously over 30 minutes every 3 weeks. Pancreatic adenocarcinoma - The recommended dose of Abraxane in combination with gemcitabine is 125 mg/m² administered intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. Non-small cell lung cancer: The recommended dose of Abraxane is 100 mg/m² administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of each 21-day cycle. The recommended dose of carboplatin is AUC = 6 mg•min/ml, on Day 1 only of each 21-day cycle, beginning immediately after the end of Abraxane administration. Refer to the full prescribing information for dose adjustments during treatment in case of haematologic (neutropenia and/or thrombocytopenia) and other adverse reactions. Administer reconstituted Abraxane suspension intravenously using an infusion set incorporating a 15 µm filter. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose. **Reference to special groups of patients:** Patients with hepatic impairment: For patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x ULN and aspartate aminotransferase [AST] ≤ 10 x ULN), no dose adjustments are required, regardless of indication. Treat with same doses as patients with normal hepatic function. For metastatic breast cancer patients and non-small cell lung cancer patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to ≤ 5 x ULN and AST ≤ 10 x ULN), a 20% reduction in dose is recommended. The reduced dose may be escalated to the dose for patients with normal hepatic function if the patient is tolerating the treatment for at least two cycles. For patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment, there are insufficient data to permit dosage recommendations. For patients with total bilirubin > 5 x ULN or AST > 10 x ULN, there are insufficient data to permit dosage recommendations regardless of indication. Patients with renal impairment: Adjustment of the starting Abraxane dose is not required for patients with mild to moderate renal impairment (estimated creatinine clearance ≥30 to <90 ml/min). There are insufficient data available to recommend dose modifications of Abraxane in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 ml/min) Older people: No additional dosage reductions, other than those for all patients, are recommended for patients 65 years and older. Paediatric population: The safety and efficacy of Abraxane in children and adolescents aged 0-17 years has not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Lactation. Patients who have baseline neutrophil counts < 1500 cells/mm³. **Warnings:** Abraxane should not be substituted for or with other paclitaxel formulations. It is an albumin-bound nanoparticle formulation of paclitaxel, which may have substantially different pharmacological properties compared to other formulations of paclitaxel. Rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have been reported. If a hypersensitivity reaction occurs, the medicinal product should be discontinued immediately, symptomatic treatment should be initiated, and the patient should not be rechallenged with paclitaxel. Bone marrow suppression (primarily neutropenia) occurs frequently with Abraxane. Neutropenia is dose dependent and a dose limiting toxicity. Frequent monitoring of blood cell counts should be performed during Abraxane therapy. Patients should not be retreated with subsequent cycles of Abraxane until neutrophils recover to >1500 cells/mm³ and platelets recover to >100,000 cells/mm³. Sensory neuropathy occurs frequently with Abraxane, although development of severe symptoms is less common. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose reduction. If Grade 3 sensory neuropathy develops, treatment should be withheld until resolution to Grade 1 or 2 followed by a dose reduction for all subsequent courses of Abraxane is recommended. For combination use of Abraxane and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold Abraxane; continue treatment with gemcitabine at the same dose. Resume Abraxane at reduced dose when peripheral neuropathy improves to Grade 0 or 1. For combination use of Abraxane and carboplatin, if Grade 3 or higher peripheral neuropathy develops, treatment should be withheld until improvement to Grade 0 or 1 followed by a dose reduction for all subsequent courses of Abraxane and carboplatin. Sepsis was reported at a rate of 5% in patients with or without neutropenia who received Abraxane in combination with gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Abraxane and gemcitabine until fever resolves and ANC > 1500 cells/mm³, then resume treatment at reduced dose levels. Closely monitor all patients for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with Abraxane and gemcitabine and promptly initiate appropriate treatment and supportive measures. Because the toxicity of paclitaxel can be increased with hepatic impairment, administration of Abraxane in patients with hepatic impairment should be performed with caution. Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression, and such patients should be closely monitored for development of profound myelosuppression. Abraxane is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, Abraxane is not recommended in patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and AST <10 x ULN). Rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving Abraxane. Most of the individuals were previously exposed to cardiotoxic medicinal products such as anthracyclines, or had underlying cardiac history. Thus patients receiving Abraxane should be vigilantly monitored by physicians for the occurrence of cardiac events. The effectiveness and safety of Abraxane in patients with central nervous system (CNS) metastases has not been established. CNS metastases are generally not well controlled by systemic chemotherapy. If patients experience nausea, vomiting and diarrhoea following the administration of Abraxane, they may be treated with commonly used anti-emetics and constipating agents. Carefully assess patients with pancreatic adenocarcinoma aged 75 years and older for their ability to tolerate Abraxane in combination with gemcitabine. Give special consideration to performance status, co-morbidities and increased risk of infections. When reconstituted, Abraxane contains 0.183 mmol sodium, which is 4.2 mg of sodium. To be taken into consideration by patients on a controlled sodium diet. **Clinically significant interactions:** Abraxane is indicated for as monotherapy for breast cancer in combination with gemcitabine for pancreatic adenocarcinoma, or in combination with carboplatin for non-small cell lung cancer. Abraxane should not be used in combination with other anticancer agents. Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cioplidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures. **Reported side effects:** The most common clinically significant adverse reactions associated with the use of Abraxane have been neutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders. Prescribers should consult the summary of product characteristics in relation to other side-effects. **Storage conditions:** Keep the vial in the outer carton in order to protect from light. Neither freezing nor refrigeration adversely affects the stability of the product. This medicinal product does not require any special temperature storage conditions. **Price: Classification:** Medicinal product subject to medical prescription. **Marketing Authorisation Numbers:** EU/1/07/426/001, EU/1/07/426/002. **Marketing Authorisation Holder:** Celgene Europe Limited, 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom. **Date of last revision:** 11/2010. **Internal ID of the printed material: INT-ABR170002**
Date of preparation: February 2017

Celgene

Scan to access our website

Cancerworld

Shaping the future of cancer care



"Away from pain" by Vito Manolo Roma for Cancerworld

Print run 16,000

Contents

Printed by
Grafiche Ambert, Verolengo (TO)

Cover by
Vito Manolo Roma

Illustrations by
Elisa Macellari, Vito Manolo Roma, Nicolò Assirelli

Published by
European School of Oncology

Direttore responsabile
Alberto Costa

Registrazione Tribunale di Roma
Decreto n. 436 del 8.11.2004

All enquiries to: ESO Editorial Office, Via Turati 29, 20121 Milan, Italy
magazine@eso.net +39 02 8546 4522

Correspondence should be sent to The Editor at editor@eso.net

Recommended by:

OECI
Organisation of European Cancer Institutes
European Economic Interest Grouping

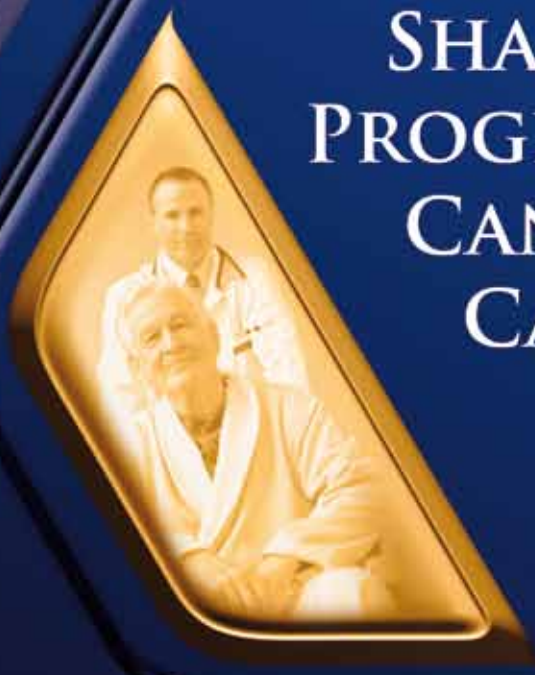
Would you like to receive a regular free copy of *Cancer World*? To receive a printed copy, please complete our online form http://bit.ly/CW-print. If you prefer to read it online, please sign up to receive weekly email alerts of new articles at http://bit.ly/CW-online. The full version can also be viewed online at www.cancerworld.net.

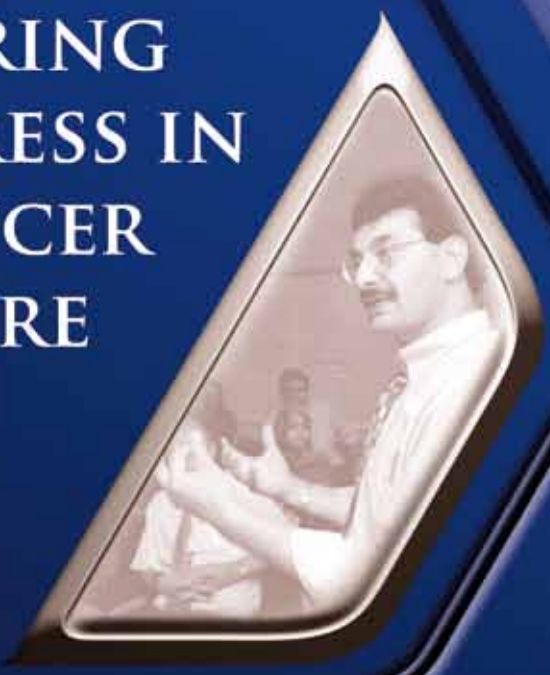
Cancer World is published five times a year by the European School of Oncology. It is distributed at major conferences, and mailed to subscribers and European opinion leaders.

European School of Oncology

Learning to care

Sharing Progress in Cancer Care





PLATINUM SPONSOR:

Bristol-Myers Squibb

Sharing Progress in Cancer Care (SPCC) is a pioneering partnership between ESO and some of the world's leading pharmaceutical companies. Unrestricted grants from SPCC partners support a spectrum of innovative projects implemented by ESO such as *CancerWorld* magazine and the Masterclass in Clinical Oncology. The SPCC partners confirmed as of February 2017 are acknowledged on this page.

GOLD SPONSORS:

HELSINN · Lilly · MERCK · Pfizer Oncology · Roche

SILVER SPONSORS:

Boehringer Ingelheim · Celgene · Genomic Health · NOVARTIS · SANDOZ a Novartis company

The elephant in the room

Alberto Costa, Editor

Ne umquam pars pro toto (Plinius). Can anyone remember a bit of Latin? This quotation was used in a slide presentation given a few weeks ago by Louis Denis, urologist and prostate cancer patient, at the congress of European Association of Urology (EAU), where he was representing the patient coalition Europa Uomo.

It means "never consider only a part for the totality", and Louis Denis' message was: "Do not focus only on our prostates, do not forget that the prostate belongs to a man." I believe there is no more important message to cancer doctors and nurses. We are so influenced by our training, by the anatomic mentality, by the so-called organ-site approach, that we seem inevitably to keep confounding the part for the whole.

Imaging (radiology but also nuclear medicine) is focusing more and more on each single 'lesion', and is putting a lot of effort into magnifying the neoplastic findings to find out everything about them, leaving little time and space to study what else we can see – How is the environment that 'contains' the tumour?

We surgeons admittedly have a very bad habit of planning our activity in terms of '*pars*': What is the programme for the theatre tomorrow? We have one thyroid, two breasts and one colon, sir.

Advocates of complementary medicine have a point there, and it is time to discuss it openly. In this issue we report on an ESO groundround dedicated to 'integrative oncology', and I encourage you to read it with attention and to think about how many of your patients have timidly asked you about unconventional remedies in recent times.

This topic is often the elephant that calmly ruminates in our outpatients room: I understand we need to kill as many cancer cells as possible, says the person in front of us, and I accept we have to cut, irradiate and bombard this enemy which is growing in me, but what can I do for the rest of my body, for my pain, my constipation, my dry skin, not to mention my chronic insomnia, my anxiety, my depression?

No question but we have to remain firm against selling any false illusions, and to challenge unproven methods when presented as an alternative to evidence-based cancer treatments.

But holistic care should not remain a term to be used only in congresses and then forgotten in our daily practice. Holistic care is a challenge, it is demanding, tiring and difficult, but it is the only way to practise oncology with dignity and success.

Pain! The denial needs to end

Uncontrolled pain can blight the lives of cancer patients and survivors. But all too often, health professionals don't ask, and patients don't tell. **Simon Crompton** looks at why this is still the case, and what can be done about it.

It isn't as if cancer pain isn't talked about. The need to manage cancer pain effectively has had a high profile since 1986, when the World Health Organization produced a three-step analgesic ladder as part of guidance aimed at bringing effective pain relief for the majority of cancer patients globally.

Since then, swathes of guidelines on treating cancer pain have been produced, including comprehensive ESMO clinical practice guidelines in 2012 covering assessment and management of mild, moderate and severe pain up to end of life. Opioids and other new pharmacological-based treatments are becoming increasingly available in European countries, as understanding grows, fears diminish and national laws and policy adapt.

But for all the profile of pain, is the experience of pain improving for cancer patients in the day-to-day reality of the clinic, hospital ward and home? The answer would appear to be no.

Cancer pain, according to WHO, includes pain caused by the cancer, pain related to the cancer (for example through lymphoedema) and pain related to treatment. But recent evidence suggests all types are undertreated.

An analysis in the *Journal of Clinical Oncology* concluded that one third of cancer patients do not receive pain medication proportionate to their pain intensity (*JCO* 2014, 32:4149–54). Another, in the *Annals of Oncology*, reviewing studies using pain management indices, concluded that nearly one in two patients with cancer pain is undertreated (*Ann Oncol* 2008, 19:1985–91).

"Despite increased attention to cancer pain, pain prevalence in cancer patients has not significantly changed over the last decade as compared to the four decades before," said Johan Haumann from the University of Maastricht's Pain Centre, writing in *Current Opinion in Supportive Palliative Care* (2017, doi:10.1097/SPC.0000000000000261).

Mitzi Blennerhassett from the UK stands witness to the long – sometimes unending – journey into cancer pain. Patient advocate, campaigner, speaker and author of an award-winning book describing her experiences with anal cancer, Mitzi started experiencing pain from the cancer before her diagnosis 27 years ago. This continued with increasingly extreme pain through chemotherapy and radiotherapy treatments, and today she still suffers daily – and often unbearable – pain.

She remembers how her requests for better analgesia during treatment were ignored, and the level of pain she was experiencing was not acknowledged until a Macmillan nurse obtained dextromoramide and later diamorphine for her. Radiotherapy staff had told her there was nothing more they could do for it. "They looked at their feet and said they were sorry but the oncologist had told them that I couldn't be prescribed anything else."

"When treatment has finished they are left to cope with the side effects"

"I was trying to be stoic. I thought I was expected to just put up with the pain as there was no opportunity to talk about it. But it also seemed that health professionals were in denial about pain, particularly when it was caused by their treatments."

She still finds it hard hold back the emotion when she remembers the pain she experienced during brachytherapy, when the wall of the anal canal repeatedly went into spasm.

Today, talking to support groups and looking through online forums of cancer patients, she can't believe how – despite all the structural reforms to cancer services and the growth of multidisciplinary teams in the UK – health professionals still seem to be in denial. Many patients still aren't being told they might experience severe pain as a result of treatment, and still aren't being asked about pain on clinic visits.

"What stands out about most patients is that when treatment has finished they are left to cope with the side effects," she says.

In denial?

Why? With so much attention, resources, and guidelines focused on cancer pain, why is cancer pain still not being addressed? The guidelines are increasingly clear and specific about what should be happening – and increasingly take account of some of the anticipated barriers, such as uncertainty about the best drugs for different cancers.

Last year, comprehensive clinical practice recommendations were published in *Critical Reviews on Oncology/Hematology* on managing pain in people with head and neck cancers undergoing chemo-radiotherapy (*CROH* 2016, 99:100–106). Severe pain is common in head and neck cancers, with half of all patients experiencing it before treatment, four out of five experiencing pain during treatment, and more than two thirds afterwards. The pain results from both malignancy and treatment, and the most frequent cause is chemo/radiation-related oral mucositis.

Aware that pain is often underestimated and undertreated in this group,

an Italian multidisciplinary group of head and neck specialists reached an expert consensus on pain management. Their resulting recommendations impressively addressed not just pain management principles, but practicalities – setting out not only what should be done when, but also which health professional has responsibility at which stage.

"Patients think the professional will ask if they are interested. And the professional thinks, if the patient has pain, they will tell us"

It seems a significant step forward from the World Health Organization's (now much debated) simple three-step approach, which just recommended a mild to strong order of drug administration.

Yet one of the authors, Carla Ripamonti, Head of Supportive Care in the Cancer Unit at Fondazione IRCCS, at Milan's National Cancer Institute, is surprisingly realistic about the impact these pain guidelines – and any others – are likely to have.

"There are many valid pain assessment tools," says Ripamonti, who also co-authored the ESMO clinical practice guidelines on cancer pain management. "But only pain specialists seem to use them. In general, too many oncologists and other physicians don't take the time to talk to patients about pain, or use the assessment tools."

She has noticed that oncologists seem to be far more knowledgeable about guidelines on nausea and vomiting than pain – possibly because they are symptoms that are likely to appear sooner than pain during treatment.

Many other key figures in cancer pain are aware of the difficulties of converting guidelines and good intentions into action in the clinic. Wendy Oldenmenger, a nurse who coordinates oncology nursing research at Rotterdam's Erasmus MC Cancer Institute, has studied in detail the barriers to good cancer pain management. Her analysis in the *European Journal of Cancer* identified knowledge deficits, inadequate pain assessment and misconceptions regarding pain as the most common obstacles (*EJC* 2009, 45:1370–80).

"We have so many guidelines, from the WHO guidelines in the 1980s onwards, but still oncology pain management isn't as it should be. There are patients with complex pain problems, and they will always be a challenge, but there's also a problem with treating basic pain on a day-to-day basis, particularly in outpatient clinics. Most of the time, nurses and physicians think they know the guidelines, but actually they don't know how to use them in daily practice."

Many nurses and physicians still have the same misconceptions about pain and analgesics as the general public, she says, fearing addiction and side effects. The problem is no longer that opioids aren't available, it's that professionals don't give them, patients don't take them, or there's not enough explanation of how to use them.

"Communication is a really big issue," says Oldenmenger. "Patients are afraid to talk about pain – they don't want to distract the physician from effective treatment. They think that the professional will ask them if they are interested. And the professional thinks, if the patient has pain, they will tell us."

Though practice varies considerably from clinic to clinic and country to country, the problem of implementing good pain management is widespread across Europe. Norway, for example, is often cited as a world leader in palliative care. But a study published last year indicated that cancer pain control in Norway did not improve at all between 2008 and 2014, with prevalence of cancer pain among inpatients at 53–55% and among outpatients at 35–39% (*Support Care Cancer* 2016, 24:2565–74). An earlier study showed that 30% of patients with severe pain did not use opioids, and some of these did not receive any analgesics at all.

The oncologists must ask

Stein Kaasa, Head of Oncology at Oslo University Hospital, Norway, and Director of the European Palliative Care Research Centre, believes that inadequate cancer pain control is an issue at all stages of cancer – primary diagnosis, treatment and long after treatment. Even the basics, such as the use of oral morphine, are often not followed, he says. At the core of the problem is oncologists' focus on the tumour, not the patient.

"During short outpatient visits between the patient and the oncologist and the surgeon, I believe that physicians don't investigate pain systematically," he says. "It's well documented that pain is under-reported in consultations because it's the physician who sets the scene – and if they focus on the tumour, then patients don't feel it's appropriate to raise the issue of symptoms. It should be the responsibility of the healthcare

"People don't want to hear"

Cordelia Galgut, a registered counselling psychologist from London, was diagnosed with bilateral breast cancer 13 years ago. Her pain started after surgery, and became more widespread and complex through radiotherapy and four years of the hormone treatment with Zoladex. Today it continues to affect her arms, abdomen, hips and legs.

"Here I am, 13 years on, seemingly cancer free, and in more pain than ever. It gets worse. It's related to my treatment, but it's very seldom acknowledged. You talk to the doctors about it, and it's swept under the carpet.

"My arms are hugely painful on both sides, and it radiates down to hips and then the legs, so I have problems walking. The scar tissue seems to have more and more effect over time.

"After my initial surgery, nobody talked about pain. The nerve pain was terrible. I was just given a load of basic painkillers, but on some level I accepted it because it was so soon after the event and I was happy to have survived. That goes on for a year or so.

"I have three very large scars. They tightened after surgery, causing more pain and abdominal tightness and affecting my diaphragm and arm mobility. I've raised the symptoms with my surgeon, oncologist, radiotherapist, and GP, and though they acknowledged that there was pain caused by the scars tightening, the attitude was: 'You're lucky to have survived' – that was all that mattered.

"And the pain has got worse, but that attitude has continued. It's as if they think: 'Conventional wisdom is that the pain shouldn't get worse, therefore it doesn't. It's either in the patient's head, or something I don't need to acknowledge because the main thing is we've kept you alive for 13 years.' People don't want to hear, therefore they don't hear."

system – and the physician specifically – to put symptom management on the agenda."

So how does pain get onto the daily routine – not just in centres of excellence, but for cancer patients throughout Europe? The hard option – and one frequently suggested when it comes to putting pain on the map – is to engrain it by making it a more intrinsic part of health professionals' basic education.

Wendy Oldenmenger estimates that on average in Europe, medical and nursing training provide just two to three hours on pain management. In some countries, medical schools include nothing at all on symptom management. This may result both in a lack of confidence in treating pain, and an implicit message to physicians that treating pain can't really be that important.

"If you aren't trained in pain, and don't know what to do about it, then you probably don't ask about it," says Stein Kaasa.

"If you aren't trained in pain, and don't know what to do about it, then you probably don't ask about it"

In Norway, palliative cancer care is now included in the medical curriculum, and the curriculum for medical oncology and radiotherapy includes developing skills in symptom management. But bringing such a fundamental national change takes time and investment.

It isn't the only option. There may be simpler paths to bringing cancer pain management towards the centre of day-to-day clinical practice. Several commentators believe that major progress could be made by providing new incentives and simple measures to embed pain assessment into routines. And simply communicating about pain in a different way could bring change.

Carla Ripamonti's disappointment that guidelines are not better used is balanced by her belief that it would be relatively easy to get them more widely implemented.

"We need to find a different approach," she says. "ESMO publishes pain guidelines in the *Annals of Oncology*, but if you look at other cancer journals, they only publish research articles. There needs to be more diffusion of the guidelines, translated into more national languages so that all physicians can easily access them."

Somehow, she says, oncologists need to be made to talk about pain in consultations. She acknowledges that oncologists often don't see patients for long periods, and pain often arises after symptoms such as nausea. But if oncologists always raised the subject there would be less chance of longer term pain problems associated with treatment toxicity, for example, being missed. Patients could then be referred to supportive or specialist pain units.

Part of the routine

Wendy Oldenmenger, however, believes there are simply not enough resources to refer more than a few cancer pain cases to specialist services. A study she carried out at two Dutch outpatient oncology departments, and published in the *Annals of Oncology* last year, showed that around 40–45% of patients reported pain and 12% registered their current pain as moderate to severe (*Ann Oncol* 2016, 27:1776–81). So she believes the issue has to be addressed within these clinics. And the most practicable way is to make pain assessment part of their whole outpatient clinic routine.

"You have to assess pain in the same way you would assess a tumour, with a scan before a consultation"

Oldenmenger proposes a system of patient pain self-assessment. As part of a multidisciplinary group, she trialled a new approach to pain at the two outpatient oncology departments. At each visit, patients were asked to register their pain intensity on a touch screen computer, and this was incorporated into medical records. Cases of untreated pain could be flagged to physicians. Patients were also provided with web-based information, to increase understanding and expose misconceptions about pain.

By the end of the six-month project, most patients reported that when they scored their pain as moderate to severe, their physician discussed these results with them. The percentage of patients with moderate to severe pain decreased from 12.5% to 8.5% over the period.

"We should integrate supportive care and pain management into oncology," says Oldenmenger. "I think we must use the new communications and technology possibilities before patients even get into their consultation."

Stein Kaasa agrees that routine collection of patient reported pain scores before a consultation is the direction to take – and that new

technology such as mobile phone apps offers huge potential.

"You have to assess pain in the same way you would assess a tumour, with an MRI or CT scan before a consultation," he says. "Then it can be incorporated into the consultation and into the decision-making process."

At the same time, he says, it is important to recognise that complex and long-term problems of pain may require referral elsewhere. Different and specialist approaches may be required for those who have been cured of cancer but suffer chronic pain as a result of surgery or radiotherapy – because long-term opioid prescription may not be possible.

"If a patient is cured but still having pain, and the oncologist doesn't know how to handle it, there should be an automatic referral to a pain team or cancer survivorship clinic."

From guidelines to practice

So if solutions are becoming clearer, how are they to be made to happen? Kaasa believes that health systems need to provide the structures to make pain management an 'essential' rather an 'added extra'. Economic incentives can be an extremely effective way to bring change.

"We know that it's challenging to change behaviour in complex health systems," he says. "In countries which use diagnostic related groupings (DRGs) to determine how much to pay for a patient's hospital stay, you could say that in order to get full payment you have to follow symptom management guidelines with specific groups of patients."

Another option is to include pain management in cancer plans – comprehensive national policies designed to reduce cancer cases and deaths and improve quality of life. Josep Borràs, professor of public health at the University of Barcelona, and one of the authors of the European Guide for Quality National Cancer Control Programmes, developed as part of the 2014 European Partnership for Action Against Cancer (EPAAC), says that pain policy needs a new emphasis.

He says that although cancer pain has been on national and international agendas for more than 20 years, the emphasis has invariably been on providing pain resources – for example changing legislation to ensure that opioids are accessible, or building palliative care teams and units. These have been the focus of most cancer plans, including EPAAC's.

"Now we need to focus more on qualitative issues and less on the quantitative approach," he says. "We need to expand the use of tools for pain management from palliative teams to clinical teams in surgical oncology, medical oncology or radiation oncology."

Currently, he knows of no national cancer plans that include these day-to-day aspects of pain management within their targets or quality measures. "It's something we need to do in the future," he says.

One model to follow might come from Ontario, Canada, where a statutory but independent cancer quality council, set up in 2002, monitors and publicly reports on cancer system performance within the province. It then makes recommendations for targeted quality improvement to ministers. Among its quality indicators are patient symptom screening, including pain, and the patient experience with symptom management.

An even greater political commitment to pain management came in Italy in 2010, when a new national law was passed, "to ensure access to palliative care and pain therapy". This requires that physicians record type and intensity of pain, analgesic therapies and clinical results.

It also encourages the availability of opioids in pharmacies, the development of pain education programmes for health professions, the growth of regional palliative care networks and quality standards for the networks. The overall impact of the law on day-to-day practice is still to be determined.

"We need to expand pain management from palliative teams to clinical teams in surgical, medical or radiation oncology"

There is no doubt that managing pain in cancer patients has achieved a high profile – and in some cases the highest political priority – over the past decade. But throughout Europe there remains the fear that policy, targets and guidance will only go so far. Something has to happen on the humdrum and human level if cancer pain is to be conquered. For Mitzi Blennerhassett it comes down to basic principles: start the conversation with the patient, and listen.

"Some patients may require palliative care from the day of diagnosis," she says. "We need more patients on the groups that draw up pain guidelines – people who really know what it's like to go through. We need more articles for clinicians which describe what it's like for patients. And we need to break through this damaging idea that you mustn't talk to patients about pain because you might frighten them. The denial needs to end."

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

esmo.org

Put your knowledge to the test

ESMO Examination

MADRID SPAIN
9 SEPTEMBER 2017

LATE REGISTRATION
20 JULY 2017

WHY TAKE THE ESMO EXAMINATION?

- Assess your knowledge in medical oncology
- Become an ESMO Certified Member
- Collect ESMO-MORA CME points

HOW TO PREPARE

- Review the ESMO Examination Trial questions online
- Access educational material online via OncologyPRO's Tumour Knowledge Portal
- Attend the ESMO Academy, 4-6 August 2017 for an interactive, in-depth update about the major topics in oncology. Reduced fees and travel grants available for attendees pre-registered for the ESMO Examination

Register now at **esmo.org**

THE ONLY THING MORE RELENTLESS THAN CANCER IS THE PEOPLE WHO FIGHT IT.

Because no two cancer patients are alike, Lilly Oncology is committed to developing a broad portfolio of therapies, including those tailored to unique patients, and meaningful support solutions that accelerate the pace and progress of cancer care.

We're determined to continue making life better for those affected by cancer. Learn more about all we do at LillyOncology.com.

Lilly | ONCOLOGY

Ending substandard treatment in lung cancer

Lung cancer kills more people in Europe than any other type of cancer, yet efforts to monitor and improve standards of treatment and care have lagged behind those of less fatal cancers, such as breast and prostate. **Marc Beishon** talked to some of the specialists who are determined to turn this around.

"A fatalistic professional approach." This is how Erik Jakobsen, a leading Danish thoracic surgeon and head of the Danish Lung Cancer Registry, describes the attitude that used to dominate thinking about treating lung cancer, and which invariably led to the conclusion that reductions in mortality would only come from better prevention and detection (*J Thorac Surg* 2013, 8:1238–47).

Understandable, possibly, given that the five-year survival rate in the latest EUROCARE study (EUROCARE-5) averaged 13% across Europe, showing only marginal improvement over previous EUROCARE cohorts.

Yet focusing on prevention and detection is of no use to the more than 400,000 people diagnosed with the disease in Europe every year. What is more, it overlooks the major disparities in outcomes that have been recorded not only between European countries but also within them. These point to considerable potential for improving outcomes by ensuring that all centres that treat lung cancer deliver treatment and care to an equally high standard.

Comparative data on cancer outcomes by hospital or health region are quite hard to come by. Those that do exist indicate some quite shocking disparities, at least in the case of lung cancer. In England, for example, one of the few countries where widespread data are available, the proportion of lung cancer patients alive after one year in 2013 varied from 55% down to just 12% among the hospitals that treat the disease, and even when outliers at the top and bottom are removed, the variation ranges from 48% to 20%.

Those figures are cited by Mick Peake, who has led several initiatives in lung cancer in the UK, including the National Lung Cancer Audit Programme, and he has also been the lead for lung cancer quality improvement.

Peake is neither an oncologist nor a lung cancer surgeon, he is a respiratory physician – a specialism that, along with epidemiology, has been taking a lead in work on quality and variation of lung cancer care in Europe. The European Initiative for Quality Management in Lung Cancer Care, for example – a task force of the European Respiratory Society – is led by German respiratory physician Torsten Blum.

Much of this work is recent and

researchers are only just starting to identify underlying reasons for such alarming inconsistency, and to put forward comparative information on the ways that lung cancer is treated.

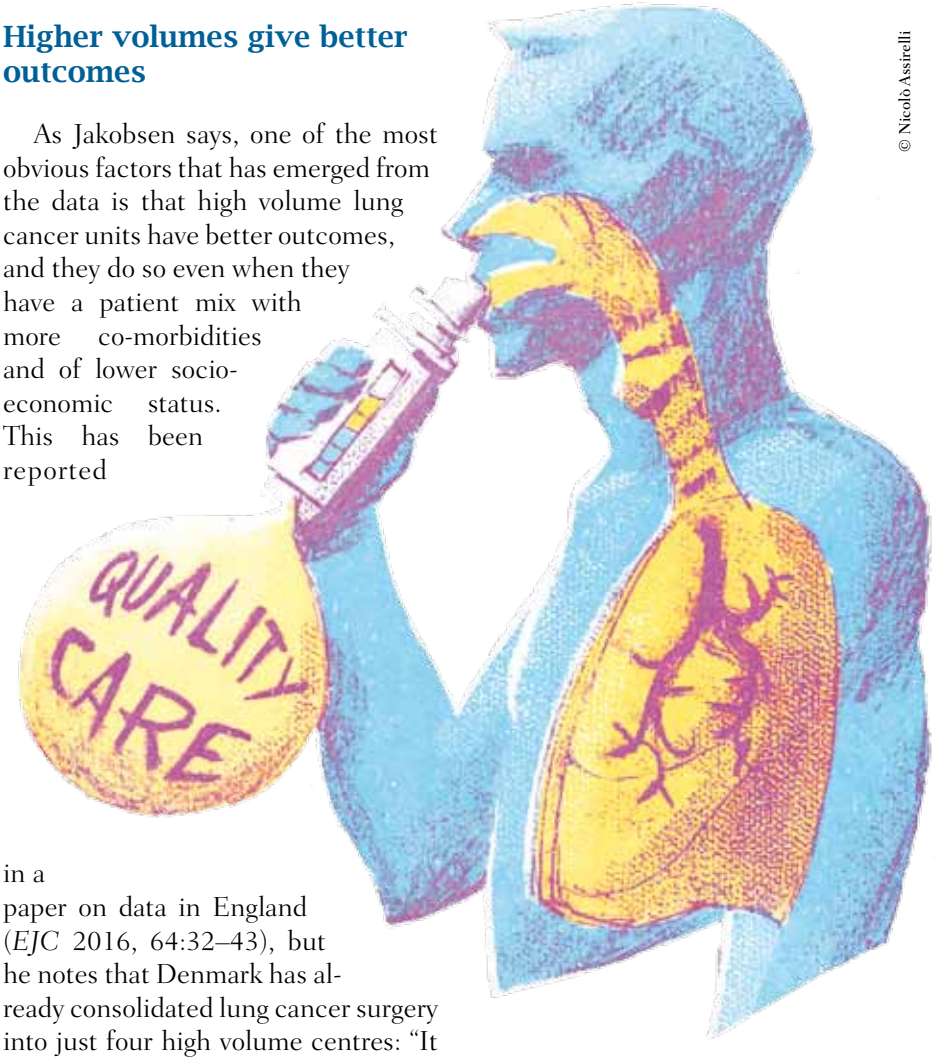
Denmark and the UK are two countries that have been particularly active in this field, not least because of their comparatively poor showing within the EUROCARE league tables. Denmark was one of the first countries to set up a lung cancer group, back in 1991. The work it did, establishing national clinical guidelines, a lung cancer registry, and a range of quality indicators, offers valuable evidence not just about the disparities in outcomes between treatment centres, but the potential for reducing those disparities and improving overall outcomes.

Findings reported by Jakobsen and colleagues in the 2013 *Journal of Thoracic Surgery* paper show that one-year survival rates increased between 2003 and 2011 from 36.6% to 42.7%, the five-year rates increased from 9.8% to 12.1% and the five-year survival rates for patients whose lung cancers were surgically resected increased by almost nine percentage points, from 39.5% to 48.1%.

The key point, says Jakobsen, is that improvements can be made independently of efforts to tackle smoking and improve early diagnosis. With colleagues including Peake in the UK, and the epidemiology team at King's College London, he has taken part in a number of studies on England, as well as Denmark, noting that one of the reasons the two countries collaborate is that they both have high quality data and are part of an international cancer benchmarking partnership set up by the UK. Few other countries, including major ones such as France and Germany, have such data, he says.

Higher volumes give better outcomes

As Jakobsen says, one of the most obvious factors that has emerged from the data is that high volume lung cancer units have better outcomes, and they do so even when they have a patient mix with more co-morbidities and of lower socio-economic status. This has been reported in a paper on data in England (*EJC* 2016, 64:32–43), but he notes that Denmark has already consolidated lung cancer surgery into just four high volume centres: "It is clear to me as a surgeon that if you have a low volume hospital – and England still has many – the chances of lower competence among the MDT [multidisciplinary team] are higher.



© Nicolò Assirelli

"For example, we have shown from the Danish registry that the quality of pre-treatment evaluation procedures is very important in outcomes; you need to ascertain the correct stage of cancer before treatment, and a problem with low volume centres is they may not have access to PET-CT and high quality staging procedures, or within a reasonable time. When you have the participation of expert radiologists, pathologists and lung physicians you get a better chance of high quality treatment."

As Jakobsen adds, it is not enough just to have an MDT meeting – it has to be provided with high quality information to make correct decisions. While Denmark has just four surgical centres, it has also been consolidating evaluation units, down from some 50 in the year 2000 to about 12.

High volume centres are also more likely to have thoracic surgeons trained in advanced procedures, including video assisted operations and organ sparing. In England, notes Jakobsen, low volume centres perform more total lung removals (pneumonectomy) as a proportion, which are associated with a higher postoperative death rate and greater

Quality indicators

Indicators suggested by various groups for the purpose of audit and benchmarking of the quality of lung cancer care include:

- Survival rates at 1,2 & 5 years
- Survival rates after surgery at 30 days and 1, 2 & 5 years
- Consideration by a multidisciplinary team
- PET-CT scan before surgery or radical radiotherapy
- Histological stage confirmation
- Seen by clinical nurse specialist
- Performance and function status assessed
- Resection rate for patients with non-small-cell lung cancer (NSCLC)
- Radical treatment rates for patients with stage I/II NSCLC
- Systematic anticancer treatment rates for patients with stage IIIB/IV NSCLC and performance status 0-1
- Active anticancer treatment rates for patients
- Chemotherapy rates for patients with small-cell lung cancer
- Waiting times from referral to receiving first anticancer treatment
- Completeness of data collection

morbidity. England's pneumonectomy rate is double that of Denmark, he says, although it has been going down.

Also associated with better outcomes is the number of patients who actually have a surgical operation – the resection rate – which again is rising in England, though for non-small-cell lung cancer (NSCLC) it remains lower than in the benchmark countries (which also include Australia, Canada, Norway and Sweden). However, Jakobsen cautions that the resection rate must be seen in the context of the overall treatment rate with curative intent, as stereotactic radiotherapy (itself not available in many locations) is a good alternative to surgery in patients with high comorbidity and low lung function. There is a similar story with chemoradiation treatment, which is often led by oncologists (and high volume centres are generally more likely to have access to the latest drugs).

"But very few countries have this data," says Jakobsen. "We are aiming to collect this in the Danish registry. Often, you have data on the treatment that was planned, but not what was actually given – about half of patients don't get their planned treatment, and this can have a big impact on survival."

About 35% of patients in Denmark are currently eligible for curative treatment, he says, "and our target is 40% for NSCLC. But because of the lack of country data we don't know how this compares with others."

As for outcomes, Jakobsen stresses that it is not just the one- to five-year survival figures that matter, but also mortality at 30 and 90 days, and high volume centres have an advantage here as well, as they are more likely to have a highly skilled, multidisciplinary post-operative team in place.

Multidisciplinarity: what it means in lung cancer

Peake takes up the theme of multidisciplinarity, saying that in England there are currently more than 150 lung cancer teams, and they cannot possibly all have fully expert professionals, and that volumes vary from smaller hospitals seeing about 50 cases up to 600 at the largest centre. Despite the UK's pioneering implementation of cancer care pathways, surgical centres have not always had specialist thoracic surgeons based at them, and surgeons have not always been available to attend MDTs. Peake says that, earlier in his career, he'd seen many patients in outlying hospitals who, in retrospect, could have been operated on had a specialist surgeon been directly involved.

Since the UK has started feeding back data from its lung cancer audit, and since nearly all patients are now discussed in a MDT, operations have more than doubled from about 3,250 in 2005 to 7,250 in 2014, he says.

Since the UK started feeding back data from its lung cancer audit, operations have more than doubled

While resection rates are still lower than other countries, as reported in the literature, like Jakobsen he expresses doubt about the quality of data from elsewhere, and also echoes the point that this is not just about surgery, as lung cancer treatment has become more specialised, with new molecular targets and stereotactic radiotherapy.

In the MDT, he also highlights the role of nurse specialists – "They often act as advocates for patients and press for a specialist opinion on a patient's fitness for treatment." There is even a study showing an association between being reviewed by a cancer nurse

specialist and a higher likelihood of receiving active treatment (*Thorax* 2011; 6:Suppl 4 A42-43).

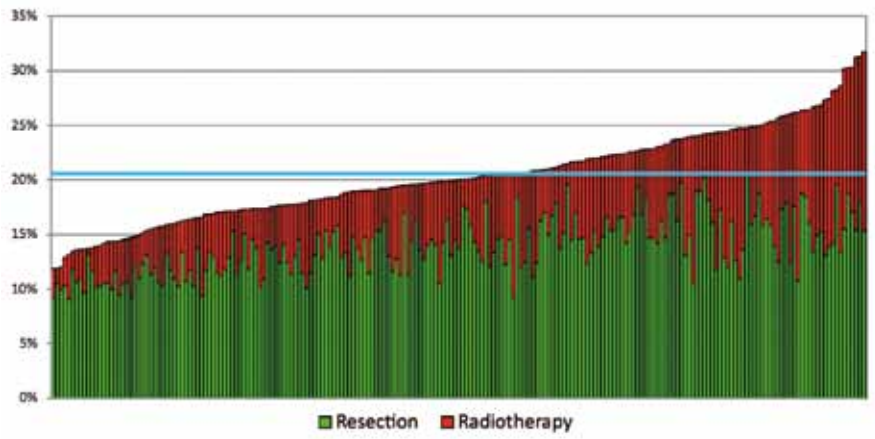
Peake has a huge amount of other data and studies at his fingertips concerning lung cancer in England, from how primary care doctors with lower threshold rates for referral can improve outcomes, to the impact that distance from hospitals, age and socioeconomic status have on treatment uptake, to trends in take up of various therapies, and indeed the role of respiratory physicians, who are also known as pulmonologists/pneumologists, or thoracic/chest physicians.

These specialists play a pivotal role say Peake and colleagues (*Respirology* 2015, 20:884-8). While countries do vary in service structure, they write, "Most patients with suspected lung cancer are initially referred to a respiratory physician for confirmation or exclusion of this diagnosis, as well as staging of confirmed lung cancer, and assessment of fitness for any potential therapy." In many instances, they add, "it is the respiratory physician who is the chair of the MDT and provides leadership and strategic direction for the team."

It is acknowledged by Peake and colleagues, though, that there is little actual 'trial level' evidence for the effectiveness of lung cancer MDTs, and even less for the role of respiratory physicians, and "conclusions are based both on common sense and clinical experience." It all points to a need to develop the evidence, although controlled trials are not likely to ever happen – which is an issue common to other cancers.

Torsten Blum, who leads the European Initiative for Quality Management in Lung Cancer Care, also stresses the role of respiratory experts. A review he co-authored, 'The lung cancer patient, the pneumologist and palliative care: a developing alliance', finds that the value of early palliative care is not being realised, and looks at how pneumologists can raise their game (*Eur Respir J* 2015, 45:211–26). He makes the point that, in Germany, respiratory physicians can also administer systemic therapy.

Treatment varies widely from place to place



> Radical treatment: 11.8% to 31.7% (IQR: 17.6%–23.1%)
> Surgery: 9.1% to 20.7% (IQR: 12.0%–15.8%)
> Radiotherapy: 0.4% to 16.4% (IQR: 4.2%–8.2%)

Quality matters. This graph, published by Public Health England, shows that people are almost three times as likely to receive radical treatment for non-small-cell lung cancer in local health services with the highest rates of radical treatment compared with the lowest. The picture is likely to be replicated in many other countries, but most do not collect or publish the data.

Source: Daniela Tataru et al. (2016) Geographical Variation in the Use of Radiotherapy and Surgical Resection for Treatment of Non-Small Cell Lung Cancer in England. National Cancer Registration & Analysis Service, Public Health England

Improving quality across Europe

The European Initiative for Quality Management in Lung Cancer Care is probably the first attempt to capture data on the quality of care across Europe. A first paper was published in 2014, detailing an extensive literature review, a baseline survey of healthcare infrastructure, benchmarking of guidelines, and the feasibility of collecting clinical data from European countries (*Eur Respir J* 2014, 43:1254–77).

As Blum says, it has confirmed the picture of widespread inequalities among countries, especially in access to radiotherapy and new targeted drugs (and now immunotherapies are also becoming important in lung cancer). "We also see differences in qualifications and specialisms of personnel. For example, we believe surgeons should specialise in thoracic surgery, but some countries don't have a board exam for it, only for general or perhaps cardiothoracic surgery," says Blum.

Waiting times for scans and treatment in the UK, which has a primary care/outpatient system, contribute to higher mortality there he feels, although Jakobsen says that waiting a bit longer for treatment is not crucial (but late diagnosis is).

In general, the paper also found that there was no other project of the same scope – most other studies were institutional or regional, and addressed single facets of the lung cancer pathway. The (open access) paper includes tables showing what type of professional delivers certain modalities, including palliative care, what infrastructure delivers care in each country, and how countries and hospitals vary in histological confirmation and surgical resection rates.

There is also detail on who makes up MDTs in the hospitals surveyed from European countries, and Blum says the task force has since carried out interviews in 25 countries to dig deeper into MDT features. "We have not published yet, but one finding is that MDTs tend to channel patients into various treatment pathways – such as surgical, palliative or systemic treatment – but then these pathways become unidisciplinary with no teamwork. There should be multidisciplinary working along the entire pathway, but this seems to be hard to do owing to lack of resources." What can be termed extended MDTs – with professionals such as psychologists and social workers – are also not in place in most countries.

The task force is aiming to publish standards for lung cancer registries and centres in Europe. "We want to define our gold standard of care – the idea is not to run a certification system but to help countries make a self-assessment to improve their care quality."

Germany, he notes, is one of the leaders in certification, including it for lung cancer in 2009. Blum's centre – Lungenklinik Heckeshorn, in Berlin – was a pilot. "Having an external auditor is helpful – we found discussion on structuring MDT meetings particularly useful. Our main criticism is that it is too focused on infrastructure and outcomes, and is lacking in process quality." As an example, he gives the delivery of systemic chemotherapy – "Do you assess every cycle to adjust dosages? How are complications managed? Standards are needed for certain processes to guarantee quality."

"Unacceptable variation remains in standards of care between organisations"

In the UK, Peake notes that a national peer-review system for cancer units is still in place, although not as in-depth as it was a few years ago when lung MDTs used to receive regular visits from peers – now it is mostly done based on data. The UK National Lung Cancer Audit for 2016 was published with commendable speed, covering patients diagnosed in 2015. It shows encouraging improvements, such as one-year survival at 38% compared with 31% in 2010, histological confirmation rates have risen, and the proportion of patients treated surgically (excluding those with small-cell lung cancer) rose to 16.8%. But "there remains wide and unacceptable variation in standards of care between organisations," the audit report notes.

Putting survival on policy agendas

Patient groups are now becoming much more vocal about the lottery that exists for care in countries. For example, the UK Lung Cancer Coalition (UKLCC) is calling for governments, commissioners and the healthcare community to work together to raise five-year lung cancer survival rates to 25% by 2025 across the UK, and has recently published a report, '25 by 25: a Ten-year Strategy to Improve Lung Cancer Survival Rates', in which it makes 20 recommendations, including the introduction of screening for groups at risk (informed by a Dutch–Belgian randomised trial on using CT scans, known as NELSON).

At the European level, LuCE (www.lungcancereurope.eu) is a relatively recent arrival to the advocacy movement. Modelled on Europa Donna, the breast cancer umbrella organisation of national members, its launch was supported by the European School of Oncology. It has followed up a position paper from 2015 with a report launched last November at the European Parliament. The 'LuCE report on lung cancer' presents the incidence, survival and mortality figures, and one of the key messages is to address inequalities that emerge from this data, especially in eastern Europe, and engage member groups in addressing concerns in their countries.

It stresses access to new treatments but recognises that they must be provided on the basis of evidence, such as by using ESMO's Magnitude of Clinical Benefit Scale. As the LuCE board members say: "Spending on lung cancer doesn't automatically translate into improved outcomes, but more effective management of available resources to provide patient-centric care, does."

The conclusion about patients with lung cancer, like those with other major cancer types, is that they need care in high quality, high volume multidisciplinary centres that help to iron out inequalities. There is much to do in prevention and early diagnosis, not least to reduce the numbers first seen in emergency departments (which vary from about 23% to 47% across Europe). But at the same time a standard of care quality for treatment centres, as

Lung Cancer Europe

Lung Cancer Europe (LuCE), the pan-European advocacy group, is calling for action to improve screening and early diagnosis, access to quality treatment, research and support for people with lung cancer. This image is part of their campaign to challenge stereotypes and stigma surrounding lung cancer, which isolates patients and can act as a barrier to seeking timely help, diagnosis and treatment.

suggested by the European Respiratory Society task force, must have wider discussion and ultimately promotion – and the emphasis should be more on patient needs rather than just raw outcome measures.

Other work in this direction includes 'Defining a standard set of patient-centred outcomes for lung cancer', a paper by the lung cancer working group of the International Consortium for Health Outcomes Measurement (ICHOM), again with Peake as one of the key movers. As the authors say, lung cancer outcome measurement has been mostly limited to survival, and there is a need to include measures of the value of treatments according to other factors such as complications, degree of health, and quality at end of life (see *Eur Respir J* 2016, 48:852–60).

And when it comes to lung cancer, addressing public attitudes and prejudices are an essential part of improving outcomes. This is not just about fatalism, and raising awareness of the disparities in the quality of treatment and the importance of seeking out the best centres. It is also, as LuCE emphasises, about challenging widely held, and ill-informed, negative attitudes that people with lung cancer 'have brought the disease on themselves' through smoking, which as LuCE says, "creates a stigma which can isolate patients, and creates barriers to seeking timely help, diagnosis and treatment, which could ultimately save lives."

EUROPEAN ONCOLOGY NURSING SOCIETY (EONS)

Working in partnership to develop and promote excellence in cancer nursing practice through education, research, leadership and support to cancer nurses across Europe.

We are…

A pan-European organisation dedicated to the support and development of cancer nurses. Through our individual members and national societies we engage in projects to help nurses develop their skills, network with each other and raise the profile of cancer nursing across Europe.

Our vision…

That all people affected by cancer across Europe will benefit from the care of well educated, well informed and highly competent cancer nurses, who will play a central role in providing support, promoting health and improving clinical outcomes.

EONS aims to...

Moving forward together to realise the potential of cancer nursing across Europe ensuring that European cancer patients will benefit from the care of well educated, perceptive and proficient cancer nurses.

RECaN aims to...

Increase the Recognition of Cancer Nursing across Europe (RECaN). This is a major Onco-Policy project, supported by ECCO using a variety of different methods including research, education, clinical leadership, nursing strategy, advocacy and policy development.

Work with us to shape a healthier future for European citizens!
Visit us at:http://www.cancernurse.eu/

MERCK

AS ONE FOR robyn

Bowel cancer, Gladstone, Australia

www.merckgroup.com

Communication – the core skill that can make or break multiprofessional care

Complex healthcare cannot succeed without effective communication between everyone involved in the patient's care, with each understanding and respecting the contribution of others. **Peter McIntyre** looks at where things can go wrong, and how to help ensure they go right.

The patient was watching the chemotherapy passing down the tube into her arm when she noticed something odd. She rang the bell at her bedside and asked the nurse: "Why is another person's name on my infusion bag?"

The nurse stopped the infusion before damage was done; but for a minute or so the wrong drug was being delivered.

This was a formative experience for Lena Sharp, then a specialist nurse and manager at the Karolinska University Hospital and now head of cancer care improvement at the Regional Cancer Centre in Stockholm and President Elect of the European Oncology Nursing Society (EONS).

She understood that even in the most prestigious institutions, things go wrong when communication fails.

Improving the way that nurses interact with each other, with doctors, other professionals and patients is one of the key missions of her presidency.

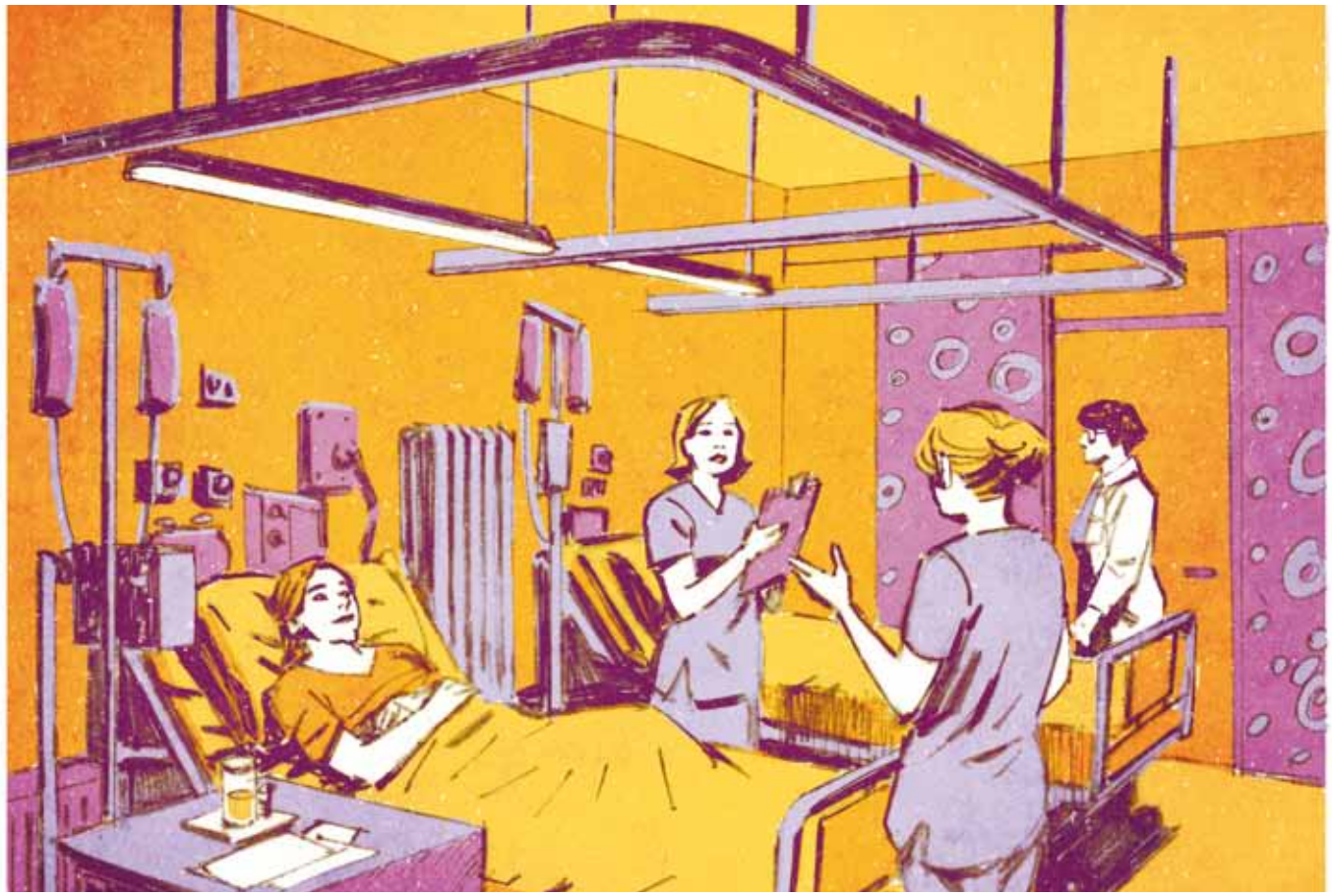
The Swedish National Cancer Plan states that all cancer patients should have someone with in-depth knowledge of cancer nursing to help them navigate the healthcare system: a contact nurse to coordinate care and clinical handovers.

However, when Lena Sharp and colleagues at the Regional Cancer Centre and Karolinska University Hospital researched contact nurses for head and neck cancer patients in Sweden, they could not find any significant patient benefits. For example, no systematic handover system or information exchange had been established between oncology and palliative care.

Sharp was not surprised. Contact nurses do not have clearly defined roles and find it difficult to balance hands-on care duties with their roles in education, information and handover. "They struggle with: 'Should we deliver chemo or should we be a contact nurse?'"

Helena Ullgren, who led this research, is one of a new breed of 11 coordinating contact nurses appointed in Sweden to work with regional cancer centres and deliver on the cancer plan. One key role is to improve the quality of communication and handovers. They visit contact nurses and try to ensure that each patient has a written care plan.

They talked to patients and family members to identify where different parts of the healthcare system were



failing to communicate. Lena Sharp says that the gaps were very visible. "It is not just between different types of care, like palliative and acute care, but also within departments, where you think that collaboration is simple and manageable."

For example, 88% of patients have at least one medication changed when their condition is reviewed at Karolinska University Hospital. However most remained unaware that this had happened, despite having a discharge meeting with their doctor.

There was also little communication between inpatient and outpatient care in the same unit. Patients could be discharged without knowing who to contact in case of problems, or they were advised to go to the emergency unit.

"These are really potent drugs we give to the patient, so a lot of dangerous side effects can occur. The patient might be in a clinical trial and the study drug not yet on the market – if they come to the ER [emergency unit] how can staff know how to handle the side effects? If outpatient nurses or doctors are unaware, that is a source of confusion and misunderstanding."

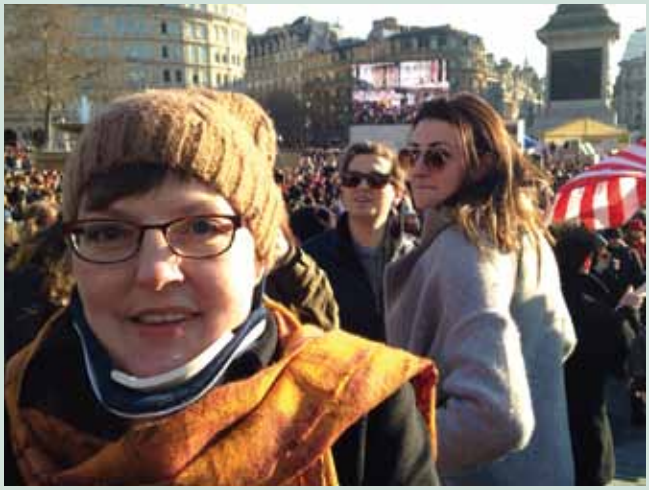
The handover

Shift handovers are a particular source of concern. Lena Sharp recalls an incident when nurses found a full chemotherapy infusion bag on a shelf in the medication room marked with the name of a patient who had been discharged a week before. The doctor had requested the chemo on the morning ward round, but the afternoon shift nurse had presumed it had already been given.

There is little hard evidence about what constitutes the best style of patient handover in a hospital. A Cochrane review team looked at the effectiveness of different nursing handover styles for ensuring continuity of information, but were unable to draw firm conclusions because of the lack of randomised controlled studies (*Cochrane Database Syst Rev* 2014 Jun 24;(6):CD009979).

Karolinska has now introduced 'person-centred nursing shift handovers' to reduce the risk of errors and increase patient awareness. Cancer nurses conduct face-to-face handovers at the bedside at the change of shifts.

Oncology ward to spinal unit… are you hearing me?



Bettina Peters went to the emergency department of a London hospital in September 2015 with severe back and neck pains. She was diagnosed with breast cancer that had spread to the bone. The day after she was admitted, the spinal surgeon fitted a halo brace to her neck as a life-saving measure, saying that the vertebra was being eaten away. The brace protected the bone but was unforgiving and uncomfortable.

"The problem was that the halo brace was whittling away my chin and jawbone. It was getting onto the bone and this became infected and needed to be cleaned. The tissue viability nurse looked at this mess and said something needs to happen. That needed to be communicated to the spinal nurse.

"I was on the oncology ward far away from the spinal unit in a different hospital, so it took about a week for the tissue viability nurse report to make it to the spinal nurse who talked to the spinal surgeon. The spinal surgeon came by after I had chased them a bit and he said I can't take it off, not even for disinfection."

Bettina Peters was in a private hospital, but after seven weeks her workplace insurance expired and she was admitted to the Royal London Hospital and then to St Bartholomew's Hospital (Barts). As there is almost no communication between the private sector and the NHS, her notes all restarted from scratch. To this day, they record the start of her treatment as admission to the Royal London.

In Barts the brace continued to be a problem. "The multidisciplinary team within the department of oncology seems to work quite well. The moment you add something else into the mix like plastic surgeons or spinal surgeons that is much more difficult. They argued over whether there was another option other than this halo brace. That went on for a while, partly because it was difficult to get input from the spinal surgery side.

"The ones really pushing this, talking to the oncology team, making sure that my issue was raised with the tissue viability nurse, and chasing up the spinal surgeon team and making this come together at the multidisciplinary meeting were the physiotherapists. They were the ones saying there needs to be another option. They found the (softer) collar I have now, after I had been wearing the halo brace for about ten weeks."

Peters is grateful for the high-quality treatment she received at Barts, but she now suffers persistent osteomyelitis, and she wonders whether an earlier change of brace would have prevented the sores that led to this condition.

> "The ones really pushing this and making this come together at the multidisciplinary meeting were the physiotherapists"

She also points to problems arising from the loss of continuity in systems where doctors below consultant level change departments every six months, as they do in the UK. Of the original team that treated her at the end of 2015, only one is still left when she returns as an outpatient.

"I was there today and met a consultant that I had not met before. They read your file and, if there is nothing of particular concern, it is fine. But if the same doctor sees you all the time, they can see if you gain weight, lose weight, look tired. If you only see these people once, they have no reference point.

"I would say that information in the notes about whether you look lively or tired or well should not be undervalued. They could take a picture of you every so often and put that with your notes. In this day and age, that would be easy."

Lena Sharp expects a forthcoming research paper to demonstrate benefits in patient care. "We have some qualitative interviews going on with patients and with staff and we see that patients feel it is reassuring. They hear that 'the nurses are talking about me – I might not understand all the technical things but they are making big deal of handing over in a safe way.'"

Anecdotal evidence also suggests that patients in hospital have lower levels of anxiety. "A very strong impression by the nurses involved is that the patients call us less frequently since we started this handover model, because they know that you are there and what is going to happen. They feel more secure so the bell rings less frequently."

Sharp says that health professionals can learn from closed-loop communication systems used by aircrews, where you look the person in the eye, repeat an order, and confirm that you understand. She also cites the Situation, Background, Assessment and Recommendation (SBAR) methodology originally developed by the US Navy for communication on nuclear submarines.

Tasks take priority over communication

Routine assessments made for newly admitted patients regarding their risk of fall are a typical example of where the communication process can fall short, says Sharp. Nurses go through a questionnaire with a patient and arrive at a risk figure based on their age, condition and the drugs they are taking. But that is often as far as the exercise goes. The Swedish researchers found that while nurses registered the risk on patient notes, they frequently failed to discuss preventative action with the patient, such as suggesting they ask for assistance when they go to the toilet.

Sharp says that nurses tend to over focus on practical tasks. "The risk figure does not mean anything if you do not do anything with it. If they did a bit more communication, then healthcare would be safer. They probably do not see how important their role is as communicators."

The problem can be exacerbated when nurses struggle to cope with heavy workloads. Sara Parreira, who works in an oncology day unit at the Fernando Fonseca Hospital in Lisbon, Portugal, says that "Unfortunately, due to staff shortages, people get really worried about what needs to be done at the time, and they prioritise action over communication. Usually there is not time for the team to talk about what needs to be done, plan interventions and reassess those interventions."

The result, she says, is that you can get wasteful duplication of efforts as two nurses address the same problem, while other problems get overlooked.

To improve communications, the nursing staff created a WhatsApp Group, "We can all chat through there about our daily issues". The nurses also meet together once a month, and there are weekly, "problem solving" meetings between the chief nurse and the head doctor.

Multidisciplinary teams

The multidisciplinary team (MDT) meeting is the most significant forum for sharing information about the diagnosis, treatment and care of cancer patients. Demonstrating the benefits of MDTs has proved difficult, because MDTs are often introduced at the same time as other improvements, as a number of reviews have pointed out.

Most clinicians, however, are strongly supportive of this approach, which makes it possible for professionals with different roles and areas of expertise to reach joint evidence-based decisions for treatment and care on the basis of all the relevant information – including personal information such as the patient's needs and priorities, how far away they live, and whether they have support at home.

A survey by a neuro-oncology team at the Royal Melbourne Hospital, Australia, put communication between team members as the single most important asset for MDT meetings. Standards of communication can vary widely, however, as a number of studies have shown, so getting the structure and conduct of the meeting right is important.

A 2011 review published in the *International Journal of Breast Cancer* (doi:10.4061/2011/831605) took a critical look at the quality of communication within some MDT meetings, reporting concerns about the passive role played by junior team members, and recommendations being conveyed to patients in an authoritarian manner, "without allowing patients the ability to fully explore all their available options."

More recent research, carried out for the Department of Health in the UK, has found that MDTs for cancer care are more decisive than for some other conditions, but they can tie up the time of dozens of professionals.

Researchers from University College, London, studied 12 MDTs in the London and North Thames area, covering cancer, heart failure, mental health and memory clinics, observing 30 meetings, interviewing team members and patients and reviewing more than 2,500 medical records.

Unexpectedly, they found that greater multidisciplinarity was not necessarily associated with more effective decision-making and implementation – clarity of purpose and agreed processes were more significant than the

number of people in the room. Their review echoed previously reported concerns, noting that: "Professional boundaries and hierarchies have the potential to undermine the benefits of multidisciplinarity." (*Health Serv Delivery Res* 2014, doi: 10.3310/hsdr02370).

Cancer MDTs, it noted, were tightly structured and chaired, and tended to be hierarchical, set up in a lecture-style format, with rows of chairs facing projector screens at the front, used to display pathology and radiology images. There was a tendency for consultants to sit at the front, with junior doctors, nurses and other members of the team further back. While team members valued a range of disciplinary perspectives, not all disciplines were perceived to have an 'equal voice'.

Rosalind Raine, professor of health care evaluation at University College, who led the research, says that hierarchical meetings are not all bad. "It is important not to take away too simplistic a message, because a hierarchical structure can work better than a flat structure. If a meeting is hierarchical but fair, and the chair knows when to draw in the social worker or nurse, then the hierarchical structure functions really well. When staff feel unable to speak, it does not work well.

"It sounds facile to say that leadership is key, but being reflexive and responsive and inclusive when appropriate, and making a decision and moving on when it isn't, is all about leadership. It does not matter who does it, although it is pretty clear that is has to be somebody clinically qualified and senior. It is about being able to make a judgement when different specialities need to be included. You need quite a lot of experience to know that."

Raine warns that there is also a need for efficiency. "The assumption is that if you have lots of people with different perspectives, then the best decision will be made taking the most important facets of that person's condition and life circumstances into account. However, there are huge complaints about the waste of time for many people's afternoons, especially in cancer MDTs, because there are sometimes 40 people mandated to be there for the whole afternoon, and some rarely contribute."

The hierarchy that separates doctors from nurses continues down the line

Patients can also feel left out of the loop. Raine does not believe it is appropriate for cancer patients to attend MDTs, but says more effort has to be made to explain how they function and what is happening. "There is very definitely a communication deficit with respect to a patient understanding how a decision has been made. When a clinician goes to a patient and says the MDT decided this, most patients have no idea what they are talking about. What the heck is an MDT? They may perceive it to be a decision made by whoever is sitting in front of them."

Respect for everyone's contribution

Hierarchy certainly can be an obstacle to good communication, says Lena Sharp, who was once patient safety coordinator at the Karolinska University Hospital, and has seen examples where nurses or nursing assistants did not speak up about patient safety, because they did not want to challenge the doctor.

According to Sharp, "the doctor–nurse game", described by psychiatrist Leonard Stein 40 years ago, still happens, where both doctors and nurses protect the view that the doctor is right, and the nurse is there to make the work of the doctor easier.

EONS is delivering a training course for nurses in Estonia in May that will encourage them to communicate better and to speak up more. "Estonian nurses report that they are sometimes told not to question what a medical colleague says, whether they are right or wrong. I am very critical of my own group, nurses, for taking this passive role and not speaking up."

The hierarchy that separates doctors from nurses continues down the line. Nurses find it easy to communicate with physiotherapists, occupational therapists and social workers, but not with healthcare assistants or cancer co-ordinators, and others of 'lower' status, says Sharp. "Patients often tell hospital porters things they don't tell anyone else. If they [the porters] don't say anything we might miss something important. All of us have to pick up on it, rather than saying 'what do you know?' as is too often the case."

"It is very much cultural change that we need. It is not a nursing problem; it is a healthcare problem."

Sara Parreira agrees that communicating 'down' the hierarchy seems to be a particular problem at the oncology day centre in Lisbon where she works. "In my experience, nurses can easily approach doctors about any patient issue, but the opposite – doctors talking to nurses about a patient's treatment plan, for instance – doesn't happen often."

Communication tends to be limited to immediate problem solving, she says. "We don't communicate trying to anticipate problems. I think we should do this more often by way of prevention...

Sometimes I feel that nurses are not considered as they should be."

There have been attempts to confront hierarchical obstacles head on, including at the Karolinska itself, where oncology consultant Kathrin Wode introduced a radical new ward round for cancer patients receiving palliative or curative treatment.

Instead of standing over patients while they lie in bed (often with other patients within earshot), a team that included the senior oncologist, the resident doctor, the nurse and assistant nurse sit in a circle in the staff dayroom and invite the patients in one by one. A dietician, physiotherapist and counsellor attend as needed, while X-rays and lab results are displayed on screen.

Wode describes how this transformed team work. "It was astonishing what happened. Before, there was a clear hierarchy. Here we came to sit together in a circle; everybody at the same level; doctor, patient, nurse, assistant nurse; human beings talking to each other and everybody having their own competence. Often as patients left the room they said, 'This was great.' They really appreciated it."

Patients who could not leave their beds were seen as before, but more patients than they expected were able to leave their beds and attend the consultation.

"Patients gained a sense of trust, they felt informed and they were more mobile. They wanted to shower before they came to the team, because they wanted to look nice. The night nurses told us that patients needed fewer tranquillisers and needed less comforting at night.

"For the staff it involved less work because we could do everything at the time and it meant less reporting time later. We gained time and the ward saved money because patients stayed on average one day less in hospital, with fewer X-rays, less medication and less staff overtime. It was great to go to work and everybody loved it. We were the only ward that had a queue of nurses wanting to work there."

The favourite ward. Radical changes to the traditional rounds at an oncology ward at the Karolinska saw patients invited into the dayroom to be part of a discussion with the senior oncologist, the resident doctor, the nurse and assistant nurse. Reported benefits included lower anxiety among patients, shorter hospital stays, lighter nursing workload… and a waiting list of nurses wanting to join the ward

"Human beings talking to each other and everybody having their own competence"

Wode admits that there was some resistance from doctors to spreading this to other wards. Research on a similar scheme in another Swedish hospital found that, although most doctors believed it improved team work, some senior doctors felt their autonomy was threatened and feared being asked questions they could not answer in front of the whole team (*J Hosp Admin* 2014, 3:127–42).

Wode has since changed jobs, but the team model continues on her former ward and she remains convinced that this is the way forward. "You have to switch something in your mind, abandon some ideas of hierarchy or power and go for it totally. It was great to work like that."

Good communication takes time and commitment and depends on professionals operating within systems that function well, Lena Sharp concludes. She had just finished a full day with her team when she spoke to *Cancer World*, and commented on the meeting that had just wrapped up, which involved 11 professionals and a patient, seated around the table. "It was a fantastic discussion. When you have the multiprofessional perspective plus the patient and you recognise each other's contribution, that is when things begin to happen."

She agrees that you cannot have this level of resources all the time, just as you cannot have 40 professionals in a room for every MDT. But she says that the cost of miscommunication is even higher. "It takes more time when you have to read up again on a patient you lost track of, or something goes wrong and you have to take the patient back. Readmission as a consequence of miscommunication is a big deal. We save a lot of time by communicating effectively."

35 years

ESO European School of Oncology

Learning to care

CLINICAL TRAINING CENTRES
FELLOWSHIP PROGRAMME

Are you a trainee oncologist looking to spend a short period in a clinical setting at a centre in Europe?

Would you like to gain further experience in your speciality and learn more about the running of a successful cancer unit?

ESO offers Clinical Training fellowships (observership or residency) at selected host centres across Europe for 3-6 months.

The following centres have been selected as ESO's Clinical Training Centres and offer various programmes for trainee oncologists:

- **St. Vincent's University Hospital**, Dublin, Ireland, under the umbrella of the University College Dublin
- **Institut Gustave Roussy**, Villejuif, France, under the umbrella of University Paris-Sud
- **Oncology Institute of Southern Switzerland**, Bellinzona, Switzerland
- **European Institute of Oncology**, Milan, Italy
- **Istituto Nazionale dei Tumori**, Milan, Italy
- **The Royal Marsden, NHS Foundation Trust**, London, United Kingdom
- **Comprehensive Cancer Centre Ulm**, Ulm, Germany
- **Champalimaud Clinical Centre (CCC)**, Lisbon, Portugal

GRANT

Successful applicants will receive the following:

- travel costs to and from country of residence
- a monthly grant of EUR 2.300 (visiting observership status) and EUR 2.500 (visiting residency status)

The application deadlines for training periods in 2018 are:

- **30th June 2017** ***(applications for the first semester in 2018)***
- **6th November 2017** ***(applications for the second semester in 2018)***

Details of the training programme offered by each centre and how to apply can be found at www.eso.net under the 'Career Development' section.

Further information
Corinne Hall, chall@eso.net

The 2018 Clinical Training Centres programme will be supported by a Fund provided by the European School of Oncology and an educational grant from **Bristol-Myers Squibb**.

FURTHER INFORMATION AT WWW.ESO.NET

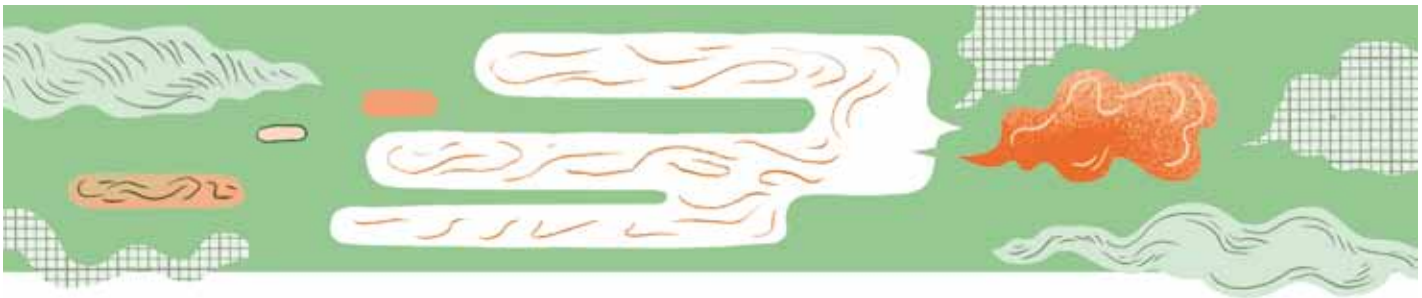
HELSINN

Building quality cancer care together

Going further to bring better todays to even more people with cancer

At Helsinn, we are delivering more treatments to lift the burden of cancer and investing in research to meet the needs of patients, for better tomorrows.

www.Helsinn.com



Ivana Božović-Spasojević: A Bordet for Belgrade

A chance to work at the heart of the trailblazing MINDACT trial gave Ivana Božović–Spasojević a memorable lesson in the value of international academic trials, and the logistics of how to run them. She spoke to **Anna Rouillard** about her efforts to use what she learnt to ramp up academic research efforts in her own country.

If you ever feel overburdened by the demands of your job, then maybe you can spare a thought for Ivana Božović-Spasojević. A consultant medical oncologist, she is part of the most overstretched cancer workforce in Europe, based as she is in Belgrade. According to Eurostat, Serbia has fewer than one cancer professional per 100,000 population – one third the ratio in Poland, and one seventh that in Sweden.

As if this were not workload enough, she is leading efforts to develop Serbia's academic cancer research capacity. She is setting up a Serbian Breast Group, connected with other research organisations in Europe and North America, with the aim to better connect with other academic groups in the region.

She is herself principal investigator in a number of academic trials. These include the POSITIVE trial, run by the International Breast Cancer Study Group (IBCSG), and an international trial on male breast cancer, sponsored by the European Organisation for Research and Treatment of Cancer (EORTC), which is looking to characterise the biology and evolution of male breast cancer, which accounts for less than 1% of all breast cancers diagnosed worldwide.

Based in the Breast and Gynaecology Oncology ward of the Institute for Oncology and Radiology of Serbia, one of four cancer centres in the country, Božović is adamant that oncologists in Serbia need to get involved in large international trials and initiatives – not least because of the increasing number of commercial trials being run in the country over the past 15–20 years.

"Having sponsored trials in Serbia is on the one hand positive, since it means that patients get access to expensive drugs for free, but on the other hand, these trials sometimes have questionable trial design, and results are sometimes misreported," she says.

Physicians are not involved in the conception, planning or design of sponsored trials, nor in the reporting of results, adds Božović, who argues that it is vital to have an equal partnership between academia and pharmaceutical companies.

Academic research is also essential for its own sake, she says, to find answers to critical questions that are important

to patients, but which hold no commercial interest. Male breast cancer, a very rare cancer, is a good example.

"I have been working in my institute for 15 years, and in total I've seen maybe 80 or 100 cases of male breast cancer. The number is too small for research. But if you collect a large number of patients willing to participate in academic research that is conducted by international collaborations, over a small period of time you are going to have big data," she says.

The POSITIVE trial, led by Olivia Pagani, is another example of a trial with scant commercial interest. POSITIVE is designed to answer questions about whether it is safe for women with early breast cancer to interrupt endocrine therapy for two years to have a child.

"This is not something pharmaceutical companies are going to be interested in researching, but it's really a hot topic," says Božović. Young female cancer patients always have questions about their fertility. They want to know how safe it is to get pregnant, and we need big, prospective, robust data in order to advise them properly."

Educated at the Bordet

Serbia suffered a massive brain drain during and after the Balkans war, leaving the country perilously low on healthcare practitioners. Today, with salary levels of around €800 a month, qualified young oncologists continue to leave for western Europe and the US, "where they have better opportunities and conditions," says Božović. "For older physicians, getting a research grant gives them a chance to work in better conditions and do high quality research. But young doctors are leaving the country in droves."

Her own career path into oncology was slightly unusual, starting in 2001 with a spell doing research in clinical pharmacology at the Belgrade national cancer research centre, where she still works. This was made possible by a postgraduate scholarship awarded by the Serbian Ministry of Health for outstanding academic achievement.

There she had the chance to work with Zora Neškovic, a leading breast oncologist and academic researcher. "She sparked my enthusiasm for academic research," says Božović.

"Professor Neškovic was PI for many academic trials in Serbia led by EORTC and IBCSG, and she paved the way for the breast cancer research we do here today."

In 2009, Božović was herself enticed to leave the country, when an opportunity arose to work as a clinical research fellow at the Jules Bordet Institute in Brussels, under the supervision of Martine Piccart and Fatima Cardoso.

It turned out to be the perfect time and place. In her first year of training she was involved in one of the great pioneering translational trials in personalised medicine, the MINDACT trial, which prospectively evaluated gene profiling as a tool for identifying which women with early breast cancer can safely forego adjuvant chemotherapy.

"I got to understand the different challenges researchers face, be they medical, logistical or legislative"

"The MINDACT trial was the most interesting trial I have ever worked on," says Božović. "Through this experience I got to understand the different challenges researchers face, be they medical, logistical or legislative. The results were published in the *New England Journal of Medicine* last year, and it was a real privilege to be listed as a collaborator."

Božović's clinical research fellowship was extended, and one year turned into three when she shifted to the Breast Data Centre as a medical advisor for ALTTO and neo-ALTTO – two large multinational trials that compared two anti-HER2 targeted therapies with different mechanisms of action, used separately or in combination, in the adjuvant and neoadjuvant setting for early breast cancer treatment.

Building capacity in Belgrade

Božović came back to Belgrade in 2012 and has drawn on her experience in Brussels to help build up academic cancer research in her own country. Her own institute, the Institute for Oncology and Radiology of Serbia (IORS), is already an international cancer research centre, with high-quality laboratories and a data centre capable of handling translational research, but as Božović says, it is hard to make progress in isolation. "On our own, we are too small to do science. Science costs money. So we need to be part of big academic networks."

Inspired by BIG (the Brussels-based Breast International Group), she created the Serbian Breast Group, an informal set-up within the IORS, which she intends to develop so as to increase Serbia's engagement in international collaborative research in breast cancer.

The Serbian Breast Group is already part of EORTC and the International Breast Cancer Study Group, but Božović's goal is for it to become part of other research organisations such as BIG. "Being part of a recognised and reputable research group is very important, because of the learning opportunities that open up when you work with experts who are at the top of their field."

"What I am really thinking about is a model similar to the one in Brussels. We need to attract young people to work exclusively in research for several years while receiving a grant. It's a win–win situation: they will learn how to do clinical and translational research – how to formulate important research questions and design and conduct trials – and we will benefit from their help."

She is a strong proponent of gaining experience abroad, and feels that a critical mass of people who go abroad and then come back is needed. "Going abroad makes young people see what it is possible to deliver. Education is so important. You are exposed to different ways of doing things and can then do things better yourself."

She concedes, however, that the conditions they can offer in Belgrade are a long way from what she experienced in Brussels. "I may be PI for several academic trials, but I still have to take care of many things by myself, including administrative tasks. I hope one day to have a well staffed organisation like BIG, and a breast data centre, where skilled and well trained people have their own roles in the research structure."

That said, Božović is highly aware that the challenge of finding time for research is by no means unique to Serbia. "The problem in academic research is that, as a clinician, you never have dedicated time for it. And this is true everywhere. It is just that in Serbia, given how overloaded we are, you really need to fight to have any time for research at all."

Serbia has a long history of collaboration with France when it comes to oncology. Many of the country's most famous physicians and prestigious opinion leaders were educated there and, in the past, oncology students spent several months in Paris through an initiative with the French embassy. Today there is ongoing collaboration in clinical research between Paris' Tenon Hospital and the Institut Curie and the National Cancer Research Centre in Belgrade, which Božović hopes will lead to Serbian physicians being able to study in France.

Ivana Božović (*centre*) with her team at the Institute for Oncology and Radiology of Serbia, in Belgrade

'I can change things'

Božović is a member of the oncology working group within the Serbian Ministry of Health, which last year published its cancer plan. It is based on the French cancer plan, but transposed for the financial situation of Serbia, and has prevention and screening as its major focus.

"In general, Serbians do quite a lot of sport, our diet is reasonably good, but, just like other countries in the Balkan region, the majority of people smoke. Some restaurants ban smoking, but these rules are useless when you see that the smoke free room is connected to the smoking room!"

"Programmes are in place for breast, cervical and colorectal cancer screening. But screening is not having the effect it should have, because awareness of cancer is painfully low and, even if we do have the equipment for mammographies, there are too few radiation oncologists to read the mammograms."

The incidence of breast cancer is around average for European countries. However, Serbia is second highest for breast cancer mortality, according to 2014 data. "This is because screening is not working well enough," Božović explains, "and breast cancer is locally advanced in 30–40% of patients, which is a huge number."

Based on EUSOMA guidelines, Serbia is accrediting hospitals that can give high quality breast cancer treatment. "Due to the centralised system of care here, some patients have to travel up to 200 km to be treated. We are trying to address this by ensuring some of the smaller hospitals offer high quality care. These hospitals may not be able to be involved in clinical trials, but at least there will be more options for patients to be treated."

One of the great achievements has been the establishment of medical oncology as a subspecialty and a clinical oncology curriculum for medical students.

"My great wish is to expand academic research in Serbia and the region and to motivate young people to be involved in it"

For Božović, education is key to the future of cancer care in Serbia. "Sometimes I think I am too ambitious, but I really do think that, together with my experienced and enthusiastic colleagues, I can change things. My great wish is to expand academic cancer research in Serbia and the region and to motivate young people be more involved in it. They are smart, they work hard and they are eager to learn. When you get them together in a team, and you educate them, maybe send them abroad for some time, you will have a fantastic team. This is my goal and I hope I'm going to realise it."

Novartis Oncology

Changing the practice of medicine

At Novartis, we use science-based innovation to address some of society's most challenging health care issues. We are passionate about discovering new ways to improve and extend people's lives.

As a leader in oncology, Novartis offers a portfolio of more than 20 approved therapies and approximately 30 compounds in development.

NOVARTIS

Novartis Pharma AG
CH-4002 Basel Switzerland

11/16 G-ONC-1150235

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

The EU and Cancer: It's time for a bold vision Mr Juncker

In 1976, a doctor, M.F. Weiner, wrote an article in *Medical Economics* titled 'Don't Waste a Crisis – Your Patient's or Your Own'. In it, he urged doctors to think about how a medical crisis can be used to improve aspects of personality, mental health, or lifestyle.

I would like to give the European Union the same advice at this moment. I fear 'Brexit' is only the most recent example of the public losing its appetite for the spirit of cooperation that gave birth to the 'European project' sixty years ago in Rome.

So what is to be done? Those of us working in cancer know the improvements that collaboration brings. That clearly refers to the vitally important collaboration across disciplines required to provide the best cancer care to patients. ECCO promotes this mission daily, most recently with the publication of Essential Requirements for Quality Cancer Care in the fields of colorectal cancer and sarcoma. However, it also refers to collaboration across countries in specialised areas of treatment such as rare cancers, now further helped by new European Reference Networks. Collaboration also means mobility of healthcare professionals to share skills across borders, and collaboration between countries in conducting cutting-edge research into new treatments, services and practices.

So from the cancer care perspective, giving in to cynicism and abandoning multinational collaboration is not the way for Europe to go. But the EU must improve both the way it works and what it prioritises if it is to inspire the public anew about the benefits of countries coming together in common cause.

A good way of thinking about this challenge could be to start from the guiding question: 'What matters most to citizens?' Survey evidence continually tells us what I think we probably all know already: health matters most. Not just our personal health, but that of the ones we love.

Credible polling by organisations like Ipsos-MORI also informs us that, year-on-year, within health, cancer is at the forefront of citizens' concerns.

So with that in mind, is it really right or sensible for the response to euroscepticism to be for the EU to do *less* on health and cancer?

Sometimes the EU (and its members) don't do enough to promote what has been achieved. In health, this includes remarkable improvements in collaboration, such as: centralised authorisation of medicines; harmonisation of clinical trial regulations; automatic recognition of professional qualifications across borders; and ground-breaking public health collaboration in areas such as tobacco control. I could continue the list, but I want to conclude.

The EU is at its best not when it is timid, shy and reticent, but when it is bold. Like any organisation, when it defies the nay-sayers, offers vision and then pursues that vision to a successful conclusion, its esteem and value is raised, and its legacy secured.

Cancer is an area where vision can be rewarded, and lasting public support secured.

I call on the EU to direct its priorities to those of the general public. There are few greater hopes among the population than the hope that we will get the better of cancer in our own time.

Europe's multidisciplinary community of cancer healthcare professionals, represented by ECCO, stands ready and willing to help shape a new and ambitious vision for the EU on cancer. Working together, across disciplines *and* across countries, much more improvement can still be achieved. A firm sign of political intent that this is what the EU wants to focus on will not only remove barriers, it will reassure the public that the EU is working on the issues that matter most to them.

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

Complementary and integrative medicine for cancer patients

Coping with the cancer and the treatment

With studies showing that around half of all cancer patients use therapies that are not part of mainstream medicine, two specialists review what complementary and integrative medicine can offer to cancer patients, and discuss the supporting evidence and use of a range of treatment options.

This grandround was first presented by Chiara Bocci, from Istituti Clinici Scientifici Maugeri – IRCCS, in Pavia, Italy, and Emanuela Portalupi, from the Association for Research and Studies in Anthroposophic Medicine, in Milan, Italy. It is edited by Susan Mayor. The webcast of this and other e-sessions can be accessed at e-eso.net.

Use of complementary and integrative medicine (CIM) in cancer has increased dramatically over the last few decades. A survey conducted around a decade ago, across a number of European countries, found the level of use varied from around one in four cancer patients to around three in every four (*Ann Oncol* 2005, 16:655–63).

'Complementary medicine' refers to therapies that work alongside conventional treatment with the aim of treating side effects associated with cancer and cancer treatment. Integrative medicine combines appropriate complementary and conventional treatments, to heal and support the patient's body, mind and spirit. Integrative medicine is interdisciplinary, using the skills of several healthcare disciplines through referral and consultation, with the aim of using the individual's capacity for self-healing in an approach that is personalised, collaborative and comprehensive.

The National Center for Complementary and Integrative Medicine (NCCIM), within the US National Institutes of Health, distinguishes

between two subgroups of complementary and integrative approaches: natural products and mind-body practices. Examples of types of complementary and integrative therapy included in the NCCIM definition can be seen in the table (*right*).

These approaches are more likely to be used by female patients, and those who are younger, white, more highly educated and on a higher income.

Women with breast cancer have particularly high rates of CIM use, with one study showing it is used by 80% of survivors treated with multiple chemotherapies and in late stage of disease (*BMC Womens Health* 2007, 7:4).

More than 80% of those who use it experience benefit, but a large proportion of patients (20–77%) do not inform their physician that they are using CIM (*Oncologist* 2012, 17:1475–81).

Patients use CIM for a wide range of reasons. These include: improving physical symptoms, supporting emotional health, boosting the immune system and improving quality of life. Some patients use CIM to relieve the side effects of conventional cancer treatments or to obtain a more holistic treatment, while others may be hoping to gain better control of their disease.

Question Why do patients not inform their physicians they are using CIM?

Answer: Patients think doctors are not interested. They think these therapies will not interfere with conventional treatment, but that is not necessarily the case. We know that there is a risk of interaction with conventional treatment in one in three patients taking herbal medicines, so it is important that patients inform physicians about the use of CIM, because it could be dangerous. Some patients think doctors are prejudiced against use of CIM so they do not want to discuss the issue.

Complementary and integrative approaches*

- Aromatherapy
- Chiropractic/Osteopathy
- Hypnotherapy/Guided Imagery
- Yoga/Meditation
- Massage
- Music and Dance therapy
- Biofeedback
- Ayurvedic medicine
- TCM [Traditional Chinese Medicine] – Acupuncture
- Homeopathy
- Phytotherapy
- Qi Gong – Tai Chi
- Reiki
- Reflexology
- Diet Supplementation

*Some of the treatments included in the definition used by the US NIH National Center for Complementary and Integrative Medicine

Guidelines on use of CIM

The European Society of Breast Cancer Specialists (EUSOMA) has published a report and recommendations on the use of complementary and alternative medicine in caring for patients with breast cancer (*Eur J Cancer* 2006, 42:1702–10; *ibid* 1711–14; *Eur J Cancer* 2012, 48:3355–77).

These recommend that all patients with breast cancer should be treated by multidisciplinary teams that provide the best chances of cure, palliation, and psychosocial and spiritual support. They advise that undergraduate and postgraduate students should be taught communication skills as a central component of professional development.

Health professionals should work together and use 'psychometric' instruments to capture, evaluate and ultimately enhance quality of life in both physical and spiritual domains. The recommendations also suggest that clinical case histories and randomised trials should contain modules that identify patients' belief systems about complementary and alternative medicine and establish whether it is being used concurrently, and support open and factual discussions about it.

There are also clinical practice guidelines on the use of integrative therapies in the supportive care of patients treated for breast cancer (*JNCI Monographs* 2014, 50:346–58), on the use of complementary therapies and integrative medicine in lung cancer (*Chest* 2013, 143 (5 Suppl):e420–36) and on exercise for cancer survivors (*Med Sci Sports Exerc* 2010, 42:1409–26).

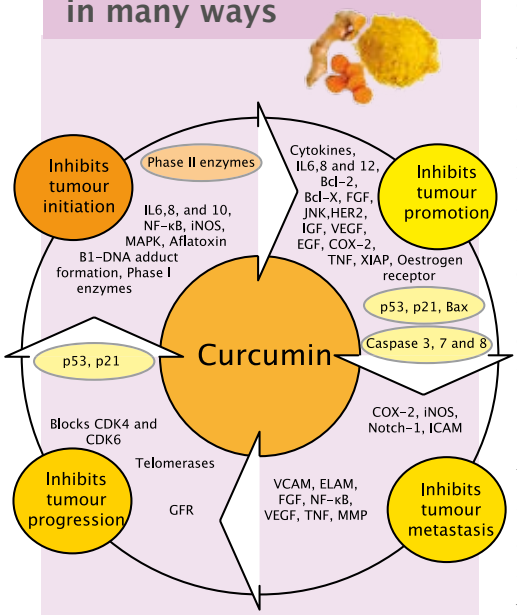
The evidence for CIM in breast and lung cancer

In a review of the evidence for CIM in breast cancer, the Society for Integrative Oncology (integrativeonc.org) graded recommendations based on evidence for a range of therapies (*JNCI Monographs* 2014, 50: 346–58).

It gave a grade A recommendation ('There is high certainty that the net benefit is substantial') for meditation, yoga and relaxation with imagery for treating anxiety and other mood disorders in breast cancer. Grade B recommendation ('There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial') was given for the use of stress management, yoga, massage, music therapy, energy conservation and meditation for treating stress, depression, fatigue and quality of life.

The recommendation for electro-acupuncture/acupressure for controlling chemotherapy-induced nausea and vomiting was rated as grade B, while that for progressive muscle

Curcumin acts on cancer in many ways



Molecular targets listed within an oval are upregulated by curcumin

All other listed targets are downregulated by curcumin

Source: C Yang et al. (2013) *Curr Pharm Des* 19:1966–73

Curcumin, the active principle in turmeric, is very pleiotropic, and can modulate intercellular signalling pathways. Studies show that it can play a role in protecting healthy tissues from harmful effects of radiation, while enhancing the radiation effect on cancer cells. Studies also suggest that it can act as a chemoprotective for healthy cells as well as a chemosensitiser, enhancing the efficacy of several types of chemotherapy drugs (*Nutr Cancer* 2010, 62:1137–41; *Target Oncol* 2014, 9:295–310)

relaxation and ginger was grade C ('There is at least moderate certainty that the net benefit is small').

More than 30 interventions, including some natural products and acupuncture for other indications, had weaker evidence of benefit, and received a grade C or D recommendation, mainly because of small study size, lack of data on long-term safety and toxicity outcomes, lack of standardised outcome measures, omission of toxicity and adverse event data, inadequate statistical methods, and lack of blinding and/or appropriate control groups. Details of the criteria for scoring the quality of the evidence are given in the Supplementary material (*JNCI Monographs* 2014, 50: 346–58).

In lung cancer, mind–body modalities were found to reduce anxiety, mood disturbance, and sleep disturbance, acute or chronic pain, and anticipatory chemotherapy-induced nausea and vomiting, and to improve quality of life (grade 2B).

Acupuncture or related techniques were suggested as adjunct treatment in patients with inadequate control of symptoms including nausea and vomiting from either chemotherapy or radiation therapy (grade 2B) and cancer-related pain and peripheral neuropathy (grade 2C) (*Chest* 2013, 143(5 Suppl):e420–36).

The Society for Integrative Oncology concluded that an evidenced-based approach to modern cancer care should integrate complementary therapies with standard cancer therapies such as surgery, radiation, chemotherapy, and best supportive care measures. Specific integrative therapies can be recommended as evidence-based supportive care options during breast cancer treatment (*JNCI Monographs* 2015, 51:98), and several complementary therapy modalities can be helpful in improving the overall care of patients with lung cancer (*Chest* 2013, 143(5 Suppl):e420–36).

It is important to be aware, however, that a range of interactions can occur between cancer drugs and phytotherapies. St John's Wort, which is widely used, particularly for mild depression, anxiety and sleep disorders, poses a particularly high risk of interactions. However, other herbal agents such as curcumin (the active principle in turmeric – see figure *left*) do not cause drug interactions.

Question: Should CIM in cancer take place only in specialised centres?

Answer: Some therapies such as guided imagery, yoga or use of ginger can be taught to patients and their families for use at home. Other therapies such as acupuncture require specialist facilities.

Question: Are there any preparations that can better prepare patients for surgery?

Answer: Some herbs that can affect coagulation, such as Ginkgo biloba, should not be used before surgery. A study in Milan has investigated Arnica in reducing blood and serum volumes collected in drainages (J Intercult Ethnopharmacol 2017, 6:1–8).

Integrative oncology in Europe

Integrative oncology in Europe does seem to differ in some respects to the US. The Tuscany Network of Integrative Medicine (Italy) was commissioned by the 2014 European Partnership for Action Against Cancer (EPAAC) to review the available evidence about the experience with integrative oncology ('Complementary and alternative medicine in cancer care: Development and opportunities of integrative oncology', epaac.eu/news/373-final-epaac-deliverables).

Emanuela Portalupi reviewed the evidence concerning anthroposophic medicine. The working group also produced a map of European centres providing integrative oncology services (*Support Care Cancer* 2015, 23:1795–806). The report considered acupuncture and

traditional Chinese medicine, herbal medicine (phytotherapy), homeopathy, anthroposophic medicine and homotoxicology. Available studies were assessed and the evidence graded for effects on quality of life and cancer symptoms in particular types of tumours.

Common concepts emerged for complementary and alternative medicine, including health being seen as a dynamic process, with conditions being seen as an imbalance and therapy being used to fight disease and to stimulate the body's self-regulatory mechanisms.

Phytotherapy (herbal therapy)

Phytotherapy is the oldest type of medicine in the world, coming from traditional medicine, but now with a modern approach. It may involve use of raw herbs or herbal preparations (purified or extracted components), based on single herbs or combinations. Studies have assessed a wide range of different herbs, with strong recommendations based on high or moderate levels of evidence (Society of Integrative Oncology grading 1A, 'strong recommendation, high-quality evidence' or 1B, 'strong recommendation, moderate-quality evidence'), that herbal medicine is effective for anxiety and depression in cancer, cancer-related fatigue, mucositis, nausea and vomiting and pain.

Acupuncture and traditional Chinese medicine

Acupuncture originated in China more than 3000 years ago, based on a holistic approach with a mind–body vision of the human being. It uses a 'map' of the human body, with specific points at which the therapist can intervene with needles, moxa and other approaches. Traditional Chinese medicine includes diet, herbs and formulae of herbs, and energetic exercises such as qi gong. The review written for EPAAC found that acupuncture was an effective treatment (Society of Integrative Oncology grading 1A or 1B) for nausea and vomiting related to chemotherapy and surgery, pain, hot flushes (due to iatrogenic menopause) and xerostomy (dry mouth).

Homeopathy and homotoxicology

Homeopathy is based on the principle of similarity (curing 'like with like'), and minimum dose, using individualised treatments that address a complex of symptoms. Homotoxicology has its roots in classical homeopathy, but is linked to pathophysiology. The evidence review found homeopathy was effective for hot flushes, side effects of radiotherapy, insomnia, anxiety and depression and diarrhoea (grading 1B).

Anthroposophic medicine

This is a model of care based on integrative medicine, enhancing the ability of the patient to self-heal, with a strong emphasis on health promotion and prevention. It was introduced in the 20th century by Rudolf Steiner and Ita Wegman, based on an integrated view of the human being, with different levels: physical, biological, emotional, spiritual and social. Anthroposophic medicine is an extension of integrative medicine, combining conventional and anthroposophic treatments. It uses pharmacological approaches including original anthroposophic mistletoe extracts, and non-pharmacological approaches, such as nursing, artistic therapies, movement therapies, nutrition and lifestyle measures, massage, biographical counselling and psychoeducational groups.

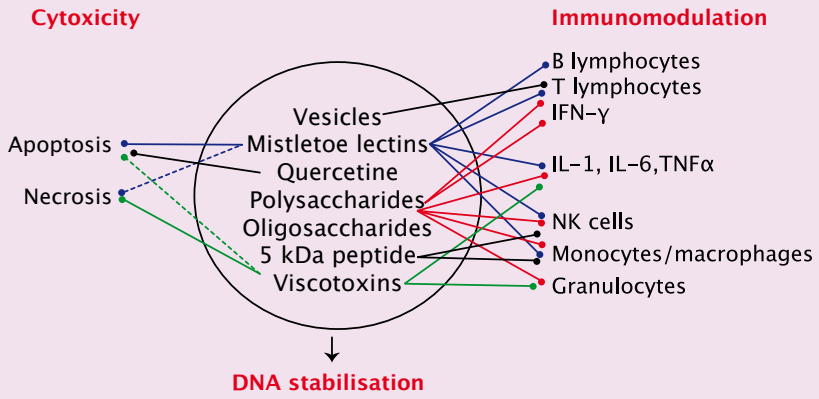
Lifestyle and self-education are central to anthroposophic medicine. A review in the *Lancet* in 1999 found a significant trend (P=0.01) for an inverse relation between the number of anthroposophic lifestyle characteristics and a reduced risk of atopy (tendency to allergic diseases) in children (*Lancet* 1999, 353:1485–8). EUROCAM published a paper in 2015 on the role of CAM, including anthroposophic medicine, in reducing antimicrobial resistance (cam-europe.eu).

Biographical issues are considered central in the healing path, seeing disease as one event in a person's biography,

Boswellia serrata resin extract for cerebral oedema

Resin extract from *Boswellia serrata*, the plant from which Indian Frankincense is derived, was given orphan designation by the European Medicines Agency in 2002 as an experimental drug with potential for treatment of cerebral oedema in patients irradiated for brain tumours (though the orphan status was withdrawn in 2006 at the request of the manufacturers). A prospective randomised trial has shown it significantly reduced cerebral oedema so could potentially be steroid sparing for patients receiving brain irradiation (*Cancer* 2011, 117: 3788–95). A larger study carried out in Milan, due to be published soon, has confirmed the benefit in patients undergoing radiotherapy for brain cancer.

Viscum album extracts in cancer



Viscum album (mistletoe) has a range of cytotoxic and immunomodulatory effects. Reviews have shown it is well tolerated, with evidence of benefit to quality of life and reduction of side effects from conventional treatments (*Eur J Med Res* 2007, 12:103–19; *Cochrane Database Syst Rev* 2008, 2:CD003297). An international oncological register, Network Oncology, based in Berlin, has collected data on the use of mistletoe in real life (Schad et al. *Forsch Komplementmed* 2013, 20:353–60).
It can be used alone as part of alternative medicine, alongside conventional and other alternative approaches, or as part of integrative medicine.

Source: A Büssing ed. (2000) Mistletoe: The Genus Viscum. Harwood Academic Publishers, the Netherlands

Further studies: **General**: *Eur J Med Res* 2003, 27:109–19; *J Exp Clin Cancer Res* 2009, 28:79; *3 Biotech* 2014, 4:13–20. **Safety:** *Integr Cancer Ther* 2015, 14:140–8; *Evid Based Complement Alternat Med* 2014, 2014:236310; *ibid* 724258. **Immunomodulatory effects:** *BMC Complement Altern Med* 2011, 11:72. **Quality of Life:** *J Altern Complement Med* 2016, 22:134–44; *Integr Cancer Ther* 2010, 9:142–57. **Survival impact:** *BMC Cancer* 2009, 9:451; *Leuk Lymphoma* 2010, 51:1414–23

and supporting individualisation of meaningfulness and therapeutic processes.

Question: Is a multimodal model compatible with the multidisciplinary approach currently used in oncology?

Answer: It is. In anthroposophic hospitals (e.g. in Berlin, Stuttgart and Herdecke in Germany, and Arlesheim in Switzerland) a multimodal approach is regularly applied, but in other general hospitals there could be a specific department providing advice (e.g. in St Gallen, Switzerland) or input into multidisciplinary discussions.

The most well-known anthroposophic approach used in cancer are *Viscum album* (mistletoe) injectable extracts. They are widely used in Europe, with some studies showing 25–60% of patients use this therapy. In cancer, *Viscum album* extracts are used differently from the previous concepts of traditional herbal medicines.

They contain more than 600 proteins, lectins, viscotoxins, polysaccharides, triterpenes and other components, which have a range of cytotoxic and immunomodulatory effects (see figure above). They can be given alone or with conventional treatments, and are used in all phases of disease, from prevention to palliative care, and in cancer survivors, where integrative approaches can be particularly important, and is often the only treatment proposed.

By 2015, 141 clinical trials of *Viscum album* had been reviewed by the Institute for Applied Epistemology and Medical Methodology IFAEMM, in Freiburg, Germany.

Recent studies showed it reduced side effects with conventional cancer therapies and improved patients' quality of life, with beneficial effects on outcome, survival and cost-effectiveness. There are no known interactions, including with main chemotherapy agents and some targeted cancer therapies.

Other approaches in anthroposophic medicine include use of external therapies, such as embrocation and compresses and oil dispersion baths (*Holist Nurs Pract* 2016, 30:216–21) and rhythmical massage, which can be helpful in influencing well-being (*Complement Ther Med* 2015, 23:685–92).

Art therapy and eurythymy therapy can support patients in rehabilitation, in feeling active and creative, and reducing fatigue, anxiety and depression during conventional oncological treatments (*Psychooncology* 2007, 16:980–4; *Complement Ther* 2013, 21 Suppl1:3–9) and lifestyle and nutrition can support general health (*FEMS Microbiol Ecol* 2014, 90:791–801).

Clinical relevance: two polar opposite examples

Breast cancer

Patients with breast cancer are generally treated on a long-term basis with conventional treatments that have side effects, so they may need approaches that can reduce these problems. Many breast cancer patients

and long-term survivors also wish to be more active and express a need for empowerment. Studies have shown the potential role for anthroposophic approaches and confirmed that patients do not abandon conventional treatments (*Forsch Komplementmed* 2006, 13: 94–100). Integrative treatment should be considered from diagnosis, through treatment and beyond to support patient wellbeing (see figure *right*).

Breast cancer patients represent the biggest group among people with cancer receiving anthroposophic medicine, with a register showing it is used by 45% of patients (*Forsch Komplementmed* 2013, 20:353–60).

Patients may use these approaches for years, looking for personal growth as well as relief from physical symptoms. Studies show a positive impact on quality of life, with improved coping, sleep, fatigue and energy, reduced cancer drug side effects, and improved ability to work and emotional and functional wellbeing.

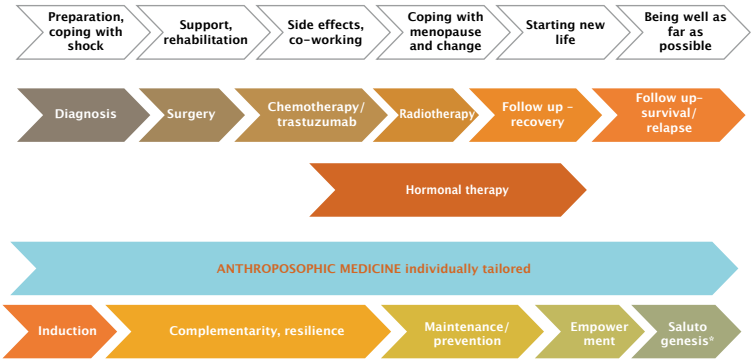
There are also synergistic effects with chemotherapy, with use of mistletoe enabling patients to maintain dosage and timing and reducing fatigue, neutropenia and neuropathy among others. In addition, there is some evidence of significant benefit in overall survival (*J Exp Clin Cancer Res* 2009, 28:79). Globally, *Viscum album* extracts and anthroposophic medicine provide a body–soul–spirit approach.

Pancreatic cancer

Patients with pancreatic cancer often have short life expectancy and poor quality of life, with limited therapeutic options. Studies with mistletoe and conventional treatment, mostly in patients with advanced disease, show a trend to improved overall survival, particularly in patients with better prognosis, together with improved quality of life (*Curr Mol Med* 2010, 10:430–9; *BMC Cancer* 2016, 16:579). Synergy has been seen with gemcitabine (*Evid Based Complement Alternat Med* 2013; 2013:964592).

A randomised trial in Serbia showed a significant and clinically relevant prolongation of overall survival of around two months and improvement in symptoms and side-effects with *Viscum album* extracts in patients with advanced pancreatic cancer (*Eur J Cancer* 2013; 49:3788–97) (see figure below) and a further randomised controlled trial of mistletoe plus chemotherapy – Mistletoe Therapy in Primary and Recurrent Inoperable Pancreatic Cancer (MISTRAL) – just started in Sweden (Karolinska).

Planning integrated treatment



Integrative oncology approaches can apply to every part of the patient's cancer journey

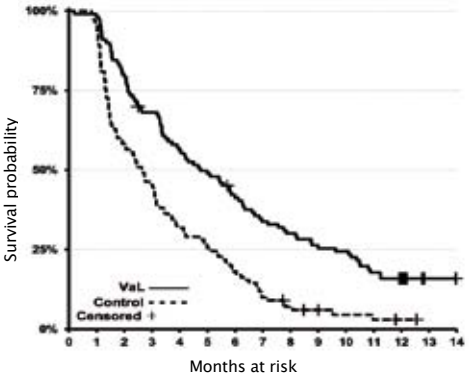
*Salutogenesis – supporting human health

Take home messages

Integrative medicine:

- Increases the range of tools to help patients cope with cancer and cancer treatments
- Is mostly co-operative, interdisciplinary and multimodal
- Is a safe and synergistic approach
- Can improve quality of life and reduce side effects of conventional treatments, which could contribute to improved overall survival and reduce costs
- Has a patient-centred perspective, directed to all aspects of human wellbeing
- Is supported by research and experience.

Viscum album extracts in advanced pancreatic cancer



Treatment with V*iscum album L.* extract showed a significant survival benefit in this prospective randomised phase III trial in 220 patients with locally advanced or metastatic pancreatic cancer, with a median overall survival of 4.8 months compared with 2.7 months for patients on no anti-cancer therapy (HR 0.49, 95%CI 0.36–0.65)

Source: W Tröger et al (2013) *Eur J Cancer* 49:3788–97, republished with permission from Elsevier

EVENTS DIRECTORY
2017 - 2018

ECCO - the European CanCer Organisation manages multidisciplinary meetings of excellence on behalf of its Members:

EVENTS	SAVE THE DATE
MCCR WORKSHOP	**17 – 23 June 2017** ***Zeist, Netherlands*** MCCRWorkshop ECCO-AACR-EORTC-ESMO Workshop on Methods in Clinical Cancer Research
2nd Special Conference EACR AACR SIC	**24 – 27 June 2017** ***Florence, Italy*** EAS2017 2nd EACR-AACR-SIC Special Conference onThe Challenges of Optimising Immuno and Targeted Therapies
EBCC 11 European Breast Cancer Conference	**21 – 23 March 2018** ***Barcelona, Spain*** EBCC11 11th European Breast Cancer Conference
EACR 25	**30 June - 3 July 2018** ***Amsterdam, Netherlands*** EACR25 25th Biennial Congress of the European Association for Cancer Research

To discover more about ECCO: **www.ecco-org.eu**

OECI
Organisation of European Cancer Institutes

ecancermedicalscience

ESO Recommended

TJ Tumori Journal

Oncology Days

OECI 39

BRNO 2017
GENERAL ASSEMBLY, SCIENTIFIC CONFERENCES AND RELATED EVENTS

Brno, Czech Republic - June 21st-23rd
Hotel International

In collaboration with

MU IBA MONKIN (MOravian Oncology Initiative)

OECI Oncology Days 2017 Programme

Wednesday June 21st - All day

- **Pathology Day**
  N-1 trial consortium: collaboration among oncologists, pathologists, bioinformatics and ethics experts

Wednesday June 21st - Afternoon

- **Accreditation and Designation Session**
  Developing Quality Criteria for Comprehensive Cancer Networks: what makes a great cancer network?

Thursday June 22nd - All day

- **Scientific Conference**
  Rising cancer prevalence as emerging challenge for oncologists

Friday June 23rd - Morning

- **OECI General Assembly 2017**

10th ANNIVERSARY Oncology Days

For more information: www.oeci.eu/Brno2017.aspx

Non-invasive metabolic imaging of brain tumours in the era of precision medicine

Sriram Venneti and colleagues examine non–invasive metabolic imaging strategies that can be used to interrogate some of the genomic alterations in brain tumours, with the ultimate goal of informing patient management.

This is an abridged version of Michelle M. Kim et al. (2016) Non-invasive metabolic imaging of brain tumours in the era of precision medicine. ***Nat Rev Clin Oncol*** *13, 725–739, doi:10.1038/nrclinonc.2016.108. It was edited by Janet Fricker and is published with permission* © *Macmillan Publishers Ltd.*

nature REVIEWS CLINICAL ONCOLOGY

Clinical management of brain cancer relies heavily on non-invasive imaging because location often prohibits tumour sampling and/or surgical resection. MRI (with or without contrast enhancement) remains the standard approach and is used to guide tissue biopsy sampling, establish diagnosis, assess progression, and evaluate therapy effectiveness.

Work is needed to exploit knowledge of brain tumour pathology and biology to develop non-invasive imaging modalities guiding diagnosis, treatment and follow-up monitoring of brain cancer.

In the personalised medicine era, we are beginning to appreciate the genetic complexity of primary brain tumours and uncover a variety of clinically relevant mutations. Such information allows identification of actionable targets and development of corresponding molecularly targeted therapies. Challenges remain in identifying, stratifying, and monitoring patients using advanced imaging technologies, and leveraging information gathered from genomics.

Cancer metabolism provides the best example of molecular imaging in cancer patients, with PET imaging and magnetic resonance spectroscopic imaging (MRS) being the principal modalities used.

PET imaging, based on biological substrates labelled with radionuclides, is highly sensitive, with signal detection limits of 10^{-11} to 10^{-12} mol/l (*Curr Pharm Biotechnol* 2010, 11:555–71). It uses the 'Warburg effect', where cancer cells generate ATP predominantly through aerobic glycolysis of glucose to lactate in the cytoplasm. The number of ATP molecules produced (2 molecules) is lower than mitochondrial metabolism (36 molecules), increasing glucose demands of cancer cells. PET imaging uses an ^{18}F-labelled glucose-

analogue tracer (^{18}F-FDG) that cannot be metabolised further than initial phosphorylation by hexokinase, and therefore accumulates in cells, indicating glucose demand.

Single-voxel MRS and multi-voxel MRS (MRSI) characterise the chemical and molecular composition of tumours based on radiofrequency signals generated by nuclear spins of magnetic-resonance-active nuclei, including ^{1}H, ^{31}P, and ^{13}C (*Semin Oncol* 2011, 38:26–41).

The capacity of oncogenes to reprogramme cellular metabolism (enabling tumour cells to survive, grow and proliferate) is emerging as a fundamental concept in cancer biology. Many oncogenes expressed in brain tumours influence specific metabolic pathways, including glucose, amino acid, and fatty metabolism.

Genomic heterogeneity of glial tumours

The updated 2016 WHO Classification of Tumours of the Central Nervous System defines two major glial tumour groups: astrocytic tumours and oligodendroglial tumours (IARC, 2016). Observations from next generation sequencing studies that adult and paediatric glial tumours are genetically distinct prompted WHO to incorporate molecular characteristics, histological type and tumour grade into the revised classification system.

For example, in adults >90% of glioblastoma multiforme (GBM) harbour genetic alterations converging on the P13K/AKT/mTOR pathway, including enhanced activation of receptor tyrosine kinases transmitting signals via this pathway (such as EGFR, PDGFRA, and MET). By contrast, high-grade gliomas in children are characterised by mutations resulting in epigenetic reprogramming, with histone H3 K27M and G34R/V mutations detected in ~60% of paediatric patients with GBMs. Thus, genetic drivers of childhood and adult gliomas are distinctly different.

Precision medicine for brain tumours

Subclassification of brain tumours into distinct groups informing management of patients beyond histological grade is another important development arising from molecular tumour studies. For example, grade IV medulloblastomas (predominantly paediatric) are classified into four molecular subtypes: Sonic Hedgehog, WNT, Group 3 and Group 4.

Next generation sequencing studies have refined understanding of brain tumours and patient care, with research opening novel avenues for targeted therapies. For example, vismodegib (an antagonist of the SHH pathway) is effective in patients with SHH medulloblastoma, but not other subtypes (*JCO* 2015, 33:2646–54).

Integrating molecular characteristics of brain tumours into therapeutic decisions is increasingly integral to patient management, with molecular features of brain cancers currently assessed using tissue samples obtained from tumour biopsy or resection. Obtaining such samples is not always feasible for pontine and brainstem tumours, owing to surgical challenges involving location. Furthermore, longitudinal assessment of serial samples is not practical due to difficulties performing repeated biopsies.

Since conventional MRI is inadequate for evaluating molecular alterations, non-invasive, metabolic imaging of brain tumours is emerging as a way to assess molecular and metabolic alterations.

Imaging glucose metabolism

Glucose is metabolised into pyruvate by glycolysis, which under aerobic conditions can be oxidised to acetyl-coenzyme A, which then enters the mitochondrial tricarboxylic acid cycle, fuelling ATP production via oxidative phosphorylation. Brain tumours typically exhibit the Warburg effect, where pyruvate is diverted from the mitochondria and converted to lactate (*NMR Biomed* 2012, 25:1234–44). Enhanced production of glycolytic intermediaries promotes tumour invasion and escape from immune cells, and glycolytic metabolism enables adaptation to low oxygen levels in hypoxic areas of the tumour.

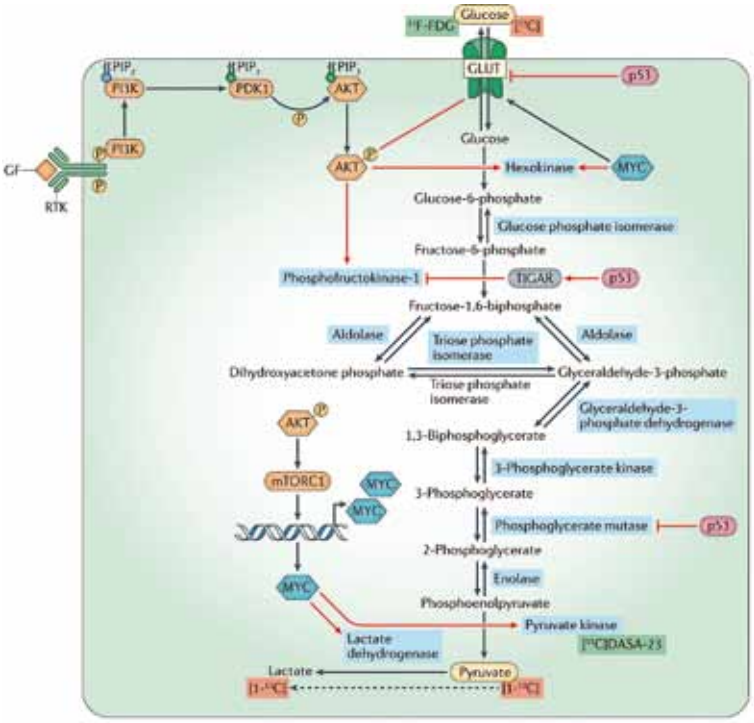
In brain tumours, the Warburg effect is controlled at several levels, including regulation by the P13K/AKT/mTOR pathway via BRAF activation.

Interestingly, many glycolytic enzyme isoforms expressed in brain development are expressed in brain tumours, but not the adult brain, e.g. HK2 and pyruvate kinase M2 (PKM2). Such observations have enabled the development of a ^{11}C-labelled PET imaging probe specific for PKM2 (*Clin Cancer Res* 2005, 11:2785–808).

^{18}F-FDG-PET imaging was one of the earliest tools measuring locations of brain glucose utilisation. However, in gliomas ^{18}F-FDG-PET has poor tumour-to-background contrast, due to high levels of glucose uptake in normal brains. Using ^{13}C-labelled glucose as a tracer (quantifying the appearance of ^{13}C-glucose in lactate or pyruvate), MRS can monitor glucose metabolism in glioma.

To overcome low signal-to-noise ratios, ^{13}C-enriched probes can be 'hyperpolarised' through exposure to low temperature microwaves, altering the Boltzmann distribution of ^{13}C, and increasing MRS detection more than 10,000 fold (*Proc Natl Acad Sci* 2003, 100:10158–63). In small animal

Oncogenic reprogramming and imaging of glycolysis in brain tumours



Red arrows depict common oncogenic signalling pathways in brain tumours, such as those involving activation of PI3K, AKT, mTOR and MYC, and those influenced by inactivating alterations in p53, which affect various aspects of glycolysis — generally increasing the glycolytic flux. PET tracers relating to this pathway are highlighted in green, and magnetic resonance spectroscopy (MRS) tracers in red. The two main substrates involved in glycolysis and related pathways that can be labelled for use as clinical imaging tracers are glucose and pyruvate (yellow ovals).

models, generation of [1-^{13}C] lactate from [1-^{13}C] pyruvate was detected in glioma xenografts *in vivo*, but not in non-tumour brain tissue.

The spectrum of metabolic imaging studies might be further expanded by spectroscopic techniques with enhanced physiological and functional information based on CEST contrast, a sensitivity enhancement mechanism by which low concentrations of solutes containing exchangeable protons that have different resonance frequencies from bulk water protons can be selectively saturated with radiofrequency energy and visualised indirectly using the water signal (*Magn Reson Med* 2011, 65:927–48).

Finally, combined PET–MRI systems are enabling a multiparametric approach to non-invasive brain tumour characterisation, although further studies are needed to optimise this approach in the clinical setting.

Imaging of IDH-mutant gliomas

Human cells express three isoforms of IDH (enzymes converting isocitrate to α-keloglutarate): IDH1, IDH2, and IDH3. IDH1 is present in the cytosol and IDH2 and IDH3 in the mitochondria. Since the metabolite D-2-hydroxyglutarate (D-2HG) is produced in IDH1/2 mutant gliomas, but not wild-type tumours, the metabolite could serve as a biomarker for diagnosis, treatment and surveillance via non-invasive imaging.

The detection of D-2HF *in vivo* using MRS correlates with better prognosis compared with patients in whom it is not detected. Sensitivity, however, depends on tumour size – 8% for small tumours versus 91% for larger tumours (*Neuro Oncol* 2016, 18:283–90). In addition, hyperpolarised-^{13}C MRS might be harnessed to probe for the enzymatic function of mutant IDH1/2 *in vivo* (*Nat Commun* 2013, 4:2429).

Imaging amino acid metabolism

Mechanisms where non-invasive imaging of brain tumours could exploit reprogramming of amino acid metabolism include:

Glutamate: Many primary brain tumours (including gliomas, meningiomas, and medulloblastomas) have altered levels of glutamate and glutamine. Tumour cells also exchange glutamate for cysteine (via the cysteine-glutamate anti-porter), raising the possibility that PET imaging of glutamate exchange could analyse brain tumours.

Glutamine: Brain tumours display increased cellular glutamine uptake and metabolism. Non-invasive *in vivo* measurement of glutamine uptake can be achieved using ^{18}F-FGln, which has been shown to increase in gliomas compared to normal brain tissue (*Sci Transl Med* 2015, 7:274ra)

Methionine: ^{11}C methionine uptake is increased in malignant cells, including gliomas. It can be useful in detecting

Take home messages from the authors

From the left: Michelle M Kim is affiliated to the Department of Radiation Oncology and Abhijit Parolia and Sriram Venneti to the Department of Pathology, of the University of Michigan Health System, University of Michigan, Ann Arbor, Michigan; Mark P. Dunphy is affiliated to the Molecular Imaging and Therapy Service of the Department of Radiology, at the Memorial Sloan Kettering Cancer Center, New York

"We have made significant progress in understanding the genetics of brain tumours. However, we have not devised ways to detect these tumours non-invasively in living patients. These genetic alterations in brain tumours can reprogramme metabolic pathways in cells. Our aim was to examine if metabolic imaging could help better understand and evaluate brain tumours in the clinic.

Our main take home messages are two-fold. First, there is great promise in metabolic imaging to detect molecular alterations. For example altered metabolism in isocitrate dehydrogenase 1/2 mutant gliomas can be detected using a technique called magnetic resonance spectroscopic imaging (MRS). Second, a lot of research will need to be done to come up with such techniques for other tumour mutations and to standardise these imaging techniques for daily clinical practice.

Clinical implications

Metabolic imaging could help with non-invasive diagnosis, monitoring and assessment of the therapeutic efficacies of treatment. This would be of enormous benefit for patients.

Further studies

The field of metabolic imaging holds great potential. We need to develop more novel techniques, and many of the existing imaging techniques, such as hyperpolarised MRS, need to be considered more carefully in order to directly impact patient care."

tumours, assessing treatment response and predicting disease recurrence.

Aspartate: Levels of NAA (synthesised in neuronal mitochondria from aspartate and acetyl-CoA) decrease in gliomas, most probably due to reduced expression of enzymes involved in NAA biosynthesis. ^{1}H-MRS can be used to detect decreases in NAA.

Imaging fatty acid metabolism

Cancer cells undertake both *de novo* fatty acid synthesis and enhanced fatty acid oxidation (*Nat Rev Clin Oncol* 2017, 14:11–31). Choline is an essential nutrient required for synthesis of phospholipids and the neurotransmitter acetylcholine, and levels of this metabolite are often increased in cancer cells, which might reflect increased rates of cell membrane turnover (*Semin Oncol* 2011, 38:26–41). Elevated total choline signals can be used clinically for primary diagnosis of low-grade and high-grade glioma, and detection of recurrent glioma versus tumour necrosis following radiation therapy.

Molecular imaging of other processes

Cell proliferation: ^{18}F-FLT-PET might be used to detect highly proliferative tumours, reflecting dependence on *de novo* thymidine synthesis and the thymidine salvage pathway.

Hypoxia: Hypoxia is a key feature of rapidly growing tumours that promotes adaptive responses (such as angiogenesis). ^{18}F-FMISO-PET enables spatial delineation of hypoxic regions of brain tumours (*J Nucl Med* 2004, 45:1851–59).

Angiogenesis: Angiogenesis is another hallmark of tumour growth. $\alpha_V\beta_3$-integrin, expressed on endothelial cells during angiogenesis, offers a target for PET scanning using ligands with high affinities for $\alpha_V\beta_3$-integrin (*Eur J Nucl Med Mol Imaging* 2010, 37:S86–103).

Metabolic imaging in patient care

In the following section, the potential for metabolic imaging to be assimilated into routine clinical care is explored.

Tumour delineation for local therapy: Use of amino-acid based PET can improve identification of most biologically aggressive components of heterogeneous low-grade and high-grade gliomas – information that could dictate subsequent therapy and reduce incomplete resection. Use of multiple imaging modalities, including multivoxel 1H-MRS and diffusion and/or perfusion MRI, can also help distinguish between heterogeneous regions of dense tumour infiltration, areas of oedema with admixed tumour cells,

and oedema not infiltrated by tumour (*Neuroradiology* 2006, 48: 622–31).

Prognostication and response prediction: In patients with low-grade glioma, ^{18}F-FET-PET time-activity curves correlate with malignant progression and survival, suggesting a prognostication role. Use of H-MRS for predicting survival outcomes has been evaluated in multiple studies in adult and paediatric patients with brain tumours, with worse outcomes observed in patients with an elevated tumour choline-to-NAA ratio before treatment or adjuvant chemotherapy.

Assessing treatment response: A variety of metabolic changes in both the tumour and microenvironment are observed following cytotoxic, radiation and antiangiogenic therapies. MRS imaging of adjuvant radiation in malignant gliomas, for example, reveals declines in mean tumour choline-to-NAA ratio that predict outcome (*Clin Invest Med* 2006, 29:201–11) Such findings open opportunities for adaptive, response-based radiation treatment.

Monitoring of resistance or progression: Both glucose and amino acid metabolism undergo reprogramming during emergence of resistance to radiation and chemotherapy. Thus, non-invasive metabolic imaging has potential to detect treatment resistance at an early stage and inform alterations in clinical care.

Molecular subgrouping: The non-invasive identification of clinically relevant (prognostic or predictive) molecular tumour subgroups offers a potential application for metabolic imaging. Use of MRS, for example, allows differentiation between SHH and Group 3/4 medulloblastomas.

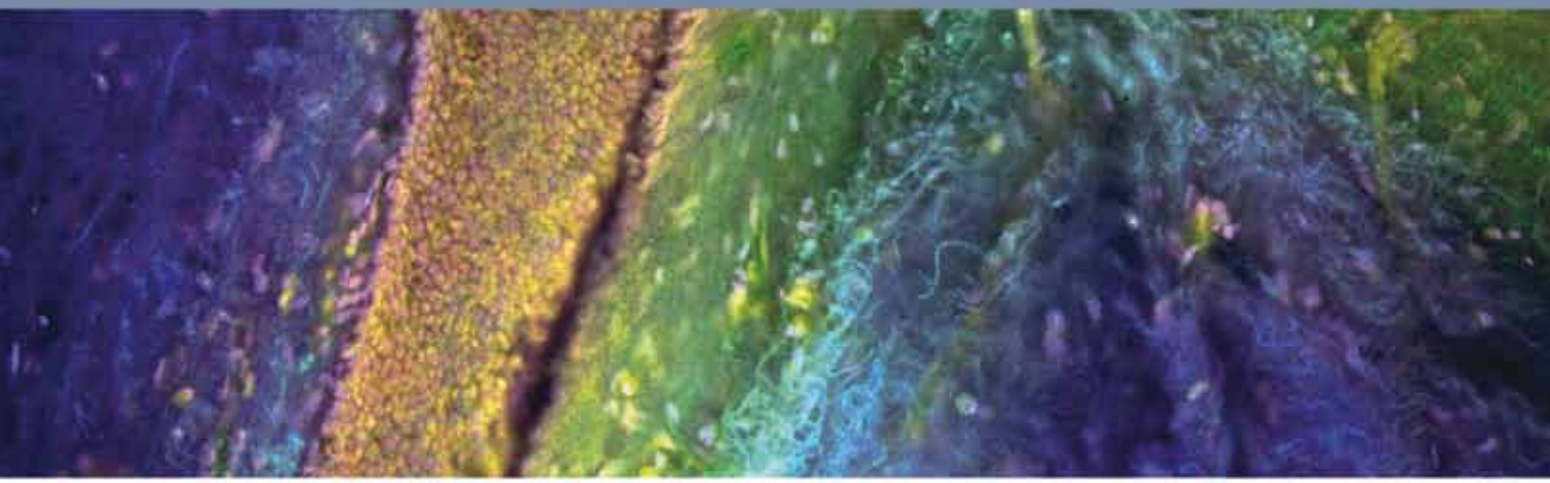
Conclusions

Altered cancer metabolism offers a unique window to integrate genomic information with advanced imaging modalities. The field has progressed, with novel techniques implemented for analysis of tumours in preclinical models and patients.

Additional work is needed to standardise these metabolic imaging techniques for routine clinical use. In combination with other functional imaging modalities, these techniques might prove complementary to conventional MRI in characterising tumour biology and metabolism, with the aim of informing patient management. Future studies based on oncogene-driven metabolic pathways, might enhance diagnosis, prognostication, treatment and surveillance of brain tumours, ultimately improving patient outcomes.

a natureresearch journal

nature REVIEWS CLINICAL ONCOLOGY



Don't miss our recently published content

Drugs that lack single-agent activity: are they worth pursuing in combination?
Bishal Gyawali and Vinay Prasad
doi:10.1038/nrclinonc.2017.27

Getting real about NCI-designated Cancer Center advertising
David Rubenson and Daniel S. Kapp
doi:10.1038/nrclinonc.2017.28

Circulating and disseminated tumour cells — mechanisms of immune surveillance and escape
Malte Mohme, Sabine Riethdorf and Klaus Pantel
doi:10.1038/nrclinonc.2016.144

Integrating liquid biopsies into the management of cancer
Giulia Siravegna, Silvia Marsoni, Salvatore Siena and Alberto Bardelli
doi:10.1038/nrclinonc.2017.14

Activating autophagy to potentiate immunogenic chemotherapy and radiation therapy
Lorenzo Galluzzi, José Manuel Bravo-San Pedro, Sandra Demaria, Silvia Chiara Formenti and Guido Kroemer
doi:10.1038/nrclinonc.2016.183

Tumour-associated macrophages as treatment targets in oncology
Alberto Mantovani, Federica Marchesi, Alberto Malesci, Luigi Laghi and Paola Allavena
doi:10.1038/nrclinonc.2016.217

A GLOBAL REVIEW OF THE mBC LANDSCAPE

2005-2015 DECADE REPORT

GLOBAL STATUS OF mBC DECADE REPORT

A comprehensive, 10-year review examining the global landscape of advanced/ metastatic breast cancer (mBC)

This report was created in collaboration with a steering committee of global, multidisciplinary mBC advisors, comprised of physicians, patient support organization leaders, and patients.

It analyzes both the progress and remaining gaps in mBC management, with a focus on:

Patient care needs | Environmental factors | Scientific developments

Explore the full report at **www.breastcancervision.com**

January 2016

Pfizer Oncology

Male breast cancer is not congruent with the female disease

Male breast cancer is almost always oestrogen receptor positive, and is traditionally treated in line with guidelines for treating hormone-sensitive breast cancers in postmenopausal women. **Ian Fentiman** questions the rationale for this approach, pointing to key biological differences between male and female breast cancers.

This is an abridged version of Ian Fentiman (2016) Male breast cancer is not congruent with the female disease. ***Crit Rev Oncol Hematol*** *101:119–124, doi: http://dx.doi.org/10.1016/j.critrevonc.2016.02.017. It was edited by Sophie Fessl and is published with permission* © *Elsevier*

Only one percent of all breast cancer cases in the western world occur in men. With such a limited number of patients, no randomised trials for male breast cancer (MBC) are carried out, and treatment standards for men have been extrapolated from trials for female breast cancer (FBC). When looking closer at the data available, it becomes clear that aspects of MBC do not fit the model that men have endocrine-sensitive tumours that behave like tumours in postmenopausal women. Differences between breast cancer in men and women are seen in their epidemiological risk factors, molecular profiles and response to systemic therapy.

Risk factors

Endocrine risk factors

The Male Breast Cancer Pooling Project pooled risk factor data from 2,400 men with breast cancer from 21 studies, and identified obesity and gynaecomastia as risk factors (*JNCI* 2014, 106:djt465). The strongest predictor of MBC risk was found to be recent BMI.

MBC is almost always oestrogen receptor positive (ER+). In a report pooling data from 1,483 patients, tumours were ER+ in 92% of patients, but HER2+ in only 5% (*Cancer Res* 2015, 75 (9):S6-05-S6-05). The frequency of FBC that are ER+ varies with menopausal status, but the proportion typically lies between 64% and 79% (*JCO* 1984, 2:1102–9). Around 10% of FBC are HER2+ (*PNAS* 2003, 100:8418–23).

Conflicting results have been reported for intratumoural aromatase; while a study of four MBC tumours found that MBC contained aromatase more

Take home messages from the author

Ian Fentiman is Professor of Surgical Oncology at the GKT School of Medicine, London

"For years, it has been argued that male breast cancer (MBC) is equivalent to female breast cancer (FBC). But the picture is much more complex. Importantly, tumour type differs between men and women. In more than 90% of MBC patients the tumour is oestrogen receptor positive (ER+). In FBC, 60–70% of tumours are ER+. The molecular profile also differs: 43% of FBC tumours are of the luminal A type, 20% luminal B, 10% HER2+ and 36% basal. The picture is completely different with MBC: 80–90% of tumours are luminal A, around 20% luminal B, and both HER2+ and basal types occur very rarely. This has implications for the treatments we should be using.

Clinical implications

Because MBC is rare, no randomised trials are carried out. Treatment recommendations are based on trials of FBC. But while aromatase inhibitors (AIs) are better for treating postmenopausal women than tamoxifen, analyses of male patients shows that men do not fare equally well when given AIs. If AIs are given to treat MBC, oestrogen production must also be blocked centrally with a GnRH analogue.

Further challenges

Collaboration is key to building our understanding of MBC. We need to work together to achieve structured treatment and carry out randomised trials to know how best to treat it."

frequently than FBC (*Horm Cancer* 2013, 4:1–11), a report of 45 cases found only a third of MBC tumours expressing intratumoural aromatase, compared with 62% of FBC tumours (*Breast Cancer Res Treat* 2007, 105:169–175; *ibid* 1998, 49:S93–S99).

Genetics

Several genes associated with a high lifetime risk of breast cancer in women have been identified. One of these, *BRCA2*, confers a significant risk in men, equating to a 7% cumulative risk of breast cancer by the age of 80 (*Am J Hum Genet* 2001, 68: 410–419). *BRCA2* mutations are much more common than *BRCA1* mutations in MBC. Compared with FBC, a larger proportion of MBC are *BRCA2* tumours (10% of MBC cases), and a smaller proportion (1%) are *BRCA1* tumours (*Breast Cancer Res Treat* 2012, 134:411–8).

Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) that influence FBC risk. Of the 12 SNPs most strongly associated with FBC, five were also strongly associated with MBC (*PLoS Genet* 2011, 9:e1002290). Two of these – rs13387042 (2q35) and rs3803882 (*TOX3*) – were even more strongly associated with MBC than with FBC.

Epigenetics

MicroRNAs are short, 21–25 nucleotide long, molecules which do not encode proteins. They bind to complementary sequences in messenger RNA and control gene expression. A comparison of miRNA expression between 23 cases of MBC and 10 of FBC showed that miRNA expression signatures differ between male and female breast cancer. MBC is characterised largely by underexpressed miRNAs (*Breast Cancer Res* 2009, 11:R58).

Molecular profile of MBC

Prognosis is significantly worse for MBC than FBC, largely due to tumour size and lymph node status (*Mod Pathol* 2002, 15:853–61). Molecular profiling shows that fewer than 1,000 genes are differentially expressed between MBC and FBC. Major processes, including energy metabolism, regulation of translation, matrix remodelling and immune recruitment are modulated differently. The androgen receptor plays a major role in MBC, while the progesterone receptor and HER2 are less important (*Breast Cancer Res Treat* 2011, 127:601–10).

The most common phenotype of MBC is luminal A, estimated to occur in 75–98% of MBC patients. This is followed by luminal B, with a frequency of 0–20%. Basal phenotype is rare, occurring in between 0% and 2% of patients, while no HER2+ tumours were found (*Breast Cancer Res* 2009, 11:R28; *Breast Cancer Res Treat* 2012, 133:949–958; *Mod Pathol* 2012, 25:398–404; *Acta Oncol* 2013, 52:102–109). An analysis of molecular subtypes of FBC in three studies shows that, in female patients, 43% of cancers are of the type luminal A, 20% luminal B, 10% HER2+ and 36% basal (*PNAS* 2003, 100:8418–23). Molecular profiles indicate that FBC and MBC are very different diseases.

Cell cycle proteins

Alterations in the expression of cell cycle proteins appear to play an important role in the development of MBC.

The kinase inhibitor proteins (KIPs) p27Kip1 and p21Waf1 negatively regulate progression of the cell cycle. Immunostaining of tumours shows that they are differently expressed in MBC and FBC (*Ann Oncol* 2002, 13:895–902).

p21Waf1 and p27Kip1 are expressed in 70% and 96% of MBC patients, respectively, while they are expressed in only 29% and 39% of FBC patients.

Chemotherapy

A comparison of US Veterans Administration data on 612 MBC patients and 2,413 FBC patients showed that patients with MBC received less chemotherapy. Median overall survival for patients with MBC was 7 years, compared with 9.8 years for patients with FBC (*Cancer* 2007, 109:1471–7).

A retrospective cohort study of 135 men treated between 1944 and 2001 showed a non-significant reduction in mortality in men with node-positive disease who were treated with adjuvant chemotherapy, mostly anthracycline-based. Survival was significantly improved in patients given adjuvant hormonal therapy (*Cancer* 2005, 104:2359–64).

Endocrine therapy

Endocrine therapy is used as adjuvant, neoadjuvant and preventive treatment in FBC. Tamoxifen is used in the treatment of women before menopause. In women after menopause, aromatase inhibitors are given as adjuvant or neoadjuvant (*Cancer* 2007, 109:1471–7).

Because of the success of tamoxifen as a treatment for early FBC, tamoxifen was also used as an adjuvant in MBC. One study of 39 men with node-positive MBC given adjuvant tamoxifen showed that five-year survival was 61%, compared with 44% in historical controls (*Br J Cancer* 1992, 65:252–4). However, a study from Sloan-Kettering Memorial Hospital showed that tamoxifen use leads to side effects in two thirds of MBC patients (*Cancer* 1994, 74:74–7). About one in four patients drop out (*ibid; Ann Oncol* 2011, 23:1471–4; *Curr Oncol* 2010, 17:17–21).

Aromatase inhibitors (AIs) are also used to treat MBC patients, especially with advanced or metastatic disease. In women, AIs are better than tamoxifen in terms of disease free survival and overall survival. However, evidence increasingly shows that AIs are less effective in male patients. While a study of 23 MBC patients who received AIs reported a partial response in 26% of patients and disease stabilisation in 57% (*Br J Cancer* 2013, 108:2259–63), a comparison of registry data in Germany of 257 MBC patients reported that the mortality rate was 1.5-fold higher among patients treated with an AI than among those treated with tamoxifen (*Breast Cancer Res Treat* 2013, 137:465–70).

To Smile

"It's got to come out, of course, but that doesn't address the deeper problem."

Santiago González-Moreno – President of ESSO (2016-2018), and Medical Director and Head of Surgical Oncology, MD Anderson Cancer Center, Madrid

Developing the next generation of researchers in surgical oncology

It is a real pleasure for me to represent the European Society of Surgical Oncology in a dedicated guest page in *Cancer World*. To feature for the first time in this magazine offers an exceptional opportunity for surgical oncologists to share our views on successes, failures, and pressing issues in our common efforts to find the best possible treatments for cancer.

In this first contribution, I would like to talk about the importance of integrating clinical research methodology in the training curriculum of surgical oncologists, especially in view of the upcoming MCCR Workshop on Methods in Clinical Cancer Research.

It is incontestable that our discipline has evolved considerably over the years, and that new surgical techniques are today very sophisticated. Innovations such as robotic surgery or the latest minimally invasive techniques do, however, need to be tested and replicated to be performed in a standardised way across Europe. Moreover, all eligible cancer patients for whom no standard of care treatment options are available should be enrolled in a clinical trial, including when it comes to evaluating surgical procedures.

It is thus self-evident that real progress in surgical oncology corresponds to an increase in the amount and quality of research in this field. There are still too few research projects assessing the quality and reproducibility of surgical oncology techniques, and only a few of them are led by our colleagues. I was once taught that research had little to do with our discipline, and that most European oncology research initiatives focus almost exclusively on the improvement of cancer medicines.

This needs to change, so a few years ago ESSO decided to take action by partnering with the European Organisation for Research and Treatment of Cancer (EORTC). Since the launch of the prospective surgical research platform SURCARE in 2013, we have started the first joint research projects on colorectal liver metastases, CLIMB and DREAM, which had positive results, and attracted a lot of interest, especially among our partners overseas – such as the Japan Clinical Oncology Group (JCOG) – and among younger colleagues.

We need to integrate a comprehensive clinical research programme in the training we provide for our young colleagues. Thanks to the involvement of EYSAC, the ESSO Young Surgeons and Alumni Club, we have been offering a research fellowship grant for some time now, to support our members who wish to expand their research experience (www.essoweb.org/youngsurgeons).

ESSO is expanding the scope of its initiatives in this field by cooperating with other societies involving young surgeons, and I am very thankful to EYSAC members for the many research initiatives they are either planning or carrying out at present, such as the recent CORSiCA study on nodal positivity before surgery in rectal cancers, and the upcoming ESSO-EYSAC Course on Surgical Clinical Trials (19-21 October 2017, Budapest).

In this era of personalised medicine, where multidisciplinary cancer treatments are key, I highly recommend the annual MCCR Workshop – a unique occasion for young surgeons to keep updated not only about the latest innovations in cancer treatments, but also on new research methodologies and practices (see http://www.ecco-org.eu/Events). “One of the best courses ever” was the *leitmotif* of ESSO members commenting on previous editions of this workshop, which always provides hands-on sessions with a faculty of highly respected oncologists from all disciplines, and offers a high scientific level platform for networking.

I am glad to note that we already have numerous enthusiastic surgical oncologists within our network ready to promote and develop meaningful research projects. This is a key point for our activity as a scientific society involved in cancer care. I am sure that, continuing in this direction, we will be able to push the boundaries of progress even further for the benefit of our patients.

www.essoweb.org

What can 'omics add to personalised risk assessment?

For a disease that has led the field of molecular biology, it is surprising perhaps that so few biomarkers have been identified that can predict a person's risk of developing cancer. Researchers are now looking at what genetics and epigenetics can add to traditional risk factors such as age, weight and family history, and at how to refine the way we interpret and use the data. **Marc Beishon** reports.

The rise of the 'omics' – especially genomics and epigenomics – has fuelled interest in stratifying people's risk of developing cancer. Virtually every tumour type now has research programmes that are identifying increasing numbers of variations associated with raised or lowered risk, to add to other biomarkers and lifestyle and environmental factors.

It is part of the drive towards personalised medicine and the goal of targeting interventions such as more frequent screening, a preventive drug, or help with lifestyle changes, to those at highest risk, while reducing overdiagnosis and the stress and costs associated with screening, for those at lowest risk.

Biomarkers of cancer risk

Efforts to identify biomarkers that reliably indicate risk of developing cancer have so far proved disappointing. The one exception may be testing for infection with cancer-causing types of the human papillomavirus (HPV).

As cervical cancers almost never occur in the absence of HPV infection, testing for the presence of cancer causing types of the virus can identify people not currently at risk. A recent study in the Netherlands, for example, suggests that the interval between screenings could be extended safely from 5 to 10 years for women aged 40 and over who test negative for HPV DNA (see *BMJ* 2016 355: i4924, and 'HPV Faster' *Cancer World* Jan–Feb 2017).

Viral and bacterial linkages with cancer, including HPV, hepatitis B/C, *Helicobacter pylori* and others, are spawning a new field called metagenomics.

Biomarkers including PSA for prostate cancer and CA125 for ovarian are also important in risk stratification, although a distinction is that they are primarily diagnostic, and indicate suspicion for an existing cancer, which may require further testing.

But while there are some obvious major risk factors such as smoking and radiation, unlike in other fields such as cardiovascular disease there has so far been limited utility for molecular biomarkers as indicators of risk, and genomic data has only added small refinements to existing risk prediction models.

This is not holding back research, judging by the volume of studies, many of which are high quality, especially in the genomics field.

Paul Pharoah, professor of clinical epidemiology at Cambridge, kick-started the genomic discussion in risk stratification as far back as 2002, with the publication of 'Polygenic susceptibility to breast cancer and implications for prevention' in *Nature Genetics* (vol 31, pp 33–36).

> **"By adding germline data in combination with other factors we have better risk prediction models"**

"We had of course known for years before about the small proportion of women who are at very high risk and are managed in family cancer clinics, before and after the *BRCA* genes were discovered. But our paper showed that there is also a distribution of inherited risk in the population and it might be possible to focus screening on those at higher risk to maximise the benefit–harm ratio."

By 2007, Pharoah and others around the world had identified a handful of common genetic variants associated with breast cancer from genome-wide association studies (GWAS). Today, more than 150 variants have been identified for breast and also for prostate cancer, which are helping refine risk models – so called 'polygenic' risk.

Major contributors to this work include the EU-funded Collaborative Oncological Gene-environment Study (COGS), which focused on genetic determinants of breast, ovarian and prostate cancer, and, more recently, the international OncoArray project, which is looking at a wider group of cancers, and is just beginning to publish its first papers.

Pharoah comments that there has been considerable pressure from funders to demonstrate the value of the genomic work. "The pressure on us is huge – research funders rightly expect that our research should have clinical translation," he says. "But we have been getting better at risk discrimination and we have shown that, while other factors can be good risk predictors, by adding germline data in combination we have better models. For example, we can say that about 20% of 50 year old women have less than half a per cent risk of dying from breast cancer in their lifetime, so the benefit of screening is very small. And that's a lot of women."

He stresses that there is no evidence that genomic data is, or will be, superior in terms of determining risk, and indeed at present simply asking about family history can tell us almost as much as all the known common genetic variants, although he makes the point that "the great advantage of genetics is that it can be measured incredibly accurately with almost no bias."

But the search for other biomarkers in the field of molecular epidemiology has been a disappointment in breast cancer, although there is some promise in hormones, and there may well be advances to come, while breast density, on the other hand, is proving to be a significant factor. "We may also be coming to the limits of what we can refine using genomic data – larger and larger studies are needed to find things with smaller and smaller effect," says Pharoah.

How strong is the signal?

The degree of 'discrimination' in determining risk is a critical factor. It measures the probability to which a model will distinguish between those who will go on to develop a disease from those who will not, and so varies from 0.5 (which would just be flipping a coin) to 1.

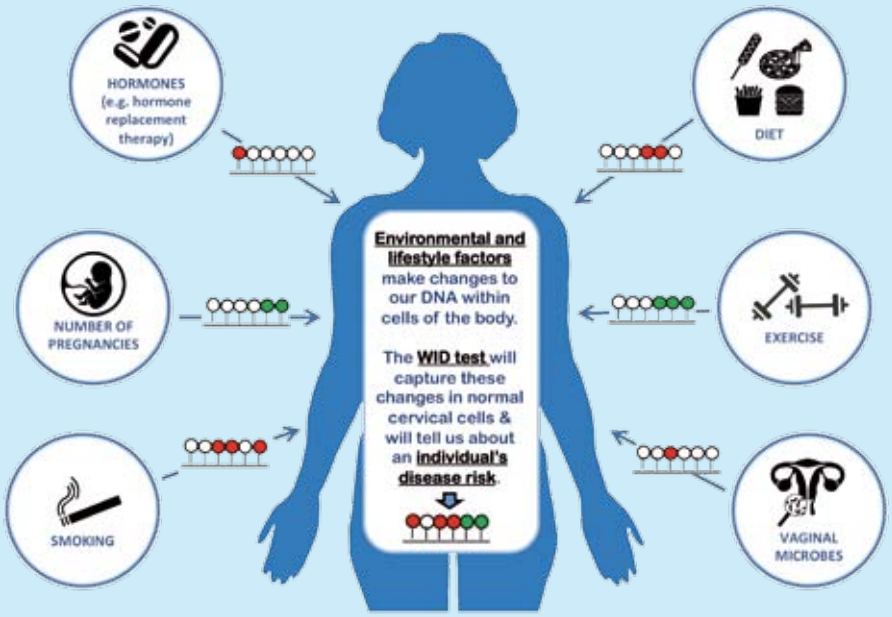
The well-known Gail breast risk model, which takes into account factors such as family history, age and weight, age of first menstrual period, whether the woman has had children, whether she has gone through the menopause, and if she is a current or past user of hormone replacement therapy, has a discrimination of 0.55, but this can rise to 0.71 once single nucleotide polymorphisms (SNPs) and breast density are added to traditional risk factors.

Mitchell Gail, who is behind the model, has commented on how modest the additions to his original model have been (see for example *JNCI* 2008, 100:1037–41 and more recently, 'Twenty-five years of breast cancer risk models and their applications' *JNCI* 2015, 107:djv042).

But Nora Pashayan, clinical reader in applied health research at University College London, points out that, although adding polygenic risk data and more non-genetic risk factors to models like Gail may result in only modest increase in discrimination accuracy, the impact could be more substantial in stratifying the population into different risk groups (for a technical explanation see *JNCI* 2014, 106: dju305).

"There is though also trade-off between improving discrimination accuracy and the user-friendliness of a model. In particular, as information on more non-genetic risk factors is needed, the more difficult it is to get complete and accurate information about them. It's why I am researching epigenetic markers that can be used as proxy for these risk factors to improve both the accuracy and ease of use of models."

The WID risk test for four women's cancers



The Women's cancer IDentification (WID) test, which is under development, uses cervical cells to detect epigenetic and metagenetic changes that go beyond genetic mutations (such as *BRCA*), to identify DNA changes associated with cancer risk that have occurred through environmental and lifestyle factors (red= raising risk, green=lowering risk). This information could be used to provide women with personalised risk prediction of developing cancers of the breast, cervix, uterus and ovaries over the following 10 years.

For more information see www.forecee.com

Four cancers, one predictive test

Epigenetics is at the centre of one of the most ambitious risk stratification projects yet, now looking to individualise screening and prevention for not one cancer, but four women's cancers – cervical, breast, endometrial and ovarian, which comprise nearly half of all cancer cases in women.

FORECEE is a four-year project launched in 2015, involving 13 European institutions, and led by surgeon Martin Widschwendter, professor of women's cancers at University College London (UCL). An EU Horizon 2020 project, it is developing a predictive test for all four cancers from a number of markers taken from a standard cervical smear, as well as from blood and cheek swabs,

with different tests for pre- and post-menopausal women.

The ambition is revealed in the inclusion not just of genetic data but also epigenetic and 'metagenetic' markers – the former being non-inherited changes due to lifestyle and environment (with the DNA methylation process being the key mechanism studied), and the latter viral and bacterial features, as with HPV.

The rationale seems straightforward – all these women's cancers have similar epidemiological and genomic risk factors and, as Widschwendter says, the most aggressive tumours such as triple negative breast and high grade serous ovarian and endometrial cancers "have a stunning molecular similarity".

Cervical cells are easy to gather from routine smear tests, and the researchers hope to show they contain markers that can be used to raise the bar in risk prediction for all the cancers. For example, in ovarian cancer, the largest ever screening trial, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), recently reported encouraging evidence of a mortality reduction, but the researchers say that while the extent of the reduction is further explored, efforts to improve risk stratification and also markers will also be needed.

Pashayan, who is a co-investigator in FORECEE (and also in breast and prostate risk projects in Canada and the US), says that the inclusion of epigenetics using cervical cells is a big step up. "When you ask about smoking and weight history, for example, you only get incomplete information – epigenetics not only measures the association of factors like these with DNA, but shows how they interact in one group, not just in silos."

The key point is that epigenetic changes far outweigh most genetic changes in cancer. In presentations, Widschwendter uses the example of smoking and DNA methylation to show how the concept can work in other cancers, both to stratify risk and to monitor prevention (given that stopping smoking starts to reverse changes to the genome).

"Epigenetics not only measures the association of environmental/ lifestyle factors with DNA, but shows how they interact"

It is also possible to make faster discoveries with genome-wide epigenetics than with SNPs from DNA, adds Pashayan, as working out the function of the latter takes time. As all four women's cancers are epithelial and hormone-sensitive, cervical cells offer tissue that is specific for markers of all. (Validation of epigenetic markers is being undertaken by a Swedish biobank of cervical samples, and cheek cell swabs are also taken as non-hormone sensitive controls.)

The project is also collecting and studying tumour samples (for more about how the epigenome works in cancer, see 'Integration of genetic and epigenetic markers for risk stratification: opportunities and challenges' – *Per Med* 2016, 13:93–95).

FORECEE researchers are confident that they will be able to develop better predictive tests based on prospectively collected samples and validated against a large cohort. The tests, which they have called Women's cancer IDentification (WID), will aim to improve the smear test's potential to detect risk of cervical cancer in pre-menopausal women and identify *BRCA* mutations, given that some women with these mutations are not currently picked up in family histories. In post-menopausal women, risk prediction of all four cancers is the aim: epigenetic changes accumulate over time, and these data will be combined with genetic profiling and usual factors such as weight and age.

A cautionary note is sounded by Pharoah, though, who says epigenetics has been studied for some time, and "there is a feeling that if there was something major we would have found it by now."

Widschwendter counters that epigenome-wide association studies (EWAS) – the equivalent of GWAS – are about to evolve. "It is true that DNA methylation and other epigenetic changes have been studied in disease tissues, such as comparing cancer tissue with normal tissue, but not in normal surrogate tissue with the intention to predict future risk."

Pashayan notes that technology advances have made this possible (see for example *Nat Rev Genet* 2011, 12:529–41).

Is it ethical, is it practical?

FORECEE is important not just because of the science it is generating, but also for the raft of practical, ethical and legal issues surrounding risk prediction testing. As an EU project it is further developing these issues following the COGS project, which set out the scope.

At a recent workshop held in Berlin, at the home of the Harding Center for Risk Literacy, a FORCEE project partner, participants heard about the results of a survey of women in five

Risk stratification – further reading

- A good summary of the issues was published in 2014: 'Stratified screening for cancer: recommendations and analysis from the COGS project' (PHG Foundation, Cambridge)
- *Cancer World* (cancerworld.net) carried an article, 'Population screening in the age of personalised medicine', on risk stratification in breast cancer in its Jan–Feb 2017 issue. A project to add is Perspective, in Canada, which is using a risk algorithm called Boadicea developed at Cambridge, UK (*Curr Oncol* 2016, 23: e615–e625)
- Latest research by Rosalind Eeles and colleagues for the NCI Genetic Associations and Mechanisms in Oncology (GAME-ON) initiative has found more SNPs associated with early onset and aggressive or indolent prostate cancer. They say men in the top 1% of a genetic risk score have a nearly six-fold higher risk for developing the disease compared with the median risk group (*JCO* 2017, 35(6S) abstract 1)
- Risk stratification is also a widely used term in stratifying treatment after diagnosis, and it also extends to survivorship. For a paper on personalised cancer follow-up, see *BJC* 2012, 106:1–5
- A first major systematic review of risk prediction models for colorectal cancer is at: *Cancer Prev Res (Phila)* 2016, 9:13–26
- Researchers in Spain have put forward a new risk model for colorectal cancer in the Spanish population. They find that modifiable risk factors have a stronger value for risk prediction than genetic susceptibility (*Scientific Reports* 2017, 7:43263)
- Newly established blood DNA methylation markers that are strongly associated with smoking might open new avenues for lung cancer screening, reports a paper from 2016 (*Clin Epigenetics* 2016, 8:127)
- Metagenomics has broadened the scope of targeting microbes responsible for inducing various types of cancers – see *Meta Gene* 2015, 5:84–89

countries, which explored their beliefs about and attitudes to the WID test.

The workshop also presented snapshots of country health systems and discussed the overall ethical and regulatory aspects of epigenetics, as well as issues surrounding the practicalities of introducing a complex test and the implications for insurance – in the US, for example, there are moves that could force people to disclose not only their own but their family's health records in workplace wellness schemes.

All these topics could have a major impact on the acceptability and feasibility of introducing yet more tests that could be offered to most women at various life stages, and no one has all the answers – brainstorming was a major activity at the workshop.

Inez de Beaufort, professor of healthcare ethics at the Erasmus Medical Centre, Rotterdam, in a talk on ethics, said that when introduced to FORECEE, women may not have associated lifestyle factors such as smoking with women's cancers, and there could be feelings of guilt and blame from others – and more than that aimed at men.

"And it's not just your health but the health of future generations," she said, noting the phenomenon of epigenetic inheritance. People should also feel free to take some risk in their lives, she said, so how far should health services try and intervene? Will there be services to help people after they have been tested? People are now bombarded with risk information and navigating yet more could be hard.

But there are also ethical issues in not giving people information about risk. Paul Pharoah says that he expressed surprise 15 years ago that women taking part in the UK breast screening programme were not informed if they were at low risk, and comments that they are still not being told about breast density and risk.

"It would be unthinkable that when you had your blood pressure or cholesterol tested you would not be told about what they mean for future risk, and indeed it would be deemed unethical," he says. He suggests that there may be concerns that the breast screening programme could be undermined if women who were told they were at low risk decided to stop attending.

"Since then we have had the major debate about the benefits of breast screening," he continues. "But despite this, there still seems to be unwillingness to really evaluate the potential of cancer risk stratification properly."

Risk is a seemingly simple word, but in the cancer world it is loaded with enormous scientific and societal connotations.

Reality check in Mumbai

Experts debate the evidence on leaving cancer care to the market

© Uttam Ghosh

How far can private and philanthropic providers meet the rapidly rising need for cancer detection, treatment and care in low- and middle-income countries? **Sandhya Srinivasan** reports on a high-profile debate involving economists, policy makers, clinicians and a range of healthcare providers.

India is a technically sophisticated country and an important player in science and medicine. It is home to a cancer centre of international standing, it has had a cancer plan for more than 30 years, and a primary healthcare system designed to operate at village and district level. And yet cervical cancer – one of the easiest to screen for and treat – still claims the lives of around 70,000 women in India every year (*Indian J Med Paediatr Oncol* 2011, 32:125–132).

Around 1.45 million Indians developed cancer in 2016, and these numbers are expected to increase steadily, according to the Indian Council of Medical Research. For the families affected, the out-of-pocket cost of paying for treatment and care has been described in one key study as 'catastrophic' in three out of four cases, with families being forced to borrow heavily and cut back on what are often already stretched daily household expenses (*Tropical Med Int Health* 2016, 21:1019–28).

Over one third of cancers are caused by tobacco use, and these, in particular, affect the poor the most. Tobacco use among men is twice as common among those with little or no formal education, and more than twice as common among the lowest wealth quintile compared to the highest.

Everyone needs access to cancer prevention, and everyone with cancer needs access to early diagnosis and, to treatment and care.

Should this healthcare be considered a right of every citizen, or a commodity to be bought and sold on the market? This was the topic of a conference organised by the Tata Memorial Centre (TMC) in Mumbai in January, under the title: "Healthcare: a commodity or basic human need?"

The public health community in India has engaged with the issue of universal access to healthcare for decades, but this was the first time it had been discussed in the context of a condition whose treatment has largely depended on highly trained doctors, sophisticated treatments and expensive drugs.

Cancer and the commitment to universal healthcare

Universal healthcare (UHC), described in a 2012 document from the Indian government's Planning Commission, is defined as "assured access to a defined essential range of medicines and treatment at an affordable price, which should be entirely free for a large percentage of the population." One element of this care, naturally, is cancer care, both prevention and treatment.

India launched its first substantive national cancer programme in 1984 with the objectives of controlling tobacco use, promoting early detection of certain cancers, improving treatment facilities, and providing palliative care. Services are meant to be available through an extensive three-tiered network of primary health centres at the village level, district hospitals for limited diagnostics as well as medical and surgical care and medical college hospitals providing specialised treatments including for cancer.

In addition, 27 regional cancer centres and eight apex cancer centres such as TMC provide specialised cancer care. Since 2012, a 'national cancer grid' has linked centres across the country to set uniform standards as well as share expertise in cancer care. In January 2017, TMC launched a 'virtual tumour board', in which experts in various fields discuss complex cancer cases and offer online opinions to centres anywhere in the network.

Palliative care is run largely by voluntary organisations and charitable foundations – though some people argue that this should be the government's responsibility.

On paper, therefore, India would seem to be doing a lot right. However, the realities on the ground, at least at present, are very different. Government services have long been starved of funds and humanpower, other than for selected programmes such as disease control and family planning.

The cancer care scenario is no different. The majority of cancers are diagnosed in an advanced stage of the disease. "In the absence of screening, nearly 70% of cervical cancer patients in India present at stages III and IV (*Indian J Med Paediatr Oncol* 2011, 32:125–132).

The same paper notes that nearly 20% of women who develop cervical cancer die within the first year of diagnosis, and the five-year survival rate is 50%. As for prevention, only the southern state of Tamil Nadu has conducted screening at the community level for some years. Systematic statewide screening and early treatment for cervical and oral cancer began in the northern state of Punjab in 2016, the same time that the national government announced plans to screen for oral, cervical and breast cancer, starting with 100 districts.

Despite its promises, the government has never made a commitment to healthcare, spending just 1.04% of its gross domestic product on health services compared to the WHO-recommended 5%, Cuba's 10.6% and Brazil's 3.8%. This amounts to only Rs 957 (€13.5) per capita, of which around 30% comes from the central government. More than 70% of healthcare expenditure (or 3.06% of GDP) is in the private sector, which operates without any regulation and is known to promote expensive, unnecessary and sometimes dangerous treatments that benefit doctors and the healthcare industry rather than patients. Private doctors don't like to be regulated, noted surgeon Sanjay Nagral at the TMC conference. As private and social insurance cover less than 20% of the population, most healthcare spending is out of pocket.

> "Public services have been systematically destroyed"

The problem, as presented at the conference by Professor T Sundararaman, Dean of the School of Health Systems Studies at the Tata Institute of Social Sciences, is that the private sector is being seen as the only option for care. "Public services have been systematically destroyed, and primary health centres, the backbone of the healthcare system, have been downsized to serve only maternal and child health."

"While India has been overtaking other countries in the progress of its real income, it has been solidly overtaken in terms of social indicators by many of the same countries"
Amartya Sen, Economist, Nobel laureate

In fact, many health activists believe that universal healthcare is just an empty slogan. Amit Sengupta of the Jan Swasthya Abhiyan, a network of community health organisations in India, writes, "The … progressive withdrawal of support to public services is part of a particular vision of UHC. Here, the role of publicly provided health services is replaced by outsourced services to the private sector. Insurance mechanisms and not public provisioning is the hallmark of this approach," (*The Hindu*, February 6, 2016).

By contrast, Cuba, which was among the national models of universal healthcare presented on the first day of the TMC conference (the others being Brazil, Japan, Iran, Thailand, Zambia and France), has publicly financed and publicly provided care.

The commitment to public health within India is seen in the southern state of Kerala, with health indicators close to those in high income countries. Kerala's infant mortality rate in 2007 was 14/1,000 live births – one-fourth the national average. The 2015-16 National Family Health Survey (based on a small sample size) reports that Kerala's infant mortality rate is now 6/1,000 live births, comparable to the US.

In addition to universal healthcare, the Kerala state government has long been committed to multiple social benefits, including a more extensive public distribution service of food grains, all of which contribute to health. It also runs the oldest, and only major community-based palliative care programme in the country.

Financial burden of treatment

Health economist Ajay Mahal reported on a study finding that median expenditure for inpatient cancer care in 2014 was $357 per hospitalisation, and that three out of four cancer patients experience catastrophic expenses – healthcare expenses that forced them to reduce routine household expenses. In more than one third of cases, the out of pocket costs of care are raised through borrowing.

While government hospital expenses were lower, patients still had to spend substantial amounts. In another paper, Mahal found that a single hospital stay for cancer treatment in a public facility cost Rs 11,659, €165, almost 50% of the average per capita income of Rs 25,320. About one quarter of that money goes on medicines. While India is a major supplier of generic drugs internationally, the price of medicines is still an enormous burden for Indians, especially poorer families.

In the absence of affordable access to cancer care, patients come from all over India to metropolitan cities, and it is common to see patients living with their families on the pavement outside the government's Tata Memorial Hospital in central Mumbai, while waiting for surgery or between treatment cycles. Even though the hospital has differential levels of payment and free services for those who cannot pay, many families must look for some money from charities, adding to the stress and anxiety of coping with this disease.

Economic growth is inversely proportionate to people's health

The need for publicly funded universal healthcare was stressed by economist and philosopher Amartya Sen when delivering the inaugural address at the conference. "While India has been overtaking other countries in the progress of its real income, it has been solidly overtaken in terms of social indicators by many of the same countries, even in the region of south Asia itself," he said. Bangladesh and Nepal have incomes much lower than India's but they have lower infant mortality rates. "A couple of decades ago, India had the second best indicators of six countries [India, Pakistan, Bangladesh, Sri Lanka, Nepal and Bhutan]. Today it has the second worst indicators of the same countries, with the worst being Pakistan."

Some of this can be attributed to the government acceptance in 1993 of World Bank prescriptions that limited public services to a package of "essential" services – contraception, immunisation and disease control – with the rest largely left to private services. Private healthcare services, well established long before 1993, have flourished over

"Industry should be approached to start new projects in public–private partnerships and the pharmaceutical industry fund department chairs in public hospitals" *Sanjay Oak, formerly Dean of Seth GS Medical College, Mumbai*

the last two and a half decades.

Among the actions Sen identified as critical to ensure universal healthcare: recognise the role of public health including social determinants of health such as nutrition, sanitation and social equity; put more government money into health – "no country has successfully provided universal health coverage without the strong support and commitment of the public health sector"; and improve the functioning of state services rather than handing them over to the private sector. He said the "private pay model", in which the government reimburses private hospitals for certain treatments for people below the poverty line, further reduced the little public money that is spent on healthcare, in addition to creating "perverse incentives" for doctors to conduct irrational treatments.

Rajendra Badwe, Director of the Tata Memorial Centre, telling the conference about how the Centre manages the care of 67,000 new patients every year, while also helping standardise care across India's 27 regional cancer centres. More than half the patients at the Centre are treated for free or at highly subsidised rates

Models of healthcare provision

Panellists in the afternoon of the first day discussed the main question of the conference – is health care a commodity or a basic human right? – debating the merits and demerits of various models of healthcare provisioning.

Sanjay Oak, formerly dean of Seth GS Medical College and King Edward Memorial Hospital in Mumbai, spoke on the public hospital, which used to provide free care for all patients, but has over the years forced patients to pay for many tests, medicines and procedures. He noted that in his 29 years in public health, "Public hospitals have never treated healthcare as a commodity." The difficulties are widespread corruption, increasing costs, and staff attrition to the lucrative private sector. His suggestions, that industry be approached to start new projects in public–private partnerships and the pharmaceutical industry fund department chairs in public hospitals, were not well received by some sections of the audience.

Rajendra Badwe, Director of the Tata Memorial Centre, described the functioning of this national cancer care institution. With the bulk of its funding coming from the government, TMC and its satellite Advanced Centre for Treatment, Research and Education in Cancer (ATREC) provide "comprehensive, state of the art" care to 67,000 new patients and 450,000 follow-ups each year. The TMC also coordinates a countrywide 'hub and spoke' network – of major public and private centres which provide specialised care, and regional units which follow up cases and run basic diagnostic and treatment services, together reaching about 50% of the cancer cases treated in the country.

Patients at TMC / ATREC pay at different rates for their care according to what they can afford, with 60% receiving free or highly subsidised treatment. Of their Rs 3 billion (€ 44 million) operational expenses for research and patient care, patients' payments amount to about Rs 1.7 billion. The government gives a fixed grant of Rs 1 billion for research and education, and also covers the shortfall of Rs 300 million.

The conference also heard from Vini Mahajan, health secretary for Punjab state since 2011. She described the government's progress in setting up a state-wide cancer control programme, supported by a special fund created in 2013 to increase infrastructure for

"Punjab set up a state-wide cancer control programme, supported by a special fund created in 2013 to increase infrastructure for cancer care"

Vini Mahajan, Health Secretary, Punjab

"The CMC model relies on salaries being low, with tight control over costs. We cannot use health to make money off people's misery"

Sunil Chandy, Director, Christian Medical College

cancer care. Expansion included new treatment facilities, some in public–private partnerships, training district hospitals in providing chemotherapy, schemes for cashless treatment, telemedicine, and recently established palliative care services through the NGO CanSupport. Screening for oral, breast and cervical cancer, using simple techniques like visual inspection with acetic acid and clinical breast examination, initially implemented in a few districts, was expanded in 2016 to cover the entire state. HPV vaccination is being conducted in districts with the highest incidence of cervical cancer.

The immediate challenge for the cancer control programme, said Mahajan, is to get information on government schemes to poor families who need it the most. Much of the Punjab programme, extensive as it is, is new, and has therefore not yet been evaluated.

A private sector model for cancer care was presented by Ajai Kumar, the CEO of Health Care Global, who described the 22 comprehensive cancer care centres it runs, which treat 700,000 new cases a year.

An independent, not-for-profit model of healthcare delivery was presented by Sunil Chandy of the Christian Medical College (CMC) in Vellore, Tamil Nadu. He talked about the Christian Medical College programme, which runs some 200 hospitals across Tamil Nadu on the principle that healthcare is a service, not a business. Poor patients' care is subsidised by those who can pay. The CMC model relies on salaries being low, with tight control over costs. "We cannot use health to make money off people's misery," said Chandy.

Another not-for-profit model, also from Tamil Nadu, is Aravind Eyecare, which was set up as a trust, and provides high quality, low cost eye care, also running outpatient services in the state's primary health centres.

The trust conducts 45% of all ocular lens replacements in the state – most of these free of charge or heavily subsidised. It manufactures its own lenses for $2, compared to the market price of $150, and runs on economies of scale. Many of its services are performed by trained high school graduates rather than doctors and nurses. Aravind's co-founder, Perumalsamy Nambaperumalsamy, said they were self-sufficient in their operational expenses, but they receive support from funding organisations, and also take the state's support for some government programmes.

The question that emerged was: how much do these models ensure people's access to care, and are they sustainable? The two non-governmental schemes work in specific circumstances for specific purposes, and both depend on personal commitment and hidden subsidies that may not be replicable. As for publicly-funded models, current government funding is inadequate. TMC, while it gets substantial government funding, charges many of its patients, and still falls short of its running costs.

Public hospitals are increasingly bridging their funding gaps by requiring patients to pay for some medicines, tests and procedures. Programmes like the National Rural Health Mission are suffering from cutbacks. State-supported insurance schemes give limited coverage and are difficult to access. Public–private partnerships and industry funding for government hospitals are likely to benefit industry more than patients. With government encouragement to private health services, most patients pay for care out of their own pocket, forcing many people to either borrow for treatment or just do without it.

There were, naturally, some heated discussions on healthcare finance. Shankar Prinja, from the Postgraduate Institute of Medical Education and Research in Chandigarh, spoke on mechanisms of financial risk protection to prevent catastrophic health expenditure – out-of-pocket expenses that affect other household spending or result in impoverishment – which affects a very large number of Indians.

Nachiket Mor, of the Bill and Melinda Gates Foundation, suggested that public health spending is low because tax collections are low. Alok Kumar of the government think tank Niti Aayog calculated that primary, secondary and tertiary services together would cost Rs 2,238 (€37) per capita which, he argued, would not be possible

"Public health spending is low because tax collections are low"

Nachiket Mor, Bill & Melinda Gates Foundation

High-tech healthcare meets abject poverty. The Tata Memorial Centre in Mumbai treats tens of thousands of patients for free, but as many patients live far away and cannot afford to rent a place to stay, they camp out on nearby pavements waiting for their next chemo or radiation treatments

through public finance alone (though it would actually be much lower than the WHO-recommended 5% of GDP). The way to prevent catastrophic health expenditure, some suggested, is to expand insurance schemes.

Professor T Sundararaman, who heads up the school of health systems studies at the Tata Institute of Social Sciences, argued strongly against the direction of the discussion. Poorer sections of the population pay a substantial amount in indirect taxes, he said, for which, at least, they should have the right to government healthcare. While 63 million Indians live below the poverty line, almost 80% of outpatient care and more than 20% of inpatient care is spent out of pocket. Echoing Amartya Sen's criticism of public insurance schemes, in which the government reimburses private hospitals for certain services, Sundararaman asked: Why should public resources go to the private sector when these procedures should be made available in government hospitals?

This is an important debate that is set to continue as India struggles to find solutions for the growing number of its citizens who are affected by cancer. The current government, however, seems set on extending its reliance on private provision, with the long awaited National Health Policy, published in mid-March, encouraging further privatisation of the healthcare sector.

"Poorer sections of the population pay a substantial amount in indirect taxes, for which, at least, they should have the right to government healthcare"

Professor T Sundararaman, Dean of Health Systems Studies, Institute of Social Science

All.Can Changing cancer care together

All.Can is a multi-stakeholder initiative set up to engage policymakers on the need to improve the efficiency of cancer care, focusing on better outcomes for patients.

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

Waste must be challenged:

20% of healthcare spending is wasted on ineffective interventions

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

Efficiency ≠ cutting costs

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

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

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

1

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

2

Investment in data to create a continuous cycle of improvement

3

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

4

Political will to focus on better outcomes for patients

To learn more about All.Can and read our policy report, visit www.all-can.org

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

Make Every Child Count

For a Brighter Future for Children and Adolescents with Cancer

Did you know cancer in Europe is the first cause of death by disease for children older than one year? And that each year there are more than 35,000 new childhood cancer cases in our region?

We at SIOPE (the European Society for Paediatric Oncology) have been active to find better cures for all children and adolescents with cancer since 1998. To reach this goal, we have been taking part in important EU projects, strengthening partnership with other organizations and advocacy groups, and achieving tangible results in the EU policy field.

We want a future where children have access to state-of-the-art treatments, no matter where they live; where the cure-rate for all types of paediatric cancers steadily grows; and where all survivors enjoy a fulfilling life without suffering from the late side effects of treatment. This is not just a dream: together with parents, patients and survivors, we defined the consensus-based SIOPE Strategic Plan 'A European Cancer Plan for Children and Adolescents' and we are working to make it a reality.

You too can be part of this: support what we do and help us to create a brighter future for children and adolescents with cancer. *www.siope.eu/donate*

SIOPE
SIOP Europe
the European Society for Paediatric Oncology

Discover more:
www.siope.eu

35 years

European School of Oncology

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ABC4

Bridging the Gap

Advanced Breast Cancer

Fourth ESO-ESMO International Consensus Conference

2-4 November 2017
Lisbon, Portugal

Coordinating Chair:
F. Cardoso, PT

Chairs:
E.P. Winer, US - L. Norton, US - A. Costa, IT/CH

Co-Chairs:
E. Senkus, PL - E. Papadopoulos, CY

Scientific Committee Members:
M.S. Aapro, CH - F. André, FR - N. Harbeck, DE

The ABC4 guidelines will be developed by ESO and ESMO

ESMO

The ABC4 conference and guidelines are endorsed by

and will be submitted for endorsement to

ESTRO European Society for Radiotherapy & Oncology

The ABC4 conference is held

with support from

BCRF

under the auspices of

OECI

UICC

and with official representatives of

ASCO American Society of Clinical Oncology

RECEIVE UPDATES AT:
www.abc-lisbon.org • #abclisbon