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Education & knowledge through people & facts

Peter Naredi

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Patients need information. Is that clear?

Kathy Redmond ■ EDITOR

The urgent quest for novel cancer treatments engages much of our attention, but could we be overlooking other opportunities for increasing patients' survival and quality of life?

One such opportunity that is increasingly gaining the attention of policy makers is improving health through improving health literacy. Defined as "the skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways which promote and maintain good health," good health literacy can play a crucial role in improving outcomes, whether it be in prevention, treatment, palliative care or survivorship.

Poor health literacy is associated with poorer general health status, increased risk of hospitalisation and a lower capacity to care for oneself and share in treatment decision making. The problem is greater among lower socio-economic groups, ethnic minorities and the elderly, and consequently these groups have much to gain by health literacy initiatives tailored to their needs.

A recent European survey has shown that one in ten patients finds the information provided by physicians difficult to understand and many more struggle to decipher the information provided on a medicine leaflet. However, the problem is under-recognised and poorly addressed by health professionals, many of whom overestimate patients' ability to understand and use health information.

As more and more cancers evolve into chronic conditions, we need to focus on how to meet the needs of cancer patients with literacy problems. As a first step we should audit patient information materials in current use to find out how far they were written with the needs of less literate patients in mind. Do they comply with the principles of clear health communication? Would they pass the clarity test if subjected to a readability assessment? Similar assessments done for other groups of patients suggest much of it would not.

There is help at hand. A number of groups have developed useful guides on how to write materials for patients with low literacy levels. Literacy experts recommend plain language, shorter sentences and larger type sizes, with a sharp contrast between the text and background. Testing draft materials on the target audience is also important. These are common-sense recommendations which should become the gold standard for the development of all patient education resources.

Health professionals can help promote health literacy by using jargon-free plain language in all their interactions with patients. They can also assess patients' literacy levels using one of the readily available and easy to administer health literacy assessment tools. This could help in tailoring information to the patient's level of understanding, in line with the current personalised approach to medicine.

These are steps we can all take right now to improve cancer outcomes, which are currently compromised by a disconnect between what professionals think patients need and what patients actually need.

Peter Naredi: a 'can do' leader for Europe's cancer surgeons

Marc Beishon

There are so many ways cancer surgeons can help improve outcomes, and Peter Naredi embraces them all. Adapting surgical approaches to the biology of a cancer, spreading best practice, using audit and transparency to raise the worst to the level of the best are things he's tried and tested in his native Sweden. As ESSO president, he now hopes to enthuse Europe's cancer surgeons to follow his lead.

As surgery is the pivotal treatment for many types of cancer – and will remain so for the foreseeable future – one might expect that the discipline of surgical oncology would be well entrenched in national practice around Europe by now, especially as so much surgery concerns cancer. But that is far from the case, reports Peter Naredi, the current president of the European Society of Surgical Oncology (ESSO). As he notes, it is only a recognised speciality in a few countries, and there is much more to the cancer surgeon's role than just carrying out operations.

"In many hospitals – such as in northern Sweden, where I am based – there may be few medical oncologists, and surgeons are most likely to be the ones leading patients through their cancer journey," he says. "What we are emphasising at ESSO is the need for surgeons to participate in quality and educational programmes to raise standards in oncology surgery, and the establishment of multiprofessional centres and regional working so that patients have the best outcomes, not just from surgery but in other areas such as diagnosis and end-of-life care."

As he adds, there is now an unstoppable movement towards auditing and publishing outcome data for hospitals and even for individual surgeons in certain countries, driven by politicians and patient groups. As a result, the variability of cancer outcomes will become more apparent. Data from registries and results from multicentre trials already show "remarkable" differences between institutions and between treatment of different tumour types around Europe, and surgeons are most often taking the lead in diagnosis and care.

It might be expected that, with surgery becoming more specialised and with many surgeons focusing only on specific areas such as urology or head and neck, the quality of cancer treatment would be an integral part of this trend. But organ-specialist surgeons do not necessarily have a detailed and up-to-date knowledge of cancer, for instance its biology and multiprofessional care, which means patients may receive suboptimal treatment, says Naredi. "What Europe lacks is the implementation of a core curriculum in surgical oncology, which we have

JOHAN GUNSÉUS/SYNK

developed at ESSO, and also the integration of organ-specialist societies and national bodies into ESSO and other cancer societies."

Promoting the ESSO core curriculum is a current priority for Naredi and colleagues, as is widening the society's membership to embrace national surgical bodies and powerful groups such as the European Association of Urology, which alone has about 12,000 members. Audit and quality assurance is another priority, for example through the European Registration of Cancer Care (EURECCA) project, which was set up by ESSO and adopted by ECCO initially to audit colorectal cancer surgery around Europe, and which could be a framework for other tumours (see www.canceraudit.eu).

Naredi, whose day job is professor of surgery at Umeå University, not far from the Arctic Circle in Sweden, is himself an ideal case study of developing surgical and multiprofessional excellence in one of Europe's outposts. Since Sweden decided to establish six regional cancer centres, each focused on key teaching hospitals, the northern region based around Umeå has become recognised as one of the more innovative, despite two other regions starting much earlier. "This is not primarily about more money," says Naredi. "Yes, we can make say a 10% improvement with more funds, but we can achieve 30% by improving what we already have in terms of the process of getting people with cancer symptoms diagnosed and treated faster and better in the right places."

As a general surgeon who specialises in the 'mid-GI' area – especially the liver and pancreas – he has helped introduce new techniques to Swedish surgical oncology. Naredi also has a research background in basic science and continues to carry out work in areas such as immunotherapy and chemotherapy resistance. And as part of a general surgical team in Gothenburg, he was routinely involved in caring for people with diseases such as stage IV melanoma. This has given him good grounding in the challenges of

improving multidisciplinary care and attracting talent to a regional university hospital.

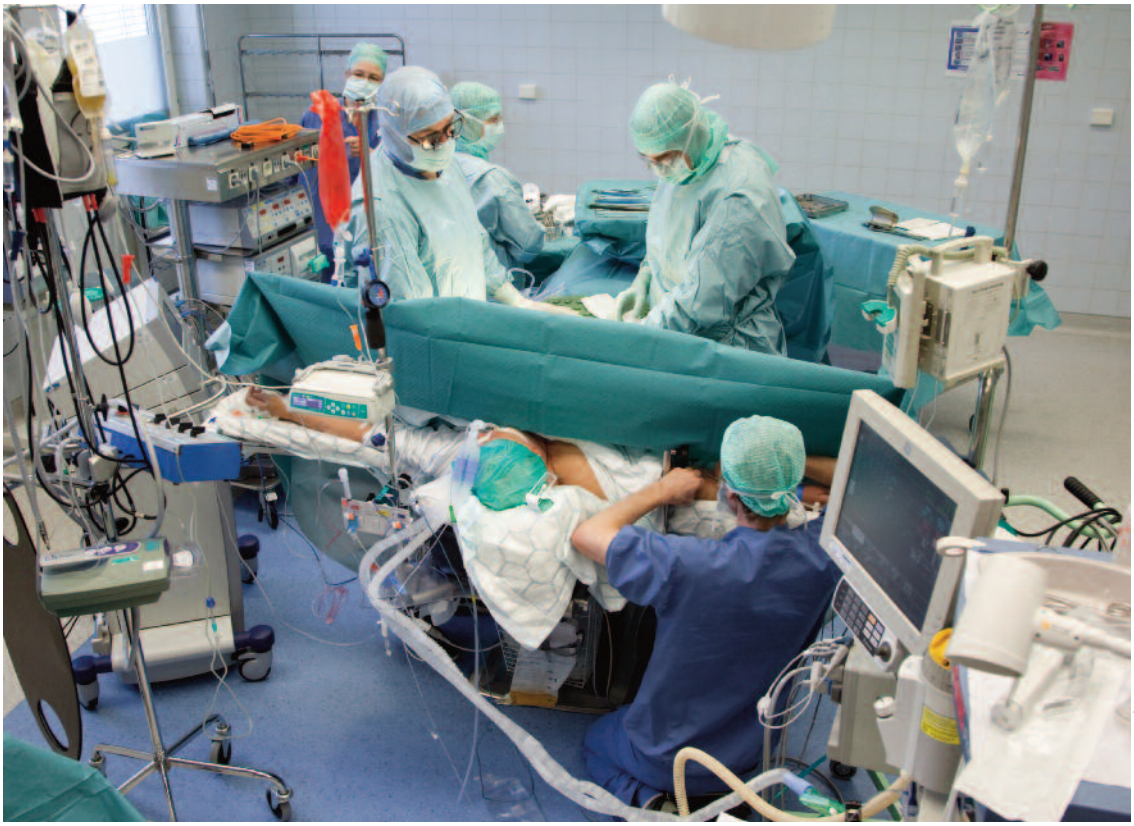
Above all, he adds, healthcare bureaucrats need to allow clinicians such as surgeons the freedom to introduce evidence-based structures that will improve cancer outcomes, and not force through change that disempowers people. Naredi speaks from experience here: he enjoyed a good deal of autonomy while at Sahlgrenska hospital in Gothenburg, one of Sweden's leading institutions, until a merger of three hospitals created too much middle management, prompting him to leave along with other colleagues.

"But for our part we need to show leadership," he says. "We are in fact running leadership courses for young surgeons in Sweden, under the Swedish Surgical Society, because our profession has to be able to tell the politicians and administrators what is best in healthcare." It's also about painting a vision of what surgeons of the future should be doing, he adds, as there is a degree of insecurity about their roles.

Naredi acknowledges that the European cancer world has not lacked strong characters, particularly from the surgery side, where there have been quite a few outspoken and sometimes controversial senior figures. But like many of the younger generation who have stepped up to senior level now in oncology, he favours a non-hierarchical, consensus-building approach that motivates rather than forces other people to participate. In his world, there is no room for the all-powerful chief surgeon who dominates decision making.

He was the first in his family to become a doctor, influenced by his mother, who worked as a Red Cross nurse. "I wanted to be an architect at first, but when I saw the kind of work I might be doing, such as interior design in banks, I knew I wanted to do something more meaningful and I've never regretted doing medicine. I chose surgery because I'm a practical person."

After a residency in Halmstad he moved to be a ward physician in the department of surgery at Sahlgrenska hospital in Gothenburg, where he was able to carve out a dual surgical and research career, focusing on cancer. "I was doing general surgery but found I was learning much more from cancer patients than say those who were having gall bladder or hip



JOHAN GUNSÉUS/SYNK

A specialist at work. A minimalist approach to treating liver metastases, which Naredi helped to develop, has resulted in significantly more patients becoming eligible for treatment

"We also need to listen to those with poor chances, to know how to provide good palliative care"

replacement operations. Everyone with cancer has a different life story and there are so many feelings involved. You have to listen carefully to improve outcomes for survivors – nine out of ten women with breast cancer in Sweden now survive. We also need to listen to those with poor chances, such as those with pancreatic cancer, where we need to know how to provide good palliative care. Treating people with stage IV melanoma, who have miserable outcomes, has taught me more than any course." Patients need one doctor who can put together a multiprofessional package, he says. "We shouldn't keep sending them to see different people to take control of their care – they need confidence in one person."

In the 11 hospitals that comprise the regional cancer centre in northern Sweden, Naredi says only two have a department of medical oncology. "Medical oncologists come to the other hospitals as consultants and may see up to 20 patients in a day, but who takes care of them afterwards? In the vast majority of cases it is the surgeon who will be seeing patients over a period of several months, which is why it is so important they have knowledge of surgical oncology."

As Naredi explains, surgical oncology is of course about excellence in treating solid tumours (although not in the brain, which is the domain of the neurosurgeon), but it also includes prevention, genetic counselling, diagnostic and staging procedures, rehabilitation and follow-up care. And treatment for the surgeon does not just mean resection, but also gaining a thorough understanding of the biology of the diseases and the use of chemo- and radiotherapy.

"At ESSO we have both a core curriculum and a European examination from the surgical section of UEMS [European Union of Medical Specialists], which takes place at either our own conference or at the European Multidisciplinary Cancer Congress every other year. I was on the committee that updated the core curriculum, which can practically be done over six years, although I could write a curriculum that would last a lifetime.

"I do not think it is important to push for more recognition of surgical oncology around Europe, but we do need to get more surgeons interested in the biology of cancer and all the other aspects of treatment and care. We need more good surgeons who understand oncology – not just dedicated surgical oncologists."

A surgeon can be specialised in one organ, say breast, but still learn about techniques developed in other areas such as the pelvis, says Naredi. All surgeons need to keep up to date now with new drugs such as targeted therapies, and the core curriculum, he emphasises, is as much about giving hospital departments a framework to be a surgical oncology teaching unit as it is about individual learning. As he points out, there is no validation and accreditation of such teaching capability as yet.

"We have tried to give the ESSO curriculum the same format as the ones from ESMO [for medical oncologists] and ESTRO [for radiation oncologists], so that ECCO's member societies have standard curricula," adds Naredi. "But as with recognition of our speciality, I'm not a big believer in thinking that you can just impose it at national level – we have to work with people who join and interact with ESSO to take it home and adapt it for their own surgical societies and institutions.

"We are not specifying detailed surgical procedures in the curriculum, just guidance on the number of procedures. The latest hands-on learning does not belong in the curriculum. For example, in Sweden we invited Bill Heald from the UK to lead sessions on TME [total mesorectal excision] for rectal surgery, which then made its way into national guidelines from our colorectal surgical society. Our aim at ESSO is to promote the tools for implementing such best practice."

Naredi himself benefited from excellent surgical mentorship at Gothenburg, but also has a strong research background, having taken up a fellowship at the University of California in San Diego, where he studied chemotherapy resistance (mainly cisplatin), and he also has a PhD in tumour blood flow. He has a long collaboration with Swedish tumour immunologist Kristoffer Hellstrand on the use of histamines

A CURRICULUM FOR SURGICAL ONCOLOGY

ESSO has put forward its core curriculum to try to tackle the *ad hoc* way in which surgeons usually receive oncology training – few countries have formal national training programmes. Naredi and colleagues note that the European Board of Surgical Qualification in surgical oncology, from the European Union of Medical Specialists, is probably the only formal qualification in Europe, but only five to ten surgeons take this exam each year.

The ESSO curriculum aims for an evidence-based approach rather than the existing 'common sense medicine' now in place, and should join successful curricula from ESTRO (the radiation oncologists) and ESMO/ASCO, they say. It includes:

- Recommendations that institutions should combine if they cannot offer access to facilities such as basic cancer biology facilities
- A minimum of three surgical oncologists who teach
- A basic scientific curriculum that includes cancer biology, immunology and principles of treatment
- Evaluating and conducting clinical studies and understanding the 'principles and pitfalls of evidence-based medicine'
- Basic clinical requirements such as diagnosis and prognosis, implementation of national guidelines, palliative surgery and management of end-of-life feelings
- Cancer surgery itself – at least 120 cancer operations is recommended, at last half done by the trainee
- Rotations in medical oncology and radiotherapy.

The full curriculum, which Naredi says will be revisited soon to see if it needs updating, was published in 2008 in *Surgical Oncology* (vol 17, pp 271–275).

and interleukin in inhibiting tumour growth, which led to Naredi being the principal investigator in several global phase III studies, although a lack of consistent interest from drug companies has meant this work has been very drawn out.

"As a young surgeon I was carrying out immunotherapy as well as surgery on patients with melanoma and renal cell carcinoma, and I kept up research in this area and in cisplatin resistance when I moved to Umeå," says Naredi. "But some other science our surgical department is involved in can seem odd – for example with colleagues in the molecular pathogenesis centre we had a paper in *Cell* in 2007 on the regulation of insulin in *C. elegans* worm cells."

Such work is way beyond the surgical oncology curriculum, although it does specify that a trainee should prepare at least one scientific paper, either original research or a review or meta-analysis.

When Naredi was in San Diego he suddenly got three great job offers: to take a senior colleague's place in Gothenburg, move with the colleague to Umeå, or stay in San Diego. "I chose to go back to Gothenburg as an assistant professor, where I could continue to benefit from great surgical leadership and also continue my research, and had some great years before the merger changes prompted me to move to Umeå."

Naredi began to specialise in liver surgery, a discipline on which he is now a leading authority, encouraged by Tore Schersten, a leading surgeon at Sahlgrenska. After focusing on conventional surgery for removing metastases, where entire lobes are usually resected, he has taken on a method pioneered in France, in particular by Bernard Nordlinger, in which smaller sections around tumours are taken rather than whole lobes, which Naredi calls the 'Swiss cheese' method.

"As long as you keep 30% of the liver you can take many different parts with this method, and we know now we do not have to leave large margins around the tumours, only up to two millimeters, not the centimeter or so we thought before. It's not that patients necessarily do better than with whole lobe resection, but we don't have to exclude as many people, and we can operate again and again on recurrences."

Even so, only one in five patients is currently suitable for resection, often after chemotherapy to shrink metastases commonly spread from colorectal cancer, but Naredi reports that, in recent years, five-year survival rates for this group have advanced from 40% to 50% in centres such as Umeå, and even to 60% in some patients, and such improvement is significant because late-stage colorectal cancer is common so there is still a large population to target. "The 'Swiss cheese' method is the result of understanding biology, and is the way we should be doing things in the 21st century. My second liver surgeon here is hardly doing any lobe resections now, and we can aim for more eli-

"The 'Swiss cheese' method is the result of understanding biology, and is the way we should be doing things"

gible patients in the future, maybe as many as one in three. It's like the way surgery for breast cancer has moved to partial removal – more is not always better for primary tumours and for metastases too. Rather than taking away more to feel safe, we must learn more about the biology. But like any recent technique, we need to market it to get it into widespread practice, just as the pharmaceutical companies market their drugs. It is more usual now, but I'm still giving talks and writing articles about it."

Naredi adds that the liver is a challenging organ with a great deal of three-dimensional complexity, which is why he was attracted to its surgery, and there are other treatments such as perfusion and ablation to consider. There is also a lot to do in trial work on liver metastases and colorectal cancer. Testing the impact of certain neoadjuvant (pre-surgery) treatments is one important area – he mentions the European EPOC study as one such trial. Other strategies that merit being tested in trials include removing metastases before the primary tumour and after chemotherapy, in the expectation that there is a better chance of eliminating cancer spread.

"My other main surgical work is in pancreatic cancer, where we have improved greatly the number of patients we can operate on. Earlier, we were doing a Whipple procedure on only a few people – now we are doing as many as 40 operations a year at Umeå. We have better work-up with MRI and CT, and surgically we have quality and skills we didn't have 15 years ago.

"But the problem of course is that we are detecting only one in five in time and, of those we operate on, only 20% are alive after five years, which is only four or five out of 100 overall. We must find it earlier and we need biomarkers and better treatments – but in Sweden as elsewhere pancreatic cancer gets very little funding and advocacy. I don't care much about a 2% increase in survival with a new drug – a huge area for research in my view lies in early detection and better use of imaging technologies, as well as effective treatments."

He notes though that there could be genuine practice-changing progress in one of his long-standing interests, melanoma, where two targeted drugs have recently been approved in the US. And on the surgical side, he mentions strong results for sentinel node trials in both breast cancer (Armando Giuliano's work in the US) and melanoma (the MSLT-I/II trials).

After escaping from Gothenburg, where he was faced with too much aimless administration, Naredi went to Umeå as an assistant professor, and then in 2003 he became a full professor and chair of the department of surgery. "It was more like a county hospital when I arrived – now it is a much larger university institution and Umeå is a fast-growing college city. I don't regret the move up here for one minute – and we have had no problem attracting young doctors and researchers here."

Apart from helping to develop the academic hospital, a key advantage, he adds, has been the ability to shape Sweden's northern regional cancer centre around its major hospital, at Umeå. "Although our government has made mistakes in forcing hospital mergers – small places still need hospitals in

JOHAN GUNSÉUS/SYNK

On the helipad. Helicopter access is essential for this regional specialist centre, which serves a huge territory, much of which is covered in snow for five months of the year

"A huge area for research in my view lies in early detection and better use of imaging technologies"

my view – the criteria for the six regional centres, such as on education, structure, research, the cancer journey and patient participation, has promoted competition on quality. We know that if we don't improve quality we could lose patients to other regions."

Naredi says there is now much effort spent on trying to iron out the weak points in multiprofessional working. Rather than just a narrow multidisciplinary tumour board, he says, there is wider participation at meetings. "I may be the one who understands liver metastases and the best way to do surgery, but we jointly make the decision as to whether the patient should have the treatment or not. We involve the patient's personal doctor, who often knows them best, and we need people such as community nurses to tell us if a patient is depressed or in pain – the rest of our approach could be great, but if we miss factors like this the person has a terrible quality of life."

JOHAN GUNSEUS/SYNK

After some struggle with the IT people, Naredi and colleagues also now have access to high-quality videoconferencing facilities, vital to bringing more people at various locations into meetings where they are all expected to play a role in decision making.

A big and stubborn challenge, as in most countries, is how to reduce the numbers of patients who are not referred or diagnosed fast enough. But Naredi feels the various elements now combining will make an impact on the roughly 1 in 10 patients for whom the process is currently not working, for instance because referrals are not made for an expert appraisal for surgery where the patient would have been eligible.

One element is use of data, which he says Sweden excels at. Cancer and death registry data are among the most complete anywhere, and hospitals can be interrogated on say tumour-specific data that are missing from the cancer registry but where cancer is present in the death database. But cancer registry data are strong and are largely driven by surgeons, notes Naredi, who mentions the colorectal surgeon Lars Påhlman in Uppsala, featured in the December 2004 issue of *Cancer World*. Påhlman has been outspoken about using an initiative he helped to develop – the Swedish rectal cancer registry in 1995 (which now also covers colon) – to cut underperforming centres and surgeons for one of the tumours for which treatment quality remains highly variable.

This had remarkable results, with surgery feedback alone promoting better outcomes for rectal than colon cancer, despite the latter benefiting from new chemotherapies. "I'm not as forceful as Lars – I think surgeons are competitive anyway and will take it on themselves to either raise their game or stop if they consistently figure at the bottom of outcomes," he says.

Palliative care is also getting its own national registry, according to Naredi. "There are more funds from government going into this now than to other cancer registries and it will help us measure where we can improve factors involved in quality of life."

He adds that the structure of the regional cancer centre allows patients to be genuinely represented at board level. "They can say if they are unhappy with the way care is managed. It's not like sending a complaint letter – they are part of the process." The general population in northern Sweden is also involved in one of the country's strongest biobanking projects. "We have 100,000 people who give blood at the ages of 40, 50 and 60, and among them we have identified people who later were diagnosed with pancreatic cancer. We have some unpublished work on possible pancreatic cancer biomarkers from this unique biobank."

And in any case Sweden does best overall for cancer according to the EUROCARE-4 dataset, so it is no surprise that other countries are looking to emulate best practice, say in tumour-specific

networks such as breast, sarcoma and colorectal.

Swedish surgeons, says Naredi, have more political clout via the Swedish Surgical Society than counterparts in the country's medical association, and he says this more heavyweight presence applies at European level too, and will help bring more surgeons into ESSO. "We have a stronger voice at European level than the organ-specialist societies, which is one reason why I feel they will want to come under our umbrella. We are talking at present to leaders of the European Association of Urology and others in head and neck, hepato-biliary and gynaecology societies and so on about their members joining ESSO – most are not currently individual members – so they can have open access to our conferences and courses as well as adding to our political voice."

ESSO currently has about 2600 members and has grown recently thanks to a policy of inviting national society members to join. The last ESSO conference in 2010 in Bordeaux attracted nearly 900 people. Naredi adds that the European Association of Urology is likely to be the first European organ-specialist group to align itself with ESSO, which could give oncology a huge boost on the continent by addressing the poor treatments that occur in some countries thanks to the 'suboptimal' oncology approach seen in certain specialities.

Like presidents of other European oncology organisations, Naredi is keen to get more young people involved, and mentions women surgeons especially. "We spend a lot of our resources now on educational events and conferences, also in collaboration with other societies. Good examples are the Flims fellowship courses and the ESO–ESSO masterclasses, which are not necessarily pitched at elementary levels but at experienced surgeons too." A young surgeons and alumni club was launched at the 2010 ESSO conference.

And like the heads of other societies, he is robust in promoting the all-round qualities of members. "I have no problem with surgeons doing systemic therapy – as many countries, like Sweden, do not have regular medical oncologists. ESMO likes to talk of the superiority of medical oncologists, but I have not seen any studies saying it is right. We are far more experienced in intraperitoneal treatments, for example. But of course in large centres it will be mostly medical oncologists administering systemic therapies, although in Sweden they are also radiotherapists. Like the UK we have the clinical oncologist speciality, and practice does vary around Europe."

That may not endear him to ESMO colleagues, and he is concerned too by the lack of trials currently run by another ECCO member, the EORTC. "ESSO does not do its own studies and we should be running them through the EORTC, but at present it has very few of the trials we are running and it needs a refresh, otherwise we may think about doing our own pan-European research."

With ESSO past-president Cornelis van de Velde now president elect of ECCO, and Naredi also an ECCO board member, surgical oncology does seem to be in the ascendancy in Europe. "I am also president of both the Swedish and Nordic surgical societies – but it is most important now to be involved at European and global level if we are going to improve oncology, and ECCO is the right organisation for unity and strength."

Naredi is married to Silvana, a fellow professor at the university, and a neuro intensive care specialist, and they have two children, one in medical school. Like many Swedes, he's big on outdoor pursuits such as cross-country skiing – just as well as even in April the river in Umeå is still frozen solid.

His plan is to continue to develop the regional centre at Umeå and especially the education and leadership side. "It takes years to get the quality you want in oncology and we must have continuity from the educational system and train young doctors to be leaders," he says. In Europe, he also has no doubt there will be a big expansion of ESSO as the organ-specialist societies come on board, and he will continue to work on educational courses and quality, such as with the European audit project. And quality also applies to time: anyone who books a meeting with Naredi that doesn't have a key objective had better watch out.

"I think surgeons are competitive anyway and will take it on themselves to either raise their game or stop"

Decision making in the treatment of gliomas

Treatment modalities for malignant gliomas have not changed greatly in recent years, but we are learning much more about how to tailor treatments to patients. This overview looks at the role of age, tumour size, performance status and various predictive and prognostic biomarkers in guiding treatment in newly diagnosed and recurrent disease.

The treatment modalities for malignant glioma have not changed a great deal over the past few years, and remain: surgery, radiotherapy and chemotherapy. Surgery is the first step and backbone in the treatment of glioma. Complete resection, debulking or biopsy allows for precise histopathological and molecular characterisation, which is essential if we are to tailor and personalise the therapy. Radiotherapy has been used for thirty years, and we know that it prolongs survival when compared with nitrosourea-based chemotherapy or best supportive care. Chemotherapy used to be the 'new kid on the block', but is now the standard of care in newly diagnosed glioblastoma, concomitantly with radiation. Its value in the upfront treatment of other subtypes is more controversial and the data are not yet conclusive. We commonly use chemotherapy (nitrosoureas and temozolomide) to treat recurrent glioma and as second- and third-line treatment.

Decision making in first-line treatment

Decisions in first-line treatment are not only about how to treat but also who to

European School of Oncology
e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these is selected for publication in each issue of *Cancer World*.
In this issue, Roger Stupp, from the University Hospital of Lausanne, Switzerland, provides an update on factors that can be used in decision-making, focusing on practical aspects and everyday questions in treating patients with malignant glioma.
Olavo Feher, of the Instituto do Cancer do Estado de São Paolo, São Paolo, in Brazil, poses questions sent in by participants during the e-grandround live presentation.
It is summarised here by Susan Mayor.

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

treat and when to treat. Prognostic and predictive markers are used to guide treatment to ensure we get the most out of it. These factors include performance status, age, tumour size and location, and resectability. There are not a lot of data on resectability, but we know resected patients do better. There are also molecular markers such as *MGMT,* LOH 1p/19q (t 1:19), and *IDH1* mutation. But to what extent do these parameters help us in everyday decisions in managing glioma ?

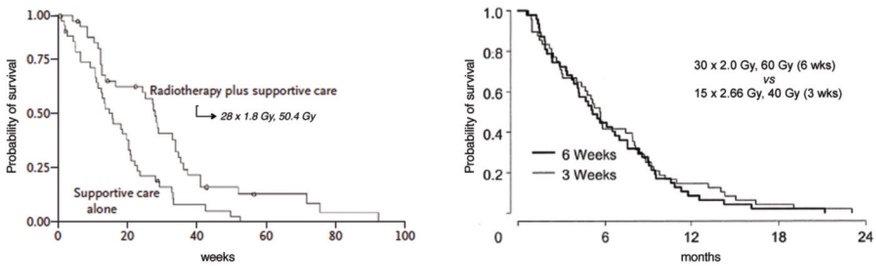
Performance status

Both WHO and Karnofsky's performance status scales are commonly used. The WHO scale has largely replaced Karnofsky in oncology because it is more reproducible; in neuro-oncology both scales remain in use. In practical terms it does not matter which one uses. Most benefit from treatment can be achieved in patients in reasonably good shape, who are alert and largely independent, and are able to come to the outpatient clinic.

Age

When we started the pivotal trial with temozolomide and radiation more than 10 years ago, patients over the age of 70 years were not considered for combined modality therapy on the grounds that their poorer prognosis and short survival would not justify a lengthy course of treatment. But a recent trial conducted by the French neuro-oncology group ANOCEF (*NEJM* 15:1527–1535) looked at the value of radiation versus supportive care in elderly patients aged over 70 years. The trial was closed early because radiation therapy improved survival over supportive care in patients even though they were considered to have poor prognosis (see figure above). A second, Canadian, randomised trial showed that hypo-fractionated radiation gives equivalent results to standard fractionated radiation in the elderly (see figure). The findings mean we can reduce exposure to radiation and the number of hospital visits for therapy in elderly patients.

RADIOTHERAPY: ELDERLY PATIENTS DO BENEFIT



Trials looking at more elderly patients have shown that this group (>70 years) does benefit from radiotherapy and that elderly patients (>60 years) can gain equivalent benefit from a lower overall dose given in fewer sessions

Source: Keime-Guibert for ANOCEF: *NEJM* (2007) 15:1527–1535

Roa et al. *JCO* (2004) 22:1583-1588. Reprinted with permission. © ASCO. All rights reserved

An analysis of subgroups from the EORTC/NCIC pivotal trial comparing temozolomide and radiation with radiation alone in patients aged 60–65 years and those aged 65–70 years shows benefits in both age groups in favour of combined treatment. The hazard ratio in the 65- to 70-years age group was less favourable than in the younger group (0.78 vs 0.64, compared to 0.63 in the whole trial population). These results do not suggest there is no value in combined modality treatment in the more elderly group, but may indicate the need to select patients who will benefit from a more aggressive approach.

The interest in elderly patients is illustrated by two randomised trials, NOA-08 and the Nordic trial, reported at ASCO last year. The NOA-08 trial compared an intensive temozolomide regimen (week on/week off) with radiation in patients aged over 65 (median age 72 years). The objective, which was to show that temozolomide is not inferior to radiation, was not attained, and toxicity with the dose-dense temozolomide regimen was higher than anticipated. With initial radiation alone a median survival of 10 months was achieved, which was reasonably good in an elderly population compared to other trials (Wick et al. ASCO 2010, abstract 2001).

The Nordic trial compared two radiotherapy regimens with temozolomide (5/28 days) in patients aged over 60 (median 70 years). Hypofractionated radiation and temozolomide seemed to be somewhat equivalent (Malmstrom et al. ASCO 2010 abstract 2002). The verdict is still out, but these studies show that if you select the right patients, radiation should be given. However, they also show that chemotherapy alone may be an alternative for some patients, such as those living far away from the hospital and those who are not in a condition to travel. The ongoing NCIC/EORTC intergroup randomised trial is looking at combined modality treatment, and as this approach worked in younger patients, I think it should also work in elderly patients, if selected correctly.

The role of surgery

Several trials have shown that patients who have complete tumour resection do better than patients who only have a biopsy. For example, the EORTC trial demonstrated that patients who had complete resection had longer survival than those undergoing only partial resection or

biopsy (see below, upper figure). A German trial aimed at increasing the complete resection rate by using fluorescent lights in the operating theatre. Results showed improved progression-free survival after complete resection, and higher rates of complete resection using this approach (see lower figure). This trial did not show longer overall survival, but at least it provided further evidence for the role of surgery. However, the extent of surgery needs to be balanced against the risks.

Question: *Considering the data in the elderly – the results of the EORTC/NCIC and the German and Nordic trials – what is your current approach in elderly fit patients with good performance status today, without results from the randomised trials?*

Answer: *If I have a fit elderly patient, I would give them combined modality treatment, possibly temozolomide chemotherapy combined with hypofractionated radiation. I would consider exclusive temozolomide chemotherapy in a patient with a methylated tumour requiring a large radiation field, particulary in an elderly and cognitively frail patient. In short, I would go with combined modality treatment outside a clinical trial if I do not have a clinical trial available.*

Question: *Would you be afraid to combine temozolomide with hypofractionated radiation?*

Answer: *No.*

Molecular markers

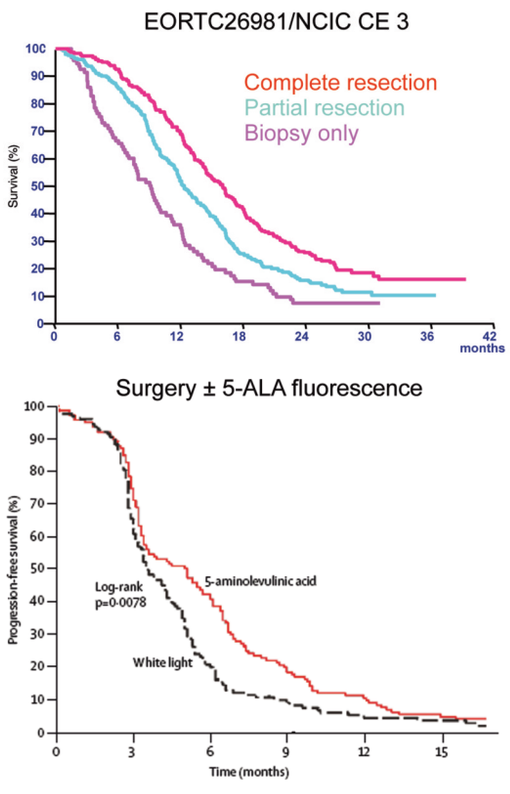
So far, we have seen that clinical factors can give a gut feeling about how to treat a patient, but we have few objective factors to use in deciding who we should treat and how. I think experience has a role here, and my answer to the last question illustrates that we sometimes deviate from the established standard of care for specific reasons, while in other situations a contemporary standard does not exist as it has never been investigated.

What of molecular markers? *MGMT* (O-6-methylguanine-DNA methyltransferase) predicts outcome – at least that's the hypothesis. It is a DNA repair protein that removes the methyl group that had been transferred from temozolomide onto guanine If the gene promoter is methylated, which is an epigenetic phenomenon affecting gene regulation, the gene is silenced. In other words, the gene is not expressed and the cell does not have the toolbox to repair the DNA damage. If this hypothesis were true, patients with a methylated *MGMT* promoter would benefit most from temozolomide chemotherapy.

Studies show that *MGMT* status predicts benefit from combined treatment. Patients with an *MGMT* methylated promoter, who are missing the tools to repair DNA damage, show most of the benefit of the addition of temozolomide, while in patients with non-methylated *MGMT,* temozolomide seems to have no, or marginal, effect on outcome (see figure overleaf).

This initial retrospective observation has recently been prospectively validated (RTOG0525; Gilbert et al. ASCO 2011, abstract 2006). We can conclude that there are two populations of tumours: those with a methylated promoter and others with a non-methylated promoter, and they may merit a different treatment strategy. In tumours with methylated *MGMT*, I think that temozolomide plus radiation should be the backbone of any proposed treatment, and should also be the backbone of any clinical trial investigating the addition of new drugs. For tumours with a non-methylated *MGMT*, we should think of options other than temozolomide, because drugs with a different mechanism of action are needed to treat these patients optimally. The difficulty is that we do not yet have a better alternative for these patients; and even the best test is never 100% predictive. Until better treatments are established, even patients with an unmethylated *MGMT* promoter will receive temozolomide and radiotherapy.

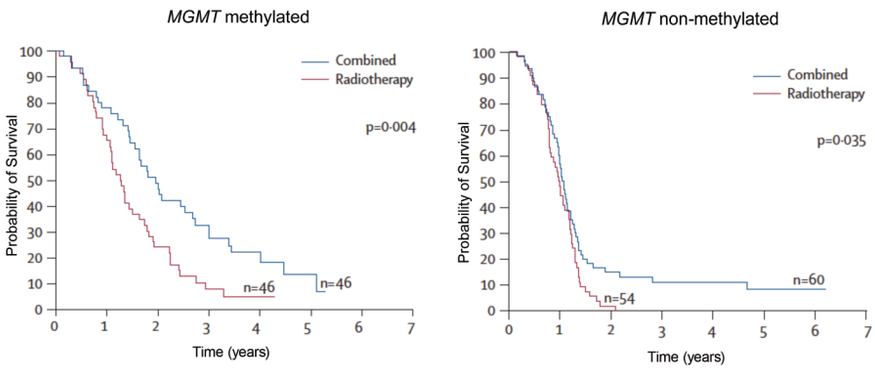
SURVIVAL AND THE EXTENT OF RESECTION



Complete resection was associated with better survival in the EORTC trial. In the German trial, fluorescence-guided surgery led to more complete resections, but complete resection was associated only with delaying disease progression and not with improved survival

Source: (top) Adapted from R Stupp et al. *Lancet Oncol* (2009) 10:459–466 (figure unpublished)
(bottom) Reprinted from Stummer et al. *Lancet Oncol* (2006) 7:392–401 © 2006, with permission from Elsevier

MGMT PREDICTS BENEFIT FROM COMBINED TREATMENT



If these results are confirmed, an alternative to temozolomide should be used in patients with non-methylated *MGMT*

Source: Reprinted from R Stupp et al. *Lancet Oncol* (2009) 10:459–466 © 2009, with permission from Elsevier

THE CURRENT STANDARD OF CARE

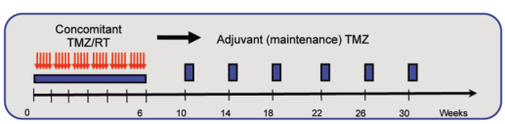
Temozolomide is given seven days a week, including weekends (tumours do not observe Sundays), while radiation is given five days a week (see figure below). With concurrent chemoradiation therapy, daily antiemetic prophylaxis is often not needed. We use a 5-HT3 antagonist only for the first few days of treatment (to avoid constipation associated with prolonged administration), before moving to a simple antiemetic like metoclopramide or domperidon.

What about anti-epileptics? These are only indicated in patients with a history of seizures and not as standard prophylaxis. It is also important to taper steroids. All too often we see patients who become weaker, not due to tumour progression but because of steroid myopathy.

THE PROGNOSTIC VALUE OF MRI

In clinical trials, MRI is usually performed four weeks after chemoradiation. However, results at this early time point are difficult to interpret and so this MRI may not have much value outside trials. The difficult issue is pseudoprogression after combined temozolomide and radiation therapy. After chemoradiation, and after radiation alone, images with increased contrast enhancement may falsely suggest tumour progression, while these changes of the blood-brain barrier reflect inflammation due to tumour breakdown and repair, and will normalise over the following months.

STANDARD OF CARE IN NEWLY DIAGNOSED GBM



RT	30 x 2 Gy, 5 days/wk	60 Gy	
TMZ	75 mg/m², 7 days/wk	max. 49 days	150-200 mg/m2 x 5 days, every 28 days, for 6 cycles
Antiemetics	5HT3 antagonist d1-3, then metoclopramide or no tx		5 HT3 antagonist (low dose) or metoclopramide
Antiepileptics	Only if seizure history		
Steroids	As needed, taper rapidly		
MRI		(X)	Approx. every 2-3 months

Six weeks of concomitant temozolomide (seven days a week, max 49 days continuously) and radiotherapy (five days a week) followed by intermittent adjuvant temozolomide is the current standard of care for all patients with glioblastoma multiforme, with supportive care to combat symptoms and side-effects and check-ups every two to three months (X = optional)

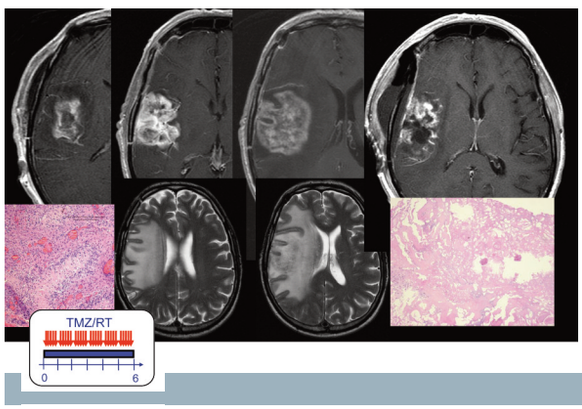
The figure opposite shows MRI scans for a patient with glioblastoma treated with temozolomide/radiotherapy in May 2008. The MRI for August 2008 shows a clear increase, with contrast enhancement, and some oedema, but we thought that it could be pseudoprogression. We continued, but an MRI in October 2008, after a longer period when we should be able to distinguish pseudoprogression from true progression, showed a further increase in tumour size, with more oedema. The patient was taken into surgery but there were no tumour cells to be seen, only necrosis. It is important to keep the phenomenon of pseudoprogression in mind, and not to take patients off treatment too early, particularly if they are clinically well.

MGMT may help in this situation. Brandes and colleagues (*JCO* 26:2192–2197) looked at patients who progressed after chemoradiation therapy but continued temozolomide further. Results showed that some patients continued to progress while others improved on MRI. Two-thirds of patients who subsequently improved had tumours with a methylated *MGMT* promoter, suggesting that pseudoprogression is more frequent in *MGMT* methylated tumours. In other words, pseudoprogression may be an expression of increased tumour breakdown rather than progression.

TREATMENT OF GRADE III (ANAPLASTIC) GLIOMA

Historically, the standard of care is radiation therapy and I think it is important to recognise that certain treatments used in the past may not have been evaluated with the same rigour as today. Data now show that we could start with chemotherapy first and then use

PSEUDOPROGRESSION ON MRI AFTER COMBINED TREATMENT



Follow-up MRI scans in patients treated with concomitant temozolomide and radiotherapy can be deceptive, and care must be taken not to assume patients are progressing when in fact they are responding

Source: MRI scans courtesy of Roger Stupp, University Hospital of Lausanne, Switzerland

radiation at progression. This could be considered for large tumours requiring extensive radiation therapy fields, or for oligos, which have a more favourable natural history and where you may want to delay radiation therapy. There are no data yet for combined modality treatment, but I know that this approach is used frequently.

A carefully conducted German trial looked at the sequence of treatment (*JCO* 27:5874–5880). It randomised patients between radiation first and chemotherapy at progression, or chemotherapy first and radiation at progression. The primary endpoint was progression the second time. Results showed no difference in overall outcome whether patients were initially treated with radiotherapy, followed by chemotherapy at first progression, or the inverse sequence. However, the use of concomitant chemoradiotherapy was not investigated (this is the subject of the ongoing EORTC-Intergroup CATNON trial). Based on these results, we may individually adapt the treatment strategy for each patient. Patients with a small tumour may best be treated with six weeks of radiation rather than a year-long chemotherapy regimen, while in larger tumours a primary treatment with chemotherapy may be considered.

MGMT in this trial was again a strong prognostic marker; however, while one might expect that tumours with a methylated *MGMT* promoter would benefit most from an approach starting with chemotherapy, time to first tumour progression was similar in these patients regardless of whether they were treated with radiotherapy first or chemotherapy first. The value of *MGMT* in grade III tumours is prognostic rather than predictive and does not readily help us chose whether to give chemotherapy or radiation therapy.

Chemotherapy for newly diagnosed anaplastic oligos

I deliberately use a term here that groups oligodendroglioma and mixed oligoastrocytoma together as 'oligos', because definition, reproducibility and trial results are not entirely consistent. As a general rule, pure oligodendroglioma, with a translocation of the gene 1;19 (LOH 1p/19q) have a distinct and prolonged natural history, and better responsiveness to both chemotherapy and radiotherapy. The above-mentioned German trial showed that patients who have an oligo component clearly do better in terms of time to first progression than patients who have anaplastic astrocytoma (*JCO* 27:5874–5880). Two randomised international trials evaluated the addition of PCV chemotherapy (procarbazine, lomustine (CCNU) and vincristine) in anaplastic glioma, including oligos, as a neoadjuvant (RTOG trial, *JCO* 24:2707–2714) or an adjuvant (EORTC trial, *JCO* 24:2715–2722). No benefit from the addition of chemotherapy could be demonstrated, even for the subset of the most chemosensitive oligos.

Individual treatment strategies should be based on tumour size, patient age and how aggressive a treatment one considers to be indicated. Primary chemotherapy may be an option for some patients with large tumours, but radiation therapy may be the best choice for small tumours; however, data do not support the unconditional preference for chemotherapy. More will be known when the ongoing international trials (CATNON coordinated by the EORTC, and CODEL, coordinated by NCCTG, and in Europe by the EORTC) have completed accrual and matured.

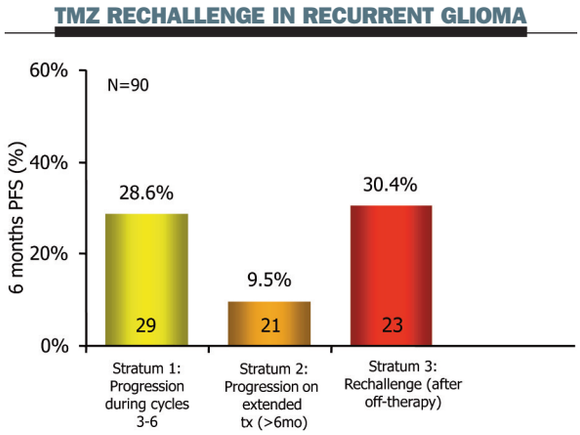
IDH mutations

IDH (isocitrate dehydrogenase) mutations were recognised a couple of years ago as an important prognostic factor for outcome. Patients with an *IDH* mutation, which usually occurs early in gliomagenesis, have a more favourable outcome than patients without this mutation. *IDH* mutation occurs in 70% or more patients with grade II and III glioma (*NEJM* 360:765–773; *JCO* 27:4150–4154). It gives us a way to identify whether a patient has a secondary glioblastoma. I would guess that many long-term survivors of recurrent glioblastoma, who do well with several lines of treatment, have *IDH* mutations.

Treatment options for recurrent glioma

While we have good data and prospective trials for the management of malignant glioma in the upfront setting, we lack large and solid trials in the recurrent setting. Decisions are individual, and depend on patients' and physicians' preferences, and availability of modalities and healthcare resources. Repeat surgery may be an option

in large tumours exerting a mass effect. A randomised trial would be needed to assess its true value, but I do not think that this is practically feasible, as it is hard to randomise patients between invasive surgery and a chemotherapy. Carmustine wafers (Gliadel) were approved for recurrent glioma undergoing repeat surgery, but the impact and use in daily practice remains limited. Approved chemotherapies include temozolomide, carmustine, lomustine and other nitrosoureas. Irinotecan (CPT11), cisplatin, carboplatin and etoposide are occasionally used, but not formally registered. Bevacizumab was recently approved in the US, but it was rejected by the European Medicines Agency (EMA). Re-irradiation is gaining in popularity, although it is not yet validated in prospective trials.



Studies exploring response to changing the dose/schedule, extending adjuvant treatment beyond the standard six cycles, or restarting temozolomide have found varying degrees of benefit

Source: Adapted from J Perry et al (for the Canadian Brain Tumor Consortium). *JCO* (2010) 28:2051-2057

Re-introduction of temozolomide, and alternative and dose-dense temozolomide schedules, are gaining in popularity. When temozolomide was approved, most patients were chemonaïve. They now all have temozolomide up front, so does it make sense to re-expose them?

A Canadian study re-challenged patients with progressive disease with temozolomide. It included patients who progressed in the early phase of adjuvant treatment, and then continued temozolomide on a different metronomic schedule (chronic non-interrupted temozolomide administration at 50 mg/m^2). Results showed almost 30% progression-free survival at six months. In patients who had been on temozolomide for more than the standard six cycles, only 10% seemed to gain benefit from staying on temozolomide. Patients who had been off treatment and then started again showed a 30% progression-free survival at six months (see figure above).

This was not a randomised trial, it was a practice treatment trial, but it tells us that patients who have been on temozolomide for a long while and progress may not benefit from re-treatment with temozolomide.

A British randomised trial looked at PCV versus temozolomide in recurrent chemonaïve (!) glioma patients not given chemotherapy during first-line radiation therapy. Results suggested that temozolomide was equivalent to PCV but not necessarily superior, although toxicity was lower (*JCO* 28:4601–4608). A second randomisation between two schedules of temozolomide – five days of 28 (standard administration schedule) and a dose-dense schedule for 21 (of 28) days showed slightly better outcomes with the five-day schedule. Similarly, the recently reported RTOG05025/EORTC/NCCTG -Intergroup trial failed to demonstrate superiority of a dose-dense temozolomide schedule in newly diagnosed glioblastoma (Gilbert et al., ASCO 2011, abstract 2006). We may have been overly optimistic about alternative temozolomide schedules.

What other alternatives do we have? A trial comparing enzastaurin with lomustine (*JCO* 28:1168–1174) provides data on lomustine in patients with recurrent disease who have failed on temozolomide and radiation. Results show overall survival of seven months, and progression-free survival of 19% at six months with lomustine – close to the 20% benchmark we set at the time with temozolomide. So, lomustine may be a better drug than we thought, often well-tolerated but with a substantial incidence of profound myelosuppression in previously treated patients.

VEGF inhibition for recurrent glioma

Use of agents targeting VEGF or VEGFR is the most recent strategy to be looked at. Data with two drugs – bevacizumab (Avastin) and cediranib (AZD2171) – have initially been particularly encouraging, giving us the kind of MRI images that get us excited! The figure opposite shows scans for a patient before and after treatment with bevacizumab and irinotecan (left-hand scans), and the tumour has almost vanished.

The right-hand scans in the same figure include similar findings from a trial by Batchelor and colleagues (*Cancer Cell* 11:83–95) for a patient treated with the VEGFR inhibitor cediranib. The scans show that the contrast enhancement disappears very rapidly. MRI scans the day before cediranib administration, the day after treatment, and after four weeks, show that the tumour had disappeared, or had started disappearing, 24 hours after giving cediranib. This is almost too good a result. It suggests that what we see with this VEGFR inhibitor is the normalisation of the vascular permeability and of the vasculature, but not necessarily a true anti-tumour effect, so some of this is a radiological

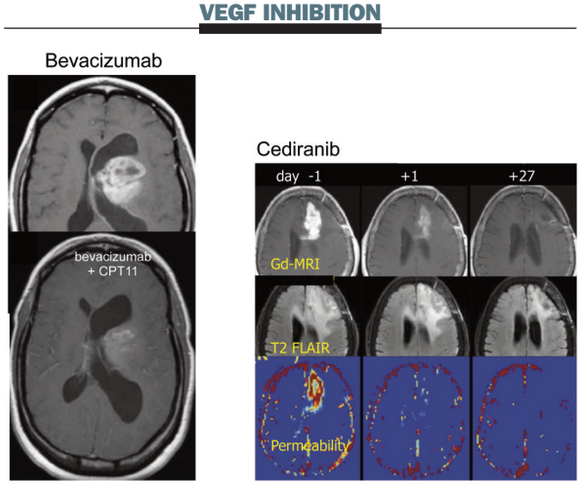
phenomenon of pseudoresponse rather than a true response. Nevertheless, regression of peritumoural oedema is real and often associated with a temporary improvement in patients well-being.

We only have limited data with these agents in brain tumours. Although bevacizumab has been approved by the FDA, this is a conditional approval on the basis of phase II data. A randomised phase II trial in which patients were randomised to bevacizumab (with irinotecan added on progression) or to bevacizumab plus irinotecan showed that the majority of patients could be spared from using steroids by treatment with bevacizumab, which is less toxic than steroids. Tumour size – as measured by contrast enhancement – decreased in the majority of patients. Results showed an overall survival of around nine months, similar in both arms. Although survival appears slightly better than with historical controls, trials with cytotoxic agents alone have shown median survival durations of seven or eight months. So bevacizumab may have some value, but largely based on a steroid-like anti-inflammatory effect, while a clear antitumour effect remains to be demonstrated. It may improve quality of life in selected patients, without necessarily prolonging survival.

For cediranib, a pan-VEGFR tyrosine kinase inhibitor, a proper randomised phase III trial was conducted. The results of the REGAL study were presented recently at the ESMO meeting. This trial randomised patients to cediranib alone, cediranib and lomustine, or placebo plus lomustine. Results showed an overall survival of around nine months in the two lomustine-containing arms, and eight months in the cediranib alone arm (ESMO 2010 abstract LBA7). Disappointingly, no benefit was seen for the combination of cediranib and lomustine. Similarly to the bevacizumab, imaging showed improvement and there was less steroid use in patients on cediranib; however, it did not translate into improved survival. Overall, a VEGF-inhibiting strategy may be of some value; however, the target population (e.g. large tumours with important peritumoural oedema and mass effect), the optimal dose and frequency of dosing, and combination with cytotoxic chemotherapy remain to be determined.

Summary

In conclusion, we have a few clinical parameters on which to make decisions on when to treat and when to withhold treatment in patients with malignant gliomas. The nihilism we have had until recently, especially in elderly patients, may be questioned, and some elderly patients may benefit from active treatment. Complete tumour resection, if feasible, is associated with improved outcome.



Images showing recurrent gliomas before and after treatment with bevacizumab (left) and cedirinab (right) show dramatic tumour shrinkage, but this may not be true response

Source: (*left*) JJ Vredenburgh et al. *Clin Cancer Res* (2007) 13:1253–59, adapted and reprinted by permission from the AACR (*right*) Batchelor et al. *Cancer Cell* (2007) 11:83–95, reprinted with permission from Elsevier

In terms of molecular markers, *MGMT* methylation status predicts benefit from alkylating agent chemotherapy in glioblastoma and is prognostic in anaplastic glioma. LOH 1p/19q characterises a subgroup of patients and tumours with a protracted natural history. *IDH* mutations occur early in gliomagenesis and are characteristic for transformed lower-grade glioma, allowing us to identify secondary gliomas that have a different genetic makeup. They may indicate a more favourable prognosis, and tumours that are more likely to respond to treatment.

Question: *We have seen overall survival of glioblastomas converging at around 21 or 22 months in a couple of late phase II trials – the NABTT trials and the UCLA trial with bevacizumab and irinotecan, and temozolomide first-line trials with glioblastomas. Do you think the survival in glioblastomas is shifting to the 20 months hallmark?*

Answer: *I think it is shifting, because patients get better care. A lot of the benefits are due to better supportive care and the fact that we do not give up, and we do repeat surgery and multiple lines of chemotherapy. It is a conglomerate of many interventions rather than just one intervention. There is always some selection bias in clinical trials. We tend to include the better patients, because the ones with the worst prognosis may not even make it to a trial. A number of trials have shown a good number of patients progress even after chemoradiation, and never make it to any further lines of treatment. This underlines the need for randomised trials, because we cannot draw conclusions based on historical controls. This shift to improved survival means we need contemporary controls to help guide decisions. The answer is randomised clinical trials.*

Beyond survival – what should new cancer drugs have to prove and how?

Anna Wagstaff

Randomised controlled trials have been the gold standard for testing new drugs, and survival is the standard by which they succeed or fail. As our understanding of cancer increases, therapies become more numerous and more complex, and patients live longer, is this still the way to get the best drugs into use most quickly? If not, is there a credible alternative?

Demonstrating in a randomised controlled trial (RCT) that a new treatment keeps patients alive for longer has long been seen as the gold standard evidence for new cancer drugs. That doesn't mean it has been uncontroversial – far from it.

On the plus side, this gold standard answers the key question for patients and doctors: "What is likely to keep me alive for longest?" It also gives payers a strong evidence base to assess the value of the drug. Using 'surrogates' for survival, such as response rate – significant tumour shrinkage – or progression-free survival (PFS) – how long the therapy holds the cancer at bay – are seen as far weaker measures. The notorious ability of cancer cells to find alternative pathways means that early indications of response are often not sustained. Surrogates are also harder to measure than survival, where the endpoint is the finality of death. It can be difficult to interpret what is happening to a tumour even on MRI, giving rise to the phenomenon of pseudoprogressions and pseudoresponses (see e-grandround in this issue for a spectacular example in gliomas). Measurement of progression is also open to variations and depends heavily on how often the patient is evaluated.

However, there is a downside to using survival as the key indicator. It means that researchers must continue a trial until enough patients have died to show a statistical difference in survival. This can be a long and expensive process, especially where the benefit is incremental – which, sadly, is often the case. If the relevant patient population is small and networking is poor, recruitment to the trial can be a very slow process.

A number bad things flow from this:

- potentially beneficial drugs are slow to reach patients who are running out of options
- the cost of the process pushes up the price of the drug, which could restrict patient access
- the time and money used in getting statistical answers could be used for other research
- the longer it takes to answer the questions posed by the RCT, the greater the risk that the question loses relevance, as the standard of care changes or greater insights are gained into the way the disease works.

There are also ethical issues about trials

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

that require patients in the control arm to die early to prove the superiority of the experimental arm, when their lives might have been extended had they been allowed to cross over to the experimental therapy as soon as it became clear that they were showing a poorer response rate or were progressing earlier.

Times are changing

There are genuine dilemmas here, with no easy answers. But a number of trends in cancer research and cancer care are now changing the terms of this debate:

Better care. For many cancers, survival times are creeping up as the result of improvement in care, including supportive care, and greater specialisation and multidisciplinary working. This is good news for patients, but means that survival endpoints take ever longer to reach.

More therapies. By the end of their lives many cancer patients will have been treated with four, five or six different 'lines' of therapy, moving on to something new each time the previous one ceased to be effective or the side-effects proved too troublesome or a new more promising drug made it to market. For each drug you can measure response rate and PFS, but death happens only once: how can you tell what contribution each drug made to overall survival?

Better organised patients. As patient groups have become more organised and vocal, it is becoming increasingly difficult to justify or recruit to trials that do not allow control patients to cross to the experimental arm once that arm has shown it does better on the PFS measure. The whole purpose of allowing crossover is to minimise the survival gap between the two arms, making it hard if not impossible to demonstrate superior overall survival.

Shrinking patient populations. Randomised controlled trials are all about numbers and statistical proof. As researchers succeed in differentiating the disease into hundreds of biologically distinct entities, the number of patients appropriate for each trial shrinks, making RCTs less of a practical option.

Decreasing toxicity. While cardiac toxicity, for instance, can still be a serious issue with some biologics, in general, newer therapies, including vaccines, have side-effects that are less threatening and less debilitating than traditional cytotoxics. The need to prove beyond doubt the survival benefit of a new drug becomes less pressing where the patients have less to lose.

Intelligent design. RCTs can give answers to specific questions even if you have no understanding of what is driving the disease, or how the drug works or in whom. Now that we understand more about the disease and drug developers invest heavily in extensive preclinical and early clinical studies to build up a clearer picture of their drug, might alternatives to lengthy RCTs be acceptable?

As cancer care and drug development move forward, should proof of overall survival benefit as shown in a randomised controlled trial still be the gold standard for new therapies? How can drug developers provide patients, doctors, regulators, trial participants and payers with the evidence they are looking for? *Cancer World* put the question to some of them.

Committed to showing survival benefit

Uday Bose is European Head of Oncology at Eisai, a Japanese pharmaceutical company that recently entered the cancer field with Halaven [eribulin], a cytotoxic, that was approved by the EMA this March for use in advanced breast cancer.

Bose questions how far overall survival is really seen as the gold standard, citing a study that showed no more than 15 out of 76 phase III studies in metastatic breast cancer published between 1998 and 2007 had overall survival as their primary endpoint, and met that endpoint (*JCO* 28:1958–1962). PFS has become an increasingly common surrogate in this setting. A consequence of this, he argues, is that while women are typically treated with four, five or even more lines of treatment, after the first two lines, doctors and patients have little evidence for survival on which to base further choices.

"I think there is a correlation between the promotion and acceptance of PFS data, because they are the primary data that are being generated. But from the research we did in preparation for our launch, the message that this is the right endpoint to be looking at, rather than overall survival, seems to have been accepted by oncologists as well."

When Eisai presented physicians with a single page showing the profile of Halaven, says Bose, their attention was immediately drawn to the PFS data – the secondary endpoint of the study. They were very interested in the overall survival data when they saw it, he says, but they didn't actually look at it until it was explicitly pointed out. "It's stark how the environment has now evolved in prescriber land that PFS is a valid surrogate, and they are quite convinced that it is a fair and a strong endpoint, even when they are presented with overall survival as primary endpoint."

Bose hopes that Eisai's success in showing overall survival benefit will challenge what he sees as a defeatist acceptance that meeting an overall survival endpoint is an unrealistic expectation in late stages of disease.

He does accept, however, that there are many situations where proving survival benefit may not be possible, and it was a delicate balancing act even in the EMBRACE trial, which demonstrated an extra two months of life for women with metastatic breast cancer who were put on Halaven as a third-line or later treatment. To make the trial more palatable to potential participants, Eisai allowed almost unconstrained 'treatment of physician's choice' (TPC) as the con-

RCTs: GOLD STANDARD OR BLUNT INSTRUMENT?

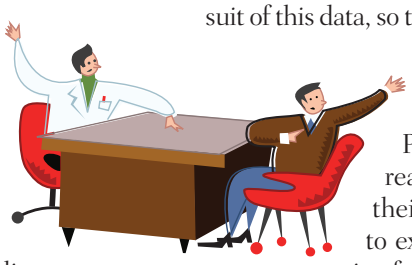
Randomised clinical trials are used to subject hypotheses such as "patients will live longer on drug A than drug B" to a statistical test. They need to recruit enough patients to show, with a high degree of certainty, that the survival difference between the trial arms really does reflect superiority of the treatment rather than having come about by chance. This measure of certainty is represented in the all-important *P*-value; $P<0.001$ being a way of saying that there is a one in a thousand chance that the survival difference shown in the trial, or an even higher difference, does not represent a real and replicable difference. The smaller the difference between the two arms, the more patients must be recruited to reach statistical significance.

Bayesian methodologies, in contrast, make use of all relevant knowledge gained through the multiple studies done during the process of drug development – on the role of the target, the ability of the drug to hit the target, the effect of hitting the target, perhaps the effect of adding a second drug, the dose levels, predictive biomarkers and so on – and can incorporate them mathematically as 'priors' into a model that presents the strength of evidence in terms of 'credible intervals', which are equivalent to the more familiar 'confidence intervals'.

Cancer World will look at Bayesian trial methodologies in greater depth in a future issue.

trol arm – including best supportive care.

As it happens, says Bose, no patients chose best supportive care – something that pleased the patient representatives, he says, "because it challenges the perception that once a woman has gone through first-/second-line treatment they give up and they don't want anything else."



Halaven is currently in a head-to-head study against capecitabine, in an earlier line of disease, after an anthracycline and a taxane. This time Eisai has chosen to use progression-free survival as a co-primary endpoint with overall survival. The company is clear, however, that whatever happens, the trial will continue until there are sufficient overall survival 'events' (i.e. enough deaths) to demonstrate a significant difference in survival. They will not do what so many phase III trials do, and publish an interim report when the number of PFS 'events' (i.e. progressions) has reached a point where they are likely to show a significant difference between the two arms, and then either stop recruiting or allow patients on the control arm to switch over to the experimental treatment.

"If we were to go out with our PFS endpoint, then in our conversations with payers, they may say, 'But you compromised the study. You had a survival endpoint, why didn't you stick with it?'"

Bose has seen exactly this happen with some other cancer drugs, and he doesn't want to repeat the mistake. There's no great ethical achievement, he points out, in stopping a trial early or allowing patients to cross over to the experimental arm on the basis of promising PFS data, if the consequence is that payers then refuse to reimburse the drug on the grounds of insufficient evidence on survival.

There are three things he would like to see happen. One is that drug developers and oncologists raise their ambitions and go the extra mile to try to get overall survival data wherever they can. The second is for a regulatory and payer environment that encourages the pursuit of this data, so that companies won't feel they could end up penalised if they have strong PFS data but fail to reach significance on their survival data, due to explicable confounding factors.

The third, which he believes is crucial to being able to give payers what they want, is the introduction of a value-based system of pricing that recognises that any given cancer drug can give different levels of benefit depending on what cancer, what stage, and what line of treatment it is used in.

Identifying your target group is the key

Oliver Kisker is vice president of global clinical development for the oncology unit at Merck-Serono, where he works with a wide variety of cancer therapies including Erbitux [cetuximab], the *EGFR* inhibitor approved for use in some colorectal cancers and squamous cell head and neck cancers, and for which Merck is now seeking approval for use in certain non-small-cell lung cancers.

Kisker shares the view that being able to show your drug improves survival is always desirable, but in some indications it is difficult to achieve: "In some areas, where few treatment options are available, it is important to demonstrate that overall survival is really better compared to the competitor. But if you have an indication where treatments are much more available, like for colorectal cancer, it will be much more difficult."

How can you prove the overall survival advantage of a drug used first line in colorectal cancer, he asks, without dictating in the protocol what patients should get not only in the first line, but also in second, third and fourth lines – which is not something physicians or patients would be likely to accept. And if you don't, then how can you stop differences in overall survival being confounded by differences in the subsequent therapies?

The answer, he suggests, is to ensure the survival benefit is sufficiently strong to show through despite the confounding impact of therapies taken after the trial. And the way to do that is to identify the patient group that derives a real benefit from the new treatment.

This is how Merck showed the survival benefit for adding Erbitux to the FOLFIRI regimen for first-line treatment of patients with metastatic colo-rectal cancer. In an undifferentiated patient population, the combined treatment showed a significant improvement in PFS, with a hazard ratio of 0.85, but the difference in overall survival failed to reach significance. However, Merck had taken tissue from the majority of its trial patients, and was able to reanalyse the data after stripping out the results from patients with a mutated *KRAS* gene. This effectively doubled the response rate figures for the wild-type (normal) *KRAS* patients; it strengthened the difference in PFS data from a hazard ratio of 0.85 to 0.696; and, importantly, the difference in overall survival became statistically significant, showing an additional 3.5 months over the control arm.

"This demonstrates you can do it," says Kisker. "It's not just a question of overall survival as a primary endpoint; it's a question of how to develop our products. We have to address, even in preclinical models, how drugs might work, what is the mode of action and what might be potential biomarkers. You then go for a phase I study, which should be used to identify patients who might

"There will always be situations where proving overall survival benefit simply isn't possible"

benefit, by including even at that stage a marker that could identify the right patients. You then use expansion cohorts [add in patients with the marker of interest] where you can see if these patients really do benefit.

"Then we have a combination of expansion cohort and biomarker, and then you go to phase II, which gives a much clearer picture of how patients might benefit based on molecular profile. Then you do additional analysis here with further markers, identify them, the right profile, the right patients, and then you go to phase III."

This is the strategy Merck is following now with all its cancer drug developments, says Kisker. In lung cancer they are looking at high levels of *EGFR* expression as a marker for response to Erbitux. And they are investigating the *MGMT* biomarker, associated with DNA repair function, as a possible predictor of response to temozolomide, which is combined with cilengitide, their experimental integrin inhibitor for first-line use in glioblastoma.

Trialling the drug only in the population that responds well not only increases the benefit you can show, but as Kisker points out, it also decreases the number of 'events' needed to prove this bigger benefit, which means trial sizes are smaller.

But no matter how well you do this work, he adds, there will always be situations where proving overall survival benefit simply isn't possible. A classic example is where you are trialling a drug for use in first line, when it has already been approved in a later setting. It is not only unethical but also impossible to deny a patient in the control arm access to the treatment once they have progressed to the point where that drug has been approved and is freely available for use. "If you have crossover you need to think about it and discuss with the regulators about the crossover effect of a drug already approved for a later stage indication."

Despite the extensive early trial work involved, however, Kisker feels that new drugs still need to prove themselves in standalone phase III RCTs. "You try to answer questions you have raised in phase I and early phase II, but in the end you need to show it in a phase III, because this is a requirement by regulatory agencies."

He doesn't rule out the possibility of extending phase IIs into the phase IIIs in the future, though it's not a design Merck currently uses. "I think it is an interesting approach, that you could carry on and reduce time to approval. But I think we would need to have further discussion with agencies, because designing studies in this way is not always accepted by agencies. This is one of the things where we need to interact with agencies to speed approval of drugs by using these kinds of designs."

Better interaction is also his solution to the question of how to satisfy the demands of payers. Kisker makes time to talk to the people who have a say over reimbursement, to discuss the issues he faces in developing a particular drug, and to find out from them what sort of data they need. "Payers are becoming more and more important, and both sides need to understand one another. They need to understand where we are, because they want to see patients benefit from therapy. We on the other hand need to see what are the points that we have to address."

He emphasises again the importance of finding the right patient group. "You need to include as early in the trial as possible personalised medicine through stratifying patients using biomarkers. If you see benefit for these patients, payers will have nothing against it."

One size does not fit all

Rafael Amado is Head of Oncology Development at GlaxoSmithKline, where current strategies include starting development with a tightly defined patient population – patients with known cancer promoting molecular alterations, such as *BRAF* mutations, for example – and developing drugs, or combinations of drugs, that will be effective in the small population of patients whose cancers are driven by those alterations.

"It's fair to insist on survival data when you are using broad-spectrum, toxic treatments which afford only small incremental benefit, as in the case of cytotoxics in most advanced cancers," says Amado, "but when you are using drugs targeted to molecularly characterised populations, which can drive large effects in surrogate endpoints, and are less toxic, I do not think that overall survival needs to remain the gold standard against which we measure new drugs. I understand that we have to show at least reasonable likelihood of clinical benefit. But if we continue to think of overall survival as the gold standard, the development process will continue to be long and cumbersome, and it will become more and more difficult to obtain it as an

endpoint. Indeed, as diseases become more chronic, waiting for survival will continue to tie up investment and resources and delay innovation."

He mentions the controversy over the use of overall survival as an endpoint in melanoma with innovative drugs such as *BRAF* and *MEK* inhibitors. These are drugs with understood mechanisms of action that have shown impressive response rates and progression-free survival in advanced melanoma. Trials are being conducted against dacarbazine – an ancient and largely ineffective cytotoxic. Carrying on the trial until enough patients die to reach statistically significant data on overall survival would rule out the possibility that PFS gains might fail to translate into longer survival, as the cancer finds alternatives to the blocked pathway – which turns out to be a real concern. But Amado says GSK would not be prepared to go down that road.

"We are developing a *MEK* and a *BRAF* inhibitor. Our randomised trials use crossover from the control to either *MEK* or *BRAF* after disease progression, or a control arm that includes an active targeted therapy, as we feel all patients in these trials should have the opportunity to access these drugs."

Amado concedes that progression-free survival is not a foolproof surrogate for overall survival. "In the field of angiogenesis for example, there have been preclinical studies showing that a rebound pro-angiogenic effect can occur after withdrawal of antiangiogenic therapy, suggesting that while a patient can respond during treatment, when one withdraws the drug the tumour may come back with a more aggressive phenotype. So I think it is incumbent on the investigators and sponsors to show that a phenomenon like this doesn't occur."

One way to do this, says Amado, is to look at whether the early difference between the overall survival (OS) data for the two arms wanes over time. "If you see OS hazard ratios that are trending progressively in the wrong direction after drug discontinuation, that should raise concerns. There are also analyses one can do looking at time to death from disease progression between test and control arms, which can help rule out a potential rebound effect," he says.

The question that should be asked, he suggests, is whether failure to meet a survival endpoint was due lack of statistical power, lack of a treatment effect, excess toxicity of the treatment arm, compromise of delivery of standard therapy, or tumour promotions such as directly or via a rebound effect. "For instance, we recently learned that the use of *EGFR* inhibiting antibodies in patients with colorectal cancer harbouring *KRAS* mutations seem to indeed shorten survival."

Amado questions the need for randomised controlled trials as the gold standard for all drug approvals, and points out that Bayesian designs are often used by sponsors and the US National Cancer Institute to do proof-of-concept trials, and are endorsed by the FDA for use in device approvals. "Traditional statistical designs have the potential to slow down drug development particularly in disease settings with small patient populations, such as for instance non-small-cell lung cancer with *ALK* translocations or *BRAF* mutations. To compound the problem, effective inhibition of some genetic aberrations may depend on blocking more than one target to ensure efficacy or prevention of resistance. The use of Bayesian statistics can also model not just the overall treatment of targeted drugs alone or in combination, but how their effects vary depending on a variety of factors, including biological heterogeneity".

The RCT approach can only really answer one or two questions at a time, says Amado, and is simply too blunt an instrument for these sorts of developments, because there are too many variables: in what type of tumour does a given drug work best, in which molecular alteration, which pathways do you target in the setting of combinations (and which plays the primary role) and what doses do you use. Many companies are therefore already relying heavily on Bayesian approaches (using modelling and probability methodology – see box p 24) to guide their proof-of-concept development, says Amado, and he expects that trend to continue.

"When you have so many variables and are trying to test a combination against a given standard, you end up with multiple-arm studies. And if you are not incorporating the knowledge that you get from every patient you end up with a large proof-of-concept trial that is often very difficult to interpret beyond the primary endpoint and safety. So eventually proof of concept is going to be more and

"The RCT is too blunt an instrument for these sorts of developments, because there are too many variables"

more iterations of trials in which arms get added on and arms get graduated or removed. We are now often using these adaptive and Bayesian designs."

Neither the EMA nor the FDA has ruled out approving a drug on the basis of evidence generated using Bayesian methodologies, and Amado hopes that the field will evolve in that direction, particularly in situations with highly biologically segmented populations where the use of novel agents result in large treatment effects. "In oncology we still have to wait for the first example of a full approval to come out of a Bayesian design. But I think that if regulators are willing to accept proof of concept based on Bayesian design as end of phase II data, it is only one step removed from accepting these designs for approval. Consider that large effects in OS mediated by a novel agent in a phase III RCT require a much higher and faster rate of death events occurring in the control arm than in the novel therapeutic arm. The question is whether allowing excess patients to die at a higher and faster rate in the control arm is appropriate when we know that the novel drug is highly active from phase II studies. For instance, when phase II studies already suggested that PFS with a novel agent is substantially longer than PFS or even OS observed with traditional chemotherapy, one could argue there is a loss of equipoise in randomising patients to the control arm".

GSK has been in discussions with regulators in US and EU to reach agreement on the design of RCTs for use in registering new combination therapies. "When using combination therapies you have to supply proof of the contribution of each compound to the benefit of the combination, and to do that one needs relatively large trials involving at least three arms. One way to decrease the size of the trial is by using a surrogate endpoint (e.g. PFS instead of OS) in one of the comparisons. Another step to simplify the development of two unapproved drugs is to use one of them as a comparator, rather than including a fourth arm for an approved standard. This can be done if the drug has significant activity as a single agent in phase II; although such a trial, if successful, would result in approval of the combination alone, it would likely not support approval of each of the agents as monotherapy."

For the payers, says Amado, the big issue may become whether paying for both drugs up front offers better value for money than using the two drugs in succession. "It is incumbent on us to demonstrate that the value of the combination goes beyond an endpoint such as progression-free survival or even overall survival, because these comparisons are done to single agents and not to sequencing multiagents." We will have to demonstrate that using combinations upfront is superior to the sequential use of each drug in terms of clinical outcomes and cost-effectiveness. In the case of *BRAF* and *MEK* it is possible that sequential use may be of no value as drugs may be cross resistant; in that case the only possible use of them would indeed be in combination.

Tailor-made trials

Hilary Calvert is director of Anticancer Drug Discovery at the University College London Partners, where he is involved in many phase I trials. He confesses to an ambivalent attitude on the need always to demonstrate overall survival benefit. Whatever else cancer patients may want from a drug, says Calvert, we can be pretty confident that they want it to make them live longer, so we do need to show that can happen,

WHAT DO PATIENTS WANT?

Cancer patients do want to live. But at what cost? As survival times increase, issues of quality of life become increasingly important, and drug developers are now encouraged, by regulators and payers, to incorporate quality of life measures into their trial designs.
How best to do this remains a problem.

- Studies show that doctors consistently rate side-effects as less significant than they are rated by patients – and it tends to be doctors rather than patients who fill in the trial forms.
- Even where patients are asked to rate side-effects on a scale, the frequency or severity may say little about how much it matters to the patient – diarrhoea may be less debilitating if you don't have to be out and about a lot; loss of feeling in the fingers, or disfiguring rashes affect people different ways. Even indicators such as whether the patient can continue working depend to some extent on what options they have.
- Patients may also have reasons to hide from their doctors the severity of side-effects if they think that telling the truth may lead to them being taken off a treatment they want to keep.
- Evidence on how patients see the trade-off between extra months of life and quality of life is scant and somewhat contradictory. A study done in 1990 showed that patients are prepared to take a greater hit on their quality of life for some extra time than their doctors (or the general public) would consider acceptable (Slevin et al., *BMJ* 300:1458–1460). A more recent study presented at the 7th European Breast Cancer Conference (Sheik-Youssouf et al., *EJC* Suppl 8:77), which looked exclusively at patients with metastatic breast cancer, suggests doctors require the offer of an additional two to six months of life as enough to consider trying a new therapy rather than the standard options, while almost two-thirds of patients want the promise of at least 10 months' additional survival.

"Cancer is just too complex and varied for golden rules or one-size-fits-all gold standards"

especially where the drug is fairly toxic. But then he cites the history of development of AIDS therapies, which took place without any of the stringent regulatory controls imposed in cancer.

"We've seen an absolute revolution in survival in HIV and they're now saying that it maybe takes five years off your expected lifespan rather than killing you within a few years. With all the enthusiasm and emphasis put on AIDS research, there's now about five different targets in the HIV system and about five different drugs available for each one. Physicians don't have any restrictions on prescribing them and nor have they ever had to prove they are value for money."

Progress in AIDS therapies was all about finding the combinations that work best, which makes it an interesting analogy to current approaches in cancer. "What they do is they look at the viral load, and they measure the changes very quickly until they find the combination that works." If AIDS research had been forced to jump through the sorts of hoops still required of cancer therapies, where you have to prove each individual drug with a set of trials for overall survival, says Calvert, they would never have progressed as fast – if at all.

He concedes, however, that AIDS, like heart disease and many other conditions, has something that cancer lacks: a good surrogate endpoint. Cancer has no equivalent of viral load or cholesterol level, which have been shown to correlate closely with survival. "Maybe the closest analogy in cancer is chronic myeloid leukaemia, where you can look for the BCR-ABL fusion, so you have a quick marker, and consequently it has been possible to develop a number of different drugs. I'm not saying it would work for all forms of cancer, but this is why I am a bit ambivalent about the very rigorous approach."

Calvert doesn't deny that approving a drug on progression-free survival can lead to wrong decisions. Iressa (gefitinib) for non-small-cell lung cancer was a case in point – it was approved by the FDA on the basis of its PFS figures, but it failed to show significant improvement in survival. This might never have become clear if there had been no requirement to show overall survival benefit. Avastin (bevacizumab) was another similar case. Calvert suggests that, given what we know about the fiendish ability of cancer cells to mutate in order to keep multiplying, the possibility that their response to being deprived of vascularisation would be to become more invasive in the search for alternative sources of blood might have been anticipated by both developers and regulators.

Which is all very well to say in hindsight, but is there any way to say in advance when disease-free or progression-free survival may be an acceptable surrogate and when it is not? "I can't think of a rule that would tell you that. Looking at a particular drug and its mechanism of action I could give you an opinion – it might well be wrong. It's a good question but a tough one."

What Calvert is saying, in effect, is that cancer is just too complex and varied for golden rules or one-size-fits-all gold standards. By the same logic, he agrees that Bayesian trial designs should replace the gold standard RCT in certain settings in the future, despite its quite formidable complexity. "I think traditional hypothesis testing methodology may well get very clumsy for things where we have a rationale for selecting quite small subsets of patients and giving them different things. We do need a mathematical logical approach that will take our subjectivity out of whether we think something is working or not. But the classical RCT with a 0.05 *P*-value and one hypothesis that you accept or reject on the basis of it may be too blunt an instrument for that."

That then leaves the question of how drug developers are going to convince regulators and payers of the risk–benefit and value of their products, without any gold standards for approval? Just like the development process, says Calvert, you have to do it on a drug-by-drug (or combination-by-combination) basis. "People need to take on board getting the right expertise onto the committee that makes the judgement [on approval or reimbursement], and really engage in a lot of detail about each drug, its mechanism, and the best way to evaluate it. I don't think there is a global solution, but if you know in enough detail how things are happening, you can come up with a good plan for each individual drug."

For the love of the job

Holland's first woman professor of medical oncology revels in a career unburdened by expectations and driving ambition

➜ Simon Crompton

Elisabeth de Vries is enjoying investigating whether we can push the potential of imaging techniques to the point where a patient's response to a drug can routinely be measured in an outpatient clinic. But she worries that the energy and creativity of her young students will be stifled by the pressures of preordained career paths.

Traditionally, women have thought differently about careers than men, says Elisabeth de Vries, the first female professor of medical oncology in the Netherlands. Women play life by ear, in the knowledge that children, family and unforeseen circumstances may get in the way of the best laid plans. Men, historically, have followed their ambitions.

So de Vries is apologetic that she can't tell me about grand plans fulfilled over her 40 year career in the Netherlands and on the international stage. But she needn't be. As a woman who edged herself to the fore of the emerging discipline of medical oncology in the '80s and '90s, and now stands at the very top of her profession, her career has real significance. De Vries, Head of Medical Oncology at the University Medical Centre in Groningen, is a Knight of the Order of the Netherlands, a visiting professor at the Dana Farber Cancer Institute in the United States, and won the ESMO award in 2009 for "an outstanding contribution to the development of oncology in Europe".

And if (as she admits) she has always had a tendency to overcommit herself, it is a mark not so much of personal ambition, as of a keenly felt responsibility on behalf of her sex.

"I've been endlessly on boards as the only female representative, and unfortunately, so many women have been needed that I simply couldn't do it all." She remembers how her work on national and international committees revealed to her just how easily (and subconsciously) gender could influence decisions; and the disbelief of male doctors when female doctors became pregnant shortly after being awarded fellowships – as if they should choose a better time.

She also points out that it wasn't so long ago that she used her initials on research papers – never her first name. In the past, she was all too aware of research in the 1990s indicating that papers

ANTOINETTE BORCHERT

submitted by an author who was obviously a woman were less likely to reach publication.

"I have the feeling that it doesn't happen any more," she says. Times are changing, and 70%–80% of medical students in the Netherlands are now female. Yet when it comes to the high-flying medical oncologists who make a name on the international stage, she suspects that men may have the highest profile for a while yet. She's found that women doctors are unwilling to blow their own trumpets even on curriculum vitae. "Men are good at this whole thing of status, whether it be the car, the house or the career. It works, and we're lacking that gene."

But de Vries is no club-wielding feminist. When I meet her, in the cavernous atrium of the University Medical Centre in Groningen – a new hospital so well organised that patients are buzzed along broad corridors in golf buggies and every patient ward has a view – she laughs about the fact that studies have shown that women doctors have smaller offices than male ones. Her own, rather spacious one, was offered soon after she had pointed this research out to colleagues. She has a good-humoured, often amazingly detached, realism about the medical world and her place in it.

Into a 'male' profession

The daughter of a paediatrician and a nurse, de Vries was exposed to hospitals from an early age and soon decided she wanted to help people and be a nurse. It was only when she went to secondary school that she realised she could be a doctor like her father. So she trained in medicine in her home town, Groningen, and having at first thought of herself as a paediatrician, she began to develop a special interest in internal medicine. She spent a few months in London, studying endocrinology at the North Middlesex Hospital, and remembers one person there who had a deep influence on her outlook.

"There was a female registrar from India, who was very beautiful, always wore beautiful silk gowns, and was very hard working. I found her a brilliant doctor. When she had to resuscitate a patient who had just come in by ambulance, she simply took up her long gown and sat on the trolley, and I realised then that, okay, maybe women shouldn't do internal medicine, but if she could do it, from India and wearing silks, then maybe I could too. She certainly influenced me."

Meet the extended family. Though she may have felt obliged to stay tied to Groningen more than she might have liked, de Vries happily combined raising two children with working her way up to professor of oncology, and even welcomed in an additional child along the way!

De Vries completed a PhD in acute leukaemia in 1982, and then spent a year as a research fellow learning more about medical oncology at the City of Hope Medical Centre, California – on the basis that, though it would be challenging, "if it didn't work out, it didn't matter because women didn't have to work anyway!"

But it did work out fine, and she returned to the Department of Medical Oncology at UMC Groningen as a senior staff member in 1983, where she has been based ever since. Her career has straddled patient care, education and influential translational research. She worked on several types of cancer, with a focus on breast cancer and neuroendocrine tumours, and is particularly interested in personalised treatments, using interdisciplinary research to improve diagnosis and treatment of a range of cancers. Her current research lines are aimed at increasing the sensitivity of tumours to anti-cancer drugs, and molecular imaging to support this.

It's molecular imaging that she wants to talk to me about, "because that's what's bothering me most". Only in the past year has she decided to concentrate on it for research because its potential is becoming clear.

The exciting potential of molecular imaging

Molecular imaging techniques allow biological processes at cellular and molecular levels to be visualised and measured in living patients. With knowledge about the heterogeneity of cancers and the need for targeted therapies increasing, imaging offers the prospect of monitoring how treatments affect the biological processes that influence cancer growth. A fluorescent or radioactive label, for example, can be added to a protein or antibody that is attracted by what is believed to be an important tumour characteristic – HER2 expression in breast cancer, for example.

What's exciting about the techniques, says de Vries, is that the scans may offer vital information on

"I realised then that, if she could do it, from India and wearing silks, then maybe I could too"

Fluorescent tracers can be detected during endoscopy or surgery, or even with handheld probes

how a patient is responding at a very early stage of treatment – within days even. This has clear implications for tailoring treatments to patients – and controlling drug budgets. She points to some spectacular longitudinal and cross-sectional scans of a patient who was injected with a radioactive tracer linked to an antibody against HER2. Yellow patches show the areas where the tracer was absorbed – patches in the liver and the bones where there are clearly metastases.

Then the patient was treated with a drug that reduces HER2 expression. A second set of scans, two weeks after treatment started, reveals that the yellow patches have contracted, and become riven with holes. The drug is affecting its target.

"It shows that the characteristics in the lesions are changing when you treat the patient. But if the treatment hadn't affected HER2 expression as the oncologist hoped, the findings might be used to inform a change of treatment."

There are implications for screening and drug development, as well as patient welfare. What's particularly interesting for de Vries at the moment is that her research, in collaboration with research centres in other countries, is indicating that, using the latest technology, fluorescence can be detected in tissue far better than originally believed. Tumour-targeted fluorescent tracers can be detected during endoscopy or surgery, or even using handheld probes that can pick up light several centimeters under tissue. This is a better option than using radioactivity, which has obvious risks for patients.

"Molecular imaging allows you to see the behaviour of the drug in the body as a whole. Is it reaching its target in the tumour? How long is it staying there? Are you dosing properly? This gives clues also to speed up drug development and decision making because you really know what's going on. You can fuse these images with CT or MRI, providing information about the characteristics of the lesion and its exact location, which is very useful for surgeons too."

As the years of research have progressed, de Vries has become persuaded that molecular imaging may be of the greatest use in developing novel therapies.

"I think it is within reach that we can label novel drugs not only with radionucleotides but also with fluorescent tracers, and then routinely check certain lesions over time in the outpatient clinic, without the need for smart people around you all the time. That would be really nice for drug development. I still have to prove it, but I have the feeling we'll make progress in the future."

Focused on the positives

De Vries likes to talk about the present rather than dig into the past or peer too far into the future. It's her current research that interests her. Equally, she's a great believer in a positive attitude, of living in the present – as an oncologist, she's all too aware of people who have put too much store on waiting until retirement to enjoy life, only to find it accompanied by illness. "Life is too short not to appreciate those important little moments that make you happy as an oncologist, like making the right decision, or a patient getting better than you expected, or your PhD students doing well."

She remains deeply influenced by Nanno Mulder, a haematologist and then oncologist, who supervised her PhD thesis in Groningen. Whatever the problem, he made it a discipline to think of ten solutions. "He is a brilliant thinker. The ideas weren't always feasible, but from ten you usually had something to choose. I think it is a huge advantage to meet people early in your career who see opportunities, not hurdles, everywhere. He certainly influenced my decision to go into oncology, and see it more as a challenge to be met, at a time when it was seen as second rate by others in internal medicine."

Some doctors in the early '80s, she recalls, thought that young internists who wanted to go into oncology were strange: why would you want to go into a specialty where there was so little to do for the patient? How things have changed, de Vries reflects. She is deeply proud of being in if not the first then the

"It is a huge advantage to meet people early in your career who see opportunities, not hurdles, everywhere"

second cohort of this new profession, and one of the very first women. She repeats again and again what a good decision she made to go into oncology.

"It's so exciting to be in a profession where every year you see change. That's now more true in oncology than other fields. It's always nice to see progress in patients, and we are now better at helping them live longer than ever before. But the other exciting thing is that biology is helping us find new mechanisms to treat cancer – though never as fast as you want to. It means you have to keep on studying and learning to acquire new insights and understanding of pathways and mechanisms. If that's what you like doing, it's wonderful that somewhere like here you can translate it into something that works in the clinic."

Despite her international outlook – de Vries has been a member of numerous EORTC and ESMO committees and is involved in the European Academy of Cancer Sciences – she has spent her entire career in Groningen, working her way up to assistant professor at the Department of Medical Oncology in 1983, then associate professor in 1989 and then full professor in 1997.

She admits to seriously considering working elsewhere many times. "Things might have been different," she says, with a touch of regret. "But everything has to fit." The needs of the family have obviously played a part in decisions to stay put. She is married to a gastroenterologist, and has two daughters now in their mid 20s – one a physical chemist specialising in nanotechnology, the other nearly qualified as a medical doctor. But childcare issues never got in the way of her career (de Vries has always worked full-time) and despite the guilt that she and other parents suffer as a result of not staying at home, she observes wryly that it has had no negative effect on her children whatsoever.

Staying in Groningen has allowed her to do what she wants to do, on the clinical, research and teaching fronts. She is a significant figure in the national cancer world, a vice chair of the Dutch Cancer Society, and a member of the Health Council of the Netherlands since 2008. It is important, she says, to present the medical perspective when high-level health policy decisions are being made. "I think that doctors have to speak up, for example, on smoking. I'm not sure that most of us like to do it, but some of us need to."

The exciting potential of young oncologists

In Groningen, a university town jam-packed with students on bicycles, it has been the medical and PhD students she teaches and supervises that have kept her feet grounded and her brain buzzing with new ideas. De Vries says that much of her research, including her work on imaging, has been fired by their creativity and knowledge of new technology. So as she looks ahead to the next couple of years, one of her main aims is to train more young people into independent doctors and scientists. But she worries about the increasing burdens being put on them.

"We have all these rules, requirements, forms to fill out, all the administrative burden associated with trials. Life for young doctors and scientists has become much more demanding from that perspective, and if they want to do research because it's inspiring and gives them the chance to see patients regularly, it's difficult to give them the same opportunities as ten years ago. I worry that we

"Doctors have to speak up, for example on smoking. I'm not sure most of us like to, but some of us need to"

"I worry that we are going to lose these people who are trying to translate findings from lab to clinic"

are going to lose these people who are trying to translate findings from lab to clinic." She believes it is her role to create a supportive setting which makes students independent but helps them over the time-consuming hurdles.

De Vries has enormous faith in the abilities of young people, if not tied down by the bonds of expectation imposed by parents and society. This faith, it turns out, is rooted in part in an unusual personal experience that also helps explain her reluctance to make plans for the future.

Around a decade ago, she explains, the family got what de Vries calls 'a borrowed daughter' – a third child who came from another home. Her youngest true daughter brought her home.

"She came from a background where people didn't go to high school, a disrupted family, and in the end my daughter thought it would be a good idea if she became part of our family, and she did." The girl was never formally adopted, but all the parties involved were happy with the arrangement. "She brought in a different background, and she made us realise that education and child-rearing seem important, but actually a lot of things children do is through their own inspiration, their own drive." The young woman has now finished a Masters degree in education and is about to become a teacher.

"So this is a gift," says de Vries. Sometimes, she points out, the best things in life are unexpected. She reflects that for young women now, starting a career in medicine or another profession, things are much harder than they were for her 30 years ago because nowadays a course is charted out and they are expected to do well. "I didn't have goals – I didn't have to reach any particular goal, so I didn't disappoint myself!" Thankfully, she didn't end up disappointing anybody.

Don't tie them down. De Vries tries to protect her students (pictured here alongside staff members) from all the expectations, rules and bureaucracy that could end up sapping their enthusiasm and creativity

Rituximab for follicular lymphoma: maintaining an open mind

Bruce Cheson

New data from the Primary Rituximab And Maintenance study provide the strongest support for the use of rituximab maintenance in patients with follicular lymphoma. However, further considerations of cost, inconvenience, toxic effects, efficacy of retreatment and lack of survival benefit should focus future clinical research on more-effective induction strategies.

Few drugs have made as great an impact on how patients with lymphoma are treated as the chimeric anti-CD20 monoclonal antibody rituximab. Chemoimmunotherapy regimens incorporating rituximab were the first strategies in decades to prolong the survival of patients with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL), follicular lymphoma and chronic lymphocytic leukaemia. Moreover, rituximab is often the platform on which newer therapies are developed. However, until all patients are cured, there remains room for improvement in our treatments.

Given the already high complete response and overall response rates with chemoimmunotherapy, one attractive strategy has been to increase the duration of response with post-induction treatment, such as maintenance rituximab. Unfortunately, maintenance rituximab has not demonstrated a benefit in patients with DLBCL or chronic lymphocytic leukaemia. Nevertheless, the use of maintenance rituximab for the treatment of follicular lymphoma is widespread. Results from the Lymphocare study suggest that 45% of patients in the USA are being treated with this strategy following chemoimmunotherapy induction.[1] Indeed, new data from the Primary Rituximab And

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Maintenance (PRIMA) study provide support for the use of maintenance rituximab,[2] and will be discussed below.

What other available data are there to support the maintenance rituximab approach? Martinelli et al.[3] randomly assigned 202 patients to four weekly rituximab infusions followed by observation or maintenance using one dose every two months for eight months. At a median follow-up of 9.5 years, 45% of previously untreated patients remained event-free in the prolonged therapy arm compared with 22% in the control arm, but with no significant survival advantage (P=0.0813).

Ardeshna and co-workers conducted a three-arm randomised trial in which patients with stages II–IV, asymptomatic, non-bulky follicular lymphoma were randomly assigned to either watch-and-wait, weekly rituximab for four doses alone, or four doses of weekly rituximab followed by two years of maintenance.[4] Time to next therapy and progression-free survival (PFS) favoured the maintenance group. The controversial conclusion was that this approach should become the standard approach. However, the follow-up was only 32 months, there was no survival advantage, and many patients might still prefer to wait until progression before initiation of therapy, when more-effective treatments might become available. Moreover, there were no data on responsiveness to second-line therapy (first systemic treatment for watch-and-wait and second systemic treatment for rituximab-treated patients). Hochster et al.[5] treated patients with cyclophosphamide, vincristine and prednisone (CVP) followed by rituximab maintenance with four weekly doses every six

months for two years. Maintenance prolonged PFS, but not overall survival. Other groups evaluated maintenance rituximab in the relapsed setting, with prolongation of response duration or PFS[6] but without a significant overall survival benefit.

However, until now, no study had addressed the most important question: does maintenance rituximab improve the outcome of patients initially treated with the standard of care – chemotherapy plus rituximab? An important publication by Salles et al.[2] of the PRIMA study addresses this issue. Indeed, the FDA approved rituximab for maintenance therapy of follicular lymphoma in January 2011, a decision based largely on results from this trial. Previously untreated patients with follicular lymphoma were treated with R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone), R-CVP (rituximab and CVP) or R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone) at the choice of the treating physician. Patients who achieved either a complete remission or partial remission were randomly allocated to either no further therapy or to rituximab maintenance every two months for two years (or until disease progression occurred). Of the 1217 patients who entered the induction phase, 503 underwent maintenance and 513 underwent observation alone. At a median follow-up of 36 months, the PFS was 74.9% in the maintenance arm compared with 57.6% in the observation arm (HR 0.55, 95%CI 0.44–0.68). The benefit was observed regardless of designated pretreatment characteristics including treatment regimen, age, sex, Follicular Lymphoma International Prognostic Index (FLIPI) or response to induction. In addition, event-free survival was improved in the group receiving rituximab maintenance. More patients were in complete remission at the end of maintenance than in the observation group. At the time of publication, there was no difference in overall survival because of the low number of events.

As maintenance rituximab consistently prolongs PFS, why not deliver it to all patients? Recognising that I am in the minority by avoiding maintenance rituximab, I will share my rationalisations. First, this therapy is expensive and time consuming. Moreover, the optimal maintenance schedule and duration are not known. In addition, there were more adverse events in the maintenance arm of the PRIMA study (56% vs 37%), notably grade 2–4 infections, with one death from fulminant hepatitis B.[2]

What is also not clear is whether maintenance provides an advantage over retreatment upon relapse. Many patients who had previously responded to rituximab respond again

to the same therapy, often with a longer response duration. Hainsworth et al.[7] randomly assigned relapsed and refractory patients to maintenance or retreatment upon relapse. Maintenance prolonged PFS, with no survival advantage.

The results of the RESORT trial (E4402; NCT00075846, which was completed in October 2008), in which patients received one weekly dose of rituximab for four weeks followed by either maintenance every three months until progression or observation with retreatment upon relapse, will be of interest to address this issue.

Second, there are toxic effects associated with maintenance rituximab including neutropenia, grade 3 and 4 infections,[8,9] and a small risk of potentially fatal, progressive multifocal leukoencephalopathy. Follicular lymphoma is a disease characterised by repeated relapses. Therefore, another concern is whether prolonged rituximab may compromise responsiveness to subsequent therapy.

In the CORAL study, Gisselbrecht and colleagues compared R-ICE (rituximab, iphosphamide, carboplatin, etoposide) versus R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), both with stem-cell transplantation in relapsed DLBCL.[10] One of the strongest predictors of inferior outcome was receiving rituximab in a previous regimen. Data from the PRIMA study on responsiveness to salvage therapies are not yet available.

One alternative might be to use another agent after induction therapy. Potential candidates include radioimmunotherapy, newer antibodies such as humanised anti-CD20s, galiximab (anti-CD80), and epratuzumab (anti-CD22), lenalidomide, small-molecule proapoptotic agents, and signaling pathway inhibitors, such as those directed against Bruton tyrosine kinase or PI3K.

Although the PRIMA study provides the strongest support yet for the use of maintenance rituximab in patients with follicular lymphoma, some of us will continue to wait until studies demonstrate an impact on survival and any further complications that may appear over time as a result of maintenance rituximab. Most importantly, the availability of newer, more-effective targeted therapies may provide a solution – if you have better induction, then maintenance becomes irrelevant.

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Practice point

Maintenance rituximab prolongs progression-free survival of patients with follicular lymphoma, but may not yet be standard therapy for all patients.

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ASTER – another flower in the diagnostic field of lung cancer?

Paul Baas

Mediastinal staging of patients with lung cancer is used to avoid futile thoracotomies. Endoscopic, oesophageal and bronchial ultrasound procedures are methods to identify involved lymph nodes. The ASTER study indicates that the sensitivity of these new techniques is high, reducing the number of futile thoracotomies and improving outcomes when combined with mediastinoscopy.

Lung cancer has a very high incidence and is the most lethal cancer type worldwide, accounting for 12.7% of the total cancers diagnosed.[1] Patients presenting with localised tumours that can be resected completely tend to achieve the best outcomes after treatment; therefore, staging of the mediastinum is of great importance. Cervical mediastinoscopy is the standard procedure to investigate the mediastinum. Under general anaesthesiology a small incision is made in the collar just above the manubrium. A videoscope is introduced and proceeds along the trachea. Lymph nodes in front or on both sides of the trachea can be visualised and sampled (paratracheal, ventral and subcarinal lymph nodes) for histological examination.

Annema et al.[2] compare the use of standard mediastinoscopy with a combination of endobronchial ultrasound (EBUS) and endoesophageal ultrasound (EUS) for mediastinal nodal staging of lung cancer; if no cancer was detected in the experimental arm, mediastinoscopy was performed. EUS and EBUS have a clear advantage over mediastinoscopy in that they provide improved coverage of the mediastinal lymph node stations (see figure).[3] Theoretically, the combination of EUS and EBUS should lead to better staging and reduction of the number of futile thoracotomies; the ASTER study examined this theory. A direct comparison of EUS and/or EBUS versus mediastinoscopy was not performed because the current guidelines indicate that mediastinoscopy is the standard of care.[4] Therefore, Annema et al.[2] included this analysis in the experimental arm to determine the additional value of the combination.

The results were as expected; the experimental arm produced better results than mediastinoscopy alone and outcomes were substantially improved when endosonography (EBUS and EUS) and mediastinoscopy were combined. With the exception of ipsilateral or contralateral disease detection, direct invasion of the tumour can be visualised more easily with endosonography than with CT or PET imaging or mediastinoscopy. Positive mediastinal lymph node samples were recorded in 41 of 118 patients in the

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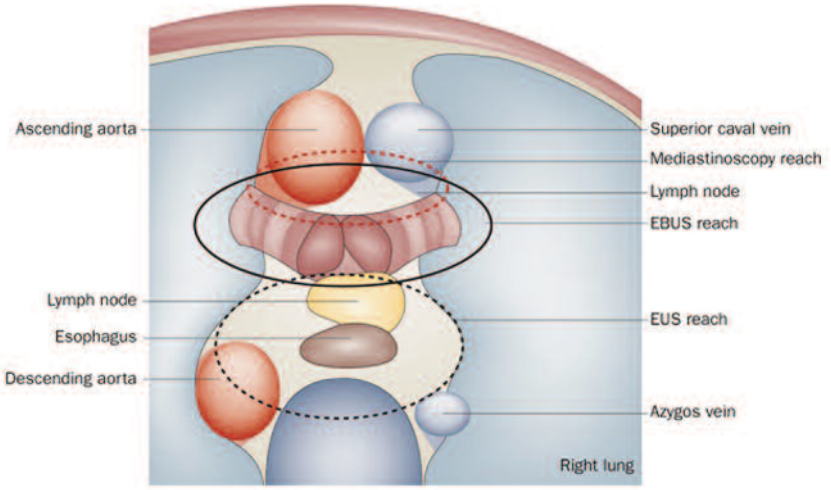
control arm and in 56 of 123 patients who underwent endosonography alone. The addition of mediastinoscopy to the experimental arm revealed an additional six lymph node metastases that had previously been missed by endosonography. The number of unnecessary thoracoscopies prevented was 21 (18%) in the experimental group compared with nine (7%) in the control arm.

The ASTER study is the first randomised trial that presents data on the sensitivity and negative predictive value of both arms. The study has many strong features; it is an investigator-initiated, multicentre, prospective study conducted in experienced centres and data are presented on an intent-to-treat basis. Features of this study have similarities to the implementation of the PET scan in the staging of lung cancer. The use of PET scanning has reduced the number of futile thoracotomies by 50%[5] and has become part of the accepted guidelines in the Western world.

Nonetheless, a number of criticisms can be made about the study by Annema et al.[2] Learning to use EBUS requires extensive training and keeping expertise at a high level requires a minimum number of cases per operator per year. Thus, identification of specific referral centres will be of importance. Coughing, patient distress and hypoxia can hamper the endobronchial procedure, leading to incomplete endobronchial or oesophageal examination. Proper patient selection for the use of midazolam or propofol anaesthesia can reduce these problems. One of the advantages of the endosonography procedure is that many institutes will use rapid on-site examination (ROSE), informing the bronchoscopist during the procedure whether or not more punctures are required. In the ASTER study, ROSE was used only in the experimental arm.[1] The limited amount of cytological material obtained by punctures is of concern when endosonography alone is performed in patients who present with positive mediastinal lymph nodes. Histology samples are preferred to test for molecular biomarkers such as *EGFR*-activating mutations, *EML4-ALK* translocations or *KRAS* mutations. This list of potential biomarkers is growing and requires a minimum amount of histological material. The cytological material obtained by punctures is, at the moment, insufficient and might increase the number of false-negative results.

The conclusion of this new approach is simple: endosonography using a combination of EBUS and EUS is here to stay and will allow a quick selection of patients suitable for major surgical interventions in lung cancer. Mortality is near zero, as is morbidity. Mediastinal bleedings are extremely infrequent and persistent hoarseness due to lesions of the recurrent laryngeal nerve has not been reported. Does this information mean that mediastinoscopy is now in its preterminal stage? Not yet. There will always be an indication for this procedure, such as the need for histological material, or in case of restaging after induction therapy when endosonography has failed to identify previously involved lymph nodes.[6,7] As applicable to surgical procedures, quality assurance, training and maintenance of expertise remain of great importance.



Transversal view of the chest at the level of the main carina. The red dotted line indicates the field approachable by mediastinoscopy; the black unbroken line for endobronchial ultrasound and the dotted black line for the endoesophageal ultrasound

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

Practice point

The combination of endoesophageal ultrasound and endobronchial ultrasound offer the physician a new and less-invasive method to stage and restage the mediastinum. Its reach is superior to that of the mediastinoscopy and future developments in molecular genetics will allow the required analysis of specimens for molecular markers.

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NEWSROUND

Selected reports edited by Janet Fricker

Cytarabine: low dose as effective as high dose in AML

➜ NEJM

Intermediate dose cytarabine was shown to be as effective as high-dose cytarabine in the treatment of acute myeloid leukaemia (AML) with less toxicity, an investigator-led study has concluded.

Cytarabine (ara-C) is one of the cornerstones of treatment for AML. Although high-dose cytarabine is now used routinely for induction and consolidation therapy it has not been compared in studies with intermediate-dose cytarabine, which could result in maximal anti-tumour effects with less toxicity.

In the current study Bob Löwenberg and colleagues, from the Erasmus University Medical Centre (Rotterdam, the Netherlands), compared outcomes for 821 patients with AML (aged 18–60 years) and 39 patients with refractory anaemia with excess blasts (RAEB), who were randomly assigned to high-dose cytarabine (n=429) or intermediate-dose cytarabine (n=431).

The high-dose group received a dose-escalated regimen of 1000 mg/m^2 of cytarabine every 12 hours in cycle 1 and 2000 mg/m^2 twice daily in cycle 2. The intermediate-dose group, received cytarabine at a dose of 200 mg/m^2 given by continuous intravenous infusion for 24 hours during cycle 1 of induction therapy and 1000 mg/m^2 by infusion for 3 hours twice daily during cycle 2 of induction therapy. For the third cycle patients with a complete response received consolidation therapy with chemotherapy (mitoxantrone–etoposide) or underwent autologous or allogeneic stem-cell transplantation.

Results show that, at a median follow-up of five years, complete remission rates were 80% for the intermediate-dose group versus 82% for the high-dose group (HR=1.14, 95%CI 0.81–1.60; P=0.45).

In the first three months there were 72 deaths in the high-dose group versus 52 in the intermediate-dose group (HR=1.41; P=0.057). However, at five years there were no significant differences between the intermediate-dose group and high-dose group in the rate of probability of relapse, event-free survival or overall survival. High-dose cytarabine provided no clear advantage for any prognostic subgroup.

After the first cycle, 61% of patients in the high-dose cytarabine group suffered grade 3 to 4 adverse events versus 51% in the intermediate-dose group (P=0.005). Specifically, skin reactions and gastrointestinal and ocular toxic effects were noted. Additionally in cycle 2, more patients in the high-dose group suffered prolonged hospitalisation and delayed neutrophil recovery, and in cycles 2 and 3 more patients in the high-dose group suffered delayed platelet recovery.

"The results suggest that the anti-

leukaemic effects of cytarabine may reach a maximum at doses well below the maximum tolerated dose," conclude the authors, adding "... the high-dose cytarabine regimen resulted in considerable toxic effects, was significantly more myelosuppressive, and required more platelet transfusions and prolonged hospitalization. Myelosuppression of high-dose cytarabine appears cumulative and is carried over to post remission chemotherapy."

■ B Löwenberg, T Pabst, E Vellenga et al. Cytarabine dose for acute myeloid leukemia. *NEJM* 17 March 2011, 364:1027–1036

Eribulin delivers overall survival benefit in metastatic breast cancer

→ The Lancet

Eribulin produced a significant improvement in overall survival in women with heavily pre-treated metastatic breast cancer when compared to treatments selected by doctors, the EMBRACE study has reported.

It is widely recognised that a great need exists for new treatments to improve overall survival in women with advanced or recurrent metastatic breast cancer, particularly those with heavily pre-treated disease. Eribulin mesilate is a non-taxane microtubule dynamics inhibitor that is a structurally modified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge Halichondria okadai.

In the phase III EMBRACE trial, led by Chris Twelves from the University of Leeds in the UK, 762 women with metastatic breast cancer who had received a median of four previous chemotherapy regimens from 135 centres in 19 countries were randomly allocated, in a 2:1 ratio, between November 2006 and November 2008, to treatment with eribulin (*n*=508) or to the treatment of physician's choice (*n*=254). The treatment of physician's choice (TPC) arm represented a mix of agents (both approved and non-approved for metastatic breast cancer) intended to mirror clinical practice at the time of the study. In the TPC arm 96% received chemotherapy, with vinorelbine, gemcitabine and capecitabine being the most frequently used agents. Patients and investigators were not masked to treatment allocation.

Results show that overall survival was 13.1 months in women assigned to eribulin versus 10.6 months in women assigned to TPC (HR=0.81, 95%CI 0.66–0.99; *P*=0.041). Furthermore, median progression-free survival was 3.7 months with eribulin versus 2.2 months with TPC (HR=0.87, 95%CI 0.71–1.05; *P*=0.137).

Asthaenia or fatigue occurred in 54% of patients on eribulin versus 40% on TPC, and neutropenia occurred in 52% of patients receiving eribulin versus 30% receiving TPC. Peripheral neuropathy was the most common adverse event, leading to discontinuation from eribulin in 5% of patients.

"This ... study establishes a potential new standard treatment for women with heavily pre-treated metastatic breast cancer, for whom there was previously no chemotherapy treatment with proven survival benefit," write the authors, adding that on the basis of the results, eribulin has received approval in the USA for patients who have received at least two chemotherapeutic regimens for the treatment of metastatic breast cancer, with previous treatments including an anthracycline and a taxane.

Eribulin, they add, has a manageable profile of toxic effects, short infusion times, and is easy to administer with no requirement for premedication to prevent hypersensitivity. Further evaluation of eribulin earlier in the natural history of breast cancer is now warranted.

■ J Cortes, J O'Shaughnessy, D Loesch, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Original text. *Lancet* 12 March 2011, 377:914–923

Small proportion of second cancers related to radiotherapy

→ Lancet Oncology

Around 8% of second cancers that develop in adult cancer survivors are related to radiotherapy, an analysis of the US Surveillance, Epidemiology and End Results (SEER) cancer registries has found. The majority of second cancers, said the authors, are attributable to lifestyle or genetics.

Radiotherapy reduces the risk of cancer recurrence, promotes tumour control, and improves survival. However, with improvements in survival, the long-term risks from radiotherapy, including the risk of developing a second cancer, have become more important.

In the current study Amy Berrington de Gonzalez and colleagues, from the National Cancer Institute (Bethesda, Maryland), undertook a comprehensive and systematic analysis of data recorded in the US SEER cancer registries on 15 solid cancer sites in adults who had been routinely treated with radiotherapy. Patients were aged 20 years or older and had been diagnosed with their first primary invasive solid cancer between January 1973 and December 2002. Due to the five-year lag between radiation exposure and solid-cancer induction, investigators excluded patients who survived less than five years from treatment.

Relative risks (RRs) for a second cancer in patients treated with radiotherapy versus patients not treated with radiotherapy were estimated using Poisson regression analysis adjusted for age, stage, and other potential confounders.

Altogether 647,672 adult cancer patients in the cohort survived for five years or longer and were followed up for a mean of 12 years. The proportion of patients who received radiotherapy as part of their initial cancer treatment varied from 23% for non-small-cell lung cancer to 79% for testicular seminomas.

Results showed that the attributable risk of a second cancer to radiotherapy was 5%

for cancers of the oral cavity/pharynx, 12% for the salivary glands, 7% for the rectum, 10% for the anus, 5% for the larynx, 6% for the lung, 15% for soft tissue, 5% for female breast, 17% for the cervix, 9% for the endometrium, 10% for the prostate, 24% for the testes, 4% for the eye/orbit, 9% for the brain and 7% for the thyroid. Overall the attributable risk was 8%.

In general, the investigators found that relative risk was highest for organs that received greater than 5 Gy, decreased with increasing age at diagnosis, and increased with time since diagnosis.

"These findings can be used by physicians and patients to put the risk of radiation-related cancer into perspective when compared with the probable benefits of the treatment," write the authors, adding that studies are now needed of secondary cancer risks related to newer radiotherapy treatments.

The strengths of the study include its systematic approach, large sample size and long-term follow-up, with the main limitation being lack of treatment randomisation, providing a potential for confounding factors.

■ A Berrington de Gonzalez, RE Curtis, SF Kry, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. *Lancet Oncol* April 2011, 12:353–360

Colonic stenting delivers no advantages over emergency surgery in malignant colonic obstructions

→ Lancet Oncology

Colonic stenting offers no decisive advantage over emergency surgery in patients with acute malignant colonic obstruction, concluded a Dutch study.

Around 7%–29% of patients with colorectal cancer present with bowel obstructions that require emergency surgery to restore luminal patency (unblock the passage). Emergency surgery is associated with mortality rates of 15%–34% and morbidity rates of 32%–64%. In the early 1990s colonic stenting was introduced to restore luminal patency in patients with malignant obstruction on the left side of the colon, with uncontrolled studies suggesting that stent placement before elective surgery decreases mortality, morbidity and the number of colostomies. Additional advantages that have been suggested for the temporary procedure are that it enabled accurate tumour staging and prevented the need for surgery in patients found to have disseminated disease.

Jeanin van Hooft and colleagues from the University of Amsterdam, in the Netherlands, set out to establish whether colonic stenting delivers better health outcomes than emergency surgery. Between March 2007 and August 2009, 98 patients with acute obstructive left-sided colorectal cancer from 25 hospitals in the Netherlands were randomly assigned in a 1:1 ratio to colonic stenting as a bridge to elective surgery (n=47) or emergency surgery (n=51).

At six months investigators found no difference between treatment groups in global health status (assessed with the QL2 subscale of the EORTC quality-of-life questionnaire). Mean global health status was 63.0 (SD 23.8) in the colonic stenting group versus 61.4 (SD 21.9) in the emergency surgery group (P=0.36). Furthermore, no difference was recorded for 30-day mortality (P=0.89), overall mortality (P=0.84), morbidity (P=0.43) and stoma rates at latest follow-up (P=0.35). The most common serious adverse events were abscess (three in the colonic stenting group versus four in the emergency surgery group), perforations (six versus none), and anastomotic leakage (five versus one).

"In this multicentre randomised trial, colonic stenting or emergency surgery did not have any distinct benefits for global health status, mortality, morbidity, other quality-of-life dimensions, and stoma rates," conclude the authors, adding that further studies are needed to establish whether specific groups of patients might have experienced greater benefit in either group.

While colonic stenting can be used as an alternative to emergency surgery, write the authors, caution should be exercised due to concerns over overt and silent perforations, which are more likely to occur with stents and might result in distant seeding of malignant cells.

In an accompanying commentary, Louis Wong Kee Song and Todd Baron from the Mayo Clinic (Rochester, Minnesota), wrote that until improvements in colonic stent design are addressed, endoscopic preoperative colonic stenting should be undertaken in selected centres and in selected patients deemed most likely to benefit.

■ J Evan Hooft, WA Bemelman, B Oldenburg et al. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. *Lancet Oncol* April 2011, 12:344–352

■ L Wong Kee Song, T Baron. Stenting for acute malignant colonic obstruction: a bridge to nowhere? *ibid*, pp 314–315

Denosumab represents treatment option for bone metastases in prostate cancer

→ The Lancet

Denosumab proved better than zoledronic acid, the standard of care, in preventing skeletal-related events in men with bone metastases from castration-resistant prostate cancer, an international phase III study has found.

Bone metastases are a major burden for men with advanced prostate cancer. Histological findings, together with analysis of bone turnover markers, suggest that excess osteoclastic activity is responsible for bone

destruction in metastatic disease. Denosumab is the first fully human monoclonal antibody developed to specifically target RANK ligand, a key mediator of osteoclast formation, function and survival. In studies denosumab has been shown to reduce bone resorption, tumour-induced bone destruction and skeletal-related events.

In the current study, led by Karim Fizazi from the Institut Gustave Roussy (Villejuif, France), investigators from 342 centres in 39 countries randomised 1904 men with castration-resistant prostate cancer and no previous exposure to intravenous bisphosphonate in a 1:1 ratio to receive 120 mg subcutaneous denosumab plus intravenous placebo (*n*=950), or 4 mg intravenous zoledronic acid plus subcutaneous placebo (*n*=951), every four weeks.

Results show that the median time to first on-study skeletal-related event was 20.7 months with denosumab versus 17.1 months with zoledronic acid (HR=0.82, 95%CI 0.71–0.95; *P*=0.0002 for non-inferiority; *P*=0.008 for superiority). Adverse events were recorded in 97% of patients on denosumab versus 97% on zoledronic acid, and serious adverse events were recorded in 63% of patients on denosumab versus 60% on zoledronic acid. The only differences were raised rates of hypocalcaemia (13%) and osteonecrosis (2%) in the denosumab group.

"We have shown that denosumab is better than the established therapy, zoledronic acid, for the delay or prevention of skeletal-related events in patients with advanced prostate cancer," write the authors, adding that two limitations of the study were that the double-dummy design did not allow them to objectively measure the benefits of subcutaneous versus intravenous administration, and that the protocol prevented them from assessing treatment benefits in patients with severe renal dysfunction at baseline.

In an accompanying commentary, Jeanny Aragon-Ching from George Washington University Medical School, describes the advantages of using denosumab over zoledronic acid.

"Denosumab is easier to give (subcutaneous) than is zoledronic acid, allowing for shorter visit times and applicability in various physicians' office settings by removing the need for an infusion clinic. Furthermore, denosumab reduces the need for management of acute phase reactions and renal monitoring or dose adjustments, although caution should be exercised with patients who have poor baseline kidney function."

Further quality-of-life and pain response data, she adds, would have been helpful, since fatigue, bone pain and asthenia were reported almost equally in both groups.

■ K Fizazi, M Carducci, M Smith et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*, 5 March 2011, 377:813–822

■ J Aragon-Ching. Unravelling the role of denosumab in prostate cancer. *ibid* pp 785–786

Success of sperm retrieval depends on chemotherapy used

➜ Journal of Clinical Oncology

Sperm retrieval using testicular sperm extraction (TESE) coupled with intracytoplasmic sperm injection (ICSI) resulted in sperm retrieval in 37% of patients who had undergone previous chemotherapy, reported a US study. The study – representing the largest series of postchemotherapy microdissection TESE–ICSI yet – found that the success of fertility techniques was related to the type of cancer that patients had originally been diagnosed with.

Advances in chemotherapy have led to greater longevity for young men, with the preservation of fertility and paternity becoming increasingly important as a quality of life issue. It has been estimated that up to two-thirds of men undergoing chemotherapy remain persistently azoospermic (no measurable level of sperm) after treatment. While men rendered persistently azoospermic have traditionally been considered sterile and referred for adoption or use of donor sperm, there is growing recognition that fertility can be salvaged with TESE–ICSI.

In the current study Peter Schlegel and colleagues, from the New York Presbyterian Hospital (US), retrospectively identified 73 patients with persistent postchemotherapy azoospermia from a series of testicular sperm extraction procedures performed between June 1995 and December 2009 by a single surgeon in 892 patients. The results show that spermatozoa were retrieved in 37% of patients (27 of 73), with an overall sperm retrieval rate of 42.9% (36 of 84). This resulted in a 57.1% fertilisation rate per injected oocyte and an overall live birth rate of 42%. Altogether there were 15 deliveries involving a total of 20 children.

When the sperm retrieval rate was stratified according to indications for chemotherapy, the highest retrieval rates were seen in patients with testicular cancer (85.7%), followed by neuroblastoma (50%), leukaemia (50%), non-Hodgkin's lymphoma (36.4%), Hodgkin's lymphoma (25.9%) and sarcoma (14.3%). "Sarcoma patients tended to have the lowest sperm retrieval rate due to high rates of exposure and higher doses of alkylating agents," write the authors.

With the mean time elapse since chemotherapy of 18.6 years, this led the authors to question whether sperm retrieval closer to the time of chemotherapy might have led to a higher success rate.

"Our data demonstrates that many men with long-term azoospermia after chemotherapy can still have their fertility salvaged with the use of assisted reproductive techniques," conclude the authors.

■ W Hsiao, PJ Stahl. EC Osterberg et al. Successful treatment of post chemotherapy azoospermia with microsurgical testicular sperm extraction: the Weill Cornell experience. *JCO* doi: 10.1200/JCO.2010.33.7808, published online 14 March 2011

Unshackling progress in the care of childhood cancers

Marc Beishon

Young cancer patients face a specific set of problems that can only be resolved through a concerted and coordinated effort by national and EU policy makers, researchers, regulators, funders and service providers. A meeting held in the run up to International Childhood Cancer Day reviewed how well we are doing, and what is urgently needed to do better.

For anyone unsure that there really is overbearing regulation on cancer research in Europe, a visit to any gathering of paediatric oncologists and others involved with child cancers would soon put them straight. In the words of one senior clinician: "We have a clinical trials directive that allows national re-interpretation, no platform for European approval, one set of rules that applies to all types of study, no adaptation to risk, overwhelming bureaucratic burden and it has been conquered by regulatory fundamentalists."

So said Stefan Bielack, medical director of paediatric oncology at Stuttgart's Olga children's hospital, speaking at a stakeholder meeting held at the European Parliament in Brussels ahead of International Childhood Cancer Day, and hosted by Slovenian MEP Alojz Peterle, himself an adult cancer survivor who has helped restart the MEPs Against Cancer (MAC) group.

The fundamentalists, Bielack explained later to *Cancer World*, are those who strictly follow the regulatory rules to be above criticism, but grow at the expense of the 'rationalists', who exercise judgement in the pursuit of better progress. The terms, he adds, are those of David Stewart at the MD Anderson in the US, and colleagues, commenting on what they see as diminishing returns from the narrow and dysfunctional 'efficacy versus safety' approach in clinical cancer research in general (for more on this see Equipoise lost: ethics, costs and regulation of cancer clinical research *JCO* 28:2925–2935).

But for paediatric oncologists like Bielack, working in an even more complex regulatory regime than in the US, the straitjacket of clinical trial regulations has reached absurd proportions for childhood cancers, which rely almost totally on investigator-driven research, given that there is a limited market to interest pharmaceutical companies. "There is too much garbage to too many recipients," he said, in reference to the seemingly unending cascade of paperwork to meet the varied requirements of a wide range of organisations that can play by different rules.

Developing cancer drugs and refining their use in children is essential, said Gilles Vassal, head of clinical and translational research at the Gustave Roussy Institute, pointing to the major role that chemotherapy has played in reaching the 80% cure rate over the last 50 years. "We need to introduce more safe and effective drugs into standard care," he said, "and there are such drugs in development – about 800 now for adults – but children are denied

SIOPE

Drug A or drug B? Europe's paediatric oncologists are leading efforts to address the many obstacles to developing evidence on the best way to treat young patients like this one; most are still being treated with therapies that have never been approved for their particular indication

access to them, which is an issue not just for oncology but for all paediatrics."

This is not for lack of trying on behalf of the paediatric oncology community, commented Ruth Ladenstein, president of SIOPE, the European Society for Paediatric Oncology. The majority of European children with cancer are treated in trials, she said, and multidisciplinary approaches to treatment have been important in driving the cure rate to its present high level. "We have more than 250 specialised centres around Europe and we've been networking since the late 1960s. About 50% of children are treated in phase I to III trials and 30% in standard treatment approaches with prospective studies, but less than 5% are in pharma-sponsored trials." Also important, she added, are the many high-level research teams dedicated to tumour biology. "This is a unique situation for an orphan disease," she said.

The message is clear – that there are centres and networks across Europe which could do much more if they had access to more new drugs and improved profiling of the many unlicensed ones already used in paediatric oncology. Vassal talked about the hopes pinned on the European paediatric regulation of 2007, which requires pharmaceutical companies to submit new adult oncology drugs for paediatric investigation plans (PIPs) to the European Medicine Agency (EMA). "But four years later, where are we? Yes the process is in place, but only 23 oncology drugs have a PIP and not all of these will be completed. We are not seeing an increase so far in the number of drugs in early-phase paediatric studies in the European Union – there are fewer than ten now, while in the US there are more than 30."

No strategy for drug development

At present, pharmaceutical companies see paediatric development as a regulatory compliance issue in Europe rather than a strategic research priority, he said, and there is no role for cooperative groups beyond contributions from individual experts. "Europe lacks a strategy for drug development for children," he added, comparing the situation with the US, where since 1997 the National Cancer Institute

has funded a programme for drug companies to make products available to cooperative groups for paediatric trials. As a result, major opportunities to address childhood cancer through the PIP programme are being missed.

Childhood cancer researchers will push for more strategic use of the European paediatric regulation (and PIPs), and of course for the reform of the clinical trials directive, which should happen in some form next year. By coincidence, on the same day of the meeting in Brussels the European Commission issued a 'concept paper' containing a 'preliminary appraisal' of the most suitable ways to address some of the key concerns in the directive, such as how risk is determined.

Jan-Willem van de Loo, scientific officer for cancer research in the health section at the European Commission, was not able to comment on the directive's reform, but he did provide an overview of the EU's commitment to supporting research and care through the various framework programme (FP) projects and networks.

Most notable, in the area of paediatric oncology, is ENCCA (European Network for Cancer in Children and Adolescents), a four-year FP7 programme coordinated by Ruth Ladenstein that aims to build sustainable research via a 'virtual institute' across Europe (for more on both Ladenstein and ENCCA see *Cancer World* March/April 2011).

Others include collaborative research projects such as PROTHETS, which looked at prognostic markers and therapeutic targets in Ewing's sarcoma, and PanCare, which is building a database on long-term childhood cancer survivors to look at trends such as late-effects.

Van de Loo highlighted the explicit focus in FP7 on investigator-driven clinical trials, and on trials to obtain marketing authorisation for paediatric use of off-label drugs – a big gap in the recent EU paediatric regulation according to Ladenstein. One example is the work of the European Paediatric Oncology Off-Patent Medicines Consortium (EPOC), which is examining the pharmacokinetics of doxorubicin – a drug that is widely used in paediatric oncology, despite the scarcity of data on correct doses for young children.

Another helpful development has been the establishment of a European Network of

A success story. Diagnosed quickly, referred to the right specialist centre, treated effectively – Olivia Ferrary described her experience of having a rare kidney cancer to show the meeting what all child cancer services should aspire to

HISPA PHOTOGRAPHY

The ear of the President. Jerzy Buzek, President of the European Parliament, was among those attending the SIOPE conference. He is pictured here (right), with fellow Poles Sidonia Jędrzejewska MEP (centre), and child cancer specialist Piotr Czauderna (left)

Major opportunities to address childhood cancer through the PIP programme are being missed

Paediatric Research run by the EMA, and tasked with promoting collaboration, as it is primarily a 'network of networks'.

Funding remains a barrier

But oncologists such as Vassal are sceptical that the current framework programme will deliver more 'calls' for cancer research funding, and Richard Sullivan, from the Centre for Global OncoPolicy in London, noted that a new report he has co-written on the state of child cancer research in Europe (see box) shows that funding remains short-term and 'fragile', and support in some member states is poor. "New mechanisms are needed for complex translational research infrastructure – we need to innovate all the time," he said.

The need to unshackle the research effort is, however, only half the story. Jerzy Kowalczyk, from the children's hospital in Lublin, Poland, talked of the need to improve the standards of care across Europe. A symposium in Lublin two years ago laid the basis for SIOPE to draw up a set of minimum European standards of care for children with cancer, and a project to identify best healthcare practices in paediatric oncology has now started under the auspices of the European Partnership for Action Against Cancer. Next steps include preparing national versions of the standards, convincing national agencies and the EU to issue regulations, and building a registry of child cancer centres.

Kowalczyk expressed disappointment that "politicians showed little interest" in the 2009 meeting, but there is an opportunity to put that right at the European Standards of Care for Children with Cancer conference on 20–21 October in Warsaw this year, led by the Polish Ministry of Health under Poland's EU presidency. Jolanta Kwaśniewska, President of the Communication without Barriers foundation, and a former 'first lady' of Poland, is a leading supporter of the meetings and of child cancer clinics in her country.

Present at the Brussels meeting were representatives of the thousands of child and teenage cancer survivors and their parents for whom good-quality services and unhindered progress in developing new therapies are so important. Olivia Ferrary talked of her experience of being successfully treated for a rare form of renal cell carcinoma at Great Ormond Street hospital in London. A video was also shown of teenagers, which came from Jimmyteens.tv, a project started at St James's hospital in Leeds, UK, where young people with cancer are given cameras to record their experiences. There are 600 such videos now from the UK and Ireland, and the producer, Claire Pope, is looking to include more from other countries.

The term 'therapeutic orphan' was first coined back in 1968 to describe the lack of drug development for children, but there does finally seem to be concerted action to improve matters substantially.

The state of paediatric research

'The state of research into children with cancer across Europe: new policies for a new decade' is a research report with input from more than 30 leading European paediatric oncologists, led by past SIOPE president Kathy Pritchard-Jones, and funded by the EU Eurocancercoms project. It looks at the funding and extent of paediatric oncology in European countries and also compares the effort with the rest of the world.

Findings include:

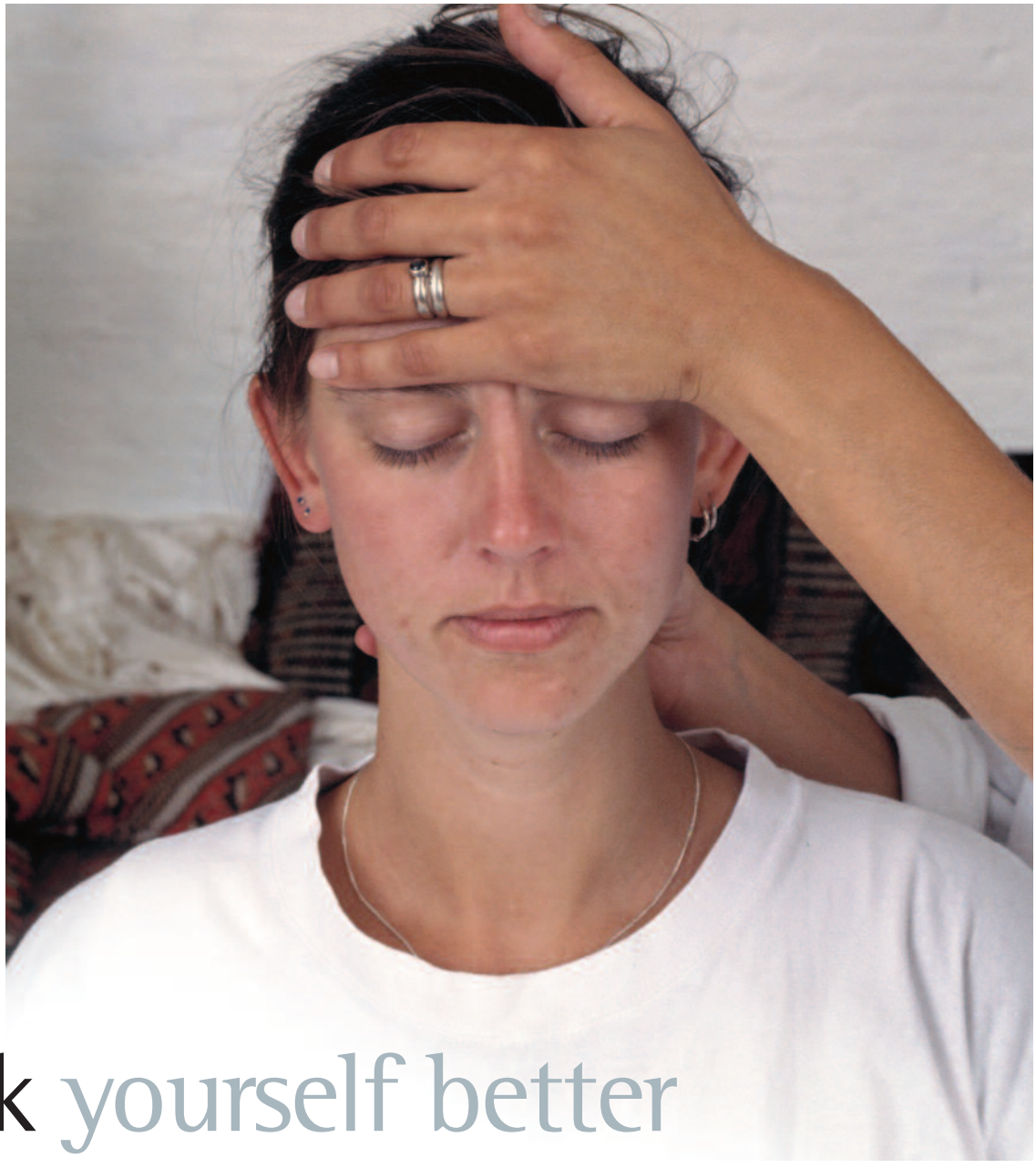
- In Europe, Sweden and the Netherlands have done the most basic paediatric oncology research but the differences between countries are not large
- Papers from the Netherlands are the most cited, followed by those from the US, the UK and Sweden
- There is relatively little collaboration between North America and Europe. However, EU member states are collaborating increasingly with each other, especially Germany and the Netherlands, and also Switzerland with France, Germany and Italy
- In most European countries except Spain, private non-profit funding sources outnumber government support, but almost half the papers bore no acknowledgement – "a marker of fragile, short-term funding"

The report includes snapshots of countries from experts, finding for example that no international trial has opened in Poland since 2007; in Italy efforts are being made to cut down the large number of centres (54) seeing child cancer, some of which have fewer than 10 patients a year; and those countries that do have strong government funding include France and Germany, whereas the UK and Sweden rely more on charitable organisations.

A survey of opinion leaders done for the report revealed the following to be priorities:

- Adequate EU funding to support a Europe-wide clinical trials network to assist with testing and dissemination of novel therapies and techniques
- A reduction of EU trial bureaucracy/regulations to remove barriers to investigator-led clinical trials, which could include a European trials bureau
- Better understanding by regulatory policy makers of the level of risk for children participating in trials (currently overestimated by insurers as well)
- The creation of a European parent/survivor organisation and a common European information portal
- The creation of a European childhood cancer epidemiological registry
- EU support for harmonising of treatments through pan-European guidelines.

The report is at www.eurocancercoms.eu



ISSAC ROSE/ALAMY

Think yourself better

Alternative medical treatments rarely work. But the placebo effect they induce sometimes does. This article, published in *The Economist* two months ago, may have a particular relevance for oncology, where understanding the science is so important that it can be easy to overlook the contribution of the human touch.

Dr Ernst believes that doctors can usefully learn from the chiropractors, homeopaths and Ascended Masters

On May 29th Edzard Ernst, the world's first professor of complementary medicine, will step down after 18 years in his post at the Peninsula Medical School, in south-west England. Despite his job title (and the initial hopes of some purveyors of non-mainstream treatments), Dr Ernst is no breathless promoter of snake oil. Instead, he and his research group have pioneered the rigorous study of everything from acupuncture and crystal healing to Reiki channelling and herbal remedies.

Alternative medicine is big business. Since it is largely unregulated, reliable statistics are hard to come by. The market in Britain alone, however, is believed to be worth around £210m ($340m), with one in five adults thought to be consumers, and some treatments (particularly homeopathy) available from the National Health Service. Around the world, according to an estimate made in 2008, the industry's value is about $60 billion.

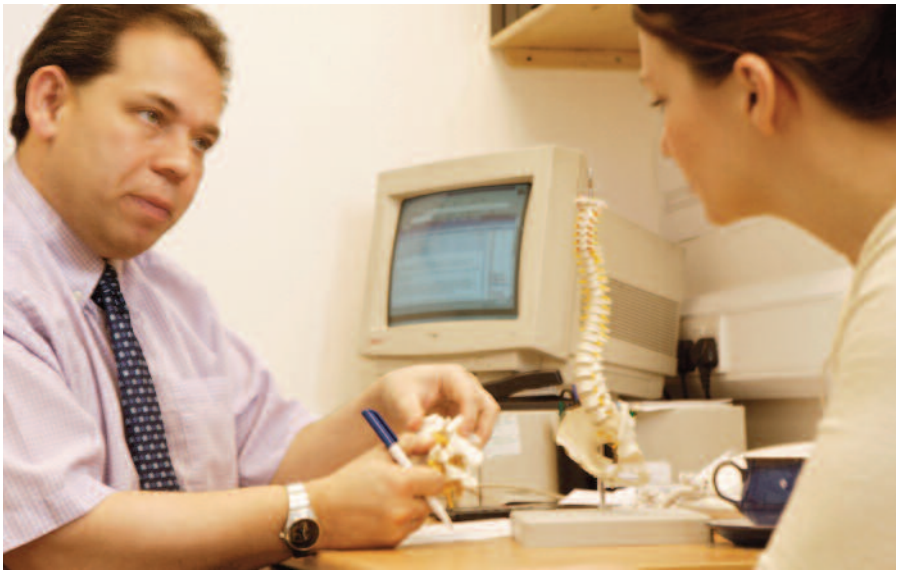
Over the years Dr Ernst and his group have run clinical trials and published over 160 meta-analyses of other studies. (Meta-analysis is a statistical technique for extracting information from lots of small trials that are not, by themselves, statistically reliable.) His findings are stark. According to his *"Guide to Complementary and Alternative Medicine"*, around 95% of the treatments he and his colleagues examined – in fields as diverse as acupuncture, herbal medicine, homeopathy and reflexology – are statistically indistinguishable from placebo treatments. In only 5% of cases was there either a clear benefit above and beyond a placebo (there is, for instance, evidence suggesting that St John's Wort, a herbal remedy, can help with mild depression), or even just a hint that something interesting was happening to suggest that further research might be warranted.

It was, at times, a lonely experience. Money was hard to come by. Practitioners of alternative medicine became increasingly reluctant to co-operate as the negative results piled up (a row in 2005 with an alternative-medicine lobby group founded by Prince Charles did not help), while traditional medical-research bodies saw investigations into things like Ayurvedic healing as a waste of time.

Yet Dr Ernst believes his work helps address a serious public-health problem. He points out that conventional medicines must be shown to be both safe and efficacious before they can be licensed for sale. That is rarely true of alternative treatments, which rely on a mixture of appeals to tradition and to the 'natural' wholesomeness of their products to reassure consumers. That explains why, for instance, some homeopaths can market treatments for malaria, despite a lack of evidence to suggest that such treatments work, or why some chiropractors can claim to cure infertility.

Despite this lack of evidence, and despite the possibility that some alternative practitioners may be harming their patients (either directly, or by convincing them to forgo more conventional treatments for their ailments), Dr Ernst also

I will help you feel better. Whether or not their treatments have any merit, the time and attention alternative therapists can spend in consultations, and their sense of assurance and belief in the therapies they are proposing, can make a real difference to the wellbeing of their patients



Neuro-imaging shows that this deception stimulates the production of naturally occurring painkilling chemicals

believes there is something that conventional doctors can usefully learn from the chiropractors, homeopaths and Ascended Masters. This is the therapeutic value of the placebo effect, one of the strangest and slipperiest phenomena in medicine.

Mind and body

A placebo is a sham medical treatment – a pharmacologically inert sugar pill, perhaps, or a piece of pretend surgery. Its main scientific use at the moment is in clinical trials as a baseline for comparison with another treatment. But just because the medicine is not real does not mean it doesn't work. That is precisely the point of using it in trials: researchers have known for years that comparing treatment against no treatment at all will give a misleading result.

Giving pretend painkillers, for instance, can reduce the amount of pain a patient experiences. A study carried out in 2002 suggested that fake surgery for arthritis in the knee provides similar benefits to the real thing. And the effects can be harmful as well as helpful. Patients taking fake opiates after having been prescribed the real thing may experience the shallow breathing that is a side-effect of the real drugs.

Besides being benchmarks, placebos are a topic of research in their own right. On May 16th the Royal Society, the world's oldest scientific academy, published a volume of its *Philosophical Transactions* devoted to the field.

One conclusion emerging from the research, says Irving Kirsch, a professor at Harvard Medical School who wrote the preface to the volume, is that the effect is strongest for those disorders that are predominantly mental and subjective, a conclusion backed by a meta-analysis of placebo studies that was carried out in 2010 by researchers at the Cochrane Collaboration, an organisation that reviews evidence for medical treatments. In the case of depression, says Dr Kirsch, giving patients placebo pills can produce very nearly the same effect as dosing them with the latest antidepressant medicines.

Pain is another nerve-related symptom susceptible to treatment by placebo. Here, patients' expectations influence the potency of the effect. Telling someone that you are giving him morphine provides more pain relief than saying you are dosing him with aspirin – even when both pills actually contain nothing more than sugar. Neuro-imaging shows that this deception stimulates the production of naturally occurring painkilling chemicals in the brain. A paper in *Philosophical Transactions* by Karin Meissner of Ludwig-Maximilians University in Munich concludes that placebo treatments are also able to affect the autonomic nervous system, which controls unconscious functions such as heartbeat, blood pressure, digestion and the like. Drama is important, too. Placebo injections are more effective than placebo pills, and neither is as potent as sham surgery. And the more positive a doctor is when telling a patient about the placebo he is prescribing, the more likely it is to do that patient good.

Despite the power of placebos, many conventional doctors are leery of prescribing them. They worry that to do so is to deceive their patients. Yet perhaps the most fascinating results in placebo research – most recently examined by Ted Kaptchuk and his colleagues at Harvard Medical School, in the context of irritable-bowel syndrome – is that the effect may persist even if patients are told that they are getting placebo treatments.

Unlike their conventional counterparts, practitioners of alternative medicine often excel at harnessing the placebo effect, says Dr Ernst. They offer long, relaxed consultations with their customers (exactly the sort of "good bedside manner" that harried modern doctors struggle to provide). And they believe passionately in their treatments, which are often delivered with great and reassuring ceremony. That alone can be enough to do good, even though the magnets, crystals and ultra-dilute solutions applied to the patients are, by themselves, completely useless.

This article was first published in *The Economist* on 19 May 2011. It is reprinted here with permission.

They offer the sort of long, relaxed consultations that harried modern doctors struggle to provide