European School of Oncology
Learning to care

# Cancerworld

Number 39, November-December 2010

## Education & knowledge through people & facts

Sara Faithfull

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HarrisDPI
www.harrisdpi.co.uk

**Printed by**
Grafiche Porpora

**Cover photograph**
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**Published by**
European School of Oncology

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Registrazione Tribunale di Roma
Decreto n. 436 del 8.11.2004

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

# Fake drugs pose a threat to Europe's cancer patients

Kathy Redmond ■ EDITOR

There is a widespread misconception that the problem of counterfeit drugs is confined to poor countries and/or lifestyle drugs such as Viagra. Yet an estimated one in five Europeans have purchased prescription drugs through illicit channels according to a recent survey by Pfizer. A quick search of the Internet reveals an abundance of cancer drugs, from Arimidex to Zometa, on sale from illegal sites. Given the WHO estimate that, in more than 50% of cases, medicines purchased from these sites will be counterfeit, and that they are being sold direct to the public without a prescription or medical guidance, there is clearly cause for concern.

Counterfeit or 'fake' drugs are unsafe because they are usually low-quality products that contain no active ingredient, the wrong dose of the active ingredient or, worse still, toxic solvents such as boric acid or rat poison. How many deaths are caused by fake medicines is not known, but the dangers are clear.

The import of fake medicines in the EU is fuelled by the potential for high profits. Over a two-month period in 2009, European customs officers seized 34 million counterfeit pills, and fake drugs have entered the legal supply chain in a number of EU countries. Fake Casodex, for instance, has been found on sale via legitimate outlets in the UK. It has been estimated that global sales of counterfeit medicines could top US$ 75 billion this year – a 90% rise over five years.

European policy makers, regulators, health authorities and pharmaceutical companies have started to wage a war against counterfeit medicines. At an EU level, a series of laws to strengthen regulation in this area is currently under discussion, which will seek to ensure that legally produced drugs have a range of recognisable safety features including anti-counterfeiting packaging (barcodes and seals). Oversight of pharmaceutical distributors and legal Internet pharmacies will be tightened. The European Parliament is also pushing for heightened awareness of the dangers of counterfeit drugs as well as stiffer penalties against drug counterfeiters. Pharmaceutical companies are looking to new technologies that can detect tampering and make it easier to verify whether drugs are legitimate.

Pressure from the US government has led the biggest sellers of domain names to screen customers for online drug sales and delete illicit online pharmacies. This process is proving difficult because rogue online pharmacies may be based in countries outside of the law enforcing jurisdiction.

There is a need to increase awareness of this problem at the level of governments as well as the public, and to enhance transnational cooperation to curb the criminal networks involved in drug counterfeiting. The cancer community should be concerned about the increasing availability of counterfeit drugs and should support current efforts to tackle this criminal activity.

# Sara Faithfull:

## unleashing the potential of cancer nursing

Marc Beishon

Specialist cancer nurses have shown what a difference they can make in supporting patients – helping them manage symptoms and maintain an acceptable quality of life. Yet many cancer nurses are still undervalued and underused, with few opportunities for specialist training and little guidance on best practice. **Sara Faithfull**, cancer nurse, researcher, teacher and past-president of Europe's cancer nursing association, EONS, is working to change all that.

Last year, cancer nurse Sara Faithfull pulled off a major coup – she ran an entire clinical session at Prevent, a conference dedicated to the adverse effects of radiation, which was organised by ESTRO, the society for Europe's therapeutic radiologists and oncologists. "I brought in physiotherapists, nutritionists, dentists, nurse researchers and clinicians – it was a multidisciplinary conference stream and was very successful in terms of contacts afterwards – most times you never hear any more," she says.

It was significant, Faithfull adds, because not only was this the first time that ESTRO had had a nurse running such a programme, but also because the battle to get nursing and other allied health professionals established at such conferences and at this level is a long way from being won.

"Afterwards the chair said to me, 'There were a lot of nurses as speakers,' and I said, 'Yes, that's because I am a nurse.' I don't think he knew I was one. Unfortunately we have not been invited to the next Prevent conference, ostensibly because it's about 'bioscience.'"

A lot of medics around Europe simply do not see nurses as clinicians and researchers in their own right, says Faithfull, and she adds that, "from that Prevent session we have developed a package for nurses on managing side-effects and built a network for those working in radiotherapy. When we get these opportunities we can get things done."

Researching and implementing interventions, especially for the increasing numbers of people living with cancer and its after-effects, is a key goal for Faithfull, and one she believes cancer nurses are ideally placed for. As a professor of cancer nursing practice at the University of Surrey in England, and immediate past-president of the European Oncology Nursing Society (EONS), she has extensive experience not only of clinical work from her own previous and current posts, but also of critical training and workforce issues around the UK and Europe.

There are, she says, major obstacles in the way of developing the scale of research needed, and in rolling it out to a large and very diverse workforce around Europe. Not least is the lack of recognition of

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the role of oncology nurses, as typified by the ESTRO experience. "It goes much deeper though – a good example was the document on the future of cancer care, 'Responding to the challenge of cancer in Europe', which was presented at the 2008 EU cancer conference in Slovenia. It had chapters on presentation, screening, drugs, psychology and so on, and while recognising the importance of oncology nurses it did not have a chapter specifically on the provision of nursing or health services."

In part, Faithfull adds, this is because oncology nurses need to play their part to get their agenda heard. In the recent European Partnership for Action Against Cancer initiative, for example, the present EONS president, Sultan Kav, stressed the importance of nurses taking part "to demonstrate the critical importance of the role of the nursing workforce in delivering good cancer-related healthcare." It is reassuring, Faithfull adds, that in meetings so far EONS has been able to ensure supportive and palliative care are part of the Partnership discussions. "It is a good opportunity to knock heads together." She is also urging engagement with national nursing societies, patient groups and political bodies "to ensure the nurse's voice is heard during key debates".

With 22,000 nurse members through national societies, EONS participates as a founding member with other cancer societies at the key ECCO event, along with patient groups. But there is still a tendency for organisers to view their presence as representative and not as a primary contributor to cutting-edge issues in cancer treatment and care. "At ECCO we should be presenting our flagship nursing science and not just rounding up a geographical input from all the countries, as research simply is not very advanced in some places."

But while research findings about the role of nurses can be compelling, Faithfull acknowledges that much more needs to be done to raise the bar of nursing research to provide evidence to convince policy makers. "Take for example the delivery of chemotherapy. You want good symptom


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**Back to better health. This high-performance testing facility in Surrey is where Faithfull and her team research how to improve rehabilitation and reduce late effects following treatment for prostate cancer, using individualised plans based on detailed cellular and cardiac function data gathered as the patients exercise in a controlled and quantifiable manner**

management, provided by those trained to take care of people – nurses. Otherwise all that development effort on drugs can be wasted if patients can't continue with treatments because of lack of support. What is more, nurses trained in symptom management and drug interactions can take responsibility for prescribing and delivering care, instead of say waiting for a doctor to give drugs such as anti-emetics. And evidence shows that nurses make fewer errors with drugs as they are more likely to follow protocols."

Another major issue is the rapidly growing population of cancer survivors. "We now have in the UK 60% of people cured or in remission for common cancers; 13% of older people have had cancer during their lives; and many will also be having ongoing treatment such as hormone therapy. Even with metastatic disease people can live for many years."

There is a pressing need, she says, for more long-term involvement of community nurses who are equipped to work, for instance, with men suffering the after-effects of prostate cancer surgery, radiotherapy and hormone therapy, such as osteoporosis, metabolic symptoms, sexual dysfunction and incontinence.

It would also be helpful to have more posts like the one Faithfull now holds, with a remit to continue as a practising clinician alongside a teaching and research role. "As a nurse, once you move into education you tend to get separated from the clinical side, while in practice in hospitals or in the community it is very rare for nurses also to work as professional researchers. Contrast that with doctors, who are mostly able to pursue a clinical academic career."

Faithfull's route into nursing was a traditional one back in the 1980s – "I wasn't very academic then. But my mother was a nurse and I used to go to her hospital to help out during the school holidays and really enjoyed it. I thought then it was a real vocation that could give you mobility."

"All that effort on drugs can be wasted if patients can't continue treatments because of lack of support"

"Specialist nurses increasingly manage therapies, which is necessary now we have a shortage of doctors"

She became a general nurse at a large hospital in London, and recognises the huge differences in nursing practice then when compared with today. "In the 1980s patients would stay in hospital for much longer and we only had 83% bed occupancy, and not much more than a drip to deal with. Today, we have the same patient–nurse ratios but now everyone is an acute case, the beds are full, and on an oncology ward many will be having highly complex treatments."

There have been accusations in the UK that, with increasing numbers of nurses becoming specialists and entering the profession with degrees, much of the old caring side of nursing has been lost. Faithfull agrees, but points out that pressure on most healthcare systems around the developed world has led to a more 'conveyor belt' approach, often with little continuity with the professionals that patients see through the course of treatment. "This doesn't mean that nurses don't care, but they have a wider range of responsibilities than in the past."

Nursing, she notes, has already become a two-tier – and in oncology, a multi-tier – profession, where many of the 'washing and caring' tasks are now carried out by auxiliary and foundation nurses, at least in the UK, while nurses at advanced levels increasingly manage therapies, "which is very necessary now that we have a shortage of doctors."

But if policy makers in healthcare systems just see nurses as 'part of the furniture', and do not value their caring skills, the quality of care nurses provide will often be poor, says Faithfull, adding, "It's also true though that nurses are good at sitting back and letting other people decide what's good for them." The answers, she believes, lie in more empowerment of, and better management skills for, senior nurses, and better multidisciplinary working. That needs to include practical matters such as improving the measurement of nursing outcomes, defining the support for patients, designing new types of follow up and improving communication, while everyday issues such as finding a parking space are often cited by patients as concerns, but are consistently overlooked.

Faithfull moved on from her general nursing position to work in neurology and a coma unit, helping people with strokes and those who had had accidents, before moving to the Royal Marsden in London, one of Europe's top cancer centres. "I joined to work in a brain tumour unit and went on to stay at the Marsden for 20 years. In oncology you see the best in people – they can be very brave in trying to overcome challenges, and you get to work with them much longer than you would with most acute care, so you have time to build relationships."

At the Marsden, Faithfull worked with Mike Brada – a former ESTRO president – on supportive care for brain tumour patients and their families. She took four months out to go to Papua New Guinea with Raleigh International – a UK charity that organises expeditions – before returning to the Marsden and deciding to do an undergraduate nursing degree at Surrey University.

"The growth in degree level and specialist nurses is of course one of the most important trends in recent years, plus the breaking down of professional boundaries between nursing and medicine. Some 13 countries in Europe now have specialist cancer nurses, and the UK NHS [National Health Service] has been a leader. But there's a big problem in the UK as our professional nursing body has not regulated it – there is no standard curriculum to study cancer nursing here."

This means that on oncology wards in the UK, and in some other countries, there can be a spectrum of specialist nurses with various titles, but no consistency on qualifications and experience, as without regulation a specialism is simply awarded on the job. "In fact across cancer nursing in the UK there are some 17 different specialist titles now in use – anyone can call themselves a specialist, but you could have two people with the same title working together but with vastly different experience."

At least in the UK there are colleges that offer courses for oncology nursing, such as Surrey. "But we have a shortage of training – there are few specialist breast, urology or haematology cancer courses, for

"Providing more skills and education is fundamental to valuing people and keeping them"

example. Mostly, you have to learn special skill sets on the job. It's the same in some other countries such as France and Spain."

Other countries though have made greater progress with developing and promoting speciality cancer nurses. Faithfull cites the US and Ireland as two countries that have taken steps to regulate speciality nursing (in Ireland, a master's qualification is needed to be an advanced nurse practitioner and this is a regulated title).

But a country that stands out as lagging behind in developing nurses is Germany. "We have nurses from Germany and other countries come to the UK to do courses, but they can be frustrated by the lack of opportunity to put their skills into practice back home. We had a German student work on a European EONS project with us here and she was amazed – she didn't realise that nurses could work at higher levels and it was very inspiring for her."

Providing more skills and education is fundamental to valuing people and keeping them, says Faithfull, and this must include nurses working outside the main cancer centres, where the opportunities for on-the-job experience is limited. "We also have to realise that many of those who are teaching nurses are coming up for retirement, certainly in the UK."

Faithfull left the Marsden in 2002 to become a director of studies for the University of Surrey's advanced practice master's programme – the faculty of health and medical science has some 1500 pre-registration nurses on its undergraduate and diploma courses, plus 3000 others pursuing postgraduate and continuing professional qualifications. In recognition of her effectiveness in translating research into education, Faithfull was awarded her professorship in 2008, and she and a small group of colleagues now focus on modules in advanced practice in cancer care, such as pain and symptom management, cancer science, advanced assessment, advanced communications skills and palliative care interventions.

During her time as EONS president, and continuing now, Faithfull is helping to develop Europe-wide training and curriculum materials that can be applied at various levels by universities and professional bodies. "For example, we want to see an arrangement along the lines of the Erasmus student exchange programme for an advanced practice oncology qualification based on our materials. Most of the modules are already there and a lot of universities are using this curriculum for their courses, but we have not achieved standardisation yet. We also want to develop materials for those at foundation level, such as community nurses, and have it all online and translated into different languages. It's important that EONS can cover different levels so those starting out don't feel it is out of their reach."

Speciality EONS curricula include breast, elderly and lung cancer care, and a recent introduction is a pilot of an online radiotherapy training course. The training work is building on successful experience with other courses that are now staple parts of the education programme such as TITAN, which aims to improve nurses' skills and knowledge when working with patients with thrombocytopenia, anaemia and neutropenia. TITAN has been running since 2004, and has been translated into various languages with grants from EONS.

Translation is still important too at conferences, adds Faithfull, because unlike physicians, nurses around Europe do not routinely have good English – though English skills are improving with the rise of graduate-level nurses.

A general modernisation of the EONS presence

"Imagine not washing during a six-week treatment, but I helped to show this was a complete myth"

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With EONS board members pictured at their Spring Convention in the Hague last April. From the left (*back row*): Birgitte Grube (President elect, Denmark), Sultan Kav (President, Turkey), Kay Leonard (Ireland), Mary Wells (UK), Anita Margulies (Switzerland) (*front row*): Dimitrios Papageorgiou (Greece), Sara Faithfull (past-President, UK)

– a new journal, better website and office, technology for e-learning and so on – has also been part of Faithfull's contribution.

What triggered all this for Faithfull was acquiring 'a bug' for research that is now feeding the appetite for education. "After I worked on brain tumours I moved into the bigger field of urology, and again was fortunate to work with prostate experts such as David Dearnley and Alan Horwich at the Marsden, focusing on radiotherapy and side-effect management, which is what I did my PhD in. I got a scholarship from Cancer Research UK ."

The evidence base for nursing is still limited, she says. "It's partly because it's not funded and partly because people just assume it's there. For example, while there are now more than 35 experimental studies in managing skin care after radiotherapy, few are large-scale randomised trials. It's much more than when I started, but it's still not a lot when you consider this is a very common problem for cancer patients receiving radiotherapy." The problem, she adds, is that nurses are not good at articulating what a difference they can make – providing the best support, to which people, at what time, and how. "We need to do much more to measure and communicate the value of our therapeutic interventions."

A question she asks students on her advanced nursing course is: Give me the evidence that a specialist nurse will have more impact than a new scanner for detecting brain tumours. "It's relatively easy for doctors to measure their worth by the number of cancers detected and treated, but how do we measure quality of survival? It's not easy, but it is possible to describe and research therapeutic nursing and to be more definite about what we provide."

Faithfull's PhD work on radiotherapy and supportive care, she says, was ahead of its time and she initially had great trouble getting grants to follow up the work as she moved into her academic career. "We had so many rejections I was on the point of giving up, but patients said it was very important and the clinicians just didn't have the answers themselves."

There is a lack of knowledge about care during treatment as well as about long-term conditions. "For example, it used to be said that people couldn't wash when they were having radiotherapy as it could cause more skin toxicity. Imagine not washing during a six-week treatment course. I hope I helped to show this was a complete myth. But getting such evidence out into practice is really difficult, not only

"We need to do more to measure and communicate the value of our therapeutic interventions"

through education but in developing guidelines and influencing practice."

Following her PhD in radiotherapy and supportive care, Faithfull went on to publish a book with colleague Mary Wells on the topic, and the launch of the pilot e-learning course on side-effects by EONS is a logical move to increase awareness among nurses. As she points out, radiotherapy, despite being delivered to more than 50% of patients, is poorly understood by the public. "There is a relatively small number of people interested in researching the side-effects – there is a tiny number of papers about it compared with say the latest technologies such as IMRT [intensity modulated radiotherapy]. And with few people specialising in adverse-effects in most countries – we only have 20 radiotherapy nurses in the UK – many nurses don't understand the side-effects and so don't know how to assess them."

Long-term effects of all types of treatment have been of particular concern to Faithfull for some time now. "There is a lot more we should be doing on health promotion, after-care and follow-up, instead of just referring people back to cancer centres to check for recurrences. Again, though, we lack evidence, as most trials are only funded for short follow-ups. We have to rely a lot on sources such as the Department of Veterans Affairs in the US, where there is follow-up for insurance purposes, and we are doing work in the UK with the National Cancer Survivorship Group, where we are looking at existing datasets, such as the GP database and current clinical research on pelvic conditions and bowel cancer to gauge toxicity."

Key ideas, she says, are to help people 'self-manage' their conditions with Internet and smartphone applications, and telephone follow-up, and to provide local multidisciplinary teams that can ensure patients do not fall into gaps in care. "I've been working with men who have had prostate cancer, as they tend to get less care than women because they don't ask for it, and so have many unmet needs. They can have radiotherapy, for example, and not realise they should be getting more help with side-effects in the community. A nurse can marshal the right people to provide targeted advice, such as exactly how to exercise, what to eat, how to get hold of continence pads, sexual and erectile dysfunction services that are available and what raised blood pressure could mean if they are on hormone therapy and so on."

Faithfull has 'hands on' involvement with men with prostate cancer research as she is currently seconded one day a week to work with community teams on cancer survivorship, funded by Macmillan, the UK's cancer relief charity. She is involved with studies on urinary management, metabolic syndrome and bone health, which included looking at diet and exercise as a way of reversing musculoskeletal changes for men on hormone therapy. Bone health is a major issue for older men with prostate cancer who are on androgen deprivation therapy, and they are at high risk of fractures, she notes, adding that in future nurses could also integrate data from new biomarkers with health screening, which could flag up those most at risk.

Health promotion in general for all cancer types is neglected, Faithfull argues. "For example, a lot of nurses think that it's not worthwhile people giving up smoking, but it can have a big impact on side-effects such as skin problems and toxicity of drugs. Yet prescriptions of nicotine patches tend not to be part of cancer treatment. We need to focus more on getting people as healthy as possible during and after their treatment." She points to work by nurses at the Karolinska in Sweden on effective smoking cessation, and to research by nurses in the Netherlands on exercise and long-term symptom management.

She also points out that not all of this work need be put on the shoulders of hard-pressed healthcare services. "A lot of men are happy to pay for things like continence pads, if they know what best to buy and where, while we need to stop thinking of everything revolving around health facilities – with staff with the right skills, places like leisure centres could do a lot."

A key obstacle in the way of better nursing evidence, she adds, is nurses have not been part of a

research tradition, and where there are studies they tend to be isolated in certain hospitals or areas. "We have to move from individuals up to teams in much bigger groups that have the capacity for larger scale research." In some of her research work, Faithfull is working with a number of cancer centres in southern England to provide this scale.

Financing research is also of course a challenge, particularly as the funding often comes from very different sources to that of care. Charities fund 31% of specialist nurse posts in England, but charity funding for research tends to go towards biomedical studies rather than supportive care projects. And while research funds are available from sources such as the Department of Health and the Medical Research Council, this money is rarely ring-fenced for nursing alone, though nurses can apply. Developing bigger, multicentre studies can therefore be very difficult, although more supportive care research is funded now, with Faithfull herself a recipient in her survivorship work.

"Nurses also have good relationships with advocacy groups – we tend to be closer to them in any case – but they rarely fund supportive or psychological research, which is a shame. It is natural to look for cures though."

Lack of large pots of funding does curtail the kind of work Faithfull would like to see more of. "With small grants there is only so much you can do – mainly descriptive work about how people feel, much of which we have already done. What we really need is interventional research that tells us more about how we improve it. This would apply to issues such as fatigue, long-term urinary problems, sexual difficulties, skin management and dressings. A proper dressing study, for example, needs a lot of money for a multidisciplinary research on a decent scale."

And yet, where the evidence does exist to make improvements, adds Faithfull, it is often not practised consistently. "A good example is pain management – we have known for years what needs to be done for some symptoms, but still surveys such as EPIC [European Pain In Cancer] show there is a huge variation and we are still not getting it right."

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The question of how to ensure good practice is implemented is something EONS is now working on with the European Health Management Association. "There is other research involved here about how to make things work, such as relationships," she says. "Nurses also often have broader skill sets than doctors to make things work better, because we are trained in the social and psychological aspects of care."

One project where a deal of supportive care is in play is Faithfull's home, an old country cottage, and her garden, both of which are her main out of work pursuits. She is married to David, a computer analyst, and has a son interested in physics.

Professional aims for the next few years are clear. "I want to see more evidence-based health promotion and supportive care in widespread use, and care provided wherever it is needed, not just in acute settings. I want the UK to regulate specialist nursing and have a clear oncology nursing curriculum and I'd like to see the EONS curriculum become the standard benchmark for national use.

"Above all we will continue to fight for the voices of nurses to be heard."

"With small grants there is only so much you can do – mainly descriptive work about how people feel"

# Cancer of unknown primary: a diagnostic and therapeutic dilemma

Cancer of unknown primary origin is difficult to manage because, even when the primary can be detected, it behaves differently to cancers of the same type and location that are discovered as primaries. Here, the lead author of ESMO's new guidelines for these tumours reviews their diagnosis and management and looks ahead to the possible role of molecular profiling.

Cancer of unknown primary (CUP) represents a heterogeneous group of metastatic tumours for which medical history, physical examination and standardised diagnostic work-up fail to identify the site of the cancer's origin at the time of diagnosis. It accounts for 3%–5% of all malignancies, so is relatively common.

The natural history of cancer of unknown primary site is quite different to cancers where the primary site is known, with an unpredictable metastatic pattern. For example, a pancreatic cancer with known primary site has a well-defined metastatic pattern, with less than a 5% chance of lung metastasis. However, as a hidden pancreatic CUP, it might have a 30%–40% chance of metastasis to the lungs.

The fundamental characteristics of CUP are:

- Early dissemination
- Clinical absence of primary site at presentation
- Generally quite aggressive
- Unpredictable metastatic pattern

**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, Nicholas Pavlidis, Professor of Medical Oncology at the University of Ioannina, Greece, reviews the challenge of diagnosing and treating cancer of unknown primary (CUP). This covers a range of cancers with different histologies where the primary cancer cannot be found. He summarises new ESMO guidelines, which outline key steps in diagnosis and treatment. Daniel Helbling, from the Onkozentrum Zurich, in Switzerland, poses questions that were sent in by participants during the e-grandround live presentation. The presentation is summarised by Susan Mayor.

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

## Histological classification of CUP

The most common histological type of CUP is adenocarcinoma, with well- to moderately-differentiated adenocarcinomas accounting for 50% of cases of CUP, and poorly or undifferentiated adenocarcinomas accounting for a further 35%. Squamous cell carcinomas account for 10% of CUP cases, while undifferentiated neoplasms, including neuroendocrine tumours, lymphomas, germ cell tumours, melanomas, sarcomas and embryonic malignancies account for 5%.

## Clinicopathological entities of CUP

CUP is not one disease. The different histological types can be considered by the organ affected:

***Liver.*** Patients with liver metastases often have adenocarcinoma. They sometimes also have metastatic signs in other organs, which is, unfortunately, the most common type of CUP.

***Lymph nodes.*** Patients with lymph node metastases in a mediastinal to retroperitoneal (midline) distribution may have undifferentiated or poorly differentiated carcinoma. Those with metastases to the axillary nodes may have adenocarcinomas, while patients with metastases in the cervical nodes could have squamous cell carcinoma, and those affected in the inguinal nodes could have undifferentiated carcinoma, squamous cell carcinoma (SCC), or mixed SCC/adenocarcinomas.

***Peritoneal cavity.*** CUP with metastases in the peritoneal cavity is termed peritoneal adenocarcinomatosis when found in females, and looks like ovarian cancer. Histologically, these cancers are papillary or serous adenocarcinomas, with or without psammoma bodies (round collections of calcium). Patients may also have malignant ascites of other unknown origin, which are usually mucin adenocarcinomas (with or without signet ring cells).

***Lungs.*** A subset of patients has lung metastases, with either pulmonary metastases or only pleural effusion. These are generally adenocarcinomas.

***Bones.*** Another subset of patients has only bone metastases, either solitary or multiple. These are adenocarcinomas of various levels of differentiation.

***Brain.*** Brain metastases can occur either singly or more than one, and are adenocarcinomas.

***Neuroendocrine tumours.*** These are generally poorly differentiated cancers mainly low-grade, with neuroendocrine features.

***Melanoma.*** Patients have undifferentiated neoplasm with melanoma features, but with no obvious primary site.

Being aware of the subsets of CUP is useful in order to classify patients into appropriate groups for treatment decisions and research purposes.

## Finding the primary site

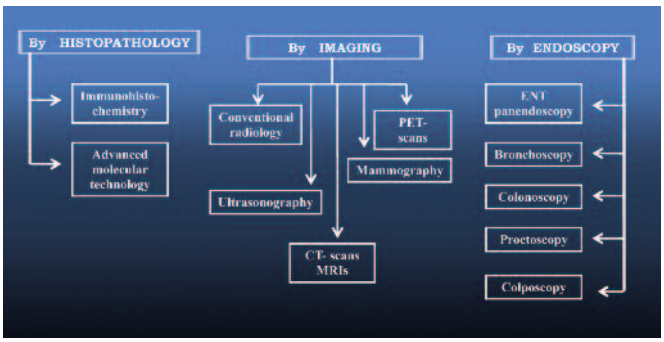
### Histopathology

The process of searching for the primary site of CUP of an adenocarcinoma origin requires good histopathology, especially immunohistochemistry, with 10 key markers generally being tested for. Routine evaluation of commonly used markers has not been shown to be of any prognostic or diagnostic assistance. Non-specific multiple overexpression of adenocarcinoma tumour markers (CEA, CA125, CA15-3, CA19-9) occurs in most CUP patients. Around 70% of CUP patients will have high serum levels of more than one tumour marker, so you cannot be sure about what you are dealing with. However, it is worthwhile to request:

- PSA in men with bone metastatic adenocarcinoma
- B-HCG and AFP in men with undifferentiated tumours (especially midline distribution)
- AFP in patients with hepatic tumours
- CA125 in women with papillary adenocarcinoma of the peritoneal cavity
- CA15-3 in women with adenocarcinoma involving only axillary lymph nodes.

The pattern of cytokeratins (CK7 and CK 20 positivity) is also very useful in determining primary cancers (see opposite). Nowadays, we also include advanced molecular technology, using gene expression to detect the primary site. This has an accuracy of 80% in locating the primary site of CUP.

**TRACKING DOWN THE PRIMARY**




Multiple strategies are needed to find the primary cancer

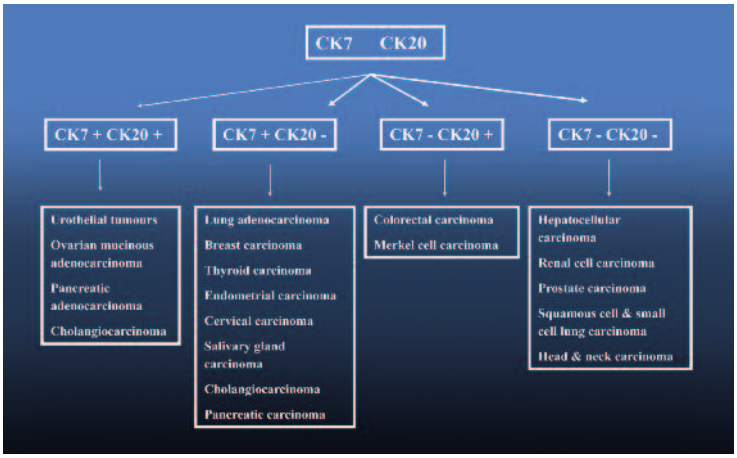
**Question:** *If CUP is discovered, do you ask the pathologist to test all of these markers?*

**Answer:** *Not all of them. In a female patient, you do not need a PSA, and GcDFP-15, which checks for hidden breast cancer, is not needed in men. You can find breast cancer in males, but it is not very common. Select markers from the list opposite to rule out the primary site.*

**WHAT IMMUNOHISTOCHEMISTRY CAN REVEAL**


*Source:* JL Dennis et al. *Clin Cancer Res* 11: 3766–3772

**WHAT CK COMBINATIONS CAN REVEAL**




**Question:** *What is the accuracy of CA125 positive serum as a diagnostic tool for ovarian cancer?*
**Answer:** *If you routinely measure epithelial markers in the serum in all patients, 70% will have more than one marker at an elevated level. If you do it in the whole population of CUP patients, it is not helpful at all. However, if you do it in the subset of patients with peritoneal disease with pathology of papillary carcinoma, it is very useful. You must be very selective. The diagnostic accuracy of CA125 alone is not good. However, immunohistochemistry in general is very useful.*
**Question:** *Are you looking for these markers during treatment as an indication of the effectiveness of therapy?*
**Answer:** *If you are dealing with subsets of CUP, you should look for the markers suggested. For example, if you are dealing with a male with midline differentiated tumour, and B-HCG + AFP levels are raised, it is useful to measure these markers during treatment. However, this occurs in only 20% of patients so is quite rare.*

## Imaging

Imaging includes conventional radiology, ultrasonography, mammography, and CT, MRI or PET scans.

A chest X-ray is used as a prerequisite before any further investigations. Barium studies are completely useless in investigating patients with CUP. CT scans are quite useful, with an accuracy of 40%, and can provide useful guidance for biopsy. Mammography is useful in investigating women with breast cancer, but has very low sensitivity. However, an MRI in breast cancer patients can increase accuracy to 60%. FDG-PET scan can be helpful, especially in patients with occult head and neck cancers or lung cancer. These areas are really sensitive to PET scan in finding the primary site.

## Endoscopy

Finally, endoscopy is sometimes useful, but not in all patients. Its use should be guided by specific symptoms or signs. For example, ENT panendoscopy should only be requested for a patient with cervical node involvement. Bronchoscopy would be indicated in patients who have a positive chest X-ray or CT scan with a cough. Colonoscopy is useful in patients with relevant symptoms or signs, with the same applying to proctoscopy and colposcopy for patients with inguinal node involvement.

**Question:** *How often do you personally use PET scans to diagnose CUPs?*
**Answer:** *I do not use it as a routine, and it is not even included in the guidelines to rule out occult head and neck cancer or lung cancer. However, if you have suspicions that your patient might have one of these cancers, you could consider it. It is still not accepted by everybody. If I have a patient with cervical lymph node presentation or some suspicions of lung cancer, I would recommend it. But do not do PET scan in all your patients.*
**Question:** *Do you recommend fundoscopy – looking at the back of the eye – as a tool in the search for CUP primary sites?*
**Answer:** *This technique would only be used frequently in the search for melanoma of unknown primary. Otherwise, I would only carry out this process in the search for a primary if I had a biopsy of metastases in the liver that showed melanoma and I could not find any skin primary. In this case, I would have to look at the retina to search for primary retinal melanoma.*

## How often is a primary tumour diagnosed?

Available data suggest that the antemortem frequency of detection of primary site by imaging, endoscopy or immunohistochemistry studies remains around 30% (*Eur J Cancer* 39:1990–2005). A study published several years ago by our group compared data from autopsy and microarray (*Eur J Cancer* 43:2026–2036). Reviewing studies from the last 55 years (1944–2000) where autopsy studies were available gave results for 884 autopsies. The primary site was found in 73% of these patients, with the most common primary sites being identified as lung (27%) and pancreas (24%).

**Question:** *Do you often find small tumours that metastasise very quickly?*
**Answer:** *Yes, this is quite common. The tissue must be sliced very finely to identify these tumours. A CUP is a tumour that metastasises abnormally quickly.*

Data from recent studies, identifying the primary site by genetic profiling or microarray, show that the accuracy of biological assignment of primaries is 50%–87%. The most common primary identified was breast cancer (15%) followed by pancreas (12.5%), bowel (12%) and lung (11.5%). It is not clear why the rates differ compared to autopsy studies.

## Treatment of CUP

In terms of treatment, there are essentially two subsets of CUP patients: the favourable prognosis subset, with better response rate, more complete responders and survival ranging from 15 to 22 months, and the poor prognosis subset, with median survival of 4 to 10 months. Favourable subsets make up only 20% of CUP patients; 80% belong to the unfavourable prognosis subset.

### CUP patients with favourable or good prognosis

The first group of patients with a good prognosis is those with poorly differentiated CUP and midline distribution. Most of these patients are men younger than 50 years who have lymph node involvement in the mediastinum and retroperitoneum, some peripheral lymph nodes and some lung metastases; 20% have elevated serum markers. The clinical evolution is, unfortunately, very rapid tumour growth. Up to 50% of these patients respond to cisplatin-based chemotherapy and around 20% are complete responders. Median survival is around 13 months, but 15% survive long-term.

The second group is women with peritoneal carcinomatosis, who present with abdominal distension, pelvic masses and ascites. Surgeons find abdominal masses with peritoneal disease and ascites, but normal ovaries with no primary tumour. Histology will show papillary serous carcinoma and patients often have elevated CA125. These patients should be treated in the same way as FIGO III ovarian cancer, with surgical cytoreduction and platinum-based chemotherapy. The response rate is up to 60%, with 30% complete responders. Median survival is around 16 months and 10% will be long-term survivors.

**Question:** *How should I treat a woman with axillary lymphadenopathy with a diagnosis of adenocarcinoma who has an increased level of CA15-3? Do you treat patients like this as metastatic breast cancer patients?*
**Answer:** *This type of patient with isolated axillary nodal metastases accounts for 0.3% of all breast cancer patients. Mammography has quite low sensitivity (20%), whereas MRI has sensitivity up to 70%. Most of these patients have N1 disease and invasive ductal carcinomas. Half are positive for ER and PR. There are not yet sufficient data about HER-2 receptors to determine the percentage. Distant metastases occur in only 2% of patients.*

*The first step in a patient with axillary lymphadenopathy is to take a biopsy and check for breast cancer. If this is the case, give standard treatment. If the biopsy is negative for breast cancer, you should perform complete axillary dissection, with, or without, breast cytoreductive surgery and radiotherapy. Chemotherapy or endocrine treatment should then be given, depending on age and menopausal status.*

**FAVOURABLE SUBSETS OF CUP**

| |
|---|
| Poorly differentiated carcinoma with midline distribution (which looks like extragonadal germ cell syndrome) |
| Women with papillary adenocarcinoma of the peritoneal cavity (which looks a bit like ovarian cancer) |
| Women with adenocarcinoma involving only the axillary lymph nodes (which looks like breast cancer) |
| Squamous cell carcinoma of the cervical lymph nodes (looks like head/neck cancer) |
| Poorly differentiated neuroendocrine tumours |
| Men with blastic bone metastases and elevated PSA (adenocarcinoma) |
| Isolated inguinal adenopathy (squamous carcinoma) |
| Patients with a single, small, potentially resectable tumour |

*Survival rates are similar to those for stage 2 or 3 breast cancer, although 25% have locoregional recurrence. The overall survival is 75% at five years and 68% at 10 years. There is no difference in survival rate between patients undergoing conservative management and mastectomy procedures. Patients with N2 disease have a worse prognosis than N1 disease.*

**Question:** *If you have suspected ovarian cancer and treat the cancer with chemotherapy, and the CA125 comes down nicely, how long will you go on with the treatment? What is the level of CA125 decline required?*

**Answer:** *You are talking about primary peritoneal disease. You do the same procedure as with ovarian FIGO III cancer patients, giving six cycles of chemotherapy. If the marker was still dropping after six cycles, I would schedule another two or three cycles to be on the safe side.*

The other good prognosis subset is patients with squamous cell cancer involving the cervical lymph nodes. These should be managed in the same way as patients with locally advanced head and neck cancer.

Surgery alone is inferior unless you have a patient with pN1 neck disease with no extracapsular extension. Radiation should be given to both sides of the neck and mucosa (entire pharyngeal axis and larynx).

Chemotherapy remains undefined, but there are encouraging results with platinum-based treatment. The five-year survival rate is 35%–55% after treatment, and there are also some long-term survivors.

Patients who have poorly differentiated neuroendocrine carcinomas should be treated with platinum-based or paclitaxel/carboplatin-based chemotherapy. The response rate is 50%–70%, with up to 25% complete responders. Median survival is around 14 months, with 24% surviving up to three years.

## CUP patients with a poor prognosis

The most common subset of patients with a poor prognosis CUP is those with liver metastases without known primary tumour. A summary of the big five trials in these patients ($n$=700) shows a response rate of less than 20% and a very poor median survival, down to five months. (*Bull Cancer* 78:725–736; *JCO* 16:2105–2112; *Clin Radiol* 57:1073–1077; *Gastroent Clin Biol* 29:1224–1232; *Cancer Treat Rev* 34:693–700).

Patients who are relatively young and have good performance status should be offered platinum-based chemotherapy for two or three cycles. If there is no response, stop treatment. A patient who is older or has a poor performance status should be given supportive care alone.

**Question:** *Which cisplatin doublet do you use and what do you use as second-line treatment for patients of unfavourable CUP subsets?*

**Answer:** *The most common first-line doublet is platinum–taxane, except for patients with a neuroendocrine tumour, where you might use etoposide at the same time. Data for second- and third-line therapy are poor. We have only data for gemcitabine and other chemotherapy. Response rates to these therapies are very poor and survival is not good. Second-line therapy still remains unsuccessful in the treatment of CUP.*

**Question:** *In a 65-year-old woman with metastatic pleural effusion and elevated CA125 but no evidence of ovarian cancer on the MRI, and no ascites, what further procedures would you do and how would you treat her? Would you do a diagnostic laparoscopy?*

**Answer:** *If a CT scan or MRI is negative, I am not going to do laparoscopy to find the primary tumour. Sometimes in primary lung cancer you might have increased serum CA125, but we never look for this. If I have a patient with pleural effusion as an unknown primary, I do a bronchoscopy first of all, to rule out lung cancer.*

*This patient belongs, by definition, to the bad prognosis subset. The two most possible good prognosis groups are breast cancer or ovarian cancer. However, if you rule out both via CT or MRI and have an MRI of the breast with no sign of tumour, I would treat this patient as belonging to the poor prognosis subset.*

## Does molecular profiling improve outcomes?

We are still unsure as to whether molecular profiling has any impact on patients' outcome, but there are two or three randomised studies investigating this. Hainsworth and colleagues in the US are conducting a phase II study in which they perform CUP investigation after conventional work-up, followed by gene expression profiling (JD Hainsworth, www.clinicaltrials.gov). They then split the patients into two groups. The first group includes patients with a specific diagnosis from gene expression profiling, who are treated accordingly. The second group is patients with no specific diagnosis, who are treated empirically for CUP with agents including platinum or a taxane. Results will be analysed to see whether guidance of treatment in patients in which gene expression profiling shows a specific primary site improves outcomes.

A retrospective study of 47 CUP patients treated with regimens for colorectal cancer showed that those with proven colorectal cancer had higher response rates (60%) and median survival (22 months) compared to those who were also treated with colorectal regimens but who had unknown primary tumours (10% response rate; six months median survival).

If prospective data show that gene profiling predicts the effectiveness of treatment, this will be very useful in determining the most appropriate treatment for these patients.

**Question:** *Do you have experience of pancreatic carcinoma in young individuals presenting as CUP? Would you treat them differently from advanced pancreatic carcinoma in the elderly? A randomised phase III trial published recently by a French group used folfirinox [5FU/leucovorin/irinotecan/oxaliplatin] against gemcitabine. There was a clear advantage in survival for individuals in the folfirinox group over three years. Would you treat CUP suspected to derive from the pancreas in young patients differently than in more elderly patients?*

**Answer:** *If you are talking about patients who had a molecular or gene profile that proved they had pancreatic cancer, it is a completely different question than suspecting a pancreatic cancer in a patient without gene profiling. You have to differentiate it. If you have patients whom you believe may have pancreatic cancer but you never proved that, you do not treat them as pancreatic cancer patients because you do not have data to support this.*

*I would give 'umbrella' treatment with platinum–taxane and treat them as a poor prognosis patient. I would not be expecting to have good results. However, if data from ongoing randomised studies show that a gene profiling diagnosis can be used to treat patients as routine patients, I would treat these patients as pancreatic cancer patients. The challenge with CUP is that there is no approved drug for its treatment and expensive drugs used to treat cancers with known primary tumours may be ineffective against CUP.*

**Question:** *In the future, will we be able to link treatment directly to the patient's genetic profile?*

**Answer:** *This is the principle. However, at the same time, we believe that patients with CUP of unfavourable prognosis (e.g. liver metastases), regardless of the discovery of the primary tumour, have low response rates. Each patient will have a specific molecular profile that can be linked to treatment, but they will not respond in the same way as those with known primary tumours. CUP patients are carrying a molecular signature that gives different behaviour, and probably respond differently to those with known primary tumour.*

A phase II trial in the US using a combination of bevacizumab and erlotinib in CUP treatment showed a fairly poor response rate, with 10% having a partial response and 61% stable disease. The median survival was 7.4 months and 33% survived up to one year (*JCO* 25:1747–1752). This answers the question of targeting treatment in these patients.

## Diagnosis and management: in summary

The new clinical practice guidelines published by ESMO for the diagnosis, treatment and follow-up of cancers of unknown primary site (*Ann Oncol* 21 (suppl 5):v228-v231) set out what you need to know in order to manage these patients. They point out that CUP patients may have a different natural history to those with known primary tumours. CUP patients do not suffer from one disease but often have more than one, and it is essential to differentiate clinical and pathological subsets.

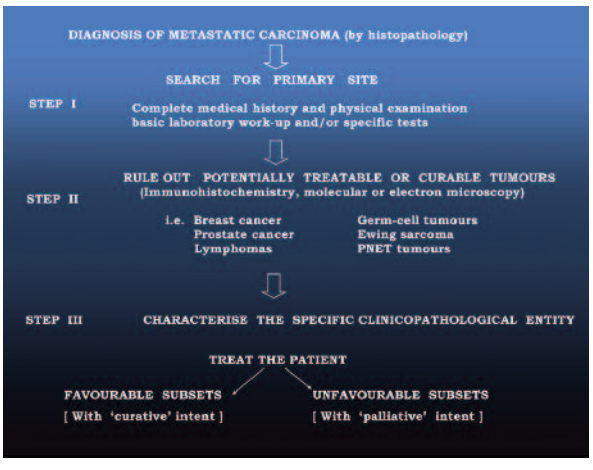
Immunohistochemistry is the cornerstone of CUP diagnosis. Molecular profiling is very useful as far as sensitivity is concerned, but we do not yet know if this will improve patients' outcomes. In terms of imaging, a CT scan and MRI are useful, especially in the detection of primary breast tumours. A PET scan is useful in finding hidden head/neck and lung cancers.

It is important to avoid spending unnecessary time and money in investigating and treating all CUP patients, as there is no benefit in this. Patients should be classified into favourable prognosis and poor prognosis subsets. For favourable subsets, locoregional treatment should be given to patients with isolated axillary lymph metastases and those with squamous cell cancer of cervical nodes.

Some of these patients – including those with poorly differentiated carcinomas of midline distribution, peritoneal adenocarcinomatosis in female patients and poorly differentiated neuroendocrine carcinomas – may also be very sensitive to chemotherapy. A combination of platinum, with or without a taxane, may achieve a response rate of 40%–70% and some prolongation of survival.

However, this is mainly in patients with good prognosis CUP and not in non-favourable subsets. In a young patient with poor prognosis CUP but with good performance status, it may be useful to provide platinum-based chemotherapy. However, you need to keep in mind that these patients have a very dismal prognosis.

**STEP BY STEP SUMMARY**



# Shining a light on nanoparticle therapy

Creative new approaches to cancer therapy deserve to be publicly celebrated. But steering the right course between simplistic talk of 'wonder drugs' and baffling readers with unnecessary scientific detail can be tricky. **Mark Henderson**, of the UK national daily *The Times*, won a Best Cancer Reporter Award for his story about a novel nanoparticle therapy, which is reprinted below.

A nanotechnology therapy that targets cancer with a 'stealth smart bomb' is to begin patient trials next year in the first clinical test of a pioneering approach to medicine.

The nanoparticle, which targets tumour cells while evading the body's immune system, promises to deliver larger and more effective doses of drugs to cancers, while simultaneously sparing patients many of the distressing side-effects of chemotherapy.

Animal studies have indicated that the treatment can shrink tumours "essentially to zero", while being better tolerated than conventional cancer treatments. Final toxicology studies are about to begin.

A trial involving about 25 cancer patients is scheduled to start within a year. If successful, it could lead to a licensed drug within five years.

Although the therapy was originally designed for prostate cancer, it is expected to be effective against other solid tumours, such as forms of breast, lung and brain cancer. Patients with some of these cancers, as well as prostate cancer, may be included in the first trial.

The technology, developed by BIND Biosciences, a company based in Cambridge, Massachusetts, should also be suitable for delivering drugs for treating other conditions, as well as for the chemotherapy agents that it has been set up to carry.

"This should be the first targeted nanoparticle delivering a chemotherapeutic to enter clinical trials," Jeff Hrkach, the company's vice-president of pharmaceutical sciences, said. "We're then looking to develop this as a broad platform that could also be used to treat cardiovascular disease, inflammation, even infectious disease."

The nanoparticle, known as BIND 014, is designed to solve three of the major challenges in drug delivery: how to ensure therapeutic molecules get to the right place in the body, how to release them slowly over several days, and how to keep the body's immune system from recognising them as foreign and destroying them.

It does this by packing drugs inside a 'special delivery parcel' developed by Robert Langer, of the Massachusetts Institute of Technology, and Omid Farokhzad, of Harvard University, who founded BIND Biosciences.

Mark Henderson

THE TIMES

**The science behind the therapy. Well-written articles explaining potentially important developments in treating cancer promote public understanding of the disease and help build confidence in, and support for, the research effort**


New attack on cancer with nano-weapon

News

How the nanotechnology therapy works

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Killer of 10,200 men each year

Bill Bryson Notes from a Large Hadron Collider

TIFFANY & Co.

## How it works

This nanoparticle's diameter is 1000 times smaller than that of a human hair, measuring about 100 nanometres – or one ten-millionth of a metre – across. It has four elements, the first of which is its payload, a common chemotherapy drug called docetaxel or Taxotere.

The docetaxel molecules are enclosed in a matrix made of a biodegradable polymer known as polylactic acid, which breaks down slowly over several days so that the drug is released gradually. This means that a single injection of nanoparticles can have a long-lasting effect.

This drug-filled 'warhead' is then covered with a 'stealth coating' of polyethylene glycol, which helps the particle to hide so that it is not attacked by elements of the body's immune system such as antibodies and macrophage cells. Normally, nanoparticles for drug delivery risk being recognised by the immune system and destroyed.

"Regular nanoparticles struggle to get through to tumours," Professor Langer said. "They get eaten by macrophages. By containing the drug within this molecule, we can avoid the macrophages."

The final element of the particle is its smart targeting system, in the form of special enzymes attached to the outer coating known as targeting ligands. These are designed to bind to a molecule found on prostate cancer cells called prostate-specific membrane antigen (PSMA), so that the particles accumulate at the site of tumours before releasing their drugs.

"It's an anchor, rather than a homing beacon," Dr Hrkach said. "If we do things right and get it to the tumour, when the particles get there they stay there.

"What's different about this delivery system is that we believe we can very explicitly target the disease site, while also protecting the nanoparticle from the body's immune system. You can get a high concentration at the site of the tumour and a lower concentration everywhere else.

"By virtue of doing that you're not exposing the body to the side-effects of chemotherapy so much, while at the same time getting larger doses of drug to the tumour."

It promises to deliver larger doses of drugs to cancers, while sparing patients many of the side-effects

Professor Langer said, "We've created a nanoparticle decorated with two molecules, one of which helps it to dodge the immune system, while the other helps it to target cancer cells."

The drug has been successfully tested against human prostate tumours grown under the skin of mice, in studies that have shown both that the drug accumulates around tumours and reduces them in size. "It's shrunk tumours in animals essentially to zero," Professor Langer said.

As the PMSA molecule targeted by the nanoparticle is also found in the blood vessels grown by many other solid tumours, it should be suitable for treating other cancers.

"We think that going after that same target with that same drug, we can not only go after prostate cancer but a considerably long list of other solid tumours," Dr Hrkach said. "The plan is to start clinical trials in the third quarter of next year. We're now transferring our efforts to manufacturing enough material for a clinical study."

The clinical trials are now scheduled to start by the end of 2010
This article was first published in *The Times* on 5 November 2009 under the title 'New attack on cancer with nano-weapon', and is reprinted here with permission

## BATTLE AGAINST A COMMON KILLER

- Prostate cancer is the most common cancer among men in Britain; it was diagnosed in 35,000 men in 2006
- About 10,200 men die of the disease each year
- Seventy per cent of men with newly diagnosed prostate cancer survive for at least five years
- About 60 per cent of cases occur in men over the age of 70
- It is usually diagnosed by digital rectal examination and/or a test for prostate-specific antigen, a protein, followed by a biopsy
- Treatments include surgery, chemotherapy, radiotherapy and hormone therapy
- Scientists have identified about two dozen genes that affect the risk of prostate cancer
- Sufferers have included François Mitterrand, the former President of France; Rudy Giuliani, the former Mayor of New York; Dennis Hopper, the actor; Frank Zappa, the singer; John Kerry, the former US presidential candidate; Linus Pauling, the scientist; and Nelson Mandela

*Sources:* Cancer Research UK, *Times* database

# Steadfast in Sarajevo

## How Hiba Basic kept services going in a city under siege

➜ Simon Crompton

Half the staff at the Clinical Centre left and 50 were killed during the siege of Sarajevo. But **Hiba Basic** stuck to her post and took over the oncology department. For three long years she used whatever was available to care for patients from all backgrounds, losing no time, once the war ended, to rebuild the department into a centre of excellence for the citizens of Bosnia Herzegovina.

Perched on a hill on the north east side of Sarajevo, is the city's century-old hospital, now part of the Clinical Centre, University of Sarajevo. It looks on quick inspection like many other European hospitals – a mix of dirty old and gleaming modern. Then you notice the bullet holes in the buildings around the main entrance. Here and there are strange splashes of missing brick and plaster, made by shell explosions. This is a hospital with a dark story of suffering, resilience and professional commitment, and at its heart is radiotherapist Hiba Basic.

During the Bosnian war between 1992 and 1995, the city was subjected to the longest siege in modern history, bombarded for three and a half years by shells and sniper bullets from forces on the hills that surround every side of the city. Around 10,000 civilians were killed. Power, water, heating, medical and food supplies were all cut off.

Yet the Clinical Centre kept going throughout. And somehow, as those injured and dying in the hostilities poured in and pulled on the hospital's dwindling resources, Hiba Basic and other staff in its oncology and radiology unit still managed to provide care and life-saving treatment for people affected by cancer.

Within months of the siege starting, half of the Clinical Centre staff left – fleeing with their families while they could. Basic, a consultant radiotherapist who became head of the hospital's Department of Radiation Oncology during the war, doesn't blame them. Living conditions became worse and escape more difficult with every week that passed. But she decided to stay and try and keep cancer services going – even though lack of electricity made radiotherapy almost impossible, and cancer drugs were in short supply.

"Just because people were dying on a daily basis from bullets and blast injuries, that didn't mean that people with cancer didn't deserve their chance of life too," says Hiba, now 64, who helped rebuild the Clinical Centre's cancer services from the ruins of the war, so that it could again serve as the country's primary oncology and radiotherapy centre.

Civilians were under fire in all parts of the city during the siege – some were killed while queuing

for bread and fresh water. Even to today's tourist, the reminder is constantly there in the dozens of new graveyards scattered around the housing areas of the city: when siege conditions make travel virtually impossible, people are buried near where they fall.

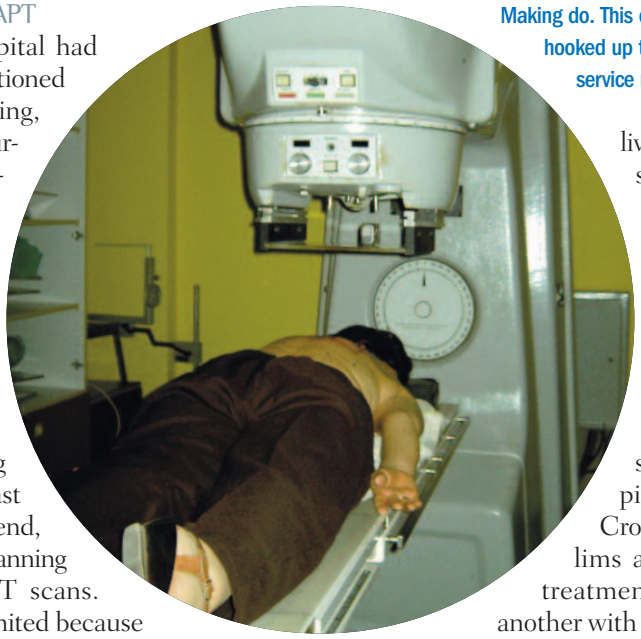
"I would queue all night for water for me and my family," says Basic, "and then in the morning I had to go and buy food under shelling and gunfire – we had to run to escape the snipers. I lived about an hour away from the hospital by foot – there was no petrol for cars. So every day on my way into work and back home, I was in danger."

On the hospital wall is a list of the 50 members of staff killed during the siege. One, a surgeon, was the husband of one of Basic's radiotherapy colleagues. He was killed by a shell as he entered an operating theatre. Looking after cancer patients became a matter of improvisation and rudimentary care.

Having wanted to be a doctor since age eight, and having studied medicine at the University of Sarajevo, Basic started her specialism in radiology and clinical oncology at the hospital in 1976, and over the years since then saw it develop its services into an Institute of Radiology and Oncology. By 1992 there were facilities for telecobalt therapy, X-ray therapy and brachytherapy, and plans to develop oncology services further, with two separate institutes for radiotherapy and medical oncology. Work began on a new hospital building to accommodate the institutes, including a new underground radiotherapy department. The war put an end to all that.

## Improvise and adapt

What power the hospital had during the siege was rationed for basic heat, cooking, washing and urgent surgery. So the only radiotherapy machine that could be used was the telecobalt machine, run from a small generator donated by the International Atomic Energy Agency. Basic had earlier pioneered new techniques of using brachytherapy in breast cancer, but this had to end, along with treatment planning and staging using CT scans. Chemotherapy was limited because of the short supply of cancer drugs.



Making do. This old telecobalt machine, hooked up to a generator, kept the service running

Yet demand for cancer care was high because there was nothing else in Bosnia. As word spread that the hospital was still providing cancer services, the United Nations Refugee Agency flew in sick cancer patients from the other besieged enclaves of Goražde and Srebrenica. With patients unable to return home, because it was simply too dangerous, most became long-term.

"We had to adapt," says Basic. "For example, in gynaecological cancers, brachytherapy is usually an unavoidable part of treatment, often in combination with external radiotherapy. But we had to replace it with external radiotherapy, because any treatment is better than no treatment. We explained all this to the patients, and they were happy just to be receiving treatment."

Chemotherapy agents came through to the hospital in small amounts from time to time, and treatment was adapted according to supply. "We naturally moved towards palliative care, because most of the patients were not in the early stages of cancer. They often became better after treatment, but they had to live here for months, and some of them died here. We buried them in the hospital cemetery." After the war, many families took the bodies of their loved ones back to be buried in their homeland.

No ethnic tensions existed in the hospital, says Basic. Serbs, Croats, and Bosnian Muslims all received the same treatment, and treated one another with respect.

"I'm a Muslim, but I tried to help everyone the same, to prolong their life, if I could, to the end of the war so that they could see their families and children who had left the city. It was right that we did this, and I know that there were Bosniaks [Bosnian Muslims] who were also treated just the same as everyone else in hospitals in Belgrade [capital of Serbia]."

## The price of isolation

Basic is clearly proud about continuing to teach students and train young doctors wishing to specialise in oncology throughout the war, so that foundations for the future of Bosnian cancer medicine were already being laid. But she was always aware that those years of isolation from the outside world, with entry and exit from Sarajevo impossible, would bring long-term consequences for health services.

"Besides the sheer fight for survival, the worst thing was the lack of information," she says. "While the rest of the outside world was making huge progress, introducing computers, talking a new language of Windows and so on, we lived in the dark."

So if what Basic and her colleagues did to

"Besides the sheer fight for survival, the worst thing was the lack of information"

# "While the outside world was making huge progress, we lived in the dark"

maintain services during the war is remarkable, so has been the rebuilding of oncology services in Sarajevo. The siege left the hospital damaged. The new building to house cancer services was unfinished. The telecobalt machine was ageing, the brachytherapy machine was damaged. And most of all, there was an enormous knowledge gap between Bosnia and other European countries.

Support came from many international organisations. The International Atomic Energy Agency provided new dosimetry equipment, a new cobalt-60 machine, repaired the brachytherapy equipment and provided experts to train local staff in working the new machines and treatment planning systems. It supported intensive training of the team of 11 radiation oncologists, three medical physicists and 10 radiographers at the department – and it is still involved in continuing education at the Institute of Oncology (as it is now known).

ESO, meanwhile, supported the education of many doctors and nurses from the unit, setting up a series of international workshops on breast cancer, starting in 2001. These later developed into the international Interconference Breast Cancer Meeting, which is held in Sarajevo every two years, and involves ECCO, Europa Donna and other organisations alongside the Clinical Centre, the Association of Oncologists of Bosnia and Herzegovina and ESO. Its aim is to bring the very latest in breast cancer research, treatment and care to the Balkan area and central and eastern Europe.

## A CENTRE OF EXCELLENCE

From having been able to treat just a few hundred people a year during the war, the Institute of Oncology is now a national centre of excellence, treating around 4800 people a year, half as outpatients. It is a well-equipped, airy centre, proud of its role in teaching undergraduate and postgraduate students, and its multidisciplinary approach to cancer diagnosis and care, involving 12 teams of professionals in the main cancer groups. Now there are plans to establish Bosnia's first breast unit in the institute. "We have some very positive support, especially from the association of women treated for breast cancer in Bosnia," says Basic.

With members of her department on the steps of the Clinical Centre. Most of those pictured here worked alongside Basic throughout the three-year siege

The return from isolation to the international world has been of personal as well as professional significance for Hiba Basic. After university, she trained in radiotherapy in Amsterdam, Utrecht, Heidelberg and Hamburg University hospitals. She has relatives in Sweden, Croatia and Germany, and her outlook has always been international. So for her, being locked away from the rest of the world was one of the worst aspects of the siege.

"At one stage, I wanted to get out, to go down the tunnel that had been dug to the airport. But I

## It is now a well-equipped, airy centre, proud of its role in teaching students, and its multidisciplinary approach

wasn't allowed to because it was only for food, soldiers and special needs. But it's strange that the moment the siege ended, I didn't want to get out any more, because I felt free. The worst thing is to be restricted in movement. Even if we had lived those three years free of danger, with the best food, the best conditions, it would still have been like living in prison."

Nevertheless, when in 1998 she was awarded a European 'Art for Care' prize for her outstanding work, and invited to Milan to receive it, it was an opportunity she couldn't refuse. She spent two days in Italy, talking to colleagues, visiting ESO, attending lectures.

"It was so exciting for me, because I was in Milan, in the normal developed world, where I thought I belonged. I was alone, and the war was finished. And yet, when I flew back, I saw below me the airport still damaged and improvised, and I could see all the houses around the airport, and none of them had a roof. They had all been destroyed. And though I was so excited, I couldn't stop myself from crying."

Since then, Basic has thrown herself into work on behalf of her profession, nationally and internationally. A member of the European radiation oncology group ESTRO and the clinical cancer research group EORTC, she has also held the top posts of both the Association of Radiologists of Bosnia and Herzegovina, and president of the Association of Oncologists of Bosnia and Herzegovina. And she has been heavily involved in running and chairing the biennial Interconference Breast Cancer Meeting.

Team work. Discussing a treatment plan with radiation oncologists and physicists

## A NETWORK OF CENTRES

She is encouraged by the developments in treatment that have occurred in Bosnia and Herzegovina in recent years. Until this spring, the Institute was the only cancer centre in the country offering radiotherapy, but units have now opened in Tuzla and Banja Luka. Well-organised chemotherapy services are now being offered in Tuzla, Banja Luka and Mostar too, says Basic. And although expensive targeted therapies are not easily available across Bosnia Herzegovina, hormone treatment is state funded for all who need it.

Yet her international awareness and appetite for clinical knowledge also makes Basic painfully aware of the ways in which her country still lags behind. Surgeons in other centres in the country are unwilling to collaborate or take a multidisciplinary approach. There is a shortage of doctors well-trained in cancer diagnostics. And a lack of trained pathologists and cytologists means that cancer diagnosis and staging are still too often based merely on tumour size and site, not on molecular biology.

In breast cancer, which is Basic's special interest, diagnosis and treatment decisions in some hospitals are still dictated by mammogram alone.

With retirement approaching, Basic finds it bittersweet to look back on what has been lost, what has been achieved, and what it still to be done in her country. She is a small bundle of energy, but acknowledges that the stresses of the past two decades have sometimes been too much for her.

"I could never have imagined living through something like this. We all lost relatives and friends," she says. "But it becomes normal. You manage."

Thankfully her immediate family was left unscathed – at least by bullets. Her son, a member of the Bosnian forces defending Sarajevo survived, "not wounded, not mad". A mechanical engineer, he now works at the airport, and is married and has two children. Her mother and brother died on the same day in 1995 – her mother in old age, her brother of a heart attack. "He wasn't killed in the war fortunately. It's easier to accept." Sadly, her husband died this September after a long-term illness. She now hopes to spend more time, in her retirement, with her grandchildren, and tending to the garden in a small holiday home owned by her family on the Bosnian coast.

Was there anything good, I ask, anything at all, that came out of the Bosnian war? She thinks hard, gives a brief and resigned laugh, thinks some more, and then shakes her head. "It is very difficult," she concludes.

The key to the future of her country, she believes, is becoming fully engaged in the European Union. Just as becoming engaged in the international community has allowed for the rebuilding of cancer services, so international political and economic engagement will finally dissipate the long-term effects of wartime isolation. But for now, she can at least consider her retirement knowing that, for hundreds of people with cancer, things would have been considerably worse if she hadn't stayed at her post and tried to make things better.

For outstanding service to cancer care. Pioneering cancer surgeon Umberto Veronesi presents the Art for Care award to Basic in Milan, 1998 – it was her first contact with 'the normal civilised world' since the war

"It's strange that, the moment the siege ended, I didn't want to get out any more, because I felt free"

# The Clinical Trials Directive: can we get it right second time around?

Anna Wagstaff

Though well-intended, the European Clinical Trials Directive severely impeded clinical research. The Commission is now trying to revise the Directive, and is inviting researchers, patient groups and others to submit concrete suggestions. But will Europe's clinical trials community be able to exert sufficient pressure at a national level to see the draft safely through the EU legislative process?

By the time the Clinical Trials Directive came into force in 2004, it was already widely suspected that what had been designed as a benign and protective intervention would result in unexpected serious adverse effects. And so it turned out.

The past five years have seen the costs, bureaucracy and time required to carry out clinical trials increase sharply and the number of trials fall, with an even sharper fall in the number of patients enrolled. Worst hit have been the type of 'academic' or investigator-driven trials that are needed to find out how, and in whom, to use existing treatments to their best effect. Bad news for patients, bad news for the European Union's stated goal of becoming a research- and knowledge-led economy, and bad news for Europe's escalating healthcare bills, paying for expensive drugs that doctors don't know how best to prescribe.

Stefan Führing is the man at the European Commission who has been charged with sorting out what the Commission recently described as "arguably the most criticised piece of legislation" in the whole body of EU legal provisions for medicines. He has spent a lot of time trying to understand how legislation that was designed to protect the public from receiving treatments based on flawed and unreliable clinical trials, and to protect the safety and the rights and dignity of patients in trials, could have led to this expensive bureaucratic snarl-up. Most of the problems, he believes, were introduced after the proposed legislation was submitted by the Commission to the European Parliament and the Council of Ministers for consideration.

Speaking at a recent conference on the Future of Academic Clinical Research hosted by the Belgian Royal Academies of Medicine, Führing explained that the differing aims of Parliament and Ministers resulted in a kind of pincer movement on the draft legislation.

"The European Parliament was very interested in raising the status of the ethics committees to the same level as the national competent authorities [national bodies with responsibility for approving trials, medical products and the use of drugs]. And the Council of Ministers was very keen on avoiding anything that would involve a kind of political centralisation – any kind of cooperation in the assess-

ment of clinical trials."

The result is that clinical trial sponsors became accountable not just to the national competent authorities in each Member State where patients are enrolled, but also to ethics committees – organised at a national level in some countries, but at local or hospital level in others – hugely increasing the amount of paperwork involved and the number of hurdles to jump through. This in turn, says Führing, means that under the current directive, "there is virtually no mechanism for cooperation between Member States in assessing the clinical trial, even if this was agreed by the all 27 Member States."

Having spent more than a year conducting a full assessment of how the directive has impacted on clinical research in Europe, the commission is now redrafting the legislation with a view to formulating a proposal by October 2011. If the redraft is to serve clinical research, patients and the public any better than its predecessor, lessons of the past must be learned. "We are open to all kinds of ideas," Führing told the conference.

## Risk-adaptive regulation

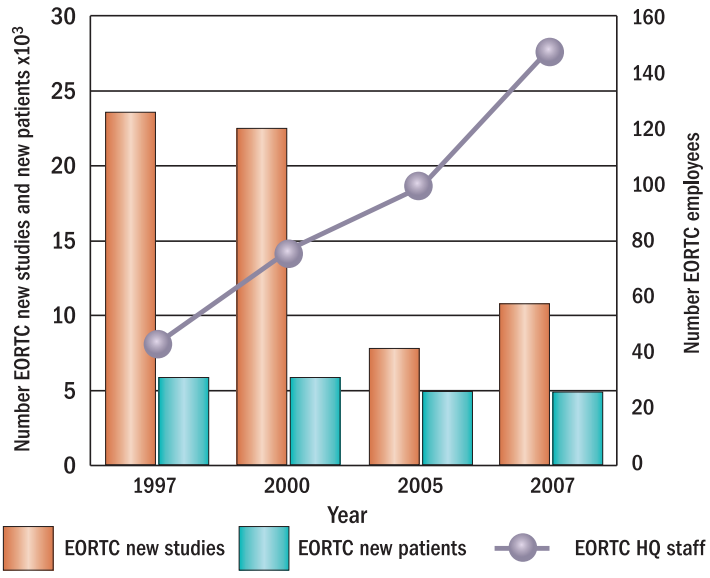
Over the past few years, many clinical researchers have been getting together in groups and forums to attempt to answer Führing's call for concrete proposals. It has not proved easy. One important principle around which a consensus has been building is that when trials involve little or no risk – for instance, an approved medicine used in an approved indication – they should not have to fulfil the same stringent regulatory requirements as more high-risk trials such as experimental gene therapy.

Such a system could substantially affect investigator-driven clinical trials, it is argued, because while four out of five clinical trials are commercial, non-commercial trials account for quite a high number of phase II trials, most of them looking at new uses (indication/population/condition) for medicines that are already authorised. Most phase IV trials (looking at how best to use approved medicines in the already licensed indication) are also sponsored by academic investigators.

An early exercise to map how such risk-adaptive regulations might work was conducted in January this year. The workshop drew participants from ECRIN (the European Clinical Research Infrastructures Network, set up in 2004), ICREL ( set up to assess the Impact on Clinical Research of European Legislation), and various European clinical research networks, including the EORTC. It sketched out the basis for categorising clinical trials into three levels of risk (see p 48), and looked at how the regulatory demands might be adapted accordingly in each of the following areas:

- Ethical review
- Assessment by national competent authorities
- Safety reporting
- Monitoring
- Requirement for a sponsor (a single body with legal responsibility for every aspect of the trial)

**FEWER TRIALS MORE RED TAPE**




**The number of new trials conducted by the European Organisation for Research and Treatment of Cancer (EORTC) plummeted from 24 in 2000 to 8 in 2005, a year after the Clinical Trials Directive came into force. This rose to only 11 new trials in 2007, despite a 50% increase in staffing levels**

*Source:* D van Vyve and F Meunier. Facing the challenge of the European Clinical Trials Directive. www.touchoncology.com. Republished with permission

The Council of Ministers was very keen on avoiding anything that would involve political centralisation

## Proposed risk categories

The Road Map Initiative for Clinical Research in Europe, held in Barcelona last January, proposed classifying clinical trials into three risk categories, which would determine how heavily they should be regulated.

**Category 1:** clinical trial on IMP [investigational medicinal product] without marketing authorisation in the EU. (Additional requirements could be proposed for trials with novelty-associated risks, as advanced therapies or first-in-human studies. This would correspond to a fourth, higher risk, category.)

**Category 2:** clinical trial on IMP with a marketing authorisation in the EU, but for another indication/population/condition. This raises the question of how to categorise low-novelty treatments, like drugs already available under a slightly different formulation (different salt, different routes of administration, slow release etc).

**Category 3:** clinical trial on IMP with a marketing authorisation in the EU, used in the licensed indication/population/condition. These trials are conducted to find the best way to use the drug.

A full report of the meeting can be found at www.ecrin.org – search for Road Map Initiative

- Insurance requirements
- Labelling (printed information that accompanies a drug specifying e.g. the batch number, and under which conditions the drug must be used)
- Documentation
- Inspections

The final report from that meeting can be found on the ECRIN website (search for 'Road Map Initiative'). As always, the devil will be in the detail, and a great deal of work will need to be done to delineate the boundaries between risk levels – concrete proposals to define exactly what is meant by terms such as 'minimal risk' and 'expedited review' can be sent on a postcard to Stefan Führing. The general principle of a risk-adaptive approach to regulation is, however, very likely to form a key part of the redraft of the clinical research directive scheduled for publication in October 2011.

### A question of interpretation

The biggest test for the redrafted legislation, however, may come in the way that it is implemented. European directives are designed to achieve certain results while leaving it up to Member States to decide precisely how to achieve them. This approach has worked reasonably well when, for instance, harmonising legislation covering the rights of people with disabilities or gender equality. It has proved a bureaucratic and administrative nightmare as a means of regulating international clinical trials, requiring trial sponsors to comply with procedures and demands that can differ widely from country to country, depending on how the directive was interpreted.

Framing some of the redrafted legislation in terms of 'regulations' which have legal force across Europe is an option, but cannot be achieved without greater support than the Council of Ministers has so far shown. Harmonisation, argues Führing, can only be achieved through building trust and forging agreement between countries on the 'nuts and bolts' of procedures and guidelines, rather than on basic principles. This is something his office has been trying to promote in a variety of ways, including:

- An ad-hoc group chaired by the Commission on implementing the Clinical Trials Directive guidelines
- A clinical trial facilitation group, chaired by Member States, which is implementing a Voluntary Harmonised Procedure, and
- An inspectors' working party, to help harmonise the interpretation and monitoring of 'good clinical practice' guidelines.

Progress in this arena could lay the basis for moving towards the sort of mutual agreement procedure that already operates for approving some drugs in Europe, whereby approval to start a new clinical trial from a competent authority in one country would open the way to approval by all.

Reporting suspected unexpected serious adverse reactions, (SUSARs), is another area with great scope for harmonisation. Currently, national competent authorities, ethics committees and the EU's own EudraVigilance all require different processes for reporting SUSARs, which involves significant additional work for the sponsors, the competent authorities and ethics committees, with no evident benefit for patients.

There may also be scope for streamlining the way insurance is dealt with. One suggestion at the Royal Academies conference was to make legislative changes to enable single deals to be nego-

Reporting suspected unexpected serious adverse reactions is an area with great scope for harmonisation

"Patients don't want to be just subjects of research, they want to be allies of research"

tiated that would cover all EU patients in a given trial regardless of where they were enrolled. An alternative suggestion is to agree guidelines with the insurance industry on risk levels, terms of cover and premiums. This could speed up and simplify proceedings and cut costs, which many delegates argued are unjustifiably high given the very strong safety record of clinical research and the strict ethical and good clinical practice controls in place. The problem is, commented one delegate, there is no one who can speak on behalf of Europe's clinical researchers in the way that the National Institutes of Health do for researchers in the US.

## Ethics committees

The hardest nut to crack will be how to streamline and harmonise the approval and monitoring of clinical trials at the level of ethics committees. Current procedures, say researchers, cause delays for no apparent benefit. Not only does approval have to be obtained in each Member State where the trial is running, but (in many countries) separate applications have to be made to each hospital where patients are enrolled. Convincing committees of the need to take biospecimens, and discussing how the privacy, dignity and rights of patients will be protected, can be particularly difficult; a lot of time is spent responding to requests from committees for detailed information. After all this, researchers may end up with a patient consent form that is 13 or 14 pages long, which can be complex and off-putting for patients to read and increases the time doctors need to spend with each patient invited to join the trial.

Proposals have been floated to change the system so that trials are referred to national ethics committees (a system already in operation in some Member States), or to go even further and have national ethics committees with mutual recognition, whereby getting approval in one Member State opens the way to approval in all. This is highly unlikely to happen. As delegates to the conference heard, Belgium alone has 200 ethics committees and they will quite understandably fight any move to undermine their independence.

After all, ethics committees are the only lay civic watchdog bodies amongst the multiple interlocking legal and administrative networks overseeing clinical research. It is surely right that the medical profession should have to explain itself to them and that they operate close to the patients where the trial is being conducted.

That said, there are clearly issues that need to be looked at. Training, first and foremost, so that ethics committee members understand the science behind today's personalised therapies. Guidelines could also be agreed to avoid repeatedly going over the same ground – a key example would be on harvesting and storing biospecimens and on procedures for anonymisation and access. These issues can take huge amounts of time to agree, even though they vary little from trial to trial. There is also scope for committees at different hospitals to work together in evaluating trials, even if this does not tie them into a single decision.

## Patient groups

The trump card in the effort to remove unnecessary shackles from clinical trials has to be the involvement of patient groups. When it comes to finding ways to improve treatments, no one has a greater sense of urgency than patients. As Kathy Oliver, Co-Director of the International Brain Tumour Alliance told delegates to the conference, "Patients don't want to be just subjects of research, they want to be allies of research."

Involve them in the design stage of protocols, and you decrease the likelihood of later problems with ethical committees and increase the chances of quick enrolment. Include them on ethics review bodies, and they will defend the rights of patients, but will also recognise the price patients pay for unnecessary delays. Involve them in drawing up consent forms, and they will help to ensure that forms are user friendly, that the language is clear and that they contain an appropriate level of detail. (You can also expect them to demand that more detailed patient-friendly information is also available elsewhere.)

In redrafting the Clinical Trials Directive, Europe has a second chance to devise a system that serves the needs of research, public and patients. Getting it right requires formulating workable proposals and then convincing the Parliament and the Council of Ministers to back them. Europe's clinical research community will need to speak with a coherent voice if it is to avoid a repeat performance of the four-year stand-off that saw the last directive batted to and fro between Parliament, Commission, and Council, becoming less and less workable with each journey. A strong alliance with Europe's patients is likely to prove very valuable.

# 200 mg/m² melphalan – the gold standard for multiple myeloma

Sergio Giralt

Palumbo and co-authors report on the results of a randomised trial comparing two doses of melphalan in patients with symptomatic multiple myeloma. Overall complete response rates, median progression-free survival and projected five-year overall survival were significantly higher among patients receiving the higher melphalan dose. These results confirm that for this patient population melphalan 200 mg/m² should remain the gold standard conditioning regimen.

Despite multiple attempts to design alternative therapies, autologous transplantation with high-dose melphalan remains the standard of care for transplant-eligible patients with multiple myeloma. A recent article by Palumbo et al.[1] reports on the results of a randomised trial that assessed treatment with two doses of melphalan in patients with newly diagnosed multiple myeloma, and was performed at Italian institutions from 2001 to 2006. The study was powered to demonstrate a 20% improvement in survival with 320 patients; however, owing to slow accrual only 298 patients participated in the trial.[1] This is the second randomised trial to confirm that melphalan 200 mg/m² should continue to be considered the gold standard conditioning regimen for patients undergoing single or tandem autologous transplant for myeloma. A previous study by Moreau et al.[2] demonstrated that melphalan 200 mg/m² was better tolerated and improved progression-free survival when compared to the combination of melphalan 140 mg/m² with 8 Gy of total body irradiation. Palumbo et al.[1] hypothesised that similar disease control could be achieved with fewer toxic effects if the dose of melphalan used for conditioning was reduced. At the time it was proposed this was an interesting question; however, since the initiation of the trial in 2001 the advent of bortezomib, thalidomide and, more recently, lenalidomide-based induction therapy for myeloma meant that this trial had lost much of its impact.

Despite the advent of novel therapies, some features of the recent Palumbo trial are worth mentioning. First, all patients received a standard combination of vincristine–adriamycin–dexamethasone as induction therapy with almost three quarters of the patients achieving at least a partial response after tandem transplants, regardless of the randomisation group. However, almost twice as many patients achieved a complete remission in the melphalan 200 mg/m² group compared with patients in the melphalan 100 mg/m² group (15% vs 8%; $P$=0.07). These results stand in contrast with the data from the studies by Cavo et al.[3] and Harousseau et al.[4] (published in abstract form) of randomised trials comparing bortezomib-based induction therapy to either thalidomide–dexamethasone or vincristine–adriamycin–dexamethasone induction displayed in the table.

If complete remission in myeloma is considered one of the most important surrogate endpoints for long-term disease control, studies that do not include modern induction therapy (such as bortezomib-based treatment) have a limited impact.[5] Despite this limitation, the Palumbo et al.[1] study is still important because it examined how much tolerance to high-dose melphalan can be improved by a 50% dose

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This article was first published in *Nature Reviews Clinical Oncology* 2010 vol.7 no.9, and is republished with permission.  doi:10.1038/nrclinonc.2010.104, www.nature.com/nrclinonc

**POST-TRANSPLANT BEST RESPONSE IN PATIENTS RECEIVING MELPHALAN CONDITIONING THERAPY**

| Study | Induction regimen | Conditioning therapy | Complete remission (%) | Very good partial remission or better (%) | Partial remission (%) |
|---|---|---|---|---|---|
| Palumbo et al. (2010)[1] | Vincristine–adriamycin–dexamethasone | Melphalan 100 mg/m$^2$ vs melphalan 200 mg/m$^2$ | 8 vs 15 ($P$ = 0.07) | 22 vs 37 | 50 vs 42 |
| Cavo et al. (2008)[3] | Thalidomide–dexamethasone vs bortezomib–thalidomide–dexamethasone | Melphalan 200 mg/m$^2$ | 20 vs 41 ($P$ <0.001) | 53 vs 75 ($P$ <0.001) | Not reported |
| Harousseau et al. (2007)[4] | Vincristine–adriamycin–dexamethasone vs bortezomib–dexamethasone | Melphalan 200 mg/m$^2$ | 28 vs 38 ($P$ = 0.127) | 50 vs 66 ($P$ = 0.021) | 88 vs 87 |

reduction. In this study, the 50% reduction in melphalan dose did not reduce transplant-related mortality (3% in each group), hospitalisation after engraftment or duration of severe (grade 3–4) neutropenia. Although the incidences of severe neutropenia and infections were higher in the melphalan 200 mg/m$^2$ group as well as the incidence of at least one nonhaematologic grade 3 or 4 adverse event, this difference was not as dramatic as the reduction in complete remissions in the 100 mg/m$^2$ group. Therefore, strategies to reduce the burden of treatment that occurs with high-dose melphalan should not focus on dose reduction (since this study demonstrates that even a 50% dose reduction was associated with similar toxic effects but a much lower complete response and disease-control rate), but rather look at other novel strategies of reducing symptom burden; rational strategies to explore would be increased stem-cell doses or the use of anti-interleukin-6 blockade treatment.[6,7]

Even with modern induction therapy and autologous transplant, many patients fail to achieve a complete remission and experience relapse before succumbing to their disease. A variety of strategies have been explored to try to improve upon the results of high-dose melphalan, including adding other agents and dose escalation with cytoprotectants, such as amifostine.[8,9] Of these, only tandem transplantation has been demonstrated in randomised trials to improve outcomes; however, more recently, the addition of post-transplant therapies with thalidomide or lenalidomide have also demonstrated efficacy and a potential survival benefit.[10]

Finally, the conclusion stated by Palumbo et al.[1] that melphalan 200 mg/m$^2$ should not be recommended for patients between the ages of 60 and 65 years is not supported by the data provided. This recommendation is based on an unplanned *post hoc* analysis of a subgroup consisting of fewer than 50 patients in each arm and was, therefore, underpowered to justify this conclusion. However, this analysis should provide impetus for studying the question of the ideal post-induction therapy for patients over 60 years of age. In summary, although associated with more toxic effects, melphalan 200 mg/m$^2$ continues to be the gold standard conditioning regimen for multiple myeloma autografts.

For future improvement of therapy in this patient population the role of single or tandem transplants in the context of bortezomib-based and lenalidomide-based therapies needs to be re-explored with large randomised trials, such as the one being planned by the International Myeloma Foundation and the Dana Farber Group as well as the recently initiated Blood and Marrow Transplant Clinical Trials Network Study looking at the role of tandem transplant versus consolidation versus maintenance therapy alone as post-transplant therapy for myeloma.

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

## Practice point

This study confirms that for patients younger than 65 years of age melphalan 200 mg/m$^2$ should remain the gold standard conditioning regimen to which other regimens need to be compared.

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*Competing interests:* The author has acted as a consultant for and received honoraria from the following companies: Celgene, Genzyme, Millenium Pharmaceuticals and Novartis

# Optimising chemotherapy and radiotherapy for anaplastic glioma

Patrick Morris and Andrew Lassman

The optimum approach for the treatment of rare anaplastic gliomas following surgical resection is uncertain. A recent study provides a greater understanding of the heterogeneous biology of these tumours and emphasises the prognostic importance of chromosome 1p19q deletion, IDH mutation and MGMT promoter methylation. The importance of radiotherapy and chemotherapy for treating these heterogeneous tumours is being elucidated for subgroups of patients.

Anaplastic gliomas are rare primary brain tumours, classified by the WHO as grade III malignant lesions. These tumours were historically grouped together with glioblastoma (WHO grade IV tumours) in clinical trials. However, anaplastic gliomas are distinct from glioblastomas, for which a clear standard of care now exists for newly diagnosed patients.[1] Anaplastic gliomas are heterogeneous, and include the spectrum of the relatively chemotherapy-sensitive anaplastic oligodendrogliomas (AOs), the more chemotherapy-refractory anaplastic astrocytomas (AAs) and mixed oligoastrocytomas (AOAs, also called anaplastic mixed gliomas). Therefore, there is a need to separate these entities, which have a varied natural history and biological characteristics, in order to define a more individualised approach to treatment.

Early analysis of two large international phase III trials showed no survival difference between treatment with radiotherapy alone, and radiotherapy before or after chemotherapy with procarbazine, lomustine and vincristine (PCV) for patients with AO

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or AOA.[2,3] Subgroup analyses, however, have yielded conflicting results depending on 1p19q deletion. Also, neither trial addressed the issue of chemotherapy alone as the first treatment or the use of temozolomide (TMZ) instead of PCV.

Against this background, Wick et al.[4] conducted the NOA-04 trial of radiotherapy versus chemotherapy in 318 patients with newly diagnosed anaplastic glioma who were randomised to receive either 60 Gy of radiotherapy or 32 weeks of chemotherapy following diagnosis by maximal surgical resection. Patients treated with chemotherapy were further randomised to either PCV or TMZ. Upon first progression, patients initially treated with radiotherapy received chemotherapy (randomly assigned to PCV or TMZ); those initially treated with chemotherapy then received radiation (exceptions discussed below). The primary efficacy endpoint was time to treatment failure (TTF), defined as progression after radiotherapy and one chemotherapy regimen (in either sequence). TTF did not differ between patients assigned first to treatment with radiotherapy or chemotherapy (42.7 months vs 43.8 months; $P$=0.28).

There have been few randomised controlled trials for patients with anaplastic gliomas and the report by Wick et al.[4] highlights the importance of large multicentre studies for these rare tumours. The authors have confirmed the significant heterogeneity of anaplastic gliomas (median TTF 29–32 months for AA versus ≥54 months for AO) and demonstrated that an age of >50 years (HR 2.6; 95% CI 1.5–4.3) and incomplete resection (HR 1.6; 95% CI 0.9–3.0) are significantly associated with shorter TTF. In addition, these results add to the growing body of evidence about the positive prognostic impact of mutations in isocitrate dehydrogenase 1 (*IDH*1) (HR 0.47; 95% CI 0.3–0.77), 1p19q codeletion (HR 0.47; 95% CI 0.3–0.83), and hypermethylation of the O6-methylguanine DNA-methyltransferase (*MGMT*) promoter (HR 0.59; 95% CI 0.37–1.1), independent of treatment.[4,5]

However, the design of the NOA-04 trial limits the broader interpretation of its results.[6] TTF was only reached after both treatment modalities had been delivered and demonstrated failure. The TTF concept – determining the impact of treatment sequence as well as treatment detail – is intriguing; however, TTF is not a typical efficacy endpoint, limiting comparison with other trials. Moreover, the protocol also called for patients without disease progression during initial chemotherapy to be re-treated with the same chemotherapy regimen at first progression, rather than radiotherapy, which was reserved for second progression. This paradigm was applicable in approximately 20% of patients. As a consequence, TTF was not uniformly defined as it included time to a differing number of relapses. Similarly, a 'modified' intent to treat (ITT) analysis, rather than a true ITT, was used, in part because 44 (14%) out of the 318 patients randomised were excluded for a variety of reasons. Although the rationale for such an approach is understandable, the results are, therefore, reported for patients 'as treated' rather than ITT – an unusual method in randomised, prospective trials.

An additional limitation of the NOA-04 trial was that only 37% of the participants (117 of the initial 318) reached TTF. The availability of fully mature data is a problem for trials that include patients with AO because many survive for over a decade. For example, median survival was not reached among patients harbouring 1p19q codeleted tumours treated with intensive PCV and radiotherapy in a randomised trial conducted by the Radiation Therapy Oncology Group, despite the 12 years that elapsed between the opening of the study and the first reported results.[3] Longer follow-up data from this trial suggests that survival may favour combined treatment in such patients.[7] Therefore, conclusions based on early analyses must be interpreted with caution.

The rarity of anaplastic gliomas also makes it difficult to accrue enough patients to allow sizable subgroup analyses. For example, in the NOA-04 trial there were only 39 patients (approximately 14% overall) with AO. Moreover, only 31 of these harboured the 1p19q codeletion. To increase the sample size for various analyses dependent on histology, the study grouped patients with AO and AOA ($n$=91) because no outcome difference was found between these histologies. However, the validity of this grouped approach depends heavily on the histologic definition of AOA, which was particularly strict in this trial – a limitation that was noted by the authors and hinders comparability with other trials. Treatment results were also not reported according to histology, *IDH* mutation, 1p19q deletion, or *MGMT* promoter methylation status, although it is likely that subgroups would be too small to draw meaningful conclusions about the respective benefit of different treatments. Similarly, the study was underpowered to compare PCV with TMZ for various subgroups, for whom recommended treatment depends at least in part on 1p19q deletion.[8]

The optimal approach to the treatment of patients with AO (or AOA) remains controversial.[8] There are limited data comparing PCV with TMZ, although the latter has been widely adopted[8] following its proven efficacy in other glioma subtypes[1] and

favourable toxicity profile. The CODEL trial (for 1p19q CODELeted tumours) is an international phase III study for patients with newly diagnosed 1p19q codeleted anaplastic glioma (most of whom will have AO). This trial (coordinated by the North Central Cancer Treatment Group as N0577) will compare radiotherapy alone versus radiotherapy in combination with TMZ versus TMZ alone.[9] Unfortunately, a comparison of TMZ with PCV is not part of that study design

For newly diagnosed AA there is reasonable consensus that postoperative radiotherapy is an important element of treatment. Although Wick et al.[4] reported no progression-free survival or TTF benefit from radiotherapy as the first treatment modality, more patients responded to radiotherapy than to chemotherapy. Similarly, more patients initially treated with chemotherapy required salvage radiotherapy compared with those initially treated with radiotherapy. Therefore, it is not clear from NOA-04 that radiotherapy and chemotherapy as the first treatment are truly equivalent.[6] The importance of initial radiotherapy is inherent in the design of the EORTC 26053-22054 Concurrent and Adjuvant Temozolomide chemotherapy for patients with NON-1p19q deleted anaplastic glioma (CATNON) intergroup study where all patients will receive radiotherapy as the backbone of initial treatment.[10] In this phase III trial, patients (most of whom will have AA) will be randomised to any of four treatment arms designed to assess the benefit of adding concurrent and/or adjuvant TMZ to radiotherapy.[10]

The NOA-04 trial clearly and importantly demonstrated that it is feasible to complete accrual to a multicentre anaplastic glioma study. The prognostic value of *MGMT* promoter methylation and *IDH* mutation also emerged, challenging future trial design to stratify by such new molecular findings, and further suggesting the importance of personalised therapy for anaplastic gliomas. Results from CATNON, CODEL and other ongoing trials for patients with anaplastic gliomas will be critical to refine the therapeutic approach by stratifying for known molecular aberrations, which should lead to more individualised treatment paradigms.

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## Practice point

Increasingly, advances in molecular biology are delineating the heterogeneity of the rare anaplastic gliomas, leading to an improved understanding of the prognostic importance of chromosome 1p19q deletion, *IDH* mutation and *MGMT* promoter methylation. The study by Wick and co-authors confirmed that chemotherapy and radiotherapy are effective treatments following optimal surgical debulking for patients with newly diagnosed anaplastic glioma. However, for subgroups of patients, the benefits of individual treatments are less clear. Therefore, randomised trials are ongoing to optimise patient outcomes by stratifying for known prognostic markers such as 1p19q deletions.

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*Competing interests:* Patrick Morris has received honoraria from the following companies: Eisai, Genomic Health, Pfizer, Haymarket Media Group, Bristol-Myers Squibb, Genentech, Novartis and Centocor Ortho Biotech. Andrew Lassman acts as a consultant for, and has received honoraria and research support from, Merck & Co. He has received research support from Keryx Biopharmaceuticals, Sigma Tau Pharmaceuticals and Genentech and acts as a consultant for Genentech, Eisai, ImClone and Cephalon

# NEWSROUND

Selected reports edited by Janet Fricker

## Olaparib shows promise in breast and ovarian cancer

➜ The Lancet

Two separate phase II proof-of-principle studies of olaparib (a novel oral PARP inhibitor) in patients harbouring *BRCA1* or *BRCA2* mutations with advanced breast cancer and recurrent ovarian cancer reported tumour response rates of 41% and 33% respectively.

In a commentary accompanying the two studies, Stephen Chan and Tony Mok, from the Chinese University of Hong Kong wrote, "These remarkable tumour response rates have undoubtedly proven the concept that a PARP inhibitor can suppress tumour growth in patients with *BRCA*-mutated cancers." The response rate, they added, was significantly better than the rate of 20% or less with cytotoxic chemotherapy. "It seems that PARP is the right target, and olaparib has successfully hit the target in both cancers," said the authors.

More than one million women worldwide are diagnosed with breast or ovarian cancer each year, with 5%–10% of them carrying germline mutations in *BRCA1* or *BRCA2*. Inside the complex of DNA repair machinery, the *BRCA* proteins play a crucial role via homologous recombination, while poly(ADP)-ribose polymerase (PARP) is a key component in base-excision repair of DNA. Preclinical studies have shown that inhibition of PARP leads to selective and significant killing of *BRCA*-mutated cells, a phenomenon which is not observed in cells with intact *BRCA* function. Olaparib is a novel, small-molecule, orally active PARP inhibitor with up to 1000-fold selective potency in isogenic preclinical models.

In the first paper Andrew Tutt and colleagues, from King's College London School of Medicine, undertook a multicentre proof-of-concept phase II study to assess the efficacy and safety of oral olaparib in women with *BRCA1* and *BRCA2* mutations and recurrent advanced breast cancer. In the study (undertaken prospectively in 16 centres in Australia, Germany, Spain, Sweden, the UK and US) women were assigned to two sequential cohorts. The first cohort ($n$=27) was given continuous oral olaparib at the maximum tolerated dose (400 mg twice daily), while the second cohort ($n$=27) was given a lower dose (100 mg twice daily). The primary endpoint was the objective response rate, assessed by use of RECIST.

Results show that the objective response rate occurred in 41% ($n$=11) of patients in the cohort assigned to 400 mg twice daily and 22% ($n$=6) in the cohort assigned to 100 mg twice daily. Toxicities associated with taking olaparib were generally found to be manageable.

"The results of this phase 2 study show that the oral PARP inhibitor olaparib at 400 mg twice daily was active even in women with *BRCA1* or *BRCA2* mutations and advanced breast cancer that was resistant to conventional chemotherapy. These findings provide proof of concept for the clinical usefulness of tumour-specific targeting of loss of *BRCA1* associated or *BRCA2* associated homologous recombination repair in patients with breast cancer," wrote Tutt and colleagues. "Importantly, there was no apparent excess toxicity with olaparib at the higher dose, which allows consideration of the use of this dose in future studies."

Notably, write the authors, response to olaparib was not restricted to patients given the least number of types of previous chemotherapy, suggesting a lack of overlap in resistance between most chemotherapy and PARP inhibitors.

In the second study, William Audeh and colleagues from Cedars Sinai Medical Center (Los Angeles, California) enrolled two sequential cohorts of women with recurrent ovarian cancer and confirmed genetic *BRCA1* or *BRCA2* mutations.

For the study (which was undertaken in 12 centres in Australia, Germany, Spain, Sweden and the USA) the first cohort ($n$=33) was given continuous oral olaparib at the maximum tolerated dose of 400 mg twice daily; while the

second cohort (*n*=24) was given continuous oral olaparib at 100 mg twice daily.

Results showed that the objective response rate was 33% (*n*=11) in the cohort assigned to olaparib 400 mg twice daily and 13% (*n*=3) in the cohort assigned to olaparib 100 mg twice daily. Olaparib was associated with predominantly mild to moderate adverse events, with the most frequently reported adverse events being nausea, fatigue and clinical diagnoses of haematological events.

"In our study, results suggest that PARP inhibition has a wide therapeutic window and sufficient tumour cell selectivity to target ovarian cancers that have defects in DNA repair by homologous recombination," write the authors.

In the accompanying commentary, Chan and Mok write, "Olaparib is potentially a new standard therapy for *BRCA*-mutated breast and ovarian cancers, yet more work is required to elucidate the mechanism of DNA repair and the best use of PARP inhibitors."

The benefits of a PARP inhibitor, they added, may not be restricted to patients with germline *BRCA* mutations. Recent data have shown that a subset of sporadic breast and ovarian cancers also harbour homologous recombination repair abnormalities as a result of epigenetic slicing of *BRCA1* or deficiencies in other components of repair. Indeed, they add, there are already preliminary data reporting clinical responses of olaparib in ovarian cancer patients without *BRCA* mutations at tumour biopsy.

One issue that remains unclear, write Chan and Mok, is how completely the PARP enzymes should be blocked to yield meaningful clinical activity.

■ A Tutt, M Robson, J E Garber et al. Oral poly(ADP-ribose) polymerase in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet* 24 July 2010, 376:235–244

■ MW Audeh, J Carmichael, RT Penson et al. Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof of concept trial. *ibid* pp 245–251

■ SL Chan, T Mok. PARP inhibition in BRCA-mutated breast and ovarian cancers. [commentary] *ibid* pp 211–212

## Training improves residents' skills in breaking bad news

→ British Journal of Cancer

Taking part in training programmes significantly improves the ability of medical residents to break bad news, a Belgian study has found. The study showed that courses in breaking bad news (BBN) skills increase the doctors' use of both assessment and supportive skills and decrease the amount of information transmitted. "Trained residents, as expected, used more open and open directive questions, more empathy and transmitted less information after training," write the authors Aurore Liénard and colleagues from the Institute Jules Bordet in Brussels, Belgium.

Breaking bad news is widely recognised as one of the most stressful and challenging communication tasks facing physicians, which impacts on their emotional states. There is growing recognition of the need for training in effective communication skills that allow doctors to manage the stress linked to the task. Recent guidelines have broken BBN into three distinct phases – preparation for the delivery of bad news, then the delivery of bad news and finally providing informational and emotional support to the patient.

Given the limited experience of BBN training for residents, Liénard and colleagues undertook the first ever study assessing in a randomised design the impact of a 40-hour training programme involving simulated patient BBN consultations. The training programme, which was spread over an eight-month period, focused on both two- and three-person consultations (where a relative accompanies the patient). A further three-hour session promoted the integration of learned communication and stress management skills. In the sessions, which were organised bimonthly in small groups of up to seven, participants were given the opportunity for predefined role plays in breaking news of a cancer diagnosis and discussing the transition from cure to palliation. They were given immediate feedback on the communication skills performed during the role plays.

In the study, 113 residents (with a mean age of 28 years) were randomised to the training programme or the waiting list. For the final analysis (after residents dropped out or were excluded from the study due to lack of attendance) 50 residents underwent the training programme and 48 were allocated to the waiting group. Communication skills were then assessed in a simulated patient consultation including a 20-minute first medical encounter, with an actress playing a 38-year-old woman given a diagnosis of breast cancer. The consultation audiotapes were then transcribed and analysed with content analysis software to indentify utterance types and contents, with utterances categorised into three main types: assessment, support and information.

Efficacy was assessed according to the time, in seconds, allocated to each of the three phases – preparation, delivery and support. Furthermore, one investigator read all the utterances and assessed whether the diagnosis was delivered precisely.

Results show that trained residents used effective communication skills more often than untrained residents. In comparison to the untrained residents, trained residents used more open questions (relative rate = 5.79; $P<0.001$); more open directive questions (RR=1.71; $P=0.003$) and more empathy (RR=4.50; $P=0.017$). Training also resulted in less information being transmitted (RR=0.72; $P=0.001$).

Furthermore, time taken in the pre-delivery phase of the consultation was increased for the trained subjects – with times showing 1 minute 46 seconds in the untrained group, and 3 minutes 55 seconds for the trained group ($P<0.001$).

"This study extends current literature on communication skills in that it shows that communication skills training programmes may improve residents' BBN skills in a simulated task," write the authors, adding that further studies are needed to assess the impact of BBN skills training on residents' BBN consultations and everyday interactions.

The authors note that trained residents used fewer emotional, medical and social words,

which allowed more room for patients to express themselves, adding that there was indeed found to be an increase in the number of emotional and medical words expressed by simulated patients.

■ A Liénard, I Merckaert, Y Libert et al. Is it possible to improve residents breaking bad news skills? A randomised study assessing the efficacy of a communications skills training program. *Br J Cancer* 13 July 2010, 103:171–177

## All vulvar cancer patients with sentinel node metastases require additional treatment

➔ Lancet Oncology

For patients with vulvar cancer, the risk of non-sentinel-node metastases increases with the size of the sentinel node metastasis, a secondary analysis of the GROINSS-V study samples has concluded. The Dutch study also found that there is no cut-off size below which chances of non-sentinel-node metastases were close to zero, leading investigators to conclude that all patients with sentinel node metastases should undergo additional groin treatment.

Currently, all patients with vulvar cancer who have positive sentinel nodes undergo inguinofemoral lymphadenectomy, irrespective of the size of their sentinel node metastases. But investigators studying other disease sites, such as breast cancer, have noted that size of sentinel lymph node metastases is of clinical significance.

Ate van der Zee and colleagues, from the University of Groningen, the Netherlands, reviewed slides from the earlier GROINSS-V study to categorise patients with T1-T2 squamous-cell vulvar cancer sentinel lymph nodes positive for metastases according to the size of their metastases. In the initial GROINSS-V study, 403 patients underwent sentinel node procedures between March 2000 and June 2006. Of these, 135 (33%) showed metastatic disease in one or more sentinel nodes.

The current analysis was limited to data from 307 (of the original 403 patients) who had undergone surgery for vulvar cancer and whose slides were available for review.

For the purposes of the current study, 723 sentinel nodes from 260 patients (2.8 sentinel nodes per patient) were reviewed. The proportion of patients with non-sentinel-node metastases increased with size of sentinel node metastasis. Non-sentinel-node metastasis was found in 1 of 24 patients with individual tumour cells and in 2 of 19 patients with metastases 2 mm or smaller, 2 of 15 patients with metastases between 2 mm and 5 mm, and 10 of 21 patients with metastases larger than 5 mm. The disease-specific survival was 69.5% for patients with sentinel node metastases larger than 2 mm compared with 94.4% for patients with sentinel node metastases 2 mm or smaller ($P$=0.001).

"The results of this study suggest that identification of sentinel-node metastasis in early stage vulvar cancer necessitates further groin treatment, regardless of the size of the metastasis," conclude the authors, adding that they did not find a cut-off size for sentinel node metastasis below which the risk of additional groin metastases became negligible.

Limitations of the study, say the authors, include: a 7% disparity between the original pathological assessment and the review; the fact that the number of metastases in each size category detected by routine pathology or ultrastaging were small; and for each groin they only assessed the largest metastatic focus in a sentinel node.

In an accompanying commentary Charles Lavenback of the MD Anderson Cancer Center in Houston, Texas, writes, "Unfortunately this recommendation means that 79 to 99% of patients who receive lymphadenectomy or radiotherapy for isolated tumour cells in an SLN biopsy will not benefit from treatment."

He adds that the question about the size of sentinel lymph node metastases requires a larger cohort of patients, which would necessitate international collaborations.

A second observational study, GROINSS-V-II, is currently investigating using radiotherapy to the groin instead of inguinofemoral lymphadenectomy as the additional treatment in vulvar cancer patients found to have positive sentinel nodes.

■ M Oonk, B van Hemel, H Hollema et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from RROSIN SS-V, a multicentre observational study. *Lancet Oncol* July 2010, 11:646–652

■ C Levenback. How important is size of sentinel lymph-node metastases in patients with vulvar cancer? [commentary]. *ibid* pp 607–608

## Chemotherapy benefits men with metastatic penile cancer

➔ Journal of Clinical Oncology

Neoadjuvant paclitaxel, iphosphamide and cisplatin benefitted men with cancer of the penis that had spread to the lymph nodes. The single-institution non-randomised phase II study found statistically significant improvements in time to progression (TTP) and overall survival (OS) among men who experienced objective responses to chemotherapy in comparison to those who did not.

While squamous cell carcinoma of the penis is uncommon in North America and Western Europe (approximately 1400 cases are diagnosed annually in the US), the condition is known to be more prevalent in Africa, South America and Asia, making it an important global health problem. Retrospective analyses of chemotherapy given as adjuvant or neoadjuvant treatment to lymphadenectomy for regional lymph node metastases have demonstrated feasibility for this multimodal approach, but have not allowed for firm conclusions about efficacy. Men with penile cancer have a low probability of surviving with lymphadenectomy alone, suggesting a multimodal approach to treatment would be desirable.

In the current study, Lance Pagliaro and colleagues, from the MD Anderson Cancer Center in Houston, Texas, performed a phase II

prospective non-randomised study of neoadjuvant chemotherapy in 30 men with stage III or IV penile squamous cell carcinoma and affected regional lymph nodes, but without distant metastases. Between April 2000 and September 2008, the patients received neoadjuvant treatment (four courses every 3–4 weeks) of paclitaxel 175 mg/m$^2$ on day 1, iphosphamide 1200 mg/m$^2$ on days 1–3, and cisplatin 25 mg/m$^2$ on days 1–3. The chemotherapy regimen was selected because it has been shown to have activity in squamous cell carcinoma of the head and neck.

Although the original intention had been to enrol 40 patients, the study was closed early as the objectives had been met and a slow accrual rate meant that several more years would have been required to reach the original target of 40 patients.

Results show that the vast majority of patients were able to tolerate the chemotherapy at full doses and on schedule, and 76.7% of them (23 patients) received all four planned courses. Of the seven patients who discontinued chemotherapy, three had rapid tumour progression, one showed hypersensitivity to paclitaxel, one had a cardiac event and two decided not to receive further treatment.

Results showed that 50% of patients (*n*=15) had an objective response (3 complete responses and 12 partial responses) and 73.3% (*n*=22) were able subsequently to undergo surgery.

At a median follow-up of 34 months, nine patients (34%) remained alive and free from recurrence. Improved time to progression and overall survival were both significantly associated with a response to chemotherapy (*P*<0.001 and *P*=0.001 respectively).

"Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy were effective in terms of the conventional response rate, time to progression and overall survival," write the authors, adding that surgery was shown to be feasible without increasing complications. This is the first prospective study of sufficient size to reliably estimate the outcomes of multimodality therapy for metastatic penile carcinoma, they say.

"We recommend the use of this neoadjuvant regimen as a new standard of care for multimodal treatment of men with regional metastatic penile cancer," the authors conclude.

■ L Pagliaro, D Williams, D Daliani et al. Neoadjuvant paclitaxel, ifosfamide and cisplatin chemotherapy for metastatic penile cancer: a phase II study. *JCO* 20 August 2010, 28:3851–3857

## Validated scale to help counsel patients with glioblastoma multiforme

➜ Journal of Clinical Oncology

A simple scale using easily obtainable preoperative data has been devised to provide objective information regarding post-surgical outcomes in glioblastoma multiforme (GBM). The US authors believe that the scale – which they validated in an additional study – will be helpful for both designing clinical trials and counselling patients regarding treatment options.

The median overall survival of patients with GBM – the most common primary intrinsic brain tumour of adulthood – has increased by only 3.3 months over the past 25 years. "This poor prognosis is largely due to the near universal recurrence of tumors after initial treatment with maximal safe surgical resection, radiotherapy and chemotherapy," write the authors, led by John Park, from the National Institute of Neurological Diseases and Stroke and the National Cancer Institute (Bethesda, Maryland).

In the study, preoperative and clinical radiographic data from 34 consecutive patients undergoing reoperation for recurrent GBM tumours at the NIH Clinical Center were analysed using Kaplan–Meier survival analysis and Cox proportional hazards regression modelling. Factors found to be associated with decreased postoperative survival (*P*<0.05) were then used to devise a prognostic scale. The scale was then validated using a separate cohort of 109 patients, who had undergone similar diagnosis and treatment at a different institution – the Brigham and Women's Hospital (Boston, Massachusetts). The sole outcome measure was survival time from the date of operation for tumour recurrence to the date of death.

The investigators found that the factors associated with poor postoperative survival were tumour involvement of prespecified eloquent/critical brain regions (*P*=0.021); Karnofsky performance status (KPS) ≤80 (*P*=0.030) and tumour volume ≥50 cm$^3$ (*P*=0.048). From this data an additive scale composed of these variables (with one point assigned for the presence of each variable) was developed that distinguished patients with good (0 points, 10.8 months); intermediate (1–2 points, 4.5 months); and poor (3 points, 1.0 months) postoperative survival.

When validation of the NIH Recurrent GBM scale was undertaken by applying it to patients treated at the Brigham and Women's Hospital, the median survival of patients with 3 points (*n*=3) was 1.9 months (95%CI 1.7–2.9 months); for patients with 1–2 points (*n*=57) it was 6.3 months (95%CI 4.8–7.9 months) and for 0 points (*n*=49) it was 9.2 months (95%CI 8.2–11.3 months).

Survival for the patients with 3 points differed significantly from those with 1–2 points (*P*<0.001, HR 3.00), as well as from those with 0 points (*P*<0.001, HR 2.97). Furthermore, survival in patients with 1–2 points differed significantly from those with 0 points (*P*=0.045, HR 1.48).

"The NIH Recurrent GBM Scale was devised and validated to generate objective information with which to advise patients with recurrent GBM tumors. In the broad health care context, it is an initial step in using comparative-effectiveness data to inform medical practices in the treatment of GBM recurrence," write the authors.

The NIH Recurrent GBM scale, they add, may also be helpful for stratifying patients for clinical trials, because of its prognostic power and ease of use. While patients with scores of 3 are unlikely to qualify for the majority of trials, those with scores of 1–2 and 0 should be enrolled or analysed in separate groups.

One limitation of the study, they note, is that it did not determine the survival benefit of reoperation per se, as all patients underwent surgery.

■ JK Park, T Hodges, L Arko et al. Scale to predict survival after surgery for recurrent glioblastoma multiforme. *JCO* 20 August 2010, 28:3844–3850