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Stella Kyriakides

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Stella Kyriakides: the torch bearer

Marc Beishon

When Dolly Triantafyllides, a prominent member of Cypriot society, contracted breast cancer in the late 1960s, she broke with traditional taboos and went public, becoming one of the island's first advocates. Many years after her death, her daughter Stella faced the same diagnosis. She took up the torch of advocacy and has been running with it ever since.

Many runners who carried the Olympic torch on its long journey to the Athens games last year publicised important causes – and none more so than Stella Kyriakides, president of Europa Donna, the European breast cancer advocacy organisation. She bore the torch as part of its leg through her home city of Nicosia, Cyprus, with supporters, wearing Europa Donna T-shirts, lining the route.

It was, she says, symbolic of her own journey as a woman who has experienced breast cancer both personally and in her family. Her mother was diagnosed with the disease in the late 1960s, when Kyriakides was a schoolchild – a time, she adds, when cancer was very much a taboo subject. "Even now it is still common to see reports of people losing their fight against the 'terrible disease', and not to see it by name," she says.

But starting with her mother, and later on in breast cancer awareness campaigns in Cyprus, Kyriakides says openness in society about the disease has slowly improved. "My mother and father were well-known people in what is still a small community, and she never tried to hide her condition," she says. "Right to the end of her life – and she lived with breast cancer for 10 years – she attended functions and got on with things. She was certainly, unknowingly, one of the first breast cancer advocates in Cyprus."

Today, thanks to Kyriakides and other Cypriot women, the country has an active national Europa Donna forum, while Kyriakides has become increasingly involved in the organisation at European level, first as vice-president, and then president in 2004. She sees Europa Donna as first and foremost a political, campaigning organisation that has done much to shape standards for breast cancer treatment and care – but still has a huge agenda on its plate.

In 2003 the European Parliament passed its first ever disease-specific resolution, laying down a 'gold standard' for pan-European breast cancer diagnosis, treatment and care. But as Kyriakides says, major variations in facilities and approaches among countries – and at regional and hospital level within countries – means that advocates

ELIGIO PAONI / CONTRASTO

"It's fine to ask for a seat at the table,
but your emotion can only get you so far"

At home with her husband Kikis and her sons Yiannis *(centre-right)* and Mihalis *(centre-left)*

"I remember waking up believing it would not be there – but of course it was"

and medical authorities need to engage in a complex picture of prioritisation and national 'politicking' if consistent improvements across Europe are to be realised.

It is an engagement that Kyriakides is well equipped to help lead. Her career to date – her 'day job' in other words – is as a child psychologist at the Archbishop Makarios hospital in Nicosia. But when she started out in 1979, psychology services for adults – let alone children – were virtually non-existent. Over 25 years, she has helped develop the shift in care of people with mental health problems from institutions to community-based rehabilitation, and set up the first child psychiatric department on the island.

But first, like many Cypriots of her generation, Kyriakides had to travel abroad to gain a university education to establish her credentials. At school, she worked as a volunteer with children to fulfil her community service requirement. "I knew then I wanted to work with children," she says. "It is fun and fascinating to see how they grow and develop, and how painfully honest they can be."

Eschewing a family tradition to study law – but with family encouragement – she duly went to the University of Reading in England to complete a degree in psychology, and then to Manchester for a Masters in Child Maladjustment. It was during her Masters that her mother died. "She was diagnosed with breast cancer when I was 11," says Kyriakides. "I often wonder if my choice of psychology is related to living through the experience of my mother's breast cancer during adolescence, and wanting to learn more about how people function. I do know I have never regretted studying psychology."

After her mother's death, she still had to complete her dissertation, which with the support of friends in England she did, and returned to Cyprus to begin work as a clinical psychologist in the Ministry of Health. "I was one of the first psychologists in Cyprus and a founder of the Cyprus Psychological Society – we were considered a strange breed at the time," she says.

Working in a mental health hospital for a number of years, she and her colleagues also helped set up the first rehabilitation programmes

and community homes for patients – sometimes using their own cars to drive them away from institutions. "I lived through the transition from institutionalisation to community mental health services. It was wonderfully exciting, but my heart was always in working with children."

Kyriakides went back to England – this time on a World Health Organization fellowship on child psychiatry at the Institute of Psychiatry – and then set up a small outpatients clinic for children in Cyprus. "I don't like to call myself a pioneer but the child psychiatry department where I now work was built from plans I held in my hand. We lobbied hard for this service. At first the department had no psychiatrists, only one psychologist – myself – and two nurses. Now we have 22 nurses, four child psychiatrists and eight psychologists. I've seen it grow day by day."

At first, Kyriakides did not expect to encounter the problems she saw while training in England, such as child abuse, thinking that Cypriot society was more close knit, with strong family ties. "But there were the same problems, although much more hidden," she says, adding that notification of abuse has now become more common since appropriate services have been in place.

Kyriakides and colleagues have also addressed the needs of children with serious medical as well as social problems. "I started working on paediatric oncology at a time when there was no children's cancer ward – they were given a room in the paediatric hospital and sometimes left there for months," she says. Now there is a range of children's specialisms at the Archbishop Makarios children's hospital, including oncology, and Kyriakides and colleagues are involved with diagnosis and care from day one.

Again, child cancer has been a taboo subject in Cyprus – and she has had to tread a careful pathway between protecting the child and the wishes of parents, and a strong belief that children do have a right to know about their disease. "Cancer takes children out of their normal journey – out of school, away from peers and affects their body image. They need to go through their treatment and also be psychologically healthy."

It is all very important and richly rewarding work that has been a cornerstone of Kyriakides' life – along with marriage and two sons, now 18 and 22.

But given her background and experience, what happened in 1996 – when she was diagnosed with breast cancer – still came as a great shock.

She wasn't unwell. Like many women, she felt a lump in her beast while showering, although because of her mother's history, she had also been having regular check-ups. It was her 40th birthday. "I chose to do what a lot of women do – nothing. I decided it would go away on its own. I remember waking up believing it wouldn't be there – but of course it was."

A visit to a doctor followed – but, as a friend, he could not believe it either, and said: forget it. "Then I was told it was a cyst and had a fine-needle aspiration – but there was no liquid and no one sent anything for biopsy. I visited a surgeon, who was complacent too. Then I called an oncologist friend in London who said it's probably nothing, but we don't leave palpable lumps in women with your history."

Back with the surgeon, Kyriakides had the lump removed – and a fast biopsy revealed that she did have breast cancer. Although she went through some denial, the whole process actually took only two weeks, but she involved only her husband and brother at the time of surgery – "I regret not telling my children earlier now," she says.

Determined to be open about her condition after the diagnosis – "I knew I had to come out with it immediately" – she went back to the hospital where she worked to see people before flying to England for a course of radiotherapy. "I could not have disappeared from hospital life for months with everyone thinking the worst was happening. But people were frozen – they couldn't believe it was happening to their Stella, whom they'd known for 15 years."

Despite her position in the medical world and her mother's breast cancer, there was a huge amount to learn. "Having a scientific background enabled me to read a lot of articles and understand the options, but to start with I didn't know what 'hormone receptor positive' was, what tamoxifen was, or what a linear accelerator was and why it was a good idea to spend three

"I needed to integrate the experience into my self and not act emotionally"

months in London on that machine and not with the cobalt option at the hospital in Cyprus."

In short, the doctors were speaking a foreign language of medical jargon – "I was surprised how little information there was in Greek, and I don't know what I would have done if I hadn't been fluent in English."

Her treatment was successful – although as she points out, being away from home having radiotherapy was a lonely time. "I spent hours walking in London, and saw so many movies. And I wondered how women in Cyprus without my level of expertise would have coped."

The seeds of her advocacy role were sown then, but it was to be a couple of years before she started. "I knew from my experience the frustration of women in Cyprus, and didn't have the European experience I have now," she says. "But first I needed to complete my treatment and focus on my family and work. I needed to integrate the experience into my self and not act emotionally, and wanted people to see me in my professional role – not a mixed front – and needed also to protect my family from what had happened."

Then, with a small group of other Cypriot women, Kyriakides formed a breast cancer awareness movement. Some 20,000 signatures were collected and presented to the country's president – "We stood in supermarkets and on the streets" – with the aim of lobbying for a national breast cancer policy.

"I'd been reading a lot about standards of excellence and what we needed to do to improve treatment," she says. "It was also about making people aware that the disease can be treated very effectively if you have early diagnosis and good care. And the message was that it affects us all – we found sponsors for advertising that actually used the words 'breast cancer'." After also giving media interviews, Kyriakides is now well known in Cyprus for her advocacy work.

At this time, the island was building its first oncology centre, and one of the consultants on the project encouraged Kyriakides to find out more about European work, in particular Europa Donna. So in 1998 she flew to the 1st European Breast Cancer Conference in Florence, where she encountered reality and shock – talks from doctors, for example, about five-year and seven-year survival rates. "I had thought: two years on and I'm cured," she says.

But there were also women standing up and asking questions, and of course the presence of Europa Donna, which has been one of the three partners behind each of the two-yearly European Breast Cancer conferences – the co-partners are the European Society of Mastology (EUSOMA) and the European Organisation for Research and Treatment of Cancer (EORTC). "Once I'd got hold of my personal feelings I was able to see the importance of putting over the views of the 'other side', and wanted to know more about Europa Donna."

Kyriakides quickly discovered that Europa Donna has a clear mission as an advocacy organisation – turning personal experience into political expertise, as she puts it – and it was not a support agency for breast cancer patients and their families. "But at times you need to advocate for change in order to safeguard basic breast care," she notes, adding that support groups are very important.

But the 10 pan-European goals formulated by Europa Donna in 1994 – which Kyriakides says remain unaltered today – have certainly proved to be agents for change, not least in the European Parliament's breast cancer resolution, which is a highly detailed call for minimum standards of screening and treatment, and ambitious targets "of creating, by 2008, the conditions required for a 25% reduction in the average breast cancer mortality rate in the EU and of reducing to 5% the disparity between the Member States in the five-year survival rate."

Carrying the torch for breast cancer patients. Supporters wearing Europa Donna T-shirts lined the route as Kyriakides carried the eternal flame through the streets of her home town, Nicosia, at last year's Olympic games

"At times you need to advocate for change in order to safeguard basic breast care"

As Kyriakides points out, the resolution is just the beginning. Getting national implementation is the key, and the realities for each of the countries in Europa Donna can vary from having few or obsolete mammographic machines up to proper screening programmes in dedicated breast units. "As for the targets, if we come out and say they are too ambitious we have shot ourselves in the foot. We are going to try – it's about putting the pressure on at European and national level."

Objections to the resolution, she says, have come from some authorities in states that feel the bar has been set too high. "But the resolution was not put together by taking the crème de la crème of two or three healthcare systems – it did take into account variabilities in Europe, and laid down the minimum standards for women with breast cancer."

Together with other advocates – in particular Karin Jöns, the Member of the European Parliament (MEP) who was rapporteur on the resolution (and who is also president of Europa Donna Germany) – Kyriakides says they will not let up the pressure, especially as there has been a large influx of new MEPs after the last round of elections. At a European level, Europa Donna has instigated an annual training programme to equip advocates with the skills and knowledge needed to lobby effectively for service improvements. The programme takes 2.5 days – the most recent was in Milan in November – and comprises a packed agenda of science and communications training and workshops.

"It's a very tight programme. We need to give information about breast cancer as a disease – its science and epidemiology – and about how to be effective as lobbyists," says Kyriakides. The toughest part of the course for most delegates – and there were 27 at Milan, each from a different Europa Donna country – is the basic science. "But if you are an advocate for, say, better screening you need to know about the biology of cancer," she says.

"It's fine to ask for a seat at the table, but your emotion can only get you so far. You're in danger of being seen as a breast cancer patient talking about your personal experience, and that's not the point. We have to put forward an educated and responsible voice. But it takes training and time."

"If we come out and say the targets are too ambitious, we have shot ourselves in the foot"

For national service improvements, it is also not enough to know about effective treatments without doing a lot of research about the resources available. Out of the European Parliament's resolution, Kyriakides says screening is clearly a priority for countries yet to introduce programmes. "But if you pick up cancer at a very early stage and you don't have the right histopathology and surgery set up, it may not be effective," she says. Likewise, all the machinery in the world makes little sense without trained radiographers. Surveys of services are crucial first-line research. At home in Cyprus, a national screening programme is now in place, but Kyriakides and colleagues have recently turned to another key issue. "Unfortunately, we do see cases of surgery that women are very unhappy about – it's a Pandora's box we had to open and we got the reaction we expected."

In 2004, Europa Donna in Cyprus went public with criticism that too many surgeons were carrying out small numbers of breast cancer surgery – and the Surgeon's Association responded with a statement along the lines of "who operates on whom is not a matter for public dialogue."

"Women should have a complete picture of their tumour type and the options available, including the type of surgery they require," says Kyriakides. "We have women – not just in Cyprus – coming out of surgery with mastectomies they may not need. I am an advocate for surgeons doing a minimum number of new cases, as the Resolution specifies. We have excellent surgeons in Cyprus – but too many are doing breast cancer operations."

It is a stand-off that surgeons are unlikely to win in the long run, as Kyriakides says the essential plank of advocacy has been laid – namely they have been collecting outcomes over a number of years. "When you decide to open up an issue, you must get your facts right." The most desirable outcome, from her viewpoint, would be the establishment of one or two dedicated breast units to handle the relatively small number of cases in the country (about 300 a year) staffed by multidisciplinary teams.

In a wider context, that Europa Donna has a 'seat at the table' is now a given – its full title, after all, is the European Breast Cancer Coalition – and it is also involved at the cutting edge of research on the global stage. Kyriakides mentions 'TransBIG', a worldwide translational research consortium run by the Breast International Group (BIG); Europa Donna sits on its steering, ethics and spreading of excellence committees.

"Our role is to help disseminate information that comes out of trials to women as quickly as possible," she says. "I think trials are much misunderstood, which is why a lot of women do not take part. They often think it's a choice between a placebo or new treatment. We have a booklet on trials in English, which we encourage national forums to translate into local languages. We certainly want more women enrolled in trials."

Breast cancer research and treatments are changing very rapidly, and progress certainly provides another powerful reason for Europa Donna's work, as all country activists, from those struggling to establish basic services up to those with well-developed infrastructures, need access

"We have excellent surgeons in Cyprus – but too many are doing breast cancer operations"

to latest information. But it is sometimes said that breast cancer receives more than its fair share of resources.

"People should realise it is getting the share it should have," says Kyriakides. "There is one new diagnosis every 2.5 minutes in the European Union and a woman loses her life every six minutes. We should always be top priority on the political agenda.

"I think too that what we have achieved in breast cancer is benefitting other types of cancer. It's not that we will make it more difficult for others to move on – they will move on with us."

That breast cancer mainly affects women (fewer men also contract the disease) has been part of the reason why advocacy has been successful, adds Kyriakides.

"I think that women organise themselves more effectively, and breast cancer affects us mainly when we are involved in multiple roles – as a mother, at work. So it has a great impact on society in general – and that means that many men have also become our strongest voices and advocates."

She comments that the first breast cancer advocacy groups evolved from the women's movement in the US – while Europa Donna itself was initially the idea of famous Italian surgeon Umberto Veronesi.

As the most recent Europa Donna president, Kyriakides' main concern is to maintain the momentum that organisation has generated, and she feels a great responsibility for advocacy work, especially as a representative at European Union level. A personal vision she has is to cater specifically for the needs of younger women with breast cancer, a group she feels face some very different issues from older women.

She has also been widely recognised for her advocacy work – in 2001, she was voted Woman of the Year in Cyprus, and was also runner-up as European Woman of the Year.

Early last year, shortly after being elected president of Europa Donna, Kyriakides suffered a second breast cancer, which required more radical treatment than before. "People say it must have been more difficult for you – it was not harder, just different as I knew what questions to ask and what to do, and I did not have the feelings of panic I had then." Crucial advice for a woman facing breast cancer, she adds, is to take your time and research the options properly.

The treatment was short enough for her to resume her work – but for a while she considered relinquishing the Presidency, as she was concerned she would not be able to effectively fulfil her role. Kyriakides spends the mornings and early afternoons as a child psychologist, catching up with e-mails and Europa Donna work later on. As the current President she has cut down her involvement in the Cyprus forum somewhat.

"Breast cancer doesn't get more than its fair share. We should always be a top political priority"

Free time she likes to keep unstructured – "I like to relax, chat with my sons, walk the dog and pass the time of day. Generally I'm a happy bouncy person."

She finds advocacy work tremendously rewarding. "If someone had said when I had breast cancer in 1996 I would be doing this now, I would have said 'no way'. It has brought out a positive and creative side in me I never knew I had, and I have also met many wonderful people.

"Someone said in one of our workshops, 'Breast cancer is the best thing that ever happened to me because it made me change my priorities,' and I see what she means. I remember after my first cancer experience seeing sunflowers outside the hospital and thinking how beautiful they were – of course, they were always like that. But you shouldn't have to go through breast cancer to feel like that."

Cancer in pregnancy: the cruellest dilemma

Anna Wagstaff

When a pregnant woman discovers she has cancer, her doctor faces a challenge with few guidelines, and little evidence of optimal treatment. The woman faces a cruel dilemma – does she lose the baby to save her life, or risk her life to try to save the baby?

Pregnant women are rarely diagnosed with cancer. The incidence is around one case in every 1000 pregnancies, but it has been rising for some time, largely due to the trend towards delaying starting a family. It poses a unique set of problems, which vary according to the stage of pregnancy, and the nature, location and stage of the cancer.

Treatment that may be essential for the mother may be fatal or highly damaging to the fetus. Achieving the best outcome possible in the circumstances is a real challenge for the physician.

40 WEEKS: THE BABY'S STORY

A normal full-term pregnancy lasts around 40 weeks. It is perfectly normal for babies to be born up to two weeks early. Delivery at 36 weeks is unusual, but, while not ideal, is considered fairly safe nowadays. In cases of real need, babies can be induced at 30 weeks in specialist units under the care of expert obstetricians, who use steroids to speed up lung development.

This is not an ideal start in life, and spending weeks in an incubator is also not the best start to any mother-child relationship. Moving the delivery date any earlier is dangerous and runs a high risk of long-term health consequences.

40 WEEKS: THE MOTHER'S STORY

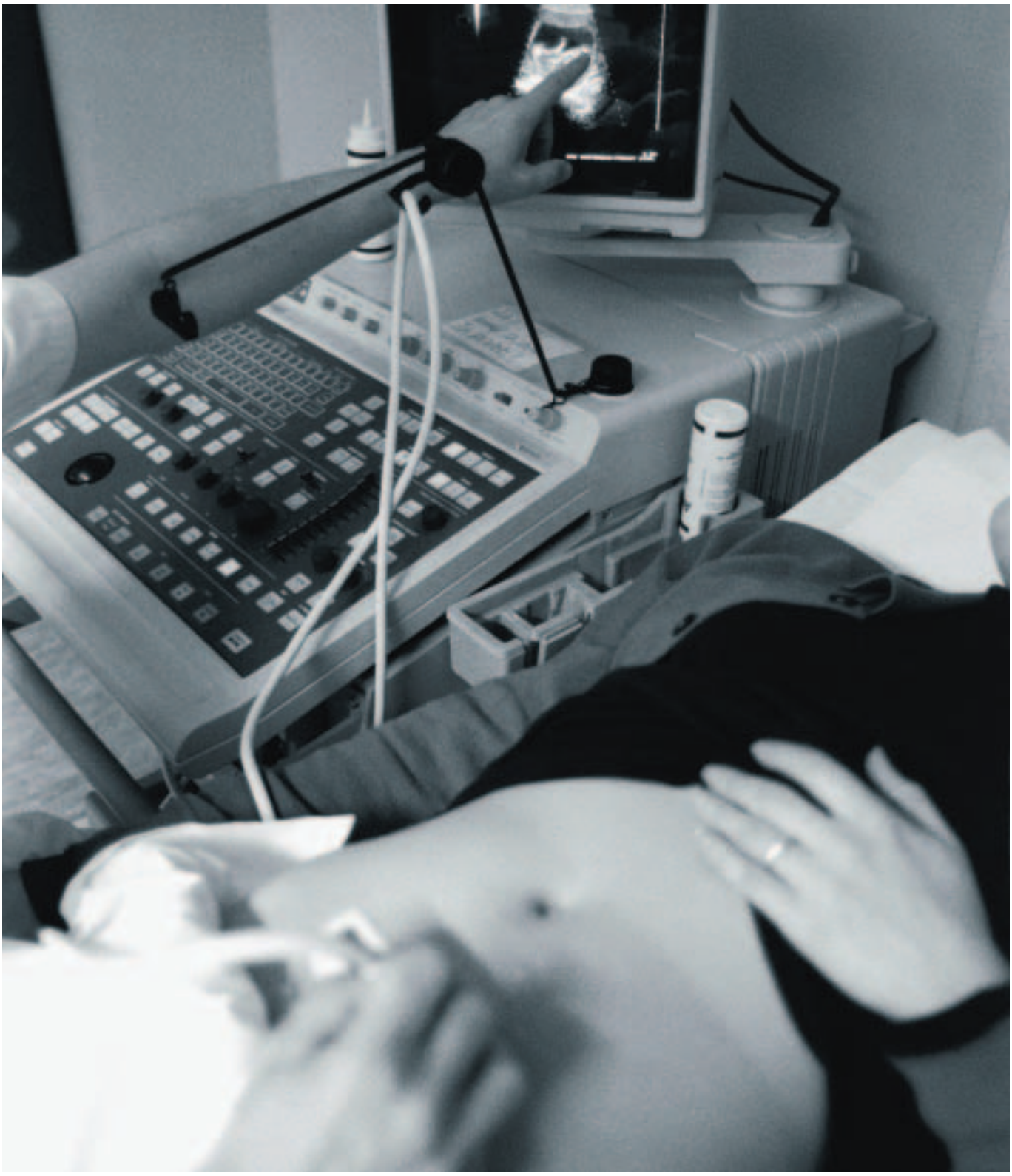
For a woman diagnosed with cancer, waiting 40 weeks for treatment could be a death sentence, particularly with high-grade, aggressive or metastatic cancers. Even in earlier or more indolent cancers, a 40-week delay would be reckless, allowing the cancer the opportunity to develop and spread into incurable disease.

THE MEDICAL DILEMMA

In this situation, there are not many options, and none of them are ideal.

One option is to delay the treatment until the child can safely be delivered. This poses a risk to the mother that may be hard to quantify. It also means she will have to care for a very premature baby while coping with the side-effects of cancer treatment. This option is more viable the lower the risk posed by the cancer and the more advanced the pregnancy.

A second option is to terminate the pregnancy to allow normal treatment to go ahead. This may be the safest option for the mother's health, but will be unacceptable to some mothers who do not accept abortion on any grounds. Leaving the mother without her baby is a particularly heavy blow given that the treatment may make it impossible for her to have any more children. This option is more likely to



OWEN FRANKEN / CORBIS / CONTRASTO

LATE DIAGNOSES

Cancer in pregnancy is often detected later because symptoms are masked by other body changes.

- Engorged breasts make it harder to detect breast cancer, and palpable lumps are often misdiagnosed as blocked milk ducts.
- Signs of cervical cancer may be misunderstood. One woman was hospitalised twice because of vaginal bleeding, wrongly attributed to complications with the pregnancy. Cervical cancer was diagnosed only after the baby was delivered by caesarean section, by which time it had spread.

Midwives and obstetricians must be aware of the need to rule out cancer when presented with these symptoms.

be considered early in pregnancy, when an abortion may be less traumatic and when the patient would otherwise have to wait a particularly long time for treatment.

A third option is to treat the cancer as effectively as possible while continuing the pregnancy and trying to minimise the risk to the fetus. The trouble is, there is still a lot we do not know about those risks.

The decision is not helped by difficulties in ascertaining how far the cancer has developed. Some staging techniques, such as certain blood tests, cervical cytology and mammography, are unreliable in pregnant women because of changes associated with pregnancy. Others, such as cone biopsy of the cervix early in pregnancy, CT scans, abdominal X-rays and any form of radionuclide imaging, are dangerous to the developing fetus. While ultrasound and MRI can be used as suitable alternatives, checking whether the cancer has spread to other organs or bones can be very difficult, and doctors may have to develop a treatment plan on the basis of an incomplete picture.

WHERE'S THE EVIDENCE?

The treatment of cancer in pregnant women is a grey area within a discipline that is increasingly dominated by evidence-based medicine built on data from ever greater numbers of clinical trials. The extra risk posed by delaying treatment a couple of months or the dangers to the fetus of, for instance, administering hydroxyurea in the first trimester are not the stuff of randomised controlled studies. New drugs are coming onto the market all the time, but there is no information about how they are likely to affect embryonic or fetal development. For this sort of information we have to rely on case reports, and it is only recently that attempts have been made to gather the information together by collecting published case reports and series or by setting up prospective registers.

Take radiotherapy. The dangers of radiotherapy to the developing embryo/fetus are relatively well known (see box) from studies after the bombing of Hiroshima and the Chernobyl disaster. While no one would contemplate delivering radiotherapy to the cervix or abdominal area during pregnancy, there is no consensus on the dangers posed by radiotherapy above the diaphragm.

Antonella Surbone, who worked as a specialist in breast cancer and pregnancy at the Memorial Sloan-Kettering Cancer Center in New York, believes that radiotherapy should not be used at all in breast cancer during pregnancy. Sibylle Loibl, from Frankfurt University Women's Hospital and the German Breast Group, is heading a study into treatment of breast cancer in pregnant women under the umbrella of the Breast International Group (BIG), with a view to drawing up international guidelines. She is also strongly opposed to the use of radiotherapy during pregnancy, but says that other experts involved in drawing up the guidelines are more open to the possibility.

RISKS OF RADIOTHERAPY

Radiotherapy is contraindicated in pregnancy, although some specialists use it above the diaphragm with abdominal shielding, particularly in later stages of pregnancy.

Therapeutic doses of 5000–6000 cGy expose the fetus to 10 cGy in early pregnancy and 200 cGy or more in later pregnancy

Doses over 2.5–5 cGy pose a high risk for malformation in early pregnancy.

Likely effects

From conception to days 9/10	lethal
Weeks 2–6	malformation, growth retardation
Weeks 12–16	mental and growth retardation, microcephaly
Weeks 20/25 to birth	sterility, malignancies, genetic defects

Treatment that may be essential for the mother may be fatal or highly damaging to the fetus

Jacek Jassem, a leading Polish oncologist who specialises in both radiotherapy and medical oncology, believes the risk is relatively small. He argues that "If you are pregnant and the cancer is located in the supraclavicular left node, you can safely radiate the patient above the diaphragm with shielding of the abdomen, even in the first trimester." He says that there is a small risk to the fetus, and he would not recommend radiotherapy lightly. However, he would consider it as an option, for instance, in cases of Non-Hodgkin's lymphoma requiring immediate treatment, if the mother did not want to abort.

These differences are reflected in analyses of case reports of breast cancer in pregnancy gathered from the literature. In some studies the majority of women were treated with radiotherapy, while in others radiotherapy was never used.

When it comes to chemotherapy, the picture is not much clearer. Given that cytotoxic drugs are designed to inhibit cell division, they could be expected to damage a developing embryo or fetus. Evidence from laboratory studies, animal tests and case reports show high levels of teratogenicity and fetal deaths for many common drugs delivered in the first trimester. The risk levels in the second and third trimesters are not well established for the majority of drugs. In the last few years some major studies have indicated that the risk is fairly low for many of the most commonly used, including the AVBD regimen (dacarbazine, bleomycine, vincristine and doxorubicin) for Hodgkin's lymphoma, a variety of standard treatments for leukaemia and Non-Hodgkin's lymphomas, and adjuvant therapy for breast cancer.

In the absence of robust evidence, many doctors are reluctant to offer opinions on the safety of these treatments. This may be good science, but some patients object that it leaves them no basis on which to take important personal decisions.

Jan G is a young (male) patient activist from Germany who has chronic myelogenous leukaemia (CML), the same cancer that affected Megan Smith (see Megan's story, p. 21). He runs the website leukaemie-online.de, about the condition, and understands patients' frustration at the lack of information. "All information is so sensitive regarding pregnancy, fertility and so on that nobody is prepared to talk about it nor publish data unless they are 100% certain.

"However, young patients are faced with those issues and have to decide on uncertainty." He has often thought about building a database where patients can publish their personal 'Glivec baby' data, for other young patients to see. "Even if the data are neither comparable nor statistically significant, it would be better than having no indicative data at all!"

RISKS OF CHEMOTHERAPY

Almost all drugs cross the placental barrier to some extent. As chemotherapeutic drugs work by inhibiting cell division, they pose a risk to the developing fetus.

Chemotherapy drugs are associated with spontaneous abortion, malformations, teratogenesis, mutations, carcinogenesis, organ toxicity and retarded development.

1st trimester

Damage is more likely to occur in the 1st trimester. The rate of chemotherapy-associated fetal malformation at this stage of development has been estimated at 12.7–17% with single-drug regimens and up to 25% with combination regimens, compared to a population rate of 1–3%. Low birth weight occurs in around 40% of cases.

2nd and 3rd trimesters

Many drugs pose a relatively low risk to the fetus in the 2nd and 3rd trimester. Some doctors prefer to wait until the development of the central nervous system is complete, around the 16th week.

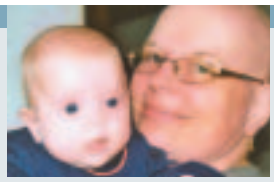
Delivery

If a baby is delivered within 2 weeks of the last chemotherapy dose there is a risk of a neutropenic baby being born to a neutropenic mother.

Breastfeeding

Breastfeeding is inadvisable for women who have recently been on chemotherapy.

Christina Brenne
Trusting her instincts



Christina Brenne was pregnant with her second child when she noticed a lump in her breast and mentioned it at a routine check up. Her midwife arranged an appointment with a doctor who told her it was a blocked milk duct. Christina was not convinced, since this was different from her previous pregnancy. The doctor reluctantly referred her to the breast clinic, but with a low priority at the back of the queue.

After six weeks she phoned to ask about the delay in her appointment. There had been a cancellation and she was called in the following day. They did a palpation, a mammogram, an ultrasound examination and a puncture biopsy.

The mammogram showed negative. The other two examinations were both positive.

She was seven months pregnant when she was told by the breast specialist that she did have cancer. The doctor said he had consulted an obstetrician and had made up his mind what to do: her baby would have to be delivered at 32 weeks so they could operate on the breast.

Sleepless night

Shocked and distressed, she spent a sleepless night before ringing the clinic to press for an alternative plan, but was told that very premature delivery was the only option. It was only at a chance visit to her General Practitioner over an unrelated problem that she learned that operating on pregnant woman was routine.

She called the clinic, demanded the name of the obstetrician who had supposedly refused the operation, and phoned him. He told her he had never raised objections, and had in fact offered to co-ordinate her care, since the operation would be done by the breast specialist surgeon at his hospital, which had a special obstetrics unit. He now repeated that offer, which she accepted.

She was given a choice between breast conserving surgery and radical mastectomy. She chose mastectomy, because she was very keen for her child to be breastfed, and the surgeon had promised that this option would avoid the need for chemotherapy.

Let down

The surgery went well and she was happy to be looked after on a postnatal ward, even though the staff were not experienced in surgical cases. However, it turned out that she had the most severe form of cancer. Despite earlier promises, she was now told that she would need to start adjuvant chemotherapy as soon as the baby was born.

Christina felt very let down. She decided to ask for the baby to be induced two weeks early, so she could use that window to breastfeed. Having originally had to fight not to have her baby delivered eight weeks early, she now found that the hospital was slightly reluctant to induce the child even two weeks early. Christina wasn't going to give up now. She won this battle, and breastfed baby Sissela for 17 days.

She gave Sissela a final feed on the hospital bed as needles were being inserted for her first treatment. Christina is now disease free. Sissela is nearing her third birthday, and her older sister Lovisa is seven. Christina's advice to other women is: "Think for yourself – is this really what you want? Always get a second, third or even a fourth opinion."

The doctor said he had consulted an obstetrician and had already made up his mind what to do

OWEN FRANKEN / CORBIS / CONTRASTO

Treating cancer in pregnant women is a grey area in a discipline led by evidence-based medicine

Where is the expertise?

The paucity of evidence on therapy options is not the only problem for doctors. There is also a very small base of expertise – few oncologists come across more than 20 or 30 of these rare cases in their entire career, most will come across far fewer. Surbone says it is important that clinicians recognise their own limitations, "If you get such a patient, try not to handle the case on your own. Refer the patient to a centre where they have experience, where they have a joint oncology/ObGyn service." If this is not possible, a close working relationship between the oncology team and the obstetrics team is vital.

The story of Megan Smith, the CML patient treated in Toronto by a leukaemia specialist working with the head of a high-risk obstetrics unit, is an example of what can be achieved (see p. 21). The story of Christina Brenne in Sweden (see p. 18), shows what can happen when breast cancer specialists don't work well with obstetricians – in this case, despite the obstetrician's advice, her specialist insisted she had no option but a very premature delivery, because he would not recommend surgery while she was seven months pregnant.

Loibl says that many German doctors insist on a very premature delivery in preference to giving the patient adjuvant chemotherapy, even in late stages of pregnancy. She attributes this to the fact that breast cancer in Germany is treated by gynaecologists, many of whom do not specialise in oncology and lack expertise in chemotherapy. As well as underlining the need for breast cancer to be treated by specialists, this illustrates the need for expertise in both obstetrics and oncology in treating a pregnant woman with cancer.

Where are the guidelines?

Many physicians would welcome guidelines to point them in the right direction. These are hard to come by, even in breast cancer, the cancer most frequently diagnosed in pregnancy. The Italian Association of Medical Oncologists is unusual; it does offer guidance on diagnosis, the use of radiation and chemotherapy, recommended surgical procedures and the importance of working with a multidisciplinary team. However, no such guidelines exist in the UK or the Netherlands – two countries that lead the field in clinical guidelines. Nor have guidelines yet been drawn up by

There is no consensus on the dangers posed by radiotherapy above the diaphragm

the European Society of Mastology.

Two separate developments may soon change this. Two years ago, Nicholas Pavlidis of the Ioannina University Hospital in Greece, wrote a paper with recommendations for the diagnosis, staging and treatment of cancers most commonly found in pregnancy and outlining the circumstances under which a termination of pregnancy should be recommended. He has now proposed that the Guidelines Task Force of the European Society of Medical Oncology (ESMO), on which he sits, draw up more formal guidelines, despite the lack of randomised studies or meta-analyses. He says that level 3 or 4 guidelines, which have lower standards of evidence, would be a great deal better than nothing.

The second new guideline initiative is spearheaded by Loibl at the University of Frankfurt. In October 2003, she called an international meeting, involving surgeons, oncologists, radiologists and breast diagnostic specialists from MD Anderson in the US, Guy's & St Thomas's in the UK, the Centro di Riferimento Oncologico in Italy and a number of German centres, to discuss and draw up international guidelines on the diagnosis and treatment of breast cancer in pregnant women. Loibl expects these to be finalised and published early this year.

The Frankfurt initiative is also running what is probably the first prospective study using a standard protocol for treating cancer in pregnancy. It involves the use of breast conserving therapy for women diagnosed with early stage breast cancer after the first trimester. The standard treatment in most countries is a radical mastectomy, on the grounds that breast conserving surgery has to be followed by radiotherapy, which is not advisable in pregnancy. Loibl's team argues that, given the trend to administer chemotherapy for between 18 and 24 weeks, there is no harm done in delaying radiotherapy until the child can be delivered at 36 weeks, and they expect the results of the trial to prove this. If correct, this would establish one of the first pieces of firm evidence in this area of medicine.

Publication over the past year or two of studies bringing together the results of substantial numbers of cases treated with a variety of drugs is another brick in the evidence base. Fedro Peccatori and a team at the European Institute of Oncology are now setting up a European registry for all patients given chemotherapy during pregnancy, in order to facilitate this process.

The mother's dilemma

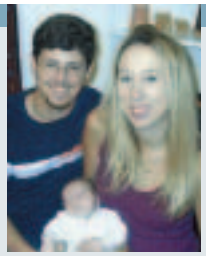
Lack of evidence, expertise and guidelines represent the challenge to professionals. Whatever the state of the evidence, there is also a painful human dilemma for the pregnant woman, or couple. The three-way choice between terminating a pregnancy, accepting treatment that may cause severe damage to the fetus, or delaying treatment with possibly life-threatening results is one that has to be made by the patient, not by doctors.

Each story is different, as shown by the following examples, which came from doctors and patients in Germany, Sweden, the Netherlands, Poland, Greece, Ireland and the UK, in the course of researching this article.

A woman diagnosed with early stage breast cancer opted for abortion and immediate treatment, because she had two young children dependent on her and was not prepared to take any chances.

A woman with three young children was discovered to have a 5-cm lump, eight weeks into her pregnancy. She underwent a radical mastectomy and

Patients object that it leaves them with no basis to take decisions of enormous personal importance



Megan Smith
Sticking to her convictions

Megan Smith was a 22-year-old biology student from Peterborough in Canada when she went to her doctor with suspected appendicitis. He told her she was pregnant. A minute later he told her that she had some form of leukaemia and she would have to terminate the pregnancy because she needed treatment right away. He said that the drugs would terminate the pregnancy anyway. "It just isn't worthwhile for you going through that stress later on."

Megan and her husband spent two distraught hours in the hospital corridor. "We didn't know what type of leukaemia it was; if I was going to be dead within a few months." They had always wanted children, and were opposed to abortion. When they told the doctor they would not terminate the pregnancy, he said he could not treat her, and referred her to a specialist oncologist in Toronto, two hours drive away.

In Toronto things started to improve. The specialist explained the disease, and spelt out the options. The only cure, he said, was bone marrow transplant, and chemotherapy, which would probably end her chances of conceiving again. He too said she needed immediate treatment and that the drugs would be highly likely to bring about a miscarriage. He strongly advised her to think about an abortion.

Megan and her husband took five minutes to decide they wanted to continue the pregnancy. They were worried that the specialist might refuse to treat Megan, as the first doctor had done. But, once they had made their decision, the doctor backed them "one hundred percent".

The specialist said that delaying treatment risked allowing the disease to accelerate out of control and would make her vulnerable to clotting. He stressed it was their choice, but he did not recommend it. He explained the risk the drugs would pose to the fetus, showing them the results of animal studies, including pictures of the deformities induced. They decided to go ahead with treatment.

Megan was given an initial high dose of hydroxyurea to bring her blood count down, followed by the lowest dose possible, to give the fetus the best chance.

Searching for information

Together with her husband, she searched the Internet to try to quantify the risk they were running. They found little about results in humans, but noted that the doses used in the animal studies were 50 times higher than she was receiving, which was reassuring.

The oncologist signed her up with the head of the high-risk obstetrics unit in Toronto, at the Mount Sinai Hospital, which runs a programme for mothers with diseases during pregnancy. The hospitals face one another across the road, and the two doctors worked closely together and tried to coordinate appointments so that Megan would not have to make too many trips to Toronto. At around 8 weeks, the specialist got the go-ahead to start Megan on Glivec (imatinib) – permission was needed on account of the cost. She was monitored constantly by both doctors, but she had to wait until the 12th week of pregnancy before it was possible to tell, using ultrasound, whether her fetus had suffered severe damage. She and her husband had decided they would agree to an abortion only if the damage was very severe, such as anencephaly. Waiting for the results was "terrorising". But the news was good, they could see signs of four limbs and a good head shape. Blood tests showed no serious genetic defects. Megan and her husband began to relax a bit.

On October 3rd, 2004, a healthy boy, Connor Charles Moore, was born, weighing 6 lbs 1 oz (2.75 kg). Following the birth Megan's blood count started to rise again; her Glivec dose was increased, and she is now stable. Megan recognises that their decision to go ahead was controversial. She knows of only five instances of babies born to women who were on Glivec, but believes they are all healthy children. Now she wants a second child.

Waiting for the results was terrorising, but the news was good

Physicians would welcome guidelines to refer to – but they are hard to come by

was found to have 20 positive nodes. She was given eight cycles of chemotherapy, but not until she reached her 3rd trimester.

A woman, pregnant with her first child, was diagnosed with high-risk breast cancer. She agreed to an abortion to allow immediate intensive treatment. The cancer was not cured and she deeply regrets losing a child that could have survived her.

A patient was diagnosed with stage 1B cervical cancer at around 18 weeks. She waited more than three months for treatment and had the child delivered at 32 weeks.

A woman was diagnosed with ovarian cancer while pregnant. She refused her gynaecologist's advice for an immediate hysterectomy and even refused chemotherapy. She had been trying to have a baby for 12 years before she became pregnant. She said: "I don't care if I die, I'm going to leave my baby to be raised by my husband or my mother." Not everyone will share those priorities … and not everyone has a husband or mother they can trust their newborn to.

These stories illustrate that there can be no right or wrong answer. Women are in different circumstances, with different priorities and facing different possible outcomes. Some women say that the child helps them cope with the cancer. Others feel that a new baby is challenging enough for a healthy woman, and that it may be too much for a woman debilitated by cancer therapy and with other young children at home, to care for a very premature newborn who may be affected by the treatment.

The biggest question is whether or not to continue with the pregnancy. But there are other difficult questions too, such as whether to induce pre-term delivery, or to risk cytotoxic treatment. If either choice is made, how early should action be taken?

Reaching a verdict

David Luesley, gynaecological oncologist at Birmingham Women's Hospital in the UK, starts consultations by outlining the extreme possibilities. "The best outcome is a healthy mother and a healthy baby; the worst outcome is two lives lost." If aiming for the first means delaying vital treatment, there is a risk the mother will die before the fetus is mature enough to survive, resulting in the worst possible outcome.

Pavlidis uses what he calls the Golden Rules, when teaching students about the treatment of cancer in pregnancy.

1. You have to benefit the mother's life
2. You have to treat curable malignant disease
3. You must protect the fetus from harmful effects
4. You must try to keep the woman's reproductive system intact

These imperatives represent, he says, an order of priority "drawn from the daily practice of a doctor's life." He emphasises, however, that it is ultimately the patient's priorities that take precedence.

In this situation there are rarely good options, just a choice between bad ones. Some doctors have ethical objections to abortion. Some may have an ethical objection to administering drugs to a pregnant woman, when there is a potentially high risk of severe damage to a fetus. Many are not happy about delaying urgent treatment for a patient at high risk.

A doctor who wishes to do best by his or her patient has to put personal preferences and convictions to one side and focus instead on helping the woman reach a decision that best reflects her own priorities.

Helping women to make that choice demands absolute honesty. Luesley says that breaking bad news to a pregnant woman is one of the hardest things a doctor has to do, and he warns against glossing over stark realities. He cites the example of a pregnant woman with ovarian cancer choosing between radical hysterectomy and chemotherapy. "You have to be clear about the likelihood of response – between 60% and 80% show a response, but a proportion relapse, and can do so quickly."

Surbone points out that you are asking a woman, at a time when she is very scared and vulnerable, to make a decision about the life of her child versus her own life versus her responsibility to this child. "She has to think about surgery and/or chemotherapy. She has to think about the practical implications, and about her relationship with her husband after a possible mastectomy. Added to all this, she now has to think about a child who could possibly grow up without her."

OWEN FRANKEN / CORBIS / CONTRASTO

It is cruel to have to decide between the risks posed to yourself and to the child you are expecting

The question is, says Surbone, whether you feel your role as a doctor is purely to provide the best information, and that offering any advice is an abuse of power, or whether, while respecting the patient's autonomy, you feel your responsibility as the expert is to offer advice in their best interest.

She herself tends to the latter view. "I first inform my patients fully. But if they ask me: What do you think I should do? I give my opinion, which depends on the case. But I always say 'This is my opinion as a physician. I'm not you, and however I try to put myself in your position I may never understand your values, and I may not share them.'"

She points out that, as the doctor, you are the expert who has the information and holds the key to the various treatment options, and you are the one who is under the least pressure. In practice, the way you present the information will influence what the patient decides.

Few situations test a doctor's ability to serve the sick as much as this one. It requires good science – evidence-based knowledge about the risks associated with the various options and a top-quality multidisciplinary team to oversee the care of mother and pregnancy. It also requires the art of the physician in communicating with the woman and judging what level of advice to offer to get the best outcome for her. Finally it requires a large measure of common humanity. It is cruel to have to decide between risks posed to yourself and to the child you are expecting, and it is unthinkable that such a decision should reflect the priorities and preferences of anyone but the woman herself.

Background reading to this article can be found in:
Cardonick E, Iacobucci A (2004) Use of chemotherapy during human pregnancy, *Lancet Oncol* 5:283-291
Germann N, Goffinet F, Goldwasser F (2004) Anthracyclines during pregnancy: embryo-fetal outcome in 160 patients. *Ann Oncol* 15:146-150
Koren G, Lishner M, Farine D (eds) (1996) *Cancer in Pregnancy. Maternal and Fetal Risks*. Cambridge University Press, Cambridge
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Surbone A, Petrek J A, Currie V E (2000) Treatment of breast cancer during pregnancy. In: Dixon J M (ed) *Breast Cancer: Diagnosis and Management*. Elsevier Science, Amsterdam London New York
And at www.germanbreastgroup.de/pregnancy and www.motherisk.org

Let's talk Chinese milk vetch

Mary Rice

'Quack remedies' have long been a thorn in the side of the medical establishment, but fear of ridicule means many patients don't tell their doctors about any additional medicines they may be using. This problem may now be compromising research results.

Complementary and alternative medicines, also known as CAMs, are becoming increasingly popular among cancer patients looking to improve their wellbeing or even find the cure that conventional medicine is still unable to promise them.

Now some scientists are beginning to question whether their use by patients taking part in trials of conventional drugs may be skewing results, or at least making outcomes less robust.

While the extent of CAM use among cancer patients still seems to be disputed in Europe, there is general agreement that it cannot be ignored, and that doctors should aid patients to disclose its use by making time to discuss the issue in a non-judgemental fashion.

"This is vital if we are to know what people are taking and figure out what effect it might have both on the individual patient and on trial results as a whole," says Gordon McVie of the European Institute of Oncology, Milan, citing a recent paediatric study where many parents had not told doctors that their children were using CAM.

Edzard Ernst, from the Peninsula Medical School, UK, and holder of the only chair in complementary and alternative medicine in the country, believes that in most European countries nearly 100% of cancer patients are using some kind of CAM. "Of course these may not be pharmacologically active – for example acupuncture or relaxation therapy," he says, adding that "this kind of therapy gives no cause for concern. Rather the opposite – massage, relaxation, aromatherapy and reflexology are particularly useful in improving quality of life and can ease the adverse effect of orthodox cancer therapies."

It is the herbal and other treatments with a pharmacological effect that worry doctors the most. "In Chinese herbal medicine, where treatment is

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It would be astonishing if there were not some major reactions with investigational agents

totally individualised and no one knows what a particular person is taking, it would be astonishing if there were not some major reactions with investigational agents," he says. "The possibilities are mindboggling."

The two men disagree over the extent of CAM use – McVie says it is nearer 40% in Europe and largely affected by social class and affluence. Studies show that those who use CAMs tend to be better educated, of higher socio-economic status, female, and younger than those who do not. "Can you imagine a 70-year-old socially deprived man with lung cancer taking relaxation classes?" he asks.

One thing they do agree on is that we need to find out more about how widely these therapies are used in cancer patients and what effect this is having on trials of new agents.

Ernst suggests that people entering cancer clinical trials should be told not to take herbal remedies of any kind without disclosing them to the investigators. "Carrying on taking CAM against the advice of the investigators could be an exclusion criterion," he says. "It would be interesting to do this in a large study and see how many people drop out. Although we have a pretty good idea about the prevalence of use, we don't yet know how many would choose CAM over conventional treatment if they were asked to make a decision to use only one. My view is that adherence to, for example, Chinese herbal medicine would be less than that to drug treatment, but this needs to be tested."

One of the biggest problems is the amount of misleading information about CAMs that patients are likely to come across on the Internet. Helping patients judge the quality of a website by suggesting what to look for is an important task for healthcare providers, says Ernst, adding that "here again it could produce useful data – it would be valuable to know the numbers of cancer patients who use information from such sites or buy CAMs for cancer online."

But patients desperate for a cure can only work with the information they have, and at the moment there is precious little authoritative evidence-based information available to them – or their doctors. This is a problem the European Organisation for Research and Treatment of Cancer has recently started to address. It has secured funding from the European Commission for a study looking for evidence-based information on CAM. With partners in many European countries, the information gained will be disseminated widely through the Internet and via cancer leagues and patient groups.

The combined effect of helping patients be more discriminating about the information they trust, and increasing the availability of more reliable evidence-based information on CAMs should go a long way towards helping patients take informed decisions. But Ernst accepts that CAMs may have an appeal beyond what the evidence merits. "What cancer patients want is a cure, and we are not providing this. Even though they know that there is no evidence that Chinese herbal medicine, for example, will cure their disease, people still continue to take it. What they may not realise is that if an effective CAM treatment emerged it would instantly be taken up by mainstream medicine, as happened with Taxol [paclitaxel], for example."

One thing patients clearly do realise, however, is that they risk being made to feel foolish and gullible if they tell their doctors about the CAMs they are using. This is a problem for the doctors trying to treat them, and for researchers trying to interpret the results of clinical trials. McVie believes what is required is a change of attitude among the medical profession.

"Giving patients the feeling that they have a real role to play and are not just there to be guinea-pigs in someone else's investigation is the most important change to be made," he says. "Using CAM is a way of taking back a bit of control over their bodies. Doctors should be aware of the widespread use of such therapies and not feel that they can simply tell their patients not to use them. It's absolutely essential that doctors understand this and avoid being superior and disapproving. The patient needs to feel sufficiently confident to be honest about exactly what he or she is taking. Clearly if parents don't feel confident in telling the doctor what they are giving their children, something has gone very wrong."

Sophie Fosså: The survival expert

Peter McIntyre

Choosing a career as a urologist in Norway was always going to be a tough option for a German woman in the 1960s, and she often felt isolated and unwelcome. But Sophie Fosså's outstanding work as a researcher gained her recognition, and eventually gave her the confidence to look beyond the purely medical needs of her patients.

Sophie Fosså is one of the most decorated oncologists in Norway, recognised internationally for her work on testicular cancer and with cancer survivors, a popular visiting Professor at the European School of Oncology, and a proud wife and mother. For someone at the top of her tree, she did not have a promising start.

She was born at the wrong time to parents whose politics were confounded and discredited. Two successive generations of her family had seen their aspirations shattered, and learning became the only treasure the growing Sophie could trust.

As a young doctor she fell into oncology by default, in a country where she was regarded with suspicion. Moreover, her focus was on science, rather than patients. As she grew more confident and happier, her attitude changed. Her research became less about tumours and more about people. Her consultations became more discursive.

She thinks deeply about her patients and about the next generation of oncologists. She has even learned to unwind a little, albeit she still works hours that make her colleagues flinch. She would like to be a better grandmother, but not yet. Her legacy will be in understanding the effects of cancer and treatment on those who survive.

Born into Nazi Germany

Sophie Gericke was born in Germany in 1941. Her mother's family had escaped revolutionary Russia where her grandfather was secretary to the Czar. Many of her relatives had been shot.

Driven by fear of Stalin's Russia, her school teacher mother became a patriotic German and a member of Hitler's National Socialists. Her father was a soldier and a convinced Nazi. By the time of Sophie's birth, her mother was having second thoughts, and in 1942 she left the Party, an act of some courage. Although both parents survived the war, their marriage did not and in 1945 they divorced. Sophie's early memories are of dreaming that the Russians were coming to kill her.

Her multilingual mother got a job translating for the British army, which allowed Sophie, her brother and two sisters to eat in the military

kitchen. Amidst the ruin of post-war Germany they were able to survive.

"We were very poor. My grandmother and mother taught us that you can lose everything in this world except what you have learned – nobody can take your knowledge from you. So our home was based on intellectual things." Her mother translated English and Russian stories for the children to read.

Sophie's ambition was to be a professor. Aged 17, she went to Münster University and then to Bonn. She fell in love with a Norwegian medical student Jon Fosså, the child of a poor farmer. She returned to Münster to take her final exams and at the age of 23 qualified as a doctor. Sophie and Jon married one week before they left for Norway.

A German in Norway

"Being German in Norway in 1964 was a problem, and the war again became important. When I came to Norway no one could accept anything positive about Germany, even people who knew that I was nothing like a National Socialist."

Her first job was in psychiatry, with troubled adolescents. She took the job because it came with a flat, and had regular hours, which her husband, by now an orthopaedic surgeon, did not. "We wanted six children and we realised that if he was on duty every third night and I did the same, it would be quite impossible. When I came down from University – I knew about diseases. Now I learned that other things were important."

In 1968 she changed direction. Feeling it was impossible to follow her first option of internal medicine, she chose oncology as second best, and moved to the Norske Radium Hospital (NRH) in Oslo. "Lots of people warned me not

"The urologists even wrote a letter of protest to my chief that I was a woman, and this was a male cancer"

"I say to these young boys, I know that you think about it, so let's talk about it"

to do oncology. They said it is so depressing. But this was a way I could have children and manage. It was a practical decision." After post-graduate training she began to specialise in urological cancer – the only specialty nobody had reserved. Bladder cancer was treated by urologists and treatment was not up to date.

"The NRH had not much contact with international colleagues, at least not for urological cancer. Chemotherapy was not used for bladder cancer. I had to find my own way and I found it through the European Organisation for Research and Treatment of Cancer (EORTC). I learned about new drugs and new ways to treat this cancer. It took a long time before my hospital accepted that I could introduce them.

"The urologists even wrote a letter of protest to my chief that I was a woman, and this was a male cancer, and I was a foreigner and not an urologist. I understood that the only way to convince them was to publish and look for support in other countries."

She did her doctorial thesis on the study of DNA in bladder cancer using cytophotometry. She worked alone, without supervision, at night after finishing her day's shift. Despite having a young family, she went to the hospital at 5 am for two hours before going swimming with her children and then going back to work. Professionally she felt isolated and unwanted.

"At one time I really thought about suicide, they went so much against me. Norway and the Scandinavian countries had a different way of life. They prioritised their leisure time. They wanted to go skiing or sailing. Very few people really understand that I still think it is fun to do research and to publish."

She was increasingly beguiled by her work. "I saw the research as compensation. I will confess that in the first ten years I was probably not the best doctor for my patients. I saw the medical problem, not the human problem." The father of one young man, wrote: "She is probably a good researcher, but she will never become a good doctor."

In the late 1970s and 1980s the awards for research began to flow, including four from the Norwegian Urological Association. She became a consultant in 1982 and achieved her childhood ambition in 1993, when she was appointed Professor. It is a title she discourages her junior colleagues from using. "I am quite an ordinary person. I don't take myself very seriously."

Fosså took an increasing interest in testicular cancer, where treatment was improving through a combination of surgery, radiotherapy and chemotherapy, especially with the introduction of cisplatin. Confident in her ability to cure these young men, Fosså became interested in their other concerns.

"The patient is scared, but in the back of their mind they wonder, 'If I survive, what kind of man will I be? Will I be able to father children?' I say to these young boys, 'I know that you think about it, so let's talk about it.' The patient will not talk about fertility and sexuality unless I raise it.

"I think young men feel secure and safe when they come to me. Most patients look at me as a kind of mother at this time."

She kept pictures of her four growing sons on display in her consulting room to reassure the young men. "They knew they would get treatment as good as in the Royal Marsden in London or in America. I take a lot of time to talk to them. They have their teddies in their bed and are like children again. Our staff and nurses understand their problems and take care of them."

She introduced a sperm bank 20 years ago. Of the 400 patients who deposited frozen sperm, only 30 have used it, as most fathered children in the usual way.

Survivor work

In 2001, Fosså opened a long-term cancer survivorship unit at the NRH. "I started with

When she received the H.M. King Olav's Research Award, Sophie Fosså knew she was truly accepted

testicular cancer patients because I had treated them for 30 years and I wanted to know the long-term effects. I also explore the mental side. I think it is very important to see what problems cancer survivors have to cope with due to the disease and their treatment.

"We have done a long-term study of 1,400 testicular cancer survivors in Norway. The quality of life for testicular cancer survivors is as good as the rest of the Norwegian male population. Sexuality is also the same. There is no difference."

She did, however, find other problems. In 2002 she published a paper in the *Annals of Oncology* showing that 20–30% of men who had been successfully treated for testicular cancer in the 1980s had decreased kidney function. In 2004, Fosså spent several months at the National Cancer Institute in the US reviewing a large number of testicular cancer cases. "We know that by giving treatment to these young men we induce new cancers after 20 years. We want to know what kind of cancers we induce after what kind of treatment. I would today be very reluctant to give radiotherapy to testicular cancer patients, which has been a routine treatment.

"I also tell the patient that they may have problems with obesity, blood pressure and cholesterol. They can do a lot through lifestyle factors and physical activity, if they know about the higher risk."

Her work on prostate cancer also demanded a human approach. "I saw patients on whom the urologists had given up. I had to understand that they only had a few months left and help them to get the best out of it. I am very clear and do not hide the prognosis. I think they have the right to know if they will die, to do the practical things they have to do. As I became older it was easier to talk about these things with my patients."

Fosså opposed moves for routine prostate screening. "The urologists wanted the PSA test for all men over the age of 50. I said that there was no scientific evidence that this would help survival. The urologists did not like that very much. Today, they understand that it was a good decision." The Norwegian Urological Cancer Group refused to recommend that Norway take part in the European Randomized Study of Screening for Prostate Cancer trial.

Fosså was gratified to read in October 2004 that Thomas Stamey, who developed the PSA test, now believes that it is overused.

She is hopeful that Taxotere (docetaxel) may be the first in a line of new drugs to prolong life in prostate cancer patients with metastases. But for those at an earlier stage of the disease there are unresolved dilemmas.

"Surgeons have become much better. But they do not operate so many cases as they did. They are very selective. The problem of urinary incontinence has decreased very much. Impotence is still a large problem. Radiotherapy also gives a high chance of impotence."

"I would today be very reluctant to give radiotherapy to testicular cancer patients"

So what advice does she give? "You have to sit down with a man and tell him all the side-effects that can be expected. It is very difficult for men to live with the idea that they have cancer but do not get treatment. Quite often he asks 'What would you do, if it was your husband?' I say, 'My husband is my husband and you are you. I would say that this or that option is best for you, but you have to decide.' Most patients want the doctor to take the responsibility, and of course we cannot. The most important thing is to find a doctor you trust and who follows the latest developments."

Fosså also sees patients with cancer of the kidney, and was one of the first in Norway to use interferon to stimulate the immune system. However, there is no effective curative treatment and no cytotoxic drugs that kill cancer cells in the kidney.

"When I started my medical education only

"Quite often a patient asks 'What would you do, if it was your husband?'"

a cure was important, but this is not true. You can do such a lot of things to relieve pain, give palliative treatment and help the relatives. Last week I saw a 95-year-old woman with a large metastasis at the neck. Her only wish is to die in peace without giving trouble to her daughter and family."

"We tell our patients very honestly whether we go for curative treatment or palliative treatment. It is essential for a good doctor patient relationship that both know what is possible and what is not."

Research and practice

Fosså does not see much distinction between research and clinical practice. "Every treatment I give, I do it as systematically as possible in order to be able to use it for research. And I always ask myself, how can I use what I learned in research on the next patient?"

Her long-term survivors' unit is expanding. Fosså sees 10 women a month who have breast cancer. She will also, over the next two years, include patients who had Hodgkin's lymphoma. "I want this long-term outcomes unit to flourish and become a national centre of competence."

Her other remaining ambition is to teach and to help young doctors. She supervises a number of PhD students and lectures. "My children think I should spend more time being a grandmother, and they probably are right. But I have my life and I am invited to conferences. My daughter in law called me to see if I could babysit. I said I can't come, I am in the USA."

In 2001 she organised a meeting in Moscow on testicular cancer, which proved highly emotional for her. "I was very happy to be in Russia. I feel a special link. I closed the conference with a picture of my mother."

Despite starting work daily at 4 am, she claims she is learning to relax. "I only work five days a week, not Saturday or Sunday! A few years ago, I learned downhill skiing, which was an adventure. The first time I went on the ski-lift, it caught my anorak and went up with me hanging from it. I fell to the ground. I told myself that if I did not try again, I would never do it. So I learned downhill skiing and I now love it. It showed me that even at my age I can do things that I never thought I could do."

Two of her four sons are doctors, and one, Alexander, is an oncologist at the Norske Radium Hospital, working on Hodgkin's disease. Her children speak German and Norwegian. One son became a German citizen, married a German girl and lives in Norway. Another married a Finnish girl and lives in Germany. A third married an English girl and lives in London. "We are a very international family."

When, in 1997, she received H.M. King Olav's Research Award, Sophie Fosså knew she was truly accepted. "It was very nice to get an award at the castle. I feel Norwegian, but a Norwegian European. I do not like nationalism, but you have to have somewhere you feel at home. For me that is Norway. When I was first here, there was always some restriction in my heart. I knew that Germans were the reason for many young Norwegian deaths. By engaging with testicular cancer, and especially fertility problems, I have assisted many young Norwegians to be alive. It gives me some comfort."

Fosså was gratified to read that the man who developed the PSA test now believes it is overused

Show me the evidence

How Else Borst-Eilers got the best out of a shrinking health budget

Anna Wagstaff

Haematologist Else Borst Eilers was handed a poisoned chalice as the Minister asked to make cuts in healthcare costs in the Netherlands. She found her salvation in the patient viewpoint, and evidence-based care.

Else Borst Eilers' first task, on becoming minister for Health, Welfare and Sport in the Dutch coalition government in 1994, was to cut public health spending. A medic by training, this was hardly the role she had envisaged when she stepped into public life. But if the job had to be done, then Dutch patients could be grateful that her hand was on the scalpel.

All over Europe, similar scenarios were being played out as two decades of spiralling public health costs combined with sluggish economies forced governments to ration health care. New accounting and budgeting systems obliged hospitals, specialist units and primary care providers to cut spending, but where and how the cuts were made was all too often the outcome of a battle between institutions and professionals defending their own territories.

Els Borst shared with most of her fellow European health ministers a desire to see the best possible health service for the money available. What gave her the edge was not so much her medical background as her work over two decades in asserting the interests of patient care over the conflicting pressures from the medical profession and the accountants.

Soft-spoken mother

Els Borst is a slightly built soft-spoken mother of three, who chose not to work full time until her children were school age. A haematologist, specialising in blood transfusion, her career didn't properly begin until she was "between 35 and 40". While working in the department of haematology in Utrecht University Hospital she had her first, reluctant, taste of power. The medical director was ill. As head of the hospital's blood bank, Els Borst was one of the few department heads on the hospital, rather than the university, pay roll. So she took on some of the director's responsibilities.

Like most hospitals at that time, the board of directors consisted of one person with medical training (the medical director), a nurse, and someone with a background in economics or administration.

"At first I hated it, but after some time I thought … well you can influence things here in this position. Everybody in a hospital is critical about how it is run. Everybody knows how to do it better. And then you are suddenly in a position where you can really make a change."

This marked the beginning of Els Borst's career in health policy, and it didn't take long for Utrecht University Hospital to start to feel the

"From time to time, it is necessary to leave your bunker and enter the political arena"

With Queen Beatrix after a visit to the Kuria hospice for terminally ill patients, as Minister of Health, in 1997

effects. Departments that were dynamic and innovative – including radiotherapy and haemo-oncology – found themselves with a greater share of the budget to fund pioneering research and trials. And strange things started happening to new appointments. Appointing new heads of department had traditionally been the domain of the university, but Els Borst argued that academics may not always be the best choice to run hospital departments. She overcame heavy resistance to win the right to sit on appointment panels, and Utrecht University Hospital became the first in the Netherlands to separate the heads of academic and hospital departments.

If an academic candidate could lead a clinical team, then the posts could still be combined. "I remember appointing the head of the neurology department. He had only published six papers in his life. He was an excellent teacher and a very good clinician, and he is still working there and is a very great success."

But not everyone was happy. "Many people wanted to have it all. They wanted all the power. To be top in research and top in the clinic. It was men more than women who complained – some of them want all the power they can get."

The patients' standpoint

At the time she would probably have phrased this more diplomatically, because, as she says, somehow you have to keep medical staff on side. "If you are in permanent battle with your medical staff – which you often see in hospitals – you get nowhere."

Her secret was always to argue her case from the standpoint of the patient. "It is not a question of making everything as cheap as possible, but how to make healthcare as good as we can." And this, she argued, meant setting priorities and working more efficiently. "If you let all those professors have their way, they would all have their own CT scanners, and that is not efficient."

Over a period of 10 years as medical director in Utrecht, Els Borst developed a great interest in how to evaluate efficiency within the health system. This was a field that was just beginning to emerge in a variety of forms in a number of countries.

Foremost among them was the guidelines movement, which started in the early 1980s in the US, and spread rapidly to Europe. Researchers in the US had been shocked to discover huge differences in rates of treatment. Most notoriously,

some doctors were five times more likely to perform a hysterectomy than others.

The medical profession suddenly found itself open to public scrutiny, as governments and health insurance providers called for guidelines. In the beginning these were drawn up through consensus. "You put ten cardiologists in a room and let them meet a few times, and they would draw up guidelines for instance for coronary bypass surgery." But this method soon proved unsatisfactory and was replaced by evidence-based guidelines.

"You say: 'Where does it work? How can you differentiate patients who will benefit from those who will not?' Consensus is all very nice, but if you have 10 cardiologists who all love intervention, they will draw up guidelines that include a much wider range of patients than if you look critically at the evidence."

Evidence-based medicine

Evidence-based medicine emerged as a defining concept in managing healthcare systems. It also gave rise to a new specialty – health technology assessment, where 'technology' included most aspects of diagnosis and treatment, as well as actual equipment. Assessors were not clinicians, but knew how to analyse the literature on clinical trials and how to do meta-analysis.

Els Borst was an enthusiastic advocate of evidence-based guidelines, and for establishing patient-led criteria for prioritising scarce resources. In the early 1980s, while medical director in Utrecht, she attended early international meetings on setting priorities and containing costs in healthcare.

As she became increasingly involved in wider policy issues, she began to move away from management. In 1986 she became vice-president of the Dutch Health Council, a government advisory body, and got her first taste of the political process. "I could see how reports I wrote were treated by the minister and by the members of parliament, and I got a feel for how political life works."

Now she was in a position to influence health policy at a national level, and she could set her own agenda. In 1987, she became the first secretary of the International Society for Health Technology Assessment, a network of organisations doing similar work – including the Institut National de la Santé et de la Recherche Médicale (INSERM) in France, the King's Fund in the UK, and the Health Councils of Australia and Canada.

Specialist centres

She lost no opportunities to argue the case for evidence-based medicine, and must surely take some credit for the Netherlands' good record on cancer treatment. In 1987, the Dutch Health Council became one of the first in Europe to advocate restricting certain cancer treatments to specialist centres with minimum annual case loads.

"We call it dividing and concentrating, and we asked the oncologists to make arrangements about how they divided the tasks between them."

Some disciplines – ear, nose and throat specialists get an honourable mention – responded well. They got together, and decided who should specialise in what. Others were less compliant. "When you talk to doctors in small hospitals they say: well it is so interesting… I want to carry out my speciality as widely as possible. They are also afraid that if they haven't treated a cancer patient for six years, they will lose their market value. Of course it is in their interests. But it is not in the patients' interests."

She cites cancer of the oesophagus as an example of an operation that is far more successful when a practitioner deals with at least 10 cases a year. But even 15 years later, a hospital was recently given a warning for continuing to operate on oesophageal cancer, despite seeing only two cases a year.

Els Borst recognises that the culture of the health service cannot be changed overnight,

"If you let all those professors have their way, they would all have their own CT scanners"

"They fear they will lose their market value if they haven't treated a cancer patient for six years"

and has told other politicians that it will take time. But she does not accept that health professionals can continue to put their own self-interest first. In 1992, she wrote a report warning the medical profession that if they did not put their own house in order, politicians would do it for them, and she pointed out that politicians know more about cutting costs than providing healthcare.

Furious reaction

Her report, *Medical Specialists at a Crossroads*, provoked a furious reaction from the profession, not least because it revealed two-fold to five-fold variations in levels of treatment by different doctors – variations that called into question the quality of patient treatment. It found over-treatment in some areas and, possibly even worse for patients, under-use of other medical interventions.

The profession realised that unless it sorted itself out, health insurers would insist on US-style managed care, in which doctors would have to get the go-ahead from the insurer for every intervention on a case by case basis. "For the first time the medical profession began to understand that the guidelines were no longer a plaything. It was becoming serious."

Politicians, desperate to find ways to economise on healthcare, loved this. Partly on the strength of the *Crossroads* report, one year later, the newly elected government offered Els Borst the poisoned chalice of Health, Welfare and Sports Minister – with a brief to cut the health budget.

Faced with the question of where to wield the axe, the issue of evidence-based treatments took on immense importance. If free healthcare had to be rationed, then clearly you want to know you are not wasting money on expensive treatments unlikely to be of benefit. "I always argued that before we set priorities in the sense of withholding treatment from those who need it, we should try to make healthcare much more effective and efficient."

Difficult decisions

She managed to get away with a series of small savings, mainly through withdrawing reimbursement from over-the-counter medicines for minor ailments – cough mixture for example. Medicines with no proven efficacy and homeopathic medicines were also taken off the list of reimbursed medicines, as were some medical aids such as elasticated stockings. Reimbursement for in-vitro fertilisation (IVF) treatment after the third attempt was also withdrawn.

Difficult decisions about serious conditions remained. Among them, the question of reimbursement for Taxol (paclitaxel), an expensive new drug that can offer around six months' extra life for patients with ovarian cancer. Her advisors argued against the drug, but in the end Els Borst decided to pay for it. "If it had been a disease of very old people with a very short life expectancy, maybe you could make a case against it, but there are so many young women who have young children, for whom a half year living longer is still important." She did, however, insist on strict guidelines on when to use the drug.

She also went against the advice of her staff in deciding to make available new anti-retroviral drugs for HIV before they had completed the full clinical trials. Even today, people still occasionally come up to her in the street to thank her for saving their lives with this decision.

However, she did exclude some treatments from reimbursement – including two that had been shown to delay the progress of Alzheimer's disease by a couple of months, and an experimental surgical treatment for Parkinson's disease.

The price of life

Els Borst has thought a great deal about what price can be put on an extra month or year of life.

BRAM GEBUYS

On a visit to a home care patient

This was not just a professional question for her. Both her husband and her brother-in-law died of cancer, and both took the decision, near the end, to forego further treatment.

She believes that when patients have options clearly spelled out – side-effects, chances of response, how many months or weeks it could give them – an increasing number opt for palliative care.

The patient is weighing up the benefits against the burdens of treatment. The minister, however, has to weigh up the benefits against the costs. In practice, Els Borst tended to go with the benefits. "To say that a few extra months of life is not worth the money is a very hard and politically dangerous thing to say. Six months may mean something very different to a mother with a young child than to an older person."

In an ideal world, she believes every patient would be correctly informed and able to choose. "There will always be some patients who are so afraid of dying that they will do anything to stay alive an hour longer – but they are the real exceptions. I don't think there are many who are asking for the stars."

Els Borst knows better than most that this is not an ideal world. Doctors find it hard to spell out bleak options even when they know their patient is not going to survive. "A doctor who abandons hope too soon is not a good doctor," she says. "But very often the patient knows that if the doctor is honest he or she is going to say that it is over. There is not much more to be done in terms of treatment. The box is empty. A good doctor starts that conversation at the moment the patient is ready for it. It is all very subtle, and it is one of the reasons why you should really have one and the same doctor during the course of your cancer."

Els Borst also has an acute appreciation of the

"Some patients will do anything to stay alive an hour longer – but they are exceptions"

value of good nurses, and during her time at the ministry the nursing profession saw lasting improvements in both status and pay. "I opened possibilities to become nurse practitioners, and to specialise and get better training. I always argued their case and sung their praises whenever I got the chance. They should work on an equal professional level with the doctor. Nurses have their own professional expertise to bring to treatment plans. One of my children is a nurse and I hear that the way they get along has completely changed. They now call doctors by their first name. It's a small thing but symbolic of the change."

The patient voice

Another important legacy from her time in office is the agreement Els Borst won to provide 30 million euros a year to support the patient voice, allocated to active, democratic organisations that not only provide good information and support for patients, but also promote public awareness and engage with the political process.

She believes patient groups have risen to the challenge of their new roles and responsibilities, and are themselves beginning to think about cost-effectiveness and evidence-based treatment. Some patient groups were once seen as the patient arm of pharmaceutical PR campaigns; now they work increasingly with the medical profession to put well-researched and well-argued cases to politicians. And today Els Borst, retired from the front line of politics, works closely with those groups as President of the Dutch Federation of Cancer Patients Organisations.

With almost maternal pride she recounts how the chair of the Breast Cancer Association recently told her that members were against the routine use of a new radiotherapy technique on the grounds that the extra cost increased much faster than the extra benefit. The feeling was, explained the chair, that the money could be better used doing something else for breast cancer patients. To illustrate her point she sketched a cost-benefit graph as she spoke!

This does not mean that state money has succeeded in co-opting the Breast Cancer Association to the government's cost-saving agenda. In fact it is running a highly effective campaign to force the Dutch health service to improve breast cancer treatment. It has given all hospitals until 1 January 2007 to comply with a set of guidelines on minimum standards of care – covering issues such waiting times, levels of expertise and choices between different interventions. The Association warns that hospitals that fail to do so will be not be used by any woman with a lump in her breast.

Nor can anyone accuse Els Borst of begrudging money to cancer services. She oversaw the biggest ever revamp of Holland's radiotherapy services during her second term in office and she still takes every opportunity to encourage other medical professionals to campaign for similar cash injections.

Medic, politician and now, in semi-retirement, President of the Dutch Federation of Cancer Patients Organisations, Els Borst recently summed up her philosophy of health care in a speech delivered to the European Society for Therapeutic Radiology and Oncology (ESTRO) on opening their conference last year:

"From time to time, it is necessary to leave your bunker, step over the fence … and enter the political arena for a short while. Because I think it is your responsibility to address the policymakers in your country when things threaten to go wrong. Your voice can be very powerful. In the first place, because you know what you are talking about. You can show the facts. And secondly, because you are not asking anything for yourselves, but for your patients. By joining forces, patient organisations and organisations of professionals can enhance their influence considerably."

State funding of 30 million euros a year to patient groups is a legacy of Els Borst's time in office

Doctors who shun guidelines get worse results

Alex Mathieson

An unhelpful straightjacket or an essential tool for optimal treatment? Some physicians still trust their own skill and judgement above all else, but new evidence shows that patients do best when their doctors follow consensus guidelines.

Compliance with consensus guidelines has been a thorny issue in oncology for some years now. At one pole is an increasingly large body of clinicians who value guidelines as indispensable tools in helping them design, deliver and evaluate treatment interventions. At the other is a more sceptical group who regard guidelines as an unwarranted intrusion into their right to treat patients in the way their knowledge and experience dictate.

And in the middle is a morass of ethical, clinical, cultural and financial issues that complicate further an already complex picture.

Debate on the rights and wrongs of guideline implementation seems set to gather pace in the wake of a recently published study on breast cancer guideline implementation from Canada. Reporting their findings in the *Journal of Clinical Oncology* (22: 18, 3685-93), Nicole Hébert-Croteau of the Institut National de Santé Publique du Québec, and colleagues, suggest that treatment according to consensus guidelines is associated with improved survival in women with breast cancer in the community.

Nicole Hébert-Croteau: The results of our study should help to increase levels of compliance with consensus guidelines

Isabelle Ray-Coquard: Findings accord with previous research, but with 1000 patients this study provides the strongest evidence yet

The study

Hébert-Croteau and her team started from the premise that, although previous work had shown 'reasonable compliance' with consensus recommendations for treatment of women with breast cancer, the impact of compliance on survival was unclear. They reviewed a cohort of women they had previously monitored for evidence of guidelines-based treatment in the 1980s and early 1990s to ascertain whether compliance with guidelines for systemic adjuvant therapy had improved survival.

Patients had been randomly selected from all new cases of node-negative breast cancer reported to the Québec tumour registry in 1988-89 and 1991–92, and to the province hospital

RISK CATEGORIES

RECURRENCE RISK CATEGORY DEFINITIONS
(ST GALLEN GUIDELINES)

Women at minimal risk of recurrence:
- Incidentally discovered small invasive tumours
- Colloid, tubular or papillary histology
- Invasive tumours measuring ≤1 cm with grade 1, 2 or unknown

Moderate risk:
- ER-positive, grade 1 or 2 invasive tumours >1 cm but ≤2 cm

High risk:
- ER-negative invasive tumours ≥1 cm (except incidentally discovered tumours of 1 cm)
- ER-positive tumours >2 cm
- Grade 3 tumours

discharge database in 1993–94. The dates were significant, as they represented the years before and after the introduction of guidelines from the National Institutes of Health (in 1990) and the St Gallen consensus conference (1992). The St Gallen guidelines were used as the set standard of care in the new study.

Data were collected from chart reviews and other sources such as radiotherapy and oncology records, pharmacy databases and interviews with attending physicians. Initial (phase 1) data collection was conducted during 1995–96 to record the disease state at diagnosis and treatment of the primary tumour, with phase 2 collection carried out in 2001–02 to gather information on recurrences and deaths. Patients were assigned a risk category for recurrence using the 1992 St Gallen criteria, which focus on tumour size, invasiveness, grade, histology, estrogen-receptor (ER) status, and mode of discovery. Risk category definitions and the treatments the authors consider to be consistent with guidelines for each risk category are set out in the boxes.

The cohort included 1,541 women. Risk of recurrence was found to be minimal in 24%, moderate in 13%, and high in 51%. Sixty-five percent of the women had received treatment consistent with the guidelines (including 98.4% of those at minimal risk) and 24.7% had not (10.3% were unknown).

It is the identified relationship between compliance with treatment guidelines and survival that gives the study such topical interest. Hébert-Croteau and her team found that survival was better in the women treated according to the guidelines, particularly among the moderate-risk category. Adjusted health ratios of death were 1.0 for women at moderate risk treated according to guidelines, and 2.3 for those who were not. For those at high risk, the ratios were 2.0 and 2.7 respectively.

The study found that not only was risk category an independent significant predictor of survival, but compliance with treatment guidelines was as well. It concludes that treatment according to guidelines is "associated with improved survival of women with breast cancer in the community", and that adoption of guidelines for treatment is "an effective strategy for disease control".

TREATMENT GUIDELINES

SYSTEMATIC ADJUVANT TREATMENTS CONSIDERED CONSISTENT WITH GUIDELINES
(ST GALLEN GUIDELINES)

Women at minimal risk:
- No treatment, or tamoxifen alone

Moderate risk:
- Tamoxifen alone

High risk:
- Chemotherapy with or without tamoxifen (women <50 years)
- Chemotherapy with or without tamoxifen (women aged 50–69 years with ER-negative tumours)
- Tamoxifen with or without chemotherapy (women aged 50–69 years with ER-positive tumours)
- Tamoxifen and/or chemotherapy (women aged 50–69 years with unknown ER tumour status)
- Tamoxifen with or without chemotherapy (women >70 years)

Patients treated within an experimental protocol were considered to have been treated according to guidelines.

Rolf Stahel: Guidelines are an option and a benchmark – we are not trying to take responsibility away from physicians

Håkan Mellstedt: Medicine is much more complicated than it used to be. We need multidisciplinary, consensus-based approaches

Study impacts

Hébert-Croteau is pleased, but not surprised, by the outcomes of the study. "I think you expect to see that treatment based on experimental research will have a positive result, but for many reasons that does not always happen," she says. "Our study shows that treatments following evidence-based guidelines can improve outcomes. It's expected, but it's nice nevertheless when you see it happen."

This is a view shared by Isabelle Ray-Coquard, who works in oncological guidelines evaluation at the Centre Léon Bérard in Lyon, France.

"I'm not surprised," she says. "There is some research on the impact of clinical guidelines on the general population, and it all suggests the same – that compliance with consensus guidelines is associated with improved survival.

"The interesting thing about the Hébert-Croteau study is the number of patients reviewed," she continues. "You can demonstrate more effectively the impact of guidelines with over 1,000 patients than you can in studies involving around 200, as has been the case with work we have done looking at the impact of guidelines adoption on patients with sarcoma and colon and breast cancer."

Guideline development

There is certainly a vibrant guidelines industry developing throughout the world. In Europe, for instance, a variety of methods have been used by different organisations to develop, disseminate and evaluate guidelines, and to try to steer clinicians away from developing their own ad hoc products (which may replicate or even contradict efforts going on elsewhere) towards a more consensual approach.

The SOR (Standards, Options, Recommendations) method of the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) adopts a programmatic approach to guideline development, and has been producing clinical practice guidelines in cancer since 1993. Its main characteristic is that the guidelines are developed by a multidisciplinary expert group who engage in thorough literature searches to produce evidence-based recommendations for practice. Each guideline focuses on all aspects of patient management, from diagnosis to supportive care. The programmatic approach encourages the process of guideline adoption, where the guideline can be endorsed for local use through the setting of local criteria. A strong 'aftercare' ethos exists, in which guideline dissemination, implementation, evaluation, reporting and updating come to the fore.

The European Society for Medical Oncology (ESMO) has also thrown its considerable weight behind cancer guideline development. It set up a guidelines task force in 1998 in response to demands from its national representatives throughout Europe,

Women at moderate or high risk had a better chance of survival if the guidelines were followed

ESMO GUIDELINES

Minimum Clinical Recommendations are available on:

Acute myeloblastic leukaemia in adult patients
Advanced colorectal cancer
Cancers of unknown primary site
Chemotherapy-induced nausea and vomiting
Chronic lymphocytic leukaemia
Chronic myelogenous leukaemia
Colon cancer
Cutaneous malignant melanoma
Oesophageal cancer
Ewing's sarcoma of bone
Gastric cancer
Haematopoietic growth factors
Hodgkin's disease
Invasive bladder cancer
Metastatic breast cancer, or locally recurrent MBC
Mixed or non-seminomatous germ cell tumours
Multiple myeloma
Newly diagnosed follicular lymphoma
Newly diagnosed large cell non-Hodgkin's lymphoma
Non-small-cell lung cancer
Osteosarcoma
Ovarian cancer
Pancreatic cancer
Primary breast cancer
Prostate cancer
Rectal cancer
Relapsed large cell non-Hodgkin's lymphoma
Small-cell lung cancer
Soft tissue sarcomas
Squamous cell carcinoma of the head and neck
Testicular seminoma

particularly from eastern and central regions, for guidelines to assist medical oncologists in their day-to-day decisions and set common standards of care and treatment throughout the continent.

The task force endorsed the principles set out in programmes such as SOR of guidelines being patient centred and evidence based, but, due to the considerable time and costs involved in developing a comprehensive clinical guideline, it opted for an approach that produces minimal clinical recommendations (MCR) for practice.

A topic for MCR development will be selected by the task force, and an authoritative author ('co-ordinator') asked to prepare a draft. The task force will review and revise the draft before forwarding it to the appropriate ESMO faculty for comment. Further revisions will be made by the task force prior to publication and dissemination. The MCR will then be updated yearly, following the same process. It's quick and straightforward, but also robust.

Rolf Stahel is chair of the ESMO guidelines task force. He believes the MCR approach is the right one to promote high standards throughout Europe. "ESMO's approach is very different from that needed to produce extensive clinical guidelines," he says. "Our aim is to produce short guidelines stating what is needed minimally to ensure good diagnosis and access to care and treatment as a means of defining the basics that should be available to patients throughout Europe," he says. "They don't preclude individual clinicians or institutions doing more. Nor are we trying to push them down people's throats – they are there as an option and a benchmark, not to take responsibility away from physicians."

Håkan Mellstedt, chair of ESMO, has been a proponent of guidelines for many years in his native Sweden, and feels they are likely to become even more important as time progresses.

"As a physician, I feel competent in diagnosis, treatment and after-care," he says. "But sometimes I ask: do I, at this moment, know the optimal treatment for this patient? That's when I can reach for the guideline, look at it, and decide. For me, guidelines are an essential support for my daily management.

"Medicine is changing so much," he continues. "Previously, it was a one-man show. The doctor took all the decisions. You could do that 30–40 years ago, because it was not so complicated. Now, everything is very complicated. You have to use multidisciplinary, consensus-based approaches – no-one has the monopoly of wisdom."

ESMO has opted for providing 'minimal clinical recommendations'

Compliance is influenced by local opinion leaders, but some still resist evidence-based approaches

Barriers to compliance

Why, then, are guidelines not adopted more widely? Hébert-Croteau believes there may be a number of reasons why clinicians are wary.

"They might be afraid of toxic side-effects, for instance, or there might be other contraindications and medical conditions that make them more cautious," she says. "We know, for example, that older women are generally treated for breast cancer less aggressively than younger women. They have other health conditions that may make them less tolerant to very aggressive treatment. The choice of the patient is also important – some women might feel very optimistic about the outcome of their disease and don't want to be treated so aggressively."

She feels these are much more likely reasons for non-compliance than the more commonly suggested one – that clinicians are, at best, not aware of guidelines' existence or, at worst, ignoring them.

"That might have been true 10 years ago, but not now," she says. "In Canada, there have been national initiatives on diseases like breast cancer that raise awareness of clinicians and patients. National guidelines have been produced, widely disseminated and updated at regular intervals. Physicians are aware of them, and the pervasiveness of the evidence-based medicine movement makes it less likely that the message will not get through. Non-compliance might be more about physicians making individual decisions based on case by case assessments."

Ray-Coquard believes that the weakness of supporting evidence in some guidelines may act as a disincentive for physicians. "Some guidelines are not evidence based, because there are no scientific data to support them," she says. "The guideline for gastrointestinal stromal tumours (GIST), for instance, is based on expert opinion, not hard evidence, because the evidence is not there. But guidelines such as this are still very important for physicians who treat the disease."

Ray-Coquard also believes that local opinion leaders have a great influence on guideline adoption. "The more you can involve the local opinion leader in the implementation of the guideline, the better the chance of it being adopted," she says. "Research has proved that medical decisions are clearly linked to the local opinion leader – if his or her views are not in accordance with the guideline, it will not be used. And there is very good evidence to suggest that some opinion leaders are not accustomed to evidence-based approaches."

The question of whether guidelines give physicians everything they need to initiate appropriate treatment has also arisen. In an editorial in the *Journal of Clinical Oncology,* commenting on Hébert-Croteau's study, Rebecca Silliman, of the Boston University Medical Center, suggests that although evidence-based guidelines are a necessary beginning, and disseminating them can influence physicians' knowledge and awareness, they are not in themselves sufficient to change practice. "What is required is a much more comprehensive approach that incorporates not only knowledge, but also builds skills and affects attitudes," she wrote.

Mellstedt agrees with this. "Today, oncology demands a multidisciplinary approach to the patient – before you take a decision on how to treat the patient, you should consult with colleagues," he says. "But as a basis, you should have guidelines, with the multidisciplinary consensus on top. The approaches are therefore complementary."

While the debate continues, Hébert-Croteau can see encouraging signs that guideline uptake is on the rise, and believes her study puts forward a strong message to clinicians to recognise the value of guidelines and use them.

"We are beginning to understand what promotes the adoption of guidelines, and what makes clinicians more receptive to them," she says. "The more prestigious the sponsoring organisation, and the more leaders in the field supporting the guideline, the better the prospects of adoption.

"There have not been many studies that have evaluated guidelines, even though they have become very popular in the last 10 or 15 years," she continues. "For whatever reason, guidelines tend to be slow to pass into practice, but if you show that they make a difference to survival, it is likely to increase the chances of compliance."

e-Lessons of yesterday point the way ahead

Christine Haran

From Harlem to Helsinki, from Stirling to Sarajevo, the Internet is being put to novel uses in the cause of cancer prevention and care. The lessons learned have now been used to map out an action plan for Cancer on the Internet.

New information and communication technologies have been used by and for cancer patients for more than a decade. But it wasn't until June 2003 that members of the cancer community first got together to formulate a common approach to Cancer on the Internet, at a conference in New York called by the European School of Oncology.

Last September a second conference was called, again in New York, which went one step further. Over the course of two days, 150 delegates from 13 countries, representing very varied levels of Internet use, shared experiences and drew up suggested areas for action under the headings: Promoting Digital Inclusion, e-Cancer Care, e-Cancer Patients, and Fostering Global Collaboration. These were incorporated into the revised New York Statement, which is published on p. 64.

"Our goal was to bring people together from all over the world who are interested in improving cancer care, from prevention to end-of-life care, using information and communication technologies," said Alex Jadad, a conference co-chair and the director of the Program for eHealth Innovation at the University Health Network and University of Toronto in Canada. "There are many success stories that people don't know anything about, and we cannot afford that… Only by sharing knowledge and learning from one another's mistakes can we move forward."

Digital inclusion

Delegates heard about a variety of initiatives in different communities across the world that aim to increase the number of people able to benefit from Internet access.

In India, doctors and nurses in underserved areas are getting access to cutting-edge information through an initiative undertaken in partnership between the WHO's Health InterNetwork (HIN) and the publishers of Indian biomedical journals. Joan Dzenowagis, project manager of the HIN, described how the project has brought computers to primary health centres in the states of Orissa and Karnataka. HIN staff worked with the community to create the infrastructure – as basic as phone lines – needed to support the computers and the Internet access, and together with local institute

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staff, they also trained more than 300 local public health personnel, so they could access and use the journal articles and other health information.

In the very different setting of Harlem, New York, a project has been running to teach consumer and healthcare providers a 'cancer education curriculum.' The aim is to provide health information in English and Spanish and teach community members how to find information online, as well as help healthcare providers identify credible health websites.

Rosemarie Slevin Perocchia, Director of the National Cancer Institute's Cancer Information Service of New York at Memorial Sloan-Kettering Cancer Center, who helped launch the project, described how she and her colleagues had got together with local groups to hold training workshops, educating 256 consumers who were residents of this underserved area and 256 health care providers from around New York City. While the workshops were successful, Perocchia reported that the project had struggled with enrolment, and observed that a 'champion', such as a local celebrity, might have helped boost participation.

Another initiative, this time in Bosnia Herzegovina, aims to provide simple, quality information to cancer patients in a language they can understand. Anes Pasic, of the Institute of Oncology at the Clinical Centre of the University of Sarajevo, described his efforts to build a cancer support webpage for his hospital's patients and their family members. The website, he says, is needed because physicians in his overburdened hospital don't always have the time needed to explain the disease as fully as they would like. Currently only around 5% of Bosnians use the Internet for health purposes. While this is likely to improve once information becomes available in their own language, the high cost of Internet access remains a problem, he said.

A series of reports from the field offered conference participants the chance to hear about other efforts around the world, including a cancer portal in Spain developed to reach people with cancer and to provide preventative information to those without cancer; a new search feature on the National Cancer Institute (NCI) website called 'Best Bets' that helps visitors find the most pertinent information; and a Danish project that assessed the usefulness of Internet support in a cancer rehabilitation centre.

Optimising cancer care

The conference also heard about innovative techniques being piloted in recent years to use information technology to improve the care of cancer patients.

In Scotland, handheld computers and cell phones were used in a study to assess patients' symptoms while they were receiving chemotherapy. Nora Kearney, a professor of cancer care at the University of Stirling, who headed up study, explained how the technology had enabled healthcare professionals to establish patterns of severity of symptoms over time and allowed them to compare how

A website in Bosnia Herzegovina provides information to cancer patients in their own language

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The 'Kardian PM' is a portable mobile electrocardiograph, which can display a cardiogram instantly, memorise it and transmit it to any medical institution through a mobile phone. Cancer patients in Scotland have used similar techniques to record and transmit information about their symptoms while on chemotherapy. The information has been used to identify best practice in symptom control in a bid to improve this essential aspect of cancer care

13–14 September 2004 2nd International Conference on Cancer on the Internet

New York Statement: Using the Internet to optimize cancer control

e-Cancer Patients

The Internet is the cornerstone of the techno-cultural revolution that is starting to transform the nature of cancer control. Patients have been at the forefront of this revolution and many are now regularly using the Internet to obtain information about their disease and its treatment, seek support from on-line patient communities and support groups, share knowledge and experiences with other patients and communicate with their professional carers and loved ones. There is a great deal of confusion and many concerns as to the quality and appropriateness of online patient resources; however, it is impossible to police the Internet. In order to address these concerns, many governmental and non-governmental organizations have developed guidelines for quality health websites and on evaluating health information on the Internet. Unfortunately, implementation of these guidelines has been patchy. Moreover, there is little or no government protection for e-consumers of health sites particularly in terms of privacy, security and confidentiality.

Suggested actions:

- Raise awareness of quality criteria for health websites that have been developed by a number of reputable agencies. Facilitate widespread dissemination of these guidelines via established networks and encourage compliance amongst cancer website developers.
- Promote research into tools that can help consumers find quality health information and undertake an inventory of currently available resources that can help patients hone their critical evaluation skills (e.g. the US National Cancer Institute's document on how to evaluate health information on the Internet, MedCIRCLE etc).
- Lobby for standards for e-health and ICTs, while maintaining freedom to innovate.
- Urge governments to take action if website providers undermine cancer patients' rights.
- Encourage sharing of best practice on running effective online patient support communities (both peer- and facilitator-led).
- Foster discussion and debate amongst all stakeholder groups on ways the healthcare sector can become more responsive to the needs of e-cancer patients.

e-Cancer Care

The Internet provides an important tool to facilitate clinical practice and cancer research. Professional access to and use of content and Internet applications is an essential part of providing appropriate cancer care; however, it has lagged for reasons of cost, effort, policy and other barriers.

Suggested actions:

- Raise awareness of ways in which the Internet can impact on diverse cancer outcomes and stimulate large-scale research in this area.
- Promote the potential of ICTs to reduce workload and costs and improve communication and continuity of care.
- Identify workable solutions to the technological, legal and attitudinal barriers to patient-physician communications via e-mail.
- Point to the usefulness of the Internet as a means of providing continuing professional education and facilitating mentorship initiatives. Encourage education providers to use web-based education approaches more widely.
- Call on the relevant authorities to include a short course on the relevance and application of ICTs in healthcare in the undergraduate curriculum and promote coverage of this topic as a fundamental component of continual medical education activities.
- Support efforts to establish clinical trials registries that are freely accessible to the public, accurate, inclusive and electronically searchable.

Participants at the International Conference on Cancer on the Internet are committed to promoting and developing the potential of the Internet in support of cancer efforts worldwide, from the global to the individual level. This statement was drafted at the first international conference in June 2003 and revised at the second conference in September 2004. The New York Statement identifies key areas for action, advocacy and collaboration in realizing the potential of the Internet for cancer control. Conference participants believe that cancer control can be improved, in all countries and for all people, through the efficient and effective use of the Internet. This applies to the whole cancer continuum from prevention through diagnosis, treatment, survivorship and palliative care. Information and communication technologies (ICT) have helped cancer control in many different ways and the benefits are being rapidly extended as the Internet grows. Internet applications and content resources for all cancer communities are an essential part of improving cancer control. This statement recognizes the significant potential benefits the Internet has for the many stakeholders involved in cancer control efforts: patients and their loved ones, citizens, health professionals, researchers, policy makers, educators and organizations.

Promoting Digital Inclusion

Internet access is becoming a reality in many countries worldwide as basic infrastructure and services continue to improve, but there are major obstacles in ensuring access is available and affordable so that all can benefit. These obstacles include cultural and economic factors, infrastructure, literacy, and language. An affordable, reliable, durable and high-speed infrastructure is required and relevant content will motivate Internet use. Moreover, skills to use and manage connectivity and content are essential. Global, national, and local efforts for e-inclusion are an important means to extend the benefits of ICTs to all citizens.

Suggested actions:

- Work beyond the cancer sector to encourage electricity and phone providers as well as government departments to improve connectivity, even in the remotest settings.
- Find local solutions for developing relevant and culturally appropriate content.
- Encourage the application of the principles of good health communication by those developing content for the Internet and raise awareness of the need to tailor online information to meet the needs of people with health literacy or other communication difficulties.
- Intensive training efforts are required to equip underserved members of the cancer community with the skills they need to use the Internet in an optimal manner.

Fostering Global Collaboration

Many organizations have as their mandate global cancer control and international activities. Their efforts can be facilitated through collaboration in developing and disseminating standards and research, sharing experience and best practice, and facilitating technology development, testing and deployment. National and international co-ordination can optimize use of limited resources and avoid duplication of effort.

Suggested actions:

- Help develop the eUICC as a global resource for collaboration.
- Identify other innovative ways to promote collaboration amongst international, regional and national cancer organizations in efforts to harness the power of the Internet in the fight against cancer. Mapping Internet-based resources created by cancer organizations worldwide should be a priority.
- Think globally; act locally – identify and support local champions to ensure the sustainability of initiatives and optimize local involvement, especially around prevention and health promotion activities.
- Explore the feasibility of establishing an international organization for people interested in collaborating on initiatives relating to Cancer on the Internet, including those targeted at low-income countries.
- Develop a workable mechanism to facilitate the sharing of best practice amongst people active in the cancer-related ICT arena.

successfully nurses in different locations were managing symptoms. A different sort of comparison, this time between US and Finnish survival statistics, was made possible through a website, www.finprog.org, which develops survival curves based on breast cancer risk factors. The creator of the website, Johan Lundin, of the Biomedical Informatics Group at the University of Helsinki, explained how it could be used by clinicians to help with treatment decision-making.

The Internet is also being used in an effort to boost participation in clinical trials, which is currently running at just 5% among US cancer patients – a situation that Cindy Lollar, of the Office of Cancer Information Products and Services and Systems at the NCI, attributed largely to the fact that around 80% of patients know nothing about them. In an effort to boost participation, said Lollar, the NCI has added to its website comprehensible summaries of open trials, together with a search facility that enables patients to search for trials relevant to their condition. Similar information has also been made available through the Cochrane Center Register of Controlled Trials (CENTRAL), which lists more than 30,000 trials.

The Internet is also being used in an effort to boost participation in clinical trials

But perhaps the most important impact of the Internet in improving cancer care, argued US Cochrane Director Kay Dickerson, has come about as a result of empowering patients. In particular, she attributed the move towards evidence-based medicine largely to pressure from patients who, thanks to the Internet, became able to take a more critical attitude towards their own treatment.

Tom Ferguson, of the Pew Internet & American Life Project, who has been championing the cause of e-patients for more than 15 years, believes that well-informed patients have a great deal to offer the cancer world. "These new medical colleagues," he says, "may help us find sustainable solutions to many of the seemingly intractable problems that now plague all modern healthcare systems."

Forward through global collaboration

Not all speakers agreed over how many online cancer patients actually visit health sites, or about how much benefit is gained by those who do. It was clear, however, that most cancer organisations across the world – around 90% according to a study conducted at the University of Toronto – are now geared up to using the Internet to fulfil their missions of providing information, promoting research, holding scientific meetings and publishing research data.

This opens up great possibilities for building global collaboration over any aspect of cancer information, care or prevention. Already 280 cancer organisations affiliated to the International Union Against Cancer (UICC), in more than 80 countries, are using the Internet for the dissemination of information, such as its tobacco control programmes. Other international cancer organisations have built their own networks.

The challenge for the future, it was argued, was not to build new networks from scratch, but to work with what we have and seek to extend existing networks. Adapting big business marketing techniques and building partnerships with technology companies are two ways in which this is being achieved.

"The Internet is already changing the way we are approaching cancer control: from the global to the personal level," said Dzenowagis from WHO, commenting on what she had heard over the two days. "We have new opportunities to work together and contribute. This conference was an important venue for highlighting some of the most promising innovations for patients and clinicians."

The sounds of silence

Negative clinical-trial results are underreported. But this may soon change.

Sometimes, no news is news. In clinical trials, where new medical treatments are tried out on human subjects, no news – an inconclusive result, indicating that the treatment is useless, or a negative one, indicating that it is harmful – can be as scientifically important as a positive result. Unfortunately, such a result is much less likely to be reported.

That is particularly true for trials sponsored by the pharmaceutical industry which, according to the American Medical Association (AMA), accounted for over 70% of the funding for such trials in America in 2002, the most recent year for which figures are available. The lack of reporting of null or negative findings is pernicious because it skews the results of so-called 'meta-analyses', which compile data from previous studies of a treatment. If only positive results are reported, then a meta-analysis risks being too laudatory.

The medical profession has been aware of this problem for a long time. However, pharmaceutical companies have a vested interest in keeping negative results quiet, so change has been slow in coming. But the proper balance between commercial confidentiality and public disclosure in the case of drugs, where ignorance can cost lives through misprescription, is different from that for, say, computer chips. The widespread government funding of basic drug research also gives the public a moral claim on the results. And a confluence of forces in the past few weeks may well succeed in pushing drug companies towards greater openness.

The times they are a changin'

The first of these forces was a legal settlement last month between GlaxoSmithKline (GSK), a British pharmaceutical company, and the state of New York. A lawsuit filed in June by Eliot Spitzer, New York's attorney-general, alleged that GSK had deliberately suppressed negative results from four clinical trials of Paxil, an anti-depressant. In the settlement, GSK agreed to post online summaries of all of the clinical trials it completed after December 27th 2000 (the date that Glaxo Wellcome merged with SmithKline Beecham).

The second force is that on September 9th the International Committee of Medical Journal Editors, a group consisting of the editors of the *Journal of the American Medical Association* (JAMA), the *New England Journal of Medicine* (NEJM), the *Lancet* and 11 other top-flight medical publications, put the screws on those who conduct clinical trials. They announced that from the middle of 2005 their journals would no longer publish the results of trials that had not been registered in advance in an independent database open to the scrutiny of all. The journal editors do not advocate a particular database, but they do point out that clinicaltrials.gov, which is run by America's National Institutes of Health, is the only one which satisfies their criteria at the moment.

At first glance, the posturing of a few scientific journals might look puny in the face of the might of the drug companies. But the editors' proposal actually has teeth, because even hard-nosed corporations value the legitimacy that publication in an important peer-reviewed journal has on their results. And although only 14 journals have signed up to the initiative so far, other journals carrying results of clinical trials typically take their lead from the journals that are spearheading it.

Defenders of the pharmaceutical industry claim that forcing the complete reporting of results might reduce the incentive to develop new drugs by revealing a firm's hand too early in the development process. But Jeffrey Drazen, the editor of the NEJM, argues that the rewards of success are so big that requiring such reporting will not stop companies from proposing trials they think have a chance of success. What it might reduce, he says, is the number of 'seeding trials'. These are trials of drugs that have already been approved for one use, and are

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Lack of reporting of null or negative findings distorts the results of meta-analyses

then tested for secondary treatments which have little hope of success. Firms use these trials as marketing tools, to put drugs into the hands of doctors in the hope that those doctors will prescribe them more often. The mere existence of seeding trials indicates that the balance between confidentiality and disclosure is skewed.

The editors' initiative will help, but it will serve only to flush out now-hidden trials so that questions can be asked about what happened to them if no public report of their results ensues. It will not force those questions to be answered. The third factor, a political one, may deal with that.

Legislation is in the works in both houses of America's Congress to reform the reporting of trials. In particular, Chris Dodd, Tim Johnson and Edward Kennedy, three Democratic senators, are expected to propose, within the next week or two,* a law that would increase compliance with existing requirements to post trial data to clinicaltrials.gov. It would probably adopt a proposal made by the AMA that registration in a central database be a requirement for the approval of human trials, as well as introducing new requirements to include trial results in the database.

The industry disputes the need for this. Caroline Loew, a spokesman for Pharmaceutical Research and Manufacturers of America (PhRMA), a trade group, claims that the industry has a "very good history of

*The bill was introduced on October 7th 2004, and was referred to the House Committee on Energy and Commerce

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The balance between confidentiality and disclosure is skewed

compliance". This is stretching the truth. As Catherine De Angelis, the editor of JAMA, points out, a group of big drug companies agreed in 1997 that they would create a centralised database. But, because there was no enforcement mechanism, they conveniently forgot about it. Furthermore, in a letter written to PhRMA in June, Henry Waxman, a Democratic congressman from California, pointed out that the industry was not even complying with existing legal requirements to post certain trials to clinicaltrials.gov. Alan Goldhammer, another spokesman for PhRMA, claims that Mr Waxman was relying on preliminary data.

Band on the run

In his letter, Mr Waxman also complains that despite PhRMA's budget of over $72.7m for lobbying the federal government, when the House of Representatives' Government Reform Committee held hearings on the issue of clinical trials and requested that an industry spokesman testify, none deigned to show up. So there are reasons to suspect that the proposal made by PhRMA on September 7th, for a new, voluntary database, is less good than it sounds. Critics point out that it will only contain summaries of the results of trials after they are completed, rather than reporting ongoing trials. It will also be restricted to trials for drugs that are being marketed in America.

Dr Goldhammer replies that this is because PhRMA has made a deliberate decision to focus on practising American physicians, who need to know only the final results for drugs sold in America, rather than on the needs of researchers. But this is shortsighted. Researchers could make good use of the more complete set of data.

Dr Goldhammer says that what his group is proposing is "delinking a registry from a results database". That sort of obfuscation seems opposed to transparency. But transparent reporting of trials looks as if it is on its way, regardless.

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