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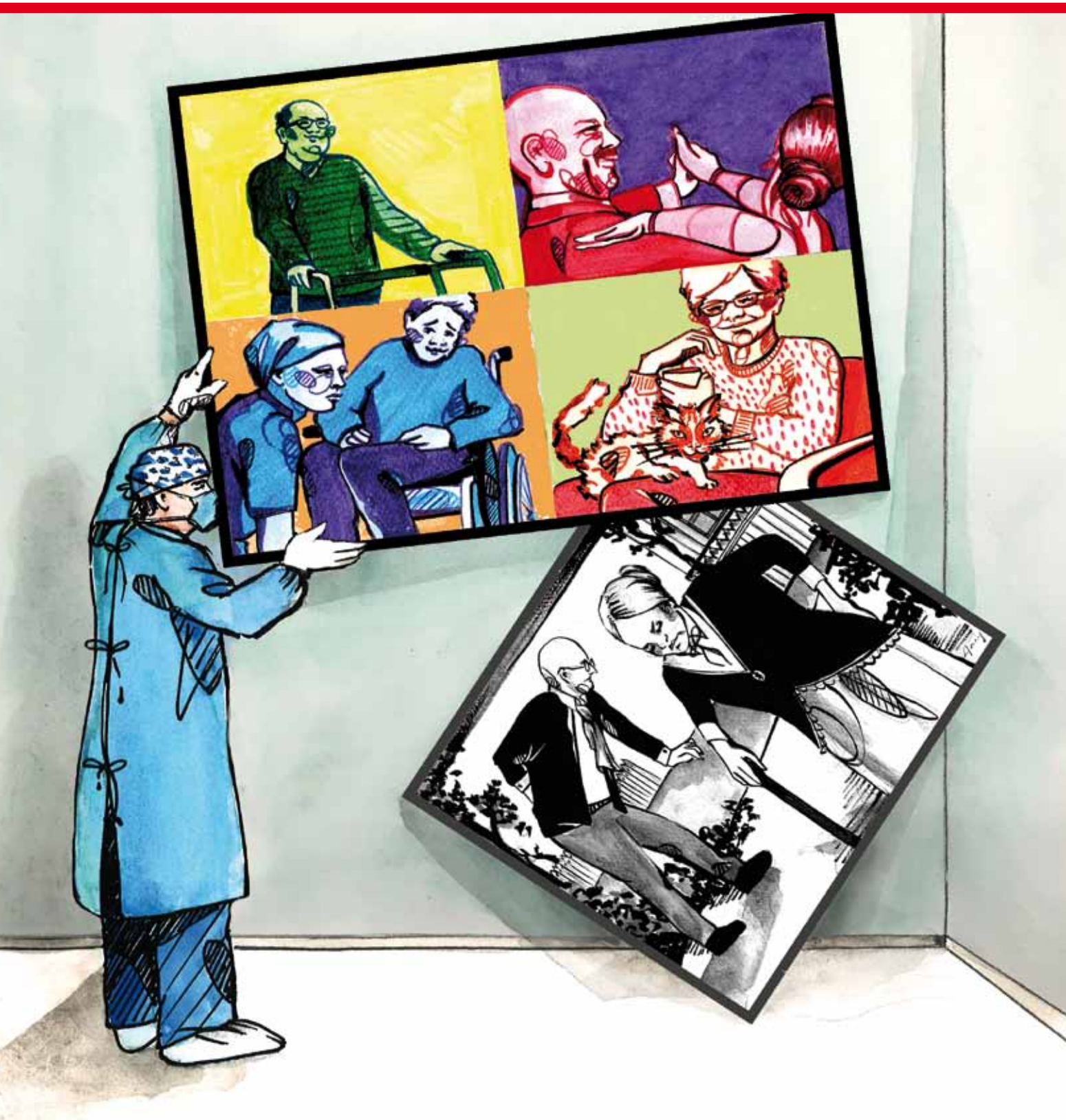

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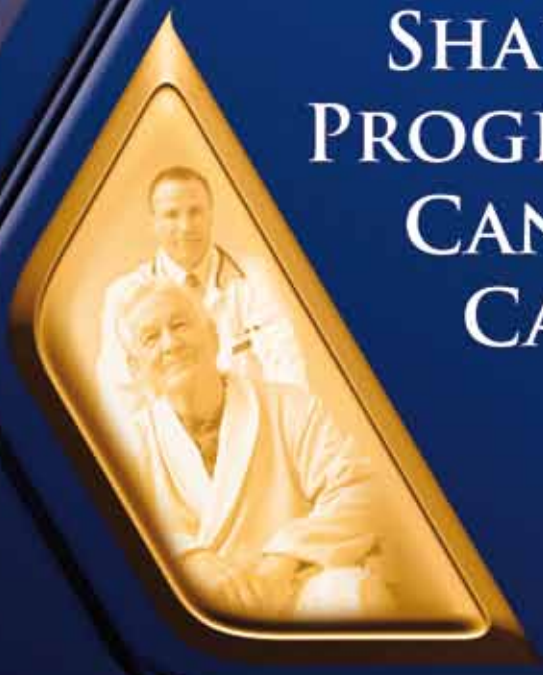
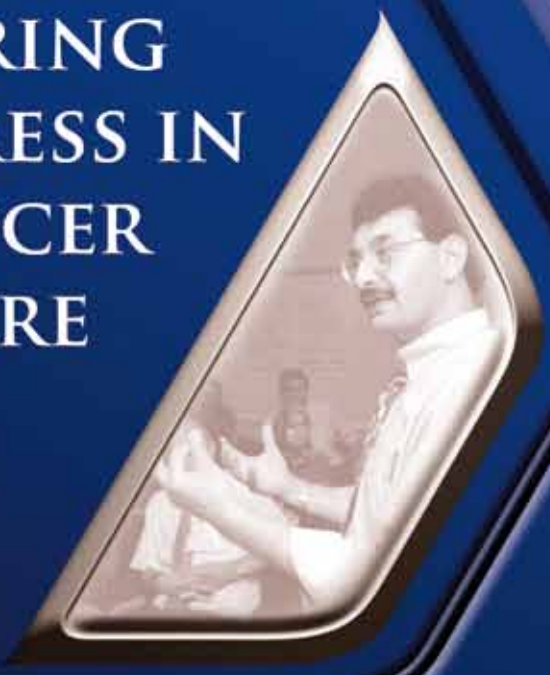
European School of Oncology

Learning to care

Sharing Progress in Cancer Care





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Old, young – does it matter?

Matti Aapro, Guest editor

Not so long ago, research protocols excluded older cancer patients based on chronologic age. Now they exclude patients with comorbidities, and as most older patients suffer additional ailments, they do not fit the protocols. But these people are looking for our help.

Reconciling real-world medicine with artificial barriers that might limit treatment of any patient without good reason is one of the tasks of geriatric oncology. We have to develop strategies that enable us to evaluate the risks and benefits of curative treatments in all our patients, not only in the 'Olympic champions' who are fit enough to enter a standard research protocol.

Progress is slow but it will certainly accelerate as awareness grows of the huge unmet need. We have to find answers based on adequate evidence, as more and more older patients are seen in hospitals and doctors' offices, not only in the aging societies of Europe but all over the world. The time-bomb of the aging population is ticking, and governments need guidance to allocate the necessary resources for this growing segment of the population. If the cancer community does not provide that guidance, older patients could end up without access to key cancer services, just as happened with kidney dialysis services two decades ago.

We need to learn from our colleagues in other areas of medicine, and especially from the real experts – the geriatricians. But in many countries they are few and far between, and in heavy demand, so true collaboration remains a challenge. The International Society of Geriatric Oncology (SIOG), a member of the European Cancer Organisation (ECCO), plays an important role here by providing guidance, developed by multidisciplinary taskforces, to the nurses and physicians who treat the growing number of cancer patients with complex health issues.

But the taskforces themselves often lack top level evidence, so their recommendations, which are published in major journals including SIOG's *Journal of Geriatric Oncology*, need to be periodically revisited as new evidence emerges. With the help of the European School of Oncology, SIOG now also organises advanced courses, attended by physicians from all over the world, to train geriatricians in basic aspects of oncology, and oncologists in the fundamentals of geriatrics.

These courses will hopefully lead to many innovative clinical research projects, to be conducted in collaboration with national groups and others like the European Organisation for Research and Treatment of Cancer. The findings should help answer the many unresolved questions about how to prevent and treat cancer in older people, and how best to care for patients and support their families and friends. They will also demonstrate that age, frailty and comorbidities do matter, and that only research that includes this growing group of patients can provide the evidence we need to provide truly personalised care, respecting the patient's goals, and recognising the risks and benefits of the suggested treatment.

Matti Aapro is a Director at the Genolier Cancer Centre, Genolier, Switzerland. He serves the International Society for Geriatric Oncology (SIOG) as Executive Board Member.

Geriatric oncology:

personalised medicine when you are old

For most of us, sooner or later, old age will bring frailty and chronic health conditions, making the task of living the life we wish progressively harder. We will want oncologists who know what different treatment options can offer people like us. **Peter McIntyre** asks: how can we do better for older patients?

"My mother believes she is immune to breast cancer," says surgeon Riccardo Audisio. "That is because they don't send screening letters to women older than 70." He hopes his mother stays safe, but suspects that if she did develop breast cancer she would probably see it as the end.

"It is a general assumption that when you are old you don't get cancer, and if you do get it, it is untreatable, which is the exact opposite of the truth. Age, *per se*, is the primary risk of developing cancer, and older cancer patients are as treatable as younger ones."

In practice, older patients do not get treated as well as younger patients and they do not survive to the same extent. There is an increasing mismatch as older age groups in Europe have a growing proportion of cancers but are less likely to be treated with surgery, chemotherapy or radiotherapy. They are much less likely to be represented in research.

Nor do older people have a voice in policy discussions about cancer. There are few special advocacy services for older people; and this is the age group most likely to trust their doctors and go along with whatever treatment is suggested.

Worse survival

The EUROCARE 5 Study showed that five-year relative cancer-specific survival in Europe (2000–2007) decreased with older age for all cancers (*Lancet Oncol* 2014, 15:23–34). The age standardised death rate for cancer was more than 12 times higher among people over 65 than for younger people (Eurostat 2015). Data from England show the rising trend of cancer deaths in the 80+ age group has the steepest trajectory.

Older patients are more likely to be admitted for cancer as a result of an emergency and more likely to be diagnosed very late (stage 4) (*Br J Can* 2015, 112, S108–S115). A study comparing colon cancer patients in England, Norway and Sweden showed excess deaths in older age groups, and most occurred within three months of diagnosis (*Gut* 2011, 60:1087–93).

Most people accumulate health problems as they age. Cancer is often treated against a background of diabetes, chronic obstructive pulmonary disease, stroke and hypertension. More than a third of people over the age of 80 are being treated for four or more medical conditions (*Lancet* 2012, 380:37–43).

However, treatments most commonly associated with cancer cure are less commonly given in this age group. The National Cancer Intelligence Network in the UK says that older patients are less likely to receive surgery, radiotherapy or chemotherapy, and most specialists say that this is the case across Europe.

Assessment

Siri Rostoft, a geriatrician at Oslo University Hospital, says that every older patient should have an assessment of some kind before treatment decisions are made. A comprehensive geriatric assessment takes about an hour, but simpler tests can be used when time is tight. The critical factor is to look at the person's condition rather than simply counting the years, as older people show great differences in physical and mental resilience, and these differences increase with age and can be predictive of outcomes.

To illustrate the point, Rostoft mentions the case of a 94-year-old woman admitted to the acute geriatric ward with fatigue and dizziness. She was found to have anaemia and bleeding due to a right-sided, narrow passage, large colon cancer. At her age, she seemed a doubtful candidate for surgery.

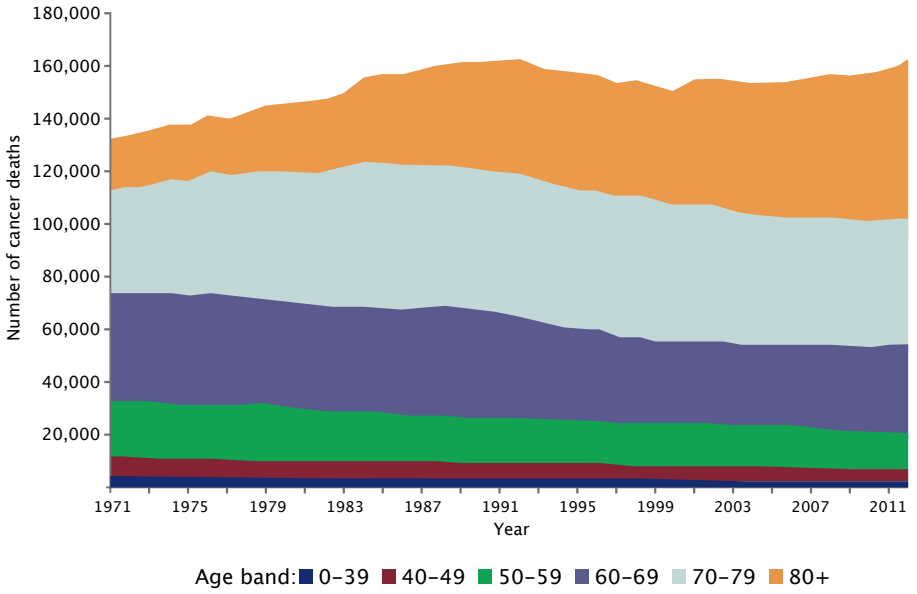
After her condition stabilised, Rostoft conducted a simple Timed Up and Go test (TUG), asking her to get up from her chair, walk three metres, return to her seat and sit down. If this takes longer than 19 seconds, the person is classified as frail and a full assessment may be needed. The 94-year-old woman insisted she wanted to take the test starting from lying on the floor, as doing it from sitting would be too easy. She completed this much more demanding test, and was passed fit for surgery.

Rostoft accepts that not every elderly patient can have a gold-standard comprehensive geriatric assessment, but even simple gait speed tests have been shown to have strong prognostic power. She points out that a fit 85-year-old in northern Europe can expect to live a further 10 years – twice as long as the five-year survival gold standard used for clinical trials.

"Oncologists may argue that there is no way they can spend one hour with a patient. But if you want to give someone chemotherapy which is extremely expensive and toxic, you have to spend enough time before you start treatment. The risk of delirium and becoming confused and not cooperating with the treatment is much higher if the patient has cognitive impairment, and you often have to do some objective tests to uncover that.

"I have experienced a few times when an oncologist calls me because the patient became confused in the ward and starts pulling out needles and refuses to do anything the doctors and nurses tell them to do. I think they should have called me before they started treatment, because maybe there were signs that could predict what would

Cancer mortality is falling – but not if you're over 80



Source: Public Health England (2014) *National Cancer Intelligence Network: Older People and Cancer*

happen, and we have interventions that may prevent delirium."

Pierre Soubeyran, a geriatric oncologist who coordinates the Geriatric Oncology Research Group at the Bergonié Cancer Institute in Bordeaux, agrees that assessing a patient's overall condition is critical.

"The older you get the more comorbidity you have and these comorbidities interact, especially medications and side effects. There can be very negative outcomes for these patients if we do not treat them correctly, because oncology treatments are toxic.

"What oncologists find most difficult are what they call the geriatric syndromes that concern nutrition, cognition, mood, mobility and functionality, which make the patient's reserves very limited. That may not be visible at first look." For example, he says, it could be dangerous to give oxaliplatin, which can cause balance problems, to someone with colon cancer who already is unsteady on their feet.

Soubeyran and his team developed the G8 assessment now adopted throughout France, asking questions about food intake, weight loss, BMI, mobility, neuropsychological status, number of medications, and self-perception of health status.

They are now working on a slightly broader assessment that can be used by an oncology team. "Oncologists are always in a hurry and the tools that geriatricians propose feel too complicated. The objective would be a 15- to 20-minute assessment performed by a nurse. What we are proposing is to make the evaluation much more methodological, clear cut and defined."

Soubeyran says that many oncologists work on the basis that if someone looks very old they should decrease the dosage, and this can lead to undertreatment. "Some patients look frail, but the evaluation shows they are not. My experience is that most of the time an evaluation leads to treatment at or close to a normal level."

However, Siri Rostoft does come across some cases of overtreatment, particularly in very frail 'young elderly' patients in their late 60s and early 70s.

"I have seen a small number of patients where, once they have started cancer treatment, it is difficult to have the discussion on when to stop. In some cases it is obvious that the patient is not benefiting, as the treatment is too aggressive and the side effects clearly outweigh the benefits. The assessment has to be individualised to aid decision making, so as not to overtreat frail younger patients or undertreat the really fit older patients."

Access to surgery

There are also concerns that elderly cancer patients are often excluded from surgical treatment. Riccardo Audisio, who is President of the European Society of Surgical Oncology and professor of surgery at Whiston Hospital, Liverpool, says that low rates of surgery for old patients in the UK reflect what is happening across the world.

"Surgery is the curative option for cancer, and there is evidence that surgery is not routinely offered to older cancer patients on the grounds of their age. There is a substantial discrimination that starts from the very beginning. A woman has had peri-rectal bleeding. She is now noticing blood in the stool but she does not tell the family. When told, the family does not tell the GP and the GP does not send her for a proper investigation because she is old.

"The most shocking thing is most older patients come with the assumption they are not fit for surgery. You have to spend a little bit of time with your

Geoff, 66 – surprised by ageism

"What surprised me most was a discussion about my treatment options. I was told that I could have surgery to remove the tumour if the cancer hadn't spread. But they explained that if I was over 70, they may not have offered to operate at all. I thought that was discriminatory, and clearly ageist. The role of the medical profession is to prolong life, no matter what age. Surgery could give someone another 20 years.

Macmillan Cancer Support. (2012) *Age Old Excuse: The under treatment of older cancer patients*

patients and clarify that surgery is not as dreadful as they expected.

"You explain that half the patients we deal with or more are their age, and anaesthesia is very safe. And surgery can be performed. In some cases I tell them, if I take the breast cancer out you can go home the same day and you can walk your dog."

Surgeons need face-to-face contact to build trust with the patient. "This is a very delicate moment. When they sign a consent form you are telling the patient 'I bet money we will get out of here quite easily' or you are telling them 'It is going to be a challenge and the risks are high'. I cannot expect a geriatrician or nurse to discuss these delicate issues for me."

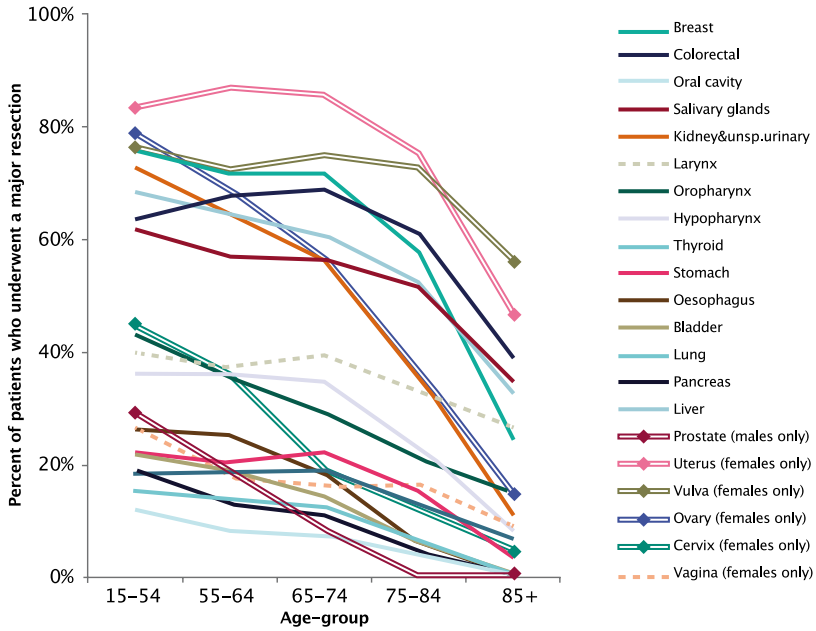
Audisio says that one reason why surgeons become cautious is because they are judged on operating mortality rates. "If you are on call over the weekend and you have three older very frail patients admitted as an emergency for bowel obstruction and you know that mortality is three times higher for an elderly emergency colorectal patient, do you operate or say, 'they are too old and too frail,' and just leave it?"

A 2016 survey by the Surgical Task Force at the International Society for Geriatric Oncology (SIOG) shows that 90% of surgeons operate for cancer regardless of age; but half would not operate on a patient with impaired cognitive status. Less than half think preoperative frailty assessment is essential, and only a third regularly collaborate with geriatricians. Quality of life and functional recovery were regarded as the most important endpoints. The study team concluded that age is not seen as a barrier to surgery, but there is a need to focus on 'prehabilitation' to achieve better functional recovery. The survey may present an optimistic picture, since the 250 surgical oncologists who responded make up only 11% of those who were asked, and possibly have more positive attitudes.

What does the patient want?

Lower rates of treatment do not seem to be due to a reluctance on the part of the patient. A 2014 report by NHS England found that older people are more likely to have confidence in doctors and nurses. Research carried out by a polling organisation for Macmillan Cancer Research in the UK, published in 2015, shows that the proportion of patients refusing cancer treatment actually falls slightly amongst older patients, with 12% refusals among

Major resections by cancer site and age in England 2006–2010



Source: Public Health England (2014) *National Cancer Intelligence Network: Older People and Cancer*

patients over 75 compared with 15% amongst 55- to 64-year-olds.

It also showed that older patients are more likely to feel they can 'cope' with cancer, and this may be driven by the desire to maintain independence. Overall, maintaining health is listed as the most important priority for most people living with cancer, but in the older retired group continued independence (44%) is just as important as maintaining health (43%).

Hearing the patient voice is especially important given the increasing understanding that patient-reported outcomes can be a very reliable indicator of how a cancer patient is progressing.

Siri Rostoft says that the only way to find out patient priorities is to ask them. "A basic thing that is often not done is to talk to the patient and to discuss it. Some patients have really strong opinions and say 'no way that I want to go through any treatment'. My impression at least is that older patients still have some paternalistic idea that the doctor knows best, and say, 'do what you think is right.' Others say, 'talk to my son or my daughter – she will know better than me.'"

Uncovering patient priorities is challenging if there is cognitive dysfunction. "Cognitive function affects physical function, and physical function is an extremely important predictor of life expectancy. It is more demanding when they cannot say clearly what they want and they don't understand. We talk to them about the cancer and treatment options, and the next day they don't remember that they have cancer."

In these cases it becomes increasingly important to include the family and care givers and take more time over explaining the options.

Pierre Soubeyran says that some older people are very skilled at hiding their confusion. He recalls a 95-year-old woman becoming very upset when asked questions designed to test her memory. "Initially when I saw the lady I did not see any cognitive problem because she was very clever and cultured and was able to circumvent the cognitive problem and answer questions. In the end, we realised that she was deeply impaired, and it was important to know that. It may change the way the patient understands what we explain."

Francesco De Lorenzo, President of the European Cancer Patient Coalition (ECPC), says there are virtually no specialist advocacy groups in Europe for elderly cancer patients, and condition-specific cancer organisations are generally not geared up to represent them. He sees as crucial providing support to family or other caregivers, who in Italy support eight out of ten older cancer patients. ECPC will be pressing the European Parliament to introduce new rights for carers and elderly people with comorbidities, who are often very severely affected by reductions in home and social care.

One of the few advocacy services for elderly cancer patients and their families is showing results, from improved clinical communications to reduced financial anxiety, improved hope for the future and enhanced self-respect. Cancer, Older People and Advocacy was launched in the UK by the Older People's Advocacy Alliance (OPAAL), with funding from the national lottery and Macmillan Cancer Support.

Operations manager Marie McWilliams says that advocates can attend hospital consultations with cancer patients and help them to understand their choices. "Sometimes people feel they should make decisions on the spot. The advocate will reassure the older person that they do not need to make a decision there and then. They might want time to digest the

Jim 73 – independence threatened

Jim has lived alone since his wife died. After he was diagnosed with cancer of the throat, he had a tracheostomy. Hospital staff wanted to send him to a nursing home as they said he could not cope at home.

"I was getting very angry because I was told that the district nurses could help me with this but none of them had been trained to do so." He was found an advocate, Richard, who talked to staff at the hospital with him. "He understood that I wanted to go home and be independent. I am not quite sure how much Richard had to do with it, but the district nurses were given a rapid training course in tracheostomy management and I was allowed home."

OPAAL (UK) and Macmillan cancer support case studies. (2014) *Every Step of the Way*

Beryl 84 – Left alone to cope

"I was shocked to be diagnosed with bowel cancer, as I'd had no symptoms or pain. I was told I'd need surgery to remove half my bowel.

I'm a widow and live on my own, so after the surgery my son came to give me a lift back to my flat. After I was discharged from the hospital, I was left to look after myself – I didn't even get a wheelchair to get down to my son's car. I wasn't offered hospital transport or help to cover the cost of taxis to and from appointments.

When I got home the first week was awful. I lost a lot of weight as I couldn't eat after the surgery. I couldn't wash myself or clean the flat, which made me feel very depressed. I had no idea who to speak to for help, and no support when I needed it the most."

Macmillan Cancer Support. (2012) *Age Old Excuse: The under treatment of older cancer patients*

information. The advocate is the calm level head who will take detailed notes.

"A lot of people who come to us are also the main carer for somebody else and put their own care and treatment to the side. We need to be aware that the person who gets the cancer diagnosis has the same issues and worries in their life they had before the diagnosis. Cancer happens to be something they add on to everything else they have in their life."

OPAAL is seeking sufficient funding to extend the service around the country to ensure that older people do not face discrimination in treatment. McWilliams says: "Those who discriminate should realise they can come become victims of discrimination too. If I am lucky I will live to be old enough to face age discrimination. Something needs to be done about it."

Left out of research

Older cancer patients are largely excluded from research. The National Cancer Patient Experience Survey in the UK showed that, while a third of patients aged 51–65 were invited to take part in research, this dropped to around 20% for those aged 75 plus. Of those who were asked, half agreed to join a research project, but only half of those who agreed were enrolled.

Ten years ago Soubeyran was part of a SIOG team who met with pharmaceutical companies to discuss how to include more elderly patients in trials. "They said it was good idea, but I did not see any changes. Probably they don't want to have frail patients who may encounter more side-effects and complications." However, he says that industry is waking up to the increasing number of old patients, and that they will benefit from a more positive approach.

The European Medicines Agency is putting pressure on industry to make clinical trials more representative of the population to be treated. The summary of product characteristics (SmPC) for each new medicine should give specific safety information and dosage considerations for elderly patients. Post-authorisation, companies will be expected to present separate information about adverse effects on patients by age band for those over 65, 75 and 85 years.

The International Society for Geriatric Oncology has been developing its own guidelines on treatment of solid tumours and haematological malignancies, which are posted on its website (www.siog.org).

Matti Aapro, a founding board member of SIOG and a Director at the Swiss Genolier Cancer Centre, says that oncologists need more guidance on risks and benefits when treating frail elderly patients. "Regrettably most studies that include elderly patients address those I call the 'Olympic champions' of oncology, as they fit all the criteria for inclusion. We need studies that look at patients who have restrictions to see how best to apply treatments without guessing on what is the best way to go."

He too sees signs of change. "In the past 20 years we have seen a steady growing interest and people have become more aware of the need for studies. Industry is now very receptive to the need for specific guidance for elderly patients."

The SIOG annual conference in Milan this November will include special sessions in collaboration with industry, to put some of these issues under the microscope. There will be a special focus on immunotherapy. Aapro says: "The question that everyone is asking is: Can we apply the new immuno-oncology drugs to the elderly? and the answer is a clear 'yes'. We have evidence that elderly patients can benefit from these types of approaches without undue toxicity."

Prehabilitation: going the extra mile

Zohra Khan, aged 71, had breast cancer in her 60s and was treated with surgery and radiotherapy. This year she was diagnosed with a neuroendocrine cancer and was assessed at the Churchill Hospital, Oxford, as a candidate for whipple surgery to remove the tumour from the top of her pancreas. To take a cardio-pulmonary exercise test, she had to get on a bicycle for the first time in her life and pedal. The test showed that her physical condition was poor, but her surgeon urged her to take some exercise and try again. For three months she has been walking every day and using an exercise bike that her daughter Jabeen installed in her front room. In September 2016 she was reassessed and was declared fit for surgery. Zohra Khan is nervous about the operation, but is delighted that the surgeon helped her to get fit.

Research is also needed to show the impact of pre-treatment assessment. Soubeyran is recruiting 1,200 patients for a randomised trial based at Institut Bergonié, supported by the French Ministry of Health, to see whether a full geriatric assessment by a geriatrician and nurse before treatment results in improved outcomes. Endpoints for this PREPARE trial will be one-year survival and quality of life. "We will consider there is a benefit if we improve survival without decreasing quality of life or if we improve quality of life without decreasing survival," says Soubeyran.

Audisio is doing something similar in the surgical field. The Go Safe trial is recruiting 360–400 cancer patients who are candidates for surgery from the UK, Italy, Netherlands, US, Canada, Germany, Switzerland and Austria. Following an initial assessment of frailty, nutrition and psychological wellbeing, they will be treated according to the judgement of their surgical oncology team and followed up at six months and a year to see if there is an association between outcomes, the original assessment, and the treatment they received.

Audisio says: "The hypothesis is that by optimising the patients' weaknesses and frailty, nutrition, depression, anaemia, cardiac and so on, we will end up with a shorter hospital stay and reduced costs, less mortality and so on."

For geriatrician Siri Rostoft, research must include cognitive function, comorbidity and functional status, both as predictors and as outcomes. "It is not only five-year survival or progression-free survival that counts; maybe functional status counts more. The new cancer drugs are extremely expensive, but maybe less toxic and we have this huge population of older cancer patients who should get them. Who will make those decisions?"

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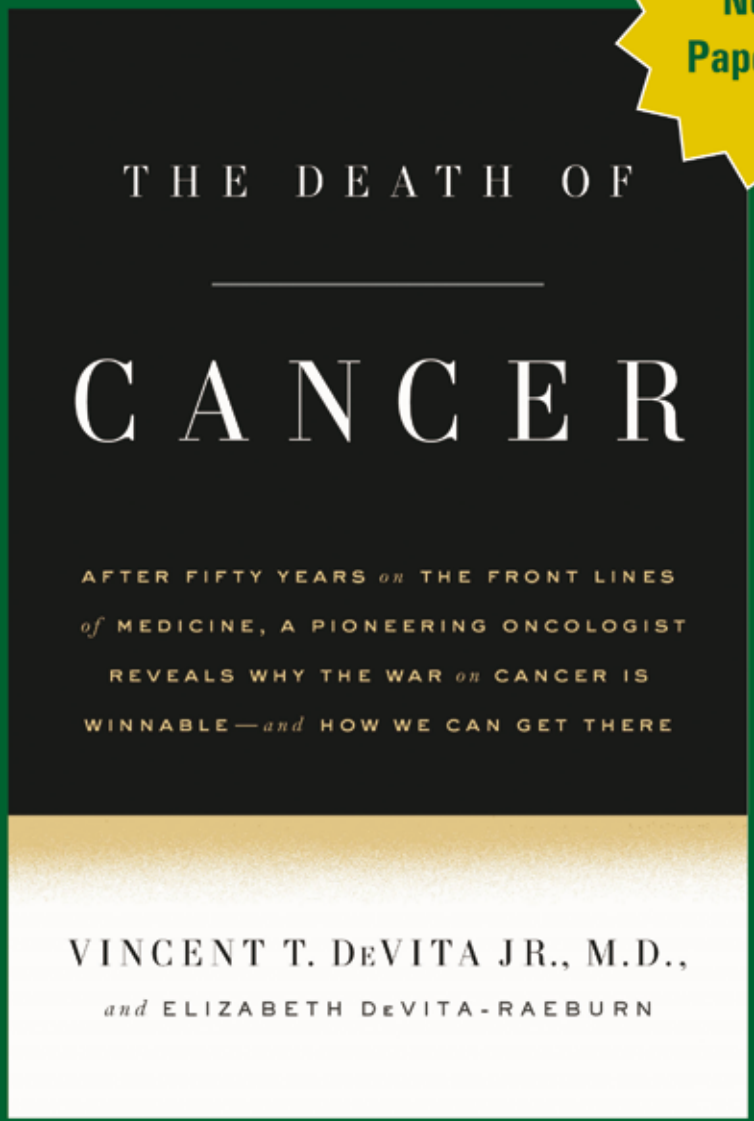

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Active surveillance: the search for greater certainty

Delaying treatment for a curable prostate cancer is an increasingly popular option among men with low risk tumours. **Simon Crompton** looks at efforts to learn more about who benefits and how to avoid delaying too long.

Active surveillance is an increasingly popular observational approach to managing low and very low risk prostate cancer. The American CaPSURE prostate cancer database indicates that its use as an initial management strategy for men in these risk categories quadrupled from one in ten to nearly four in ten between 2009 and 2013.

The approach, which gives men with localised prostate cancer the opportunity to avoid or delay radical treatments, is now regarded as quite different to watchful waiting.

While the aim of treatment administered after watchful waiting is to control the cancer, treatment after active surveillance has the aim of cure.

There are other differences. Active

surveillance involves a schedule of assessments and tests such as PSA (prostate specific androgen) tests, biopsies and clinical examination.

Watchful waiting, which will more commonly apply to men with a life expectancy of less than 10 years, involves clinic visits and PSA testing.

The field has specialised rapidly in the past 15 years, with the European School of Oncology taking a lead in extending knowledge – organising three conferences gathering expertise in urology, radiology, biology, psychology and public health (see p19). The growth in interest has coincided with mounting concern about overtreatment in prostate cancer.

And now there is new evidence of how effective active surveillance can be. This September, the *New England Journal of Medicine* published the first results from a major trial that compared treatment outcomes in 1,643 men with localised prostate cancer (doi: 10.1056/NEJMoa1606220).

They indicated that men survive just as long with active surveillance as with radical prostatectomy surgery and radiotherapy.

The ProtecT (prostate cancer testing and treatment) trial, led by the universities of Oxford and Bristol and involving nine centres, followed patients whose localised cancer had been detected after PSA tests.

It found that 10-year prostate-cancer-specific survival was 99% whichever treatment approach was assigned.

However, after six years, twice as many men who had surgery experienced continence and sexual problems compared to those who had active monitoring and radiotherapy. And radiotherapy caused more bowel problems than surgery or active monitoring.

When treatment does more harm than good

For many men, prostatectomy, radiotherapy and brachytherapy are likely to produce effects far worse than their cancer ever would.

Studies indicate that around two men in every ten have long-term urinary incontinence following radical prostatectomy, and between three and seven men in every ten who undergo radical prostatectomy or external beam radiation therapy will develop impotence after treatment.

In contrast, recent studies of men with low risk prostate cancer indicate that fewer than one in ten of them on active surveillance programmes have died of the disease after 15 years.

There is excitement among much of the prostate cancer community about advancing this field, and in so doing offering many men the prospect of a long and fulfilled life free of treatment side effects. Yet it is an emerging art, with consensus and evidence on eligibility and the best monitoring approaches elusive.

The thinking behind active surveillance

Unlike many other malignancies, prostate cancer often grows slowly and consistently over time, sometimes producing no symptoms at all. Autopsy studies have shown that as many as eight in ten men in the 60- to 80-year age group who die of other causes have cancer in their prostates without even knowing it.

Epidemiological studies have also indicated that many men have indolent and asymptomatic prostate cancer that should not require treatment.

And yet there always remains the possibility that any diagnosed prostate cancer will grow rapidly, metastasise and become lethal.

Active surveillance is an approach that attempts to straddle these difficult poles. It is based on the assumptions that:

- All prostate cancer treatments, including those directed at minimal disease, are often associated with significant side effects and costs.
- It is possible to distinguish indolent prostate cancers from those that will lead to symptoms, metastases and death.
- After biopsy, active surveillance patients can be reclassified as being at higher risk of disease progression, and receive treatment, without reducing the chance of cure.
- For some people, the burden of living with disease is less than living with the effects of unnecessary treatment.

For clinicians, active surveillance involves three key decision-making areas:

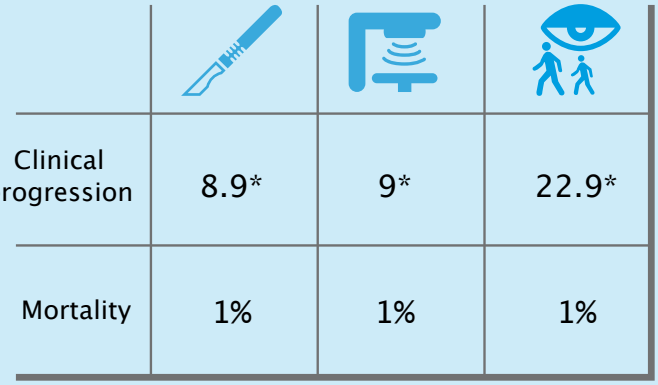
- Is the patient at low or very low risk of progression?
- How will the patient be monitored during active surveillance?
- How will it be decided whether treatment should start?

Does it work?

Since active surveillance is a relatively new approach, conclusive evidence about its value is still scarce. Large randomised trials are underway, most significantly the ProtecT trial.

The first results from the ProtecT study, indicating that surgery, radiotherapy and active surveillance all result in a similar mortality rate

Results of the ProtecT trial



Clinical progression	8.9*	9*	22.9*
Mortality	1%	1%	1%

Ten-year outcomes from the ProtecT trial, which randomised men with low risk localised prostate cancer to surgery, radiotherapy or active surveillance, showed that, while clinical progression was more likely in men managed by active surveillance (22.9* vs around 9* for surgery and radiotherapy), the chances of dying of prostate cancer were equally low for all three management options, at 1%

**Per 1000/person years*

Source: FC Hamdy et al (2016) *NEJM*, published online 14 September 2016, doi:10.1056/NEJMoa1606220

of around 1% after ten years, lend strong support to active surveillance as a treatment approach.

However, after ten years the study did find evidence of more cancer progression and metastases in men assigned to active surveillance than those assigned to surgery and radiotherapy.

A *New England Journal of Medicine* editorial accompanying the ProtecT results said this meant that, if a man wanted to avoid metastatic prostate cancer, "monitoring should be considered only if he has life-shortening coexisting disease such that his life expectancy is less than the 10-year median follow-up of the current study."

Until the ProtecT results, evidence has mainly come from observational studies. These have consistently found a low rate of progression to metastatic disease or death in patients on active surveillance. The majority of patients in the studies do not go on to require treatment.

In a prospective study from Toronto looking at 993 men managed with active surveillance since 1995, there was a 95% metastasis-free survival rate after ten years (most were low risk but 20% were classed as intermediate risk). At Johns Hopkins University, a study of 1,298 men on active surveillance revealed a prostate cancer mortality of just 0.4% after 15 years.

However, differing survival rates are partly a reflection of which patients are selected for active surveillance: mortality is likely to be small when only the lowest risk groups are admitted to this approach. Inclusion criteria vary from centre to centre.

Evidence on quality of life is encouraging. A new analysis of data from four military centres participating in the Center for Prostate Disease Research Multicenter National Database found that, apart from a slight difference in bowel function, health-related quality of life outcomes for patients on active surveillance were no different from those in men without prostate cancer during the three years of follow up.

Balancing risks and benefits

Active surveillance performs a balancing act between reducing over-treatment and reducing the risk of death. And although the potential benefits are great, there are risks: particularly that the window of curability is missed and that switching to curative treatment comes too late.

As Lionne Venderbos from Erasmus University pointed out at ESO's recent active surveillance conference in Milan, this has potential legal and ethical ramifications – so patient involvement in decision making is absolutely essential.

How do you minimise risk while also bringing benefits to the maximum number of men? The answer lies in selecting the right people for active surveillance, but the criteria used are still a matter of debate.

Selecting the right tumours for active surveillance

The difficulty of differentiating low risk 'pussy cat' indolent tumours from the high risk 'tiger' tumours has always run central in prostate cancer management decisions. There are no

definitive indicators of low risk tumours, so there are no definitive indicators for the tumours most suitable for active surveillance.

This means that different centres and studies have different criteria. However, according to Laurence Klotz, Professor of Surgery at the University of Toronto, all inclusion criteria will have the following in common:

- the cancer will be at an early clinical stage (extent)
- there will be a relatively low serum PSA reading (volume)
- the tumour's Gleason score will indicate it is well, or moderately, differentiated (grade or clinical behaviour).

Other clinical measures that are often used to determine whether the tumour is low risk include:

- the number/percentage of positive cores on original biopsy
- the extent of tumour involvement within a biopsy core
- the PSA density
- the PSA kinetics.

Selecting the right people for active surveillance

The likelihood of cancer causing death depends not only on the extent and aggressiveness of the tumour but on patient characteristics, particularly age, co-morbidities and life expectancy. The ethnicity of a patient may also be a consideration. In African Americans, for example, prostate cancer has a significantly earlier age of onset, higher PSA levels, worse Gleason scores, and more advanced stage at presentation. Studies indicate that this population has a higher rate of unfavourable findings at prostatectomy than other ethnic groups.

According to Athene Lane, Reader in Trials Research at the University of Bristol, selection of patients for active surveillance may also be enhanced by knowledge of their psychological status at diagnosis. Around two men in ten move off active surveillance without evidence of clinical progression, and the reasons may be psychological.

Prospective active surveillance patients need good decision-making aids, according to Lara Bellardita, Clinical Health Psychology Consultant at the IRCCS Istituto Nazionale dei Tumori Foundation, Milan, Italy. "Active surveillance involves a complex decision-making process and it is highly influenced by physicians' preferences and ability to engage the patient in shared decision making" she says.

Debate about eligibility criteria

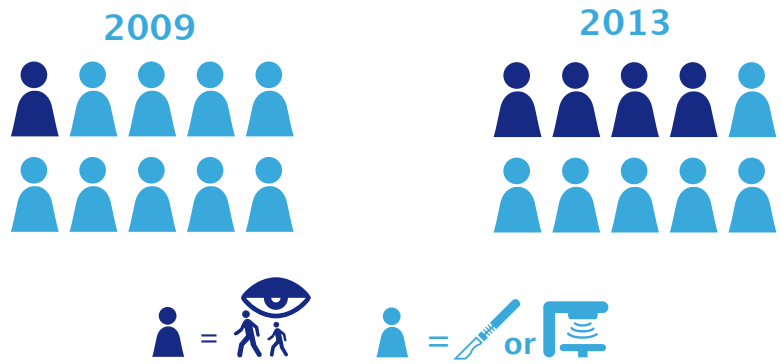
In the absence of long-term studies characterising the type of disease and person suitable for active surveillance, researchers are trying to find new predictors of disease progression to support risk-based selection. Existing prediction models help but, as Ewout Steyerberg from the Centre for Medical Decision Making at Rotterdam's Erasmus University has pointed out, much stronger predictors are needed to separate low risk from high risk patients.

At ESO's recent active surveillance conference in Milan, participants discussed the merits and difficulties of expanding active surveillance beyond people with low and very low risk cancers, where it is agreed that the approach works well.

Laurence Klotz provided details from Toronto illustrating the challenge. In a study of 980 patients, a highly restrictive approach selecting only very low risk patients resulted in a 15-year mortality of 0.5%. An inclusive approach, including all low risk and selected intermediate risk patients, resulted in a 15-year mortality of 5%. But excluding Gleason 7 patients from this group would have brought down the figure to 2%.

Karim Touijer, Attending Surgeon

An increasingly popular option



Data from the US show a rapid rise in men opting for active surveillance in preference to surgery or radiotherapy, between 2009 and 2013, from 1 in 10 to 4 in 10
Source: CaPSURE national registry of men with prostate cancer diagnosed at 45 urology practices across the United States, cited by MR Cooperberg and PR Carroll (2015) *JAMA*: 314:80–2

The UK NICE Protocol for Active Surveillance

Time	Test
At enrolment in active surveillance	MRI scan if not previously performed
Year 1	
Every 3–4 months	measure PSA
Throughout	monitor PSA kinetics
Every 6–12 months	digital rectal examination
At 12 months	prostate rebiopsy
Years 2–4	
Every 3–6 months	measure PSA
Throughout	monitor PSA kinetics
Every 6–12 months	digital rectal examination
Year 5 and every year until active surveillance ends	
Every 6 months	measure PSA
Throughout	monitor PSA kinetics
Every 12 months	digital rectal examination

National Institute for Health and Care Excellence (2014) *Prostate Cancer: Protocol for Active Surveillance. CG175*. National Institute for Health and Care Excellence, London

at Memorial Sloan-Kettering Cancer Center, said that if active surveillance were to be used for higher risk cancers, with high volume and Gleason readings of 3+4, there was a need for better prognostication. Klotz, Touijer and many other prostate cancer specialists believe that the use of MRI scans, fusion-guided biopsy and biomarkers all offer opportunities to refine patient selection (see developments in active surveillance, below).

Surveillance strategy

Despite a multitude of guidelines, there is no consensus on the best strategy for managing prostate cancer with active surveillance.

The main priority in all strategies is to detect evidence of reclassification or progression. This regular monitoring is likely to include:

- serum PSA testing
- digital rectal examination
- repeat prostate biopsy.

There are as yet no clinical studies that define the best testing intervals and criteria to trigger active intervention.

According to Leonard Bokhorst from the Department of Urology at Erasmus University, the Netherlands, the goal of follow-up testing is threefold: to filter out incorrect selection (reclassification); to filter out tumours that progress; and to do so with the minimum amount of harm to the patient. So the frequency of testing should be tailored to the individual – based not only on the risks and benefits but also the demands and discomfort caused by procedures such as biopsy.

What should trigger reclassification of a tumour during surveillance and prompt the start of treatment? Cohort studies show large variations in criteria, says Antti Rannikko, senior consultant urologist at Helsinki University Hospital, Finland. "Most rely on repeat biopsies to monitor grade of the disease," he says. "The volume of the disease is generally monitored with biopsy-based surrogates, such as number of positive biopsies, and PSA-based surrogates, such as free PSA and PSA doubling time."

According to Peter Carroll, Professor and Chair at the Department of Urology, University of California, the growing global demand for active surveillance means there is an urgent need to refine surveillance protocols. He believes the use of MRI imaging will play an important part in this, particularly in decisions on when to upgrade tumours and begin intervention.

Current guidelines on active surveillance

There are some guidelines that attempt to identify both the patient groups for whom active surveillance is an appropriate option and the surveillance strategy itself. These include:

- The American Urological Association (AUA) Guideline for the Management of Clinically Localized Prostate Cancer (US)
- The European Association of Urology (EAU) Guidelines on Prostate Cancer
- The Cancer Care Ontario Guideline, endorsed by the American Society of Clinical Oncology (Canada)
- National Comprehensive Cancer Network Guidelines for Prostate Cancer (US)

- The National Institute for Health and Care Excellence (NICE) Guideline on Prostate Cancer, including a protocol for active surveillance (UK).

A summary of the protocols published by NICE (UK) and Ontario Care (Canada) are shown as examples, in the boxes on this and the facing page.

The GAP 3 project

Definitive answers about how to select men for active surveillance and then successfully monitor them are likely to come from large studies analysing existing data from men with prostate cancer – and in particular a major study funded by the Movember Foundation, known as the Global Action Plan 3 project, or GAP3. Movember supports five GAP projects, but GAP3 specifically addresses selection for active surveillance.

It aims to create global consensus through studying the cases of 14,000 men across 19 institutions worldwide. This is the largest prostate cancer active surveillance database, comprising the majority of the world's active surveillance patient data.

Two years into the project, all the data from participating centres has been uploaded into a central database. Each patient's clinical history and data from biospecimens, imaging and biomarkers is being analysed.

This analysis will feed into a simultaneous expert review of all current active surveillance guidelines available around the world, leading to a new consensus guideline setting out which patients are suitable for active surveillance, and which are the most effective ways of monitoring them.

The end result will be a web-based platform, based on the guidelines and using risk-based modelling derived from the new analysis, to help clinicians decide which patients are suitable for active surveillance.

Perhaps just as importantly, says Sophie Bruinsma, the researcher from Erasmus Medical Centre who is coordinating the project, it will also provide some reassurance to men that they have made the most sensible, risk-based decision about their disease.

Developments in active surveillance: MRI

With increasing recognition that PSA testing is a blunt tool in both diagnosis and monitoring – which has also led to a skyrocketing of prostate cancer diagnoses in the Western world – more tests are being added to the armoury.

Imaging techniques such as multiparametric MRI and the use of new biomarkers hold particular potential in both enhancing diagnostic accuracy and monitoring prostate cancer, though as Laurence Klotz has pointed out, both are "promising but imperfect".

Multiparametric MRI scanning has four potential roles in active surveillance.

First, at diagnosis, it provides information on various aspects of tissue make-up including cell density. Second, it can be helpful in guiding confirmatory biopsies after a negative first biopsy but rising PSA levels. Third, it has a role in guiding repeat biopsies. Finally, during follow up, it can be used to assess any change in the cancer and trigger repeat biopsies.

However, debate continues about the exact value of multiparametric MRI in active surveillance. It was a key area of discussion at ESO's recent conference in Milan. Jochen Walz, Head of the Department of Urology at Marseille's Institut Paoli-Calmettes Cancer Centre, emphasised that only high-quality imaging can improve the

The Ontario Cancer Care Protocol for Active Surveillance

- Active surveillance is recommended for most patients with low-risk (Gleason score of 6 or less) localised prostate cancer.
- Some patients with low-volume, intermediate-risk (Gleason 3 + 4 = 7) prostate cancer may be offered active surveillance.
- Factors including age, prostate cancer volume, patient preference, and ethnicity should all be taken into account in decisions.
- Surveillance protocols should include PSA testing, digital rectal examinations, and serial prostate biopsies.
- Additional scanning and genomic tests may have a role in patients with unclear findings.
- Patients who are reclassified to a higher risk category (Gleason score of 7 or more), or who have significant increases in tumour volume, should be offered active therapy.

The full Cancer Care Ontario guideline, as endorsed by the American Society of Clinical Oncology, can be found at http://jco.ascopubs.org/content/34/18/2182.full

"I was just thankful that, you know, that it is being monitored and…if it does start going a bit wild then I'm obviously in the right place to have it sorted..."

"They do just ask how do you feel and whether it's giving you any trouble. When I go to [hospital] if I am a little worried and I do talk to them, they put me at my ease."

" I would put it at the back of [my] mind but some days it'd come to the front and I do start thinking then."

"You think you can handle it but it's always there niggling away in your mind."

"Just a routine now, don't think much to it really, so that's the way it is... I'm fine with it. I don't fret on it, I'm not anxious about it. I just wait to see what happens."

Quotes are taken from interviews with 22 men with early prostate cancers being managed with active surveillance, as part of a qualitative study within the ProtecT trial. The interviews were carried out face-to-face or by telephone

management of active surveillance patients.

Multiparametric MRI is helpful to guide biopsy, but its use in monitoring patients on active surveillance needs to be defined, said Caroline Moore, Senior Lecturer at the Division of Surgical and Interventional Science, University College London.

Peter Caroll and Michael Leapman described how the use of multiparametric MRI had had an impact in the active surveillance of men with low to intermediate risk prostate cancer at the University of California San Francisco.

In a study of 1,480 men, they concluded that it was a useful diagnostic and staging modality for men with newly diagnosed prostate cancer, particularly when used in conjunction with ultrasound to guide biopsy (MRI and ultrasound fusion guided biopsy). And during surveillance, fusion guided biopsy improved detection of clinically significant prostate cancer in a proportion of men.

However, the benefits of serial imaging as a means of surveillance are still unclear and under-researched.

Caroline Moore pointed to methodological difficulties involved in studying serial imaging. She said that "radiological progression" was hard to measure over time, because of changes in scan quality, physical changes in the patient and natural variations in measurements.

"We need a multi-institutional analysis using an agreed minimal data set on repeat multiparametric MRI to answer questions of natural variation and tumour size kinetics," she said.

Developments in active surveillance: molecular markers

The use of new chemical and genetic markers to monitor disease and help predict its course is now being seen as another tool with potential for active surveillance.

According to Bruce Trock, Professor of urology, epidemiology, oncology and environmental health sciences at the Johns Hopkins School of Medicine,

in Baltimore, measuring circulating biomarkers may help determine eligibility for active surveillance, providing a basis for reclassifying tumours (and possibly beginning treatment) and providing prognostic clues.

Some biomarkers may capture the heterogeneity of tumours better than biopsy. However, few have been properly evaluated.

Both blood and urine biomarkers hold potential, for example:

- Blood: various characteristics of PSA (kinetics and isoforms)
- Urine: PCA3 and TMPRSS2-ERG.

Examining these sorts of molecular markers may have a particular role in increasing clinicians' confidence that the right patients are being selected for active surveillance, according to Sigrid Carlsson, Assistant Attending Epidemiologist at Memorial Sloan Kettering Cancer Center in New York.

Current prostate cancer guidelines from the European Association of Urology (2015) state that, while biological markers and genomic analysis are promising, "further study data will be needed before such markers can be used in standard clinical practice."

However, Antti Ranniko, a urologist from the University of Helsinki, is optimistic that both molecular testing and multiparametric MRI scanning will hold increasing importance in active surveillance.

"Initial reports of multiparametric MRI's negative predictive value of close to 100% for clinically significant cancer seem promising for active surveillance," he said in Milan. "Also, initial reports on genetic tests to predict cancer outcome are noteworthy, and it is tempting to speculate that the future triggers for reclassification will largely rely on multiparametric MRI and genetic biomarkers."

Active Surveillance Conference

Every two years the European School of Oncology hosts an expert conference gathering latest evidence on active surveillance and the technologies that may improve selection and monitoring of low risk prostate cancer patients. It is held in collaboration with the European Association of Urology and the patient advocacy group Europa Uomo, and attracts urologists, oncologists, radiologists, psychologists and public health experts from around the world.

The 4th Conference on Active Surveillance for Low Risk Prostate Cancer will be in 2018.

More information is available on the prostate cancer programme page at www.eso.net.

The patient perspective

How do patients respond to active surveillance? Recent reviews of quality of life under active surveillance indicate that overall quality of life is good in the first few years of surveillance, with low levels of anxiety and depression.

A systematic review led by Lara Bellardita from the IRCCS Istituto Nazionale dei Tumori Foundation, Milan, found that quality of life scores were equal to, or better than, those for patients who had undergone radical treatment.

Another review of both active surveillance and watchful waiting evidence, led by Gregory Carter from the School of Medicine and Public Health at the University of Newcastle, Australia, concluded that decisional conflict was low and decisional satisfaction high.

New results from the ProtecT trial on patient reported outcomes indicate that, although active surveillance patients report fewer adverse effects from treatment than those undergoing surgery or radiotherapy, over six years the health related quality of life scores (including anxiety and depression) for all three groups of patients were similar.

Athene Lane, from the University of Bristol, says that interviews with patients being managed with active surveillance as part of the trial have showed that they particularly benefit from peer and partner support, as well as from positive experiences with health professionals and recognition of their uncertainty and emotional responses.

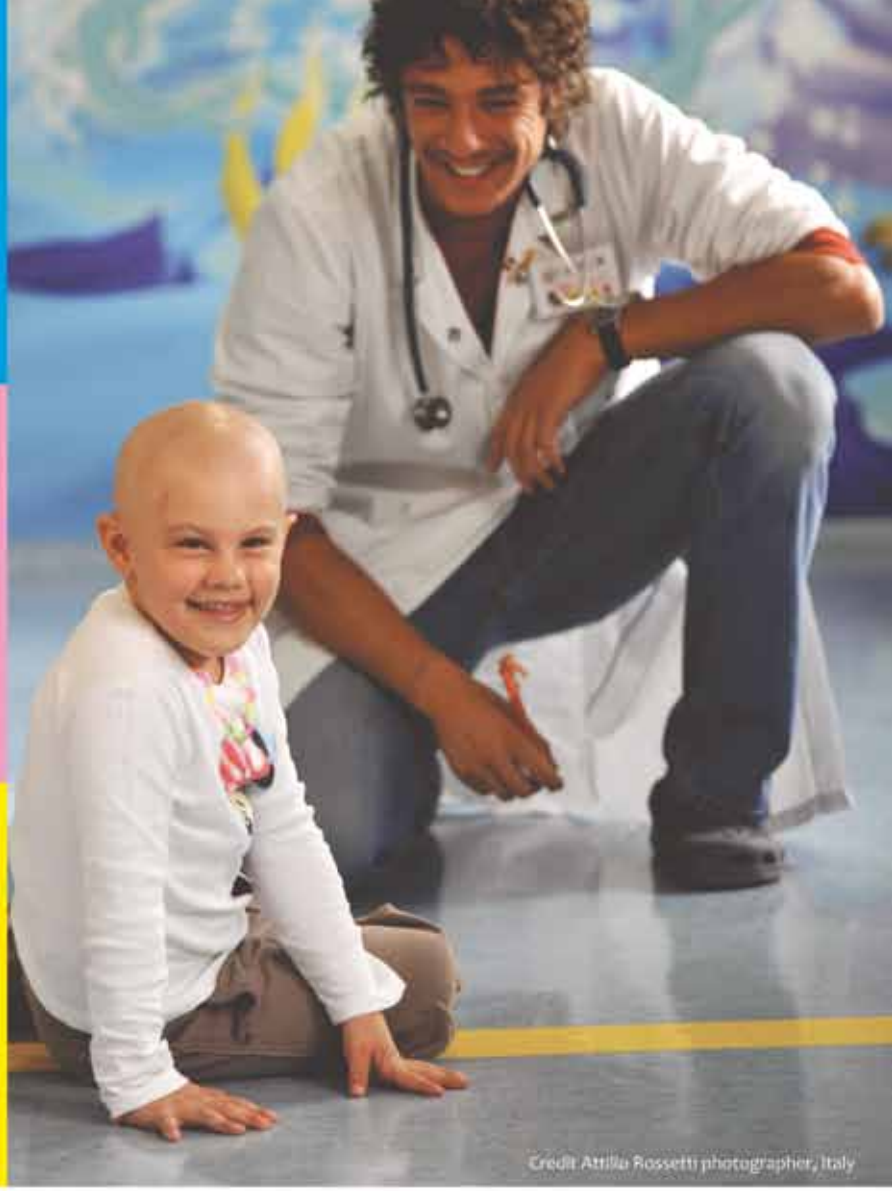
Some of the men interviewed indicated that they trust clinicians to monitor their disease closely, and that initial worries preceding PSA tests reduce with time.

One respondent who had been on active surveillance for five years said: "It's just a routine now. I don't think much to it really, it's the way it is… I just wait to see what happens."

SIOPE Society Day

27th January 2017

RAI Congress Centre Amsterdam the Netherlands



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Essential requirements for quality cancer care

In the previous issue of *Cancer World* I discussed the need for defining multidisciplinary organisational criteria on how to deliver optimal cancer care to each patient and for quality performance indicators that can help measure the efficacy of existing clinical guidelines.

Since June, ECCO has taken significant steps forward with its project on essential requirements for quality cancer care (ERQCC), starting with two tumour types: colorectal cancer and bone and soft tissue sarcomas.

In April 2016, ECCO member societies appointed their high-level experts to participate in the ERQCC multidisciplinary working groups on colorectal cancer and bone and soft tissue sarcomas. These groups gather together medical oncologists, radiologists, surgeons, patient advocates, representatives of oncology institutes, nurses, pharmacists and psychologists. The first meetings of the working groups – consensus days – took place in Brussels at the end of May 2016, where agreement was reached on a draft list of ERQCC for each tumour type.

The draft is now with the member societies for their contributions, and later this year the working groups will meet again to finalise the two ERQCC manuscripts. The manuscripts will be submitted for publication in the *European Journal of Cancer* before the end of 2016.

The ERQCC project aims to:

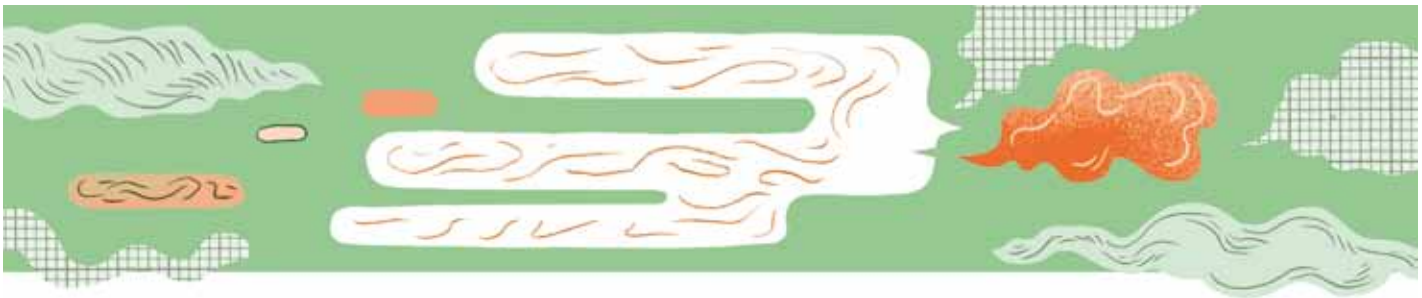
- Improve outcomes for cancer patients in Europe through the adoption and implementation of essential requirements for quality cancer care in Europe;
- Complement existing clinical guidelines and improve their efficacy;
- Shape the policy environment at European and national levels to improve quality of cancer care across Europe and decrease inequalities in cancer outcomes.

ECCO strongly believes that the essential requirements for quality cancer care will be influential in improving cancer care in Europe, and will work very well alongside current clinical guidelines. We will take every opportunity to engage with relevant stakeholders, including EU institutions and member states, to promote the results of the ERQCC project.

The success of ERQCC will depend on the level of awareness and the influence of ERQCC on national policies and practice. Policy efforts by national organisations will therefore be a determining factor.

The ERQCC results will be presented during the ECCO2017 European Cancer Congress in Amsterdam on 27–30 January 2017. Join us and participate in a lively discussion!

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



Silke Gillessen: tackling uncertainties and access in advanced prostate cancer

Prioritising collaboration over self-interest is the way to learn about who gets the best from which treatments in the complex world of advanced prostate cancer. Silke Gillessen talked to **Simon Crompton** about how she is trying to bring people together to make it happen.

Prostate cancer is lethal. With medics increasingly aware of the prevalence of indolent prostate cancer and the need to avoid overtreatment, there is a danger that this important reality gets overlooked.

Silke Gillessen is a Swiss medical oncologist who has spent the last 15 years working with, and trying to improve the lives of, men with advanced prostate cancer. The instigator of a ground-breaking consensus conference held in 2015, she has established herself over the past decade as a leading force in getting better treatment for advanced prostate cancer higher on the international research agenda.

And when I talk to her, the message she wants to convey to all the cancer community is that the deadly seriousness of prostate cancer is easily forgotten.

"It is one of the most misunderstood cancers," she says. "A lot of people still think: 'Oh yes, prostate cancer is smouldering, and it affects older men so there are rarely any problems. But that is not true. In most Western countries it is the second most common cause of cancer death in men, and as soon as someone develops metastases, it is most of the time lethal. I don't think this is something that has reached the general medical community."

Nor, she says, is there sufficient appreciation that age is not what it used to be. Effective novel diagnostics and treatments for older populations should be a priority because more people over 65 are active and working than even 20 years ago. More emphasis on prolonging and improving life in elderly patients is urgently needed.

This may help explain why advanced prostate cancer is not well understood. It has undoubtedly been neglected, says Gillessen. The situation has parallels with care for other advanced cancers. For example, the new Global Status of Advanced/ Metastatic Breast Cancer report, published by the European School of Oncology in conjunction with Pfizer, reveals there are still substantial gaps in care, lack of access to resources and support, and poor treatment outcomes for women with advanced breast cancer. But while filling those gaps is now well and truly on the international agenda in

"We could advance better if we worked as a community, and this is particularly important in prostate cancer, where multi-disciplinary work is crucial"

advanced breast cancer, the same cannot be said of prostate cancer. Gillessen wants to make things happen.

She remembers how, three years ago, she was sitting having a coffee with her colleague, Aurelius Omlin, at the Kantonsspital, St Gallen, in Switzerland, where she is Senior Oncology Consultant specialising in genitourinary tumours and head of the Oncology Clinical Trials Unit. They started discussing how the arrival of new treatment options in the past five years, such as abiraterone and enzalutamide, was improving survival and quality of life for men with metastatic prostate cancer, but how difficult it was to counsel patients about the best sequence of approved treatment options in the absence of reliable evidence on best choice of first-line therapy.

"And when we started looking deeper into it, we were surprised how many other questions and topics there are where there is no high level evidence or data," she says.

Her response was to organise a major meeting, bringing some of the world's top prostate cancer experts to St Gallen – an event analogous to the international Breast Cancer Consensus Conference that has taken place there since 1978. The objective was to acknowledge uncertainty, yet find agreement on best clinical practice nonetheless.

"We were surprised how many other questions and topics there are where there is no high level evidence or data"

"If you don't have good evidence, the second best you can have is consensus from experts in the field, so that's why we did it."

The result was the inaugural St Gallen Advanced Prostate Cancer Consensus Conference (APCCC), held in March 2015.

It resulted in an influential set of expert recommendations on the daily management of advanced prostate cancer. It also cemented Gillessen's reputation as someone who is bringing change in the treatment and care of people with advanced prostate cancer by bringing people together, encouraging discussion and confronting some of the traditional boundaries that prevent progress.

Getting knowledge out there

"Maybe it's because I'm Swiss, or female, or both, but I don't think we should compete. What I'm for is a unified community that really tries to do the best for our patients. I think we could advance better if we worked as a community and this is particularly important in prostate cancer, where multidisciplinary work is crucial in my eyes."

Interestingly, the consensus conference came up with some remarkably clear recommendations for what clinicians should do, even given the uncertainty surrounding existing evidence. For example, there was consensus (i.e. at least 75% agreement) among the 41 experts that it was wrong to treat men with metastatic castration-sensitive prostate cancer with high doses of bone-targeted drugs like bisphosphonates or denosumab to reduce the incidence of skeletal related events.

"It is not recommended because there are side effects and no proven benefits," says Gillessen. "Two big trials evaluating zoledronate in this situation show this. But when I've given talks, I'd say 50–70% of oncologists or urologists do this. One of the reasons is that there is so much pressure from pharmaceutical companies."

"If you haven't got centralised medicine, then let's get the knowledge out there, so that people know where to look and who to call"

There are other examples of common practice which the experts disapproved of – for example, stopping life-prolonging treatment in men with castration-resistant prostate cancer on the basis of a PSA rise alone. "It's important that these messages get into the cancer community," she says. The areas of agreement were published in the *Annals of Oncology* in June last year.

"If findings are to have an effect on patients, it can only be done by spreading knowledge. A lot of men don't get the right treatment, or don't have access to leading treatments. Treating physicians in many countries don't have a lot of experience in treating men with advanced prostate cancer, because they are not in specialist centres and are sometimes only seeing a few prostate cancer patients a year. If you haven't got centralised medicine, then let's go for the second best and get the knowledge out there, so that people know where to look and who to call."

Uncertainty remained in some areas of discussion at St Gallen. The experts could not agree, for example, on the optimal dose, schedule and duration of osteoclast-targeted therapies. And there was also little agreement on the best way of diagnosing and treating oligometastatic disease.

But these areas are as important as those where there was agreement, argues Gillessen. They will become a focus of discussion at future St Gallen advanced prostate cancer consensus conferences – the next is planned for March next year (www.apccc.org).

Finding answers

They also provide a research agenda for advanced prostate cancer. One important area where there is considerable uncertainty, for example, is in the use of imaging to stage and monitor prostate cancer. There are new sophisticated techniques, using PET/CT or whole body MRI, but research correlating better imaging with better clinical outcomes is missing. Research on patient quality of life during and following treatment is also lacking. "A lot of my patients tell me that their quality of life is more important to them than quantity of life, so there should be much more focus on it."

Why are there such gaps in research on advanced prostate cancer? Gillessen isn't sure it has anything to do with advanced disease somehow being less 'sexy' than other fields. She says it has more to do with regulations getting in the way of important international trials that don't involve new drugs. "The administration is crazy, and it's probably got worse over the past 20 years. It's a political issue: academic trials have to carry out exactly the same administrative work as the pharmaceutical industry, but we don't have the resources. A lot of it is over-regulated and I'm not sure it's really helping the patient."

Yet Gillessen refuses to dwell on the fact that her field has not attracted the research funding or professional

Pooling expertise

The 2015 Advanced Prostate Cancer Consensus Conference brought together 41 clinicians and researchers from 17 countries to discuss key uncertainties in caring for patients with advanced prostate cancer, with a view to reaching consensus positions to guide clinical practice in the absence of robust evidence. The resulting expert recommendations complement evidence-based guidelines, and will aid discussions between men with prostate cancer and physicians when faced with management decisions. The second APCCC conference will be held in St Gallen on 9–11 March 2017. You can register or find further information at www.apccc.org.

focus that it should have in the past. "Maybe it has been neglected, but a lot of pharmaceutical companies and some charities are interested now, and there are now a lot of phase III trials and it will be improving more and more in the coming years."

Remembering her own professional beginnings, she knows how far things have come. The frustration of seeing how little there was available for advanced prostate cancer patients proved a driving force in her career.

Making a difference

According to her mother, Gillessen decided she wanted to become a doctor while accompanying her brother to his vaccinations at the age of four. Her parents – both research chemists – always emphasised to her that anything was possible in terms of a career, and in 1992 she qualified as a doctor at the University of Basel. She started in general medicine, then moved to internal medicine at the Thurgauer Schaffhauser Höhenklinik hospital, Davos, Switzerland, where she worked with her first prostate cancer patients.

"I still remember one or two patients that were very close to my heart, but we didn't have anything for them apart from hormonal treatments. It was very frustrating. You felt this connection with patients and you felt you should be able to do something. But there was this big hole. It really started from there."

So although Gillessen spent time as an immunology researcher at Roche in the United States and in the Dana-Farber Cancer Institute in Boston, she missed working with patients and she returned to Switzerland to work in

oncology, first in Basel and then in St Gallen. She became a consultant in oncology and haematology at the Kantonsspital in 2001 and senior consultant in 2008.

The patients she has treated have been one of the biggest influences on her throughout her career. "You have the opportunity to develop long-term relationships with people who have cancer," she says. "I appreciate what you learn from prostate cancer patients – how they accept what is happening and handle it." She also, she says, simply gets on well with men, both as work colleagues and patients.

"I appreciate what you learn from prostate cancer patients – how they accept what is happening and handle it"

That has proved an asset working in the men's world of genitourinary medicine. But Gillessen has never seen her gender as a barrier. Her mother was an inspiration: she was one of only a handful of women in her generation who obtained a PhD. But also influential were other women physicians who specialised in genito-urinary oncology, and excelled.

"Seeing people like Maha Hussain [Professor of Medicine and Urology, University of Michigan, USA] or Cora Sternberg [Chair, Department of Medical Oncology, San Camillo Forlanini Hospital, Italy] give fantastic talks at ASCO and European conferences, at a time when there weren't many Swiss women in academic research, really showed me you can do it if you're a woman. They were role models."

Tackling the 'who needs what' question

Today, the research priority has to be finding better markers to predict the course of prostate cancer and help determine who will respond best to which treatments, she says.

"We need biomarkers which tell us whether, when someone has a PSA relapse after curative treatment, it's just local or systemic. We need biomarkers to tell us which are the really high-risk prostate cancers that require multimodality treatment, and which are the ones where one treatment is likely to be enough."

"We need real predictive factors saying who is responding to hormone treatment, who is responding to chemotherapy, who is responding to PARP inhibitors. It is a very important challenge."

She has worked in the field herself, having patented a new method of determining potential biomarkers and drug targets, together with colleagues at the Swiss Federal Institute of Technology (ETH) Zürich and the Kantonsspital St Gallen. And there is much hope elsewhere, she says. Lung cancer has shown the way forward, with new predictive factors identifying which mutational changes drive disease and are targetable.

In advanced prostate cancer, there is promise in AR-V7 testing, which seems to predict whether patients with castration-resistant prostate cancer will respond to novel endocrine agents such as enzalutamide and abiraterone. And the work of Johann de Bono at the Institute of Cancer Research, London, on alterations in DNA repair genes predicting response to PARP inhibitors, looks very promising. "There is a lot of light on the horizon," she says.

Tackling the access question

One of the focuses of her own research has been finding cheap yet effective treatments that might be made widely available in resource-poor countries – and in poor populations in higher income countries such as the United States. But finding financial support has been difficult.

For example, a trial at St Gallen has begun looking at the use of platins (as opposed to more expensive PARP inhibitors) in men with prostate cancer with mutations in their DNA repair genes. There are already some data suggesting that platins are effective, and they are cheap because they are out of patent. But because platins are generic, pharmaceutical companies are not interested in testing them, and it has taken "a very long time" to find trial funding. Gillessen looks to the UK, where funding from the Medical Research Council means that purely academic trials of 'not sexy' drugs can get funding.

"I think there are a lot of old drugs out there that are interesting and would be cheap, but it's very difficult to run trials," she says. "It's about providing global access to drugs. This is a very important topic in every cancer." (For more on this problem see: Too affordable: how do we overcome the drug repurposing paradox? *Cancer World* Sept–Oct 2016).

Similarly, she is involved in trials investigating the use of metformin – another very cheap drug – in treating castration-resistant and castration-sensitive prostate cancer, with the

Treating advanced prostate cancer

- Localised prostate cancer is normally treated with active surveillance or surgery and/or radiotherapy.
- If the prostate cancer has advanced beyond the capsule of the prostate gland or has metastatised, the treatment is likely to include hormone therapy.
- Prostate cancers need testosterone to grow, and hormone therapy, administered by tablets, injections or surgical castration, shrinks or slows advancing tumours by lowering levels of testosterone. This is called androgen deprivation therapy (ADT).
- ADT only holds prostate cancers for so long. Tumours that are still responding to hormone therapy are called castration-naive. Tumours that are no longer responding are castration-resistant.
- Once a cancer has become castration-resistant, there are still treatment options. There is an increasing number of novel drugs, but the best options, combinations and timings are still debated.

hope of additionally mitigating some of the adverse effects of androgen deprivation therapy.

She is also involved in planning a trial investigating the benefits of providing commonly available drugs such as aspirin and statins to patients with castration-resistant prostate cancer. This too might help reduce side effects and prolong survival. The research is planned to run under the PEACE initiative (Prostate Cancer Consortium in Europe), a recently established initiative that aims to foster cross-border networks of investigators.

"In the end it all comes back to the fact that advanced prostate cancer is a very heterogenous disease, and we have to find subgroups that respond to certain treatments. We have shown that we can prolong survival, and our patients live longer and better than they did 10 years ago. But we obviously want to improve that further."

Only collaboration will get answers

Collaboration, and letting go of self-interest, are key to making this happen, argues Gillessen. She has a broad perspective on life: she loves art, classical music, theatre, and mountain hiking with her architect husband. She enjoys good food, wine and conversation with friends who are artists as well as scientists. And she has an acute awareness of the bigger picture. "We are not the centre of the world," she says. "There are other things too. Health is extremely important, but so is our environment. We have to try and not be so self-centred, and think about future generations."

Perhaps this wide-reaching outlook is why she can see above narrow professional perspectives, and is determined to keep on promoting equity and the type of constructive pooling of expertise that the first St Gallen consensus conference exemplified.

"Health is important, but so is our environment. We have to try and not be so self-centred, and think about future generations"

"There are a lot of patients, and a lot of open questions, and there's room for all of us," she says. "In small surroundings, with friendly people – like at my hospital – collaborative work works perfectly. But it's fantastic if you can do that at a higher or international level too, and we're trying to do that, starting to talk to people in organisations such as EAU, ESMO, EORTC and ESTRO, and trying to do research together on a European level.

"It takes time, but I think it's more fruitful than competing. It's not about little kingdoms, it's about trying to work together, do the best for our patients and make the best use of the resources we have."

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Why most clinical research is not useful

It makes no sense to perform clinical research that has no relevance to patient care, so why do we do it, and how can we stop? **John Ioannidis** ponders the problem and offers some suggestions.

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Practicing doctors and other health care professionals will be familiar with how little of what they find in medical journals is useful. The term 'clinical research' is meant to cover all types of investigation that address questions on the treatment, prevention, diagnosis/screening, or prognosis of disease or enhancement and maintenance of health. Experimental intervention studies (clinical trials) are the major design intended to answer such questions, but observational studies may also offer relevant evidence. 'Useful clinical research' means that it can lead to a favorable change in decision making (when changes in benefits, harms, cost, and any other impact are considered) either by itself or when integrated with other studies and evidence in systematic reviews, meta-analyses, decision analyses, and guidelines.

There are many millions of papers of clinical research – approximately 1 million papers from clinical trials have been published to date, along with tens of thousands of systematic reviews – but most of them are not useful. Waste across medical research (clinical or other types) has been estimated as consuming 85% of the billions spent each year[1]. I have previously written about why most published research is false[2] and how to make more of it true[3]. In order to be useful, clinical research should be true, but this is not sufficient. Here I describe the key features of useful clinical research (see table) and the current state of affairs and suggest future prospects for improvement.

Making speculative, blue-sky research more productive represents a partly intractable problem, given the unpredictability of such research, but significantly improving clinical research – and developing tools for assessing its utility or lack thereof – appears conceptually more straightforward.

Features of clinically useful research

Problem base

There is higher utility in solving problems with higher disease burdens. However, context is important. Solving problems with low prevalence but grave consequences for affected patients is valuable, and broadly applicable useful research may stem from studying rare conditions if the knowledge is also relevant to common conditions (e.g. discovering the importance of the proprotein convertase subtilisin-kexin type 9 [PCSK9] pathway in familial hypercholesterolemia may help develop treatments for many other patients with cardiovascular disease). Furthermore, for explosive epidemics (e.g. Ebola), one should also consider the potential burden if the epidemic gets out of control.

Conversely, clinical research confers actual disutility when disease mongering[4] creates a fictitious perception of disease burden among healthy people. In such circumstances, treated people, by definition, cannot benefit, because there is no real disease to treat.

Data show only weak or modest correlations between the amount of research done and the burden of various diseases[5,6]. Moreover, disease mongering affects multiple medical specialties[4,7,8].

Context placement and information gain

Useful clinical research procures a clinically relevant information gain[9]: it adds to what we already know. This means that, first, we need to be aware of what we already know so that new information can be placed in context[10]. Second, studies should be designed to provide sufficiently large amounts of evidence to ensure patients, clinicians, and decision makers can be confident about the magnitude and specifics of benefits and harms, and these studies should be judged based on clinical impact and their ability to change practice. Ideally, studies that are launched should be clinically useful regardless of their eventual results. If the findings of a study are expected to be clinically useful only if a particular result is obtained, there may be a pressure to either obtain that result or interpret the data as if the desired result has been obtained.

Most new research is not preceded or accompanied by systematic reviews[10,11]. Interventions are often compared to placebos or normal care, despite effective interventions having previously been demonstrated. Sample-size calculations almost always see each trial in isolation, ignoring other studies. Across PubMed, the median sample size for published randomized trials in 2006 was 36 per arm[12]. Nonvalidated surrogate outcomes lacking clinical insight[13] and composite outcomes that combine outcomes of very different clinical portent[14] are often utilized so that authors can claim that clinical studies are well powered. The value of 'negative' results is rarely discussed when clinical studies are being designed.

Features to consider in appraising whether clinical research is useful

Feature	Questions to Ask
Problem base	Is there a health problem that is big/important enough to fix?
Context placement	Has prior evidence been systematically assessed to inform (the need for) new studies?
Information gain	Is the proposed study large and long enough to be sufficiently informative?
Pragmatism	Does the research reflect real life? If it deviates, does this matter?
Patient centeredness	Does the research reflect top patient priorities?
Value for money	Is the research worth the money?
Feasibility	Can this research be done?
Transparency	Are methods, data, and analyses verifiable and unbiased?

Pragmatism

Research inferences should be applicable to real-life circumstances. When the context of clinical research studies deviates from typical real-life circumstances, the question critical readers should ask is, to what extent do these differences invalidate the main conclusions of the study? A common misconception is that a trial population should be fully representative of the general population of all patients (for treatment) or the entire community (for prevention) to be generalizable. Randomized trials depend on consent; thus, no trial is a perfect random sample of the general population. However, treatment effects may be similar in nonparticipants, and capturing real-life circumstances is possible, regardless of the representativeness of the study sample, by utilizing pragmatic study designs.

Pragmatism has long been advocated in clinical research[15], but it is rare. Only nine industry-funded pragmatic comparative drug effectiveness trials were published between 1996 and 2010 according to a systematic review of the literature[16], while thousands of efficacy trials have been published that explore optimization of testing circumstances.

Studying treatment effects under idealized clinical trial conditions is attractive, but questions then remain over the generalizability of the findings to real-life circumstances. Observational studies (performed in the thousands) are often precariously interpreted as able to answer questions about causal treatment effects[17]. The use of routinely collected data is typically touted as being more representative of real life, but this is often not true. Most of the widely used observational studies deal with peculiar populations (e.g. nurses, physicians, or workers) and/or peculiar circumstances (e.g. patients managed in specialized health care systems or covered by specific insurance or fitting criteria for inclusion in a registry). Eventually, observational studies often substantially overestimate treatment effects[18,19].

Patient centeredness

Useful research is patient centered[20]. It is done to benefit patients or to preserve health and enhance wellness, not for the needs of physicians, investigators, or sponsors. Useful clinical research should be aligned with patient priorities, the utilities patients assign to different problems and outcomes, and how acceptable they find interventions over the period for which they are indicated. Proposed surrogate outcomes used in research need to closely correlate with real patient-relevant outcomes for patients in the clinic.

There is currently a heightened interest in patient-centered research, as exemplified by the Patient-Centered Outcomes Research Institute (PCORI), which was launched in 2012 in the United States to foster research relevant to patient needs[21]. Similar activities are ongoing in the United Kingdom and elsewhere. However, patients are still rarely involved in setting research priorities, despite the frequent mismatch between patient priorities and research agenda. Patients and physicians are frequently bombarded with information that tries to convince them that surrogates or other unimportant outcomes are important – such short-cuts either have commercial benefits or facilitate fast publication and academic advancement.

Value for money

Good value for money is an important consideration, especially in an era of limited resources, and this can be assessed with formal modeling (value of information)[22]. Different studies may require very different levels of financial investment and may differ substantially in how much we can learn from them. However, the benefits of useful clinical research more than offset the cost of performing it[23].

Most methods for calculating value for money remain theoretical constructs. Practical applications of value-of-information methods are counted in single digit numbers[24,25]. Clinical research remains extremely expensive, even though an estimated 90% of the present cost of trials could be safely eliminated[26,27]. Reducing costs by streamlining research could do more than simply allow more research to take place. It could help make research better by reducing

the pressure to cut corners, which leads to studies lacking sufficient power, precision, duration, and proper outcomes to convincingly change practice.

Feasibility

Even if all other features are met, some studies may be very difficult or practically impossible to conduct. Feasibility of research can sometimes be difficult to predict up front, and there may be unwarranted optimism among investigators and funders.

Many clinical trials are terminated because of futility. Twenty-five percent of the trials approved by six research ethics committees between 2000 and 2003 in Canada, Germany, and Switzerland were discontinued[28], and the discontinuation rate was 43% for a cohort of surgical trials registered between 2008 and 2009[29]. For other types of research, feasibility problems are less accurately known but probably even more common.

Transparency (trust)

Utility decreases when research is not transparent, when study data, protocols, and other processes are not available for verification or for further use by others. Trust is also eroded when major biases occur in the design, conduct, and reporting of research.

Only 61% of trials published in clinical journals in 2010 had been registered[30], and rates are much lower for nonregulated interventions[31] (e.g. 21% and 29% for trials published in psychological or behavioral[32] and physical therapy[33] journals, respectively). Only 55/200 (28%) of journals that publish clinical trials required trial registration as of 2012[34]. Few full protocols are registered, analysis plans are almost never prespecified, and the full study data are rarely available[35]. Trust has been eroded whenever major subversion of the evidence has been uncovered by legal proceedings[36] or reanalysis[37] with different conclusions (e.g. as in the case of neuraminidase inhibitors for influenza)[38]. Biases in the design, analysis, reporting, and interpretation remain highly prevalent[39–41].

How often is each utility feature satisfied in studies published in major general medical journals and across all clinical research?*

Feature	Studies Published in Major General Medical Journals	All Clinical Research
Problem base	Varies a lot	Minority
Context placement	Varies per journal (uncommon to almost always)	Uncommon
Information gain	Majority	Rare
Pragmatism	Rare	Rare
Patient centeredness	Rare/uncommon	Rare
Value for money	Unknown, rare assessments	Unknown, rare assessments
Feasibility	Almost always	Majority
Transparency	Rare/uncommon (data sharing)**, almost always (trial registration), uncommon (other study registration)	Rare/uncommon, except for trial registration (still only a minority)

*Rare: satisfied in <1% of studies; uncommon: satisfied in 1%–20% of studies; minority: satisfied in 20%–50% of studies; majority: satisfied in 50%–80% of studies; very common: satisfied in 80%–99% of studies; almost always: satisfied in >99% of studies. For supporting evidence for these estimates, see references cited in the text.
**The situation is improving in recent years for clinical trials.

Other considerations

Uncertainty. Some uncertainty may exist for each of the features of clinical research outlined above, even though it is less than the uncertainty inherent in blue-sky and preclinical investigation.

Uncertainty also evolves over time, especially when research efforts take many years. Questions can lose their importance when circumstances change. In one of my first papers, a systematic review of zidovudine monotherapy[42], the question was extremely relevant when we started work in 1993 and still important when the paper was accepted in late 1994. However, by the time the study was published in mid-1995, the question was of no value, as new highly effective regimens had emerged: clinical utility was demolished by technological advances.

Other sources of evidence besides trials. Observational studies often add more confusion rather than filling the information deficits[18,19]. Meta-analyses, decision analyses, and guidelines cannot really salvage the situation based on largely useless studies and may add their own problems and biases[43–45].

Focusing on major journals. Some clinicians prefer to read only research published in major general medical journals (*The New England Journal of Medicine*, *The Lancet*, *BMJ*, *JAMA*, and *PLOS Medicine*). However, these journals cover a tiny minority of published clinical research. Out of the 730,447 articles labeled as "clinical trial" in PubMed as of May 26, 2016, only 18,231 were published in the major medical journals. Most of the articles that inform guidelines and clinical practice are published elsewhere.

Studies in major general medical journals may do better in terms of addressing important problems, but given their visibility, they can also propagate more disease mongering than less visible journals. Clinical trials published in major medical journals are larger on average (e.g. median sample size 3,116 and 3,104, respectively, for papers published in *The Lancet* and *BMJ* in September 2007[46]). However, the small clinical trials published in major general journals actually have more exaggerated results, on average, than equally small studies published elsewhere[47].

The Lancet requires routinely systematic placement of the research in context for trials, and increasingly, major journals request full protocols for published trials. Pragmatism, patient centeredness, assessments of value for money, and transparency and protection from bias remain suboptimal for most clinical research published in major journals (see table, p33).

Overall picture

Ultimately, no utility feature is met by the majority of clinical research studies, perhaps with the exception of feasibility (see table). Studies that meet all utility features or almost all of them are extreme rarities, even in the most highly selective journals.

Improving the situation

The problem of nonuseful research should not be seen as a blame game against a specific group (e.g., clinical researchers) but instead should be seen as an opportunity to improve. The challenges and the problems to solve involve not only researchers but also institutions, funding mechanisms, the industry, journals, and many other stakeholders, including patients and the public. Joint efforts by multiple stakeholders may yield solutions that are more likely to be more widely adopted and thus successful[3].

Clinical research workforce and physicians

The clinical research workforce is huge: millions of people have coauthored at least one biomedical paper, and most have done so only once[48]. Students, residents, and clinical fellows are often expected to do some research. This exposure can be interesting, but trainees are judged on their ability to rapidly produce publications, a criterion that lends itself badly to the production of the sort of large, long-term, team-performed studies often needed to inform us about health, disease, and health care. Such researchers can become exploited as low-paid or volunteer personnel[49], and an untrained, noncommitted workforce cannot produce high-quality research. Other perverse recipes in clinical research include universities and other institutions simply asking for more papers (e.g. least publishable units) instead of clinically useful papers and clinical impact not being a formal part of the publication metrics so often used to judge academic performance.

Instead of trying to make a prolific researcher of every physician, training physicians in understanding research methods and evidence-based medicine may also help improve the situation by instilling healthy skepticism and critical thinking skills.

The industry–regulator dipole and academic partners

The industry and regulators are a closely connected dipole in licensing drugs and other products. Industry responds to regulatory requirements, and regulatory agencies increasingly act as both guardians of the common good and industry facilitators. This creates tension and ambiguity in mission.

Industry should be enabled to better champion useful clinical research, with regulators matching commercial rewards to clinical utility for industry products, thus helping good companies outperform bad ones and aligning the interests of shareholders with those of patients and the public. Regulatory agencies may need to assume a more energetic role towards ensuring the conduct of large, clinically useful megatrials. Current research funding incentivizes small studies of short duration that can be quickly performed and generate rapidly publishable results, while answering important questions may sometimes require long-term studies whose financial needs exceed the resources of most currently available funding cycles. Partnerships with patient-centered research initiatives[50] and academia can potentially solve some of the challenges of designing and implementing more pragmatic trials[51].

One should acknowledge that even for streamlined randomized trials, the cost may be substantial if multiple such trials require support by public funds. The industry may still participate by contributing funds towards a common pool of resources under public control for trials conducted by nonconflicted academic investigators. One to two

percent of the sales of blockbuster drugs diverted in such a pool[52] could earmark ample funding.

Funding agenda for blue-sky, preclinical, and clinical science

Discovery research without prespecified deliverables – blue-sky science – is important and requires public support. However, a lot of 'basic' investigation does have anticipated deliverables, like research into developing new drug targets or new tests. This research may best be funded by industry and those standing to profit if they deliver a product that is effective. Much current public funding could move from such preclinical research to useful clinical research, especially in the many cases in which a lack of patent protection means there is no commercial reason for industry to fund studies that might nevertheless be useful in improving care. Reallocation of funds could help improve all research (basic, preclinical, and clinical) (see table above).

Journals

Journals can be very influential is setting standards of acceptable research. External groups could also appraise the clinical utility of the papers published in journals. For example, one could track a 'Journal Clinical Usefulness Factor' scoring some features mentioned above.

Patients and related advocacy groups

Patients and related advocacy groups stand to gain most by an increase in clinically useful research. These groups can influence positively the utility of research when they are savvy about science-in-the-making and protected from biased influences. Public media and related commentators of health news[53] may also help by focusing on the need to obtain clinically useful research and not compromise for less.

Funding of different types of research:
Prespecified deliverables, utility, current funders, and ideal funders

Type of Research	Prespecified Deliverables	Utility	Current Major Funder	Ideal Major Funder
Discovery "blue sky" science	No (high uncertainty by default)	Possible, but in entirely unpredictable ways, maybe decades later; very high failure rate per single idea/project explored	Public (e.g., NIH)	Public (e.g. NIH)
Applied preclinical research	Yes (uncertainty is substantial, but goals should be set)	Possible; substantial failure rate in single projects, but eventually the accumulated efforts should pay off	Public (e.g., NIH)	Entrepreneurs and industry who will profit if they deliver something that truly works; current public funding in this area should shift to clinical research instead
Clinical research	Yes (uncertainty is usually manageable, explicit goals should be set)	Yes; results should be sufficiently useful regardless of whether they are "positive" or "negative" (even if some particular results end up being more useful than others)	Industry	Public (e.g., NIH, PCORI); industry may contribute some funds to a common funding pool; regulatory agencies and universities/ research institutions should safeguard the independence of research and may steer overall agenda

NIH, National Institutes of Health; PCORI, Patient-Centered Outcomes Research Institute

Conclusion

Overall, not only are most research findings false, but, furthermore, most of the true findings are not useful. Medical interventions should and can result in huge human benefit. It makes no sense to perform clinical research without ensuring clinical utility. Reform and improvement are overdue.

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References: *References cited in this article can be accessed in the online version of the article at www.cancerworld.net*

Summary points

- Blue-sky research cannot be easily judged on the basis of practical impact, but clinical research is different and should be useful. It should make a difference for health and disease outcomes or should be undertaken with that as a realistic prospect.
- Many of the features that make clinical research useful can be identified, including those relating to problem base, context placement, information gain, pragmatism, patient centeredness, value for money, feasibility, and transparency.
- Many studies, even in the major general medical journals, do not satisfy these features, and very few studies satisfy most or all of them. Most clinical research therefore fails to be useful not because of its findings but because of its design.
- The forces driving the production and dissemination of nonuseful clinical research are largely identifiable and modifiable.
- Reform is needed. Altering our approach could easily produce more clinical research that is useful, at the same or even at a massively reduced cost.

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Primary therapy of early hepatobiliary and pancreatic cancers: a review of the latest evidence

The state of the art on the diagnosis and management of cancer of the pancreas and hepatobiliary system was the focus of the 3rd St Gallen Gastrointestinal Cancer Conference, held earlier this year under the auspices of the EORTC. **Jonas Feilchenfeldt** reviews the highlights.

This grandround was first presented by Jonas Feilchenfeldt, from the National Center for Cancer Care and Research (NCCCR), Doha, Qatar, as a live webcast for the European School of Oncology. It is edited by Susan Mayor. The webcast of this and other e-sessions can be accessed at e-eso.net.

The St. Gallen International Gastrointestinal Cancer Conference takes place every two years under the auspices of the European Centre for Research and Treatment of Cancer. This year it looked at primary therapy of early GI cancers, with a focus on hepatobiliary and pancreatic cancers. A webcast of the two-day programme can be accessed at www.oncoconferences.ch. What follows are selected highlights of some of the key presentations.

Discriminating pancreatic cystic neoplasms: histopathological and molecular features

Irene Esposito (Essen, Germany) considered how to discriminate between pancreatic cystic neoplasms, drawing on a case series of 788 consecutive pancreatic resections that included 86 patients with cystic lesions of the pancreas (*HPB Surgery* 2015, doi.org/10.1155/2015/847837). During surgery the group found that 61% had intraductal papillary mucinous neoplasms (IPMNs), and a smaller proportion, 16.2%, had serious cystic neoplasms, while 15.1% had mucinous cystic neoplasms. The question is: which of these lesions need to be operated on and which can be followed by a 'watch and wait' policy?

The radiological classification of

IPMNs divides them into two main types:

- Main duct – which includes several types, with pancreatic IPMNs having the worst prognosis; 30–50% of lesions of this type are associated with cancer. This type of IPMN should not be managed with a watch and wait approach.
- Branch duct – including gastric IPMNs, which have a good prognosis, meaning that a watch and wait approach may be better than surgery.

Clinical relevance of pancreatic cystic neoplasms: treatment or watchful waiting?

Beat Gloor (Bern, Switzerland) considered how to manage pancreatic cystic neoplasms, comparing surgery to watchful waiting. Historically, cystic lesions or IPMNs were classified according to their size, and decisions were taken on this basis, with recommendations published in 2010 (*Pancreatology* 2006, 6:17e32). A second major consensus – the Sendai Guidelines, which were developed by a Japanese consortium (*Pancreatology* 2012, 12:183–197) – focused on high-risk features: a solid component, ductal dilatation and mural nodule, to help clinicians decide whether an IPMN lesion is high risk and should be operated on.

There is no debate about IPMNs that have a bad prognosis – they should be operated. However, the situation is different for side-branch IPMNs, which have a good prognosis; here there is a debate about whether to watch and wait or operate. One of the key publications challenging this classification is a study by Stefan Fritz et al. of 512 consecutive operated patients with IPMNs at the European Pancreas Centre, led by Professor Büchler. The study included 148 patients with Sendai-negative branch duct type IPMNs, who should not have been operated on based on this classification. However, 26% of them were found to have high-grade dysplasia or invasive cancer.

If the group had not operated on these 148 apparently low-risk patients, they would not have discovered that 26% of them required surgery. A further 29% had main duct involvement, even though imaging had indicated they had side-branch IPMNs – and main duct IPMNs should undergo surgery (*Ann Surg* 2014, 260:848–55, discussion 855–6). This study of real-life clinical practice taking a more aggressive approach to surgery challenged the notion that the Sendai guidelines represent good practice.

The thoughtful but provocative report drew criticism from the pancreatic group at the Memorial Sloan Kettering Cancer Center (*Ann Surg* 2014, 259:e45). They have a much lower number of Sendai-negative IPMNs but they do have some, even though there should be none based on the guidelines. They reported quite notable postoperative mortality of 2%. They felt that operating on the large number of patients, as reported by Fritz et al., could not be justified, and advocated a watchful waiting policy in this situation.

Gloor recommended that, in general, mucinous neoplasms and main duct IPMNs should be operated. For IPMNs not in this category, discussion should focus on: where the lesion is located – for example, for lesions in the pancreatic tail, surgery would not mean whole pancreatic resection; the patient's performance status; and the centre's surgical expertise. I consider this recommendation quite pragmatic, and we can adapt this according to a centre's practice and the number of patients undergoing resection.

Question: What do you think personally? If patients think they may have a pancreatic tumour, they usually want to have it removed. What do you say to these patients?

Answer: The paper from the Büchler group showing so many cases that, in the end, should have been operated, might suggest the guidelines are very defensive. But, on the other hand, I was surprised to see the high mortality rate. In my centre, where we operate on fewer cases, we would probably be more cautious in operating, weighing up whether the mortality justifies this, and recognising that the complication rates may potentially be higher in a smaller centre. Expert centres can probably deviate from guidelines and still have acceptable outcomes.

Question: How do you watch these patients if you don't operate? Would you see them every three months? What's your policy?

Answer: In our centre we decide on a case-by-case basis. Endoscopic ultrasound and MRI play an important role, but there is no clear recommendation on how frequently this should be done.

Improving outcomes: a case for neoadjuvant radiochemotherapy

Karin Haustermans (Leuven, Belgium) reviewed the role of neoadjuvant radiochemotherapy in pancreatic cancer. This is sometimes rather neglected, with oncologists often stressing the role of chemotherapy. In terms of clinical presentation of pancreatic cancer:

- 10–15% of patients are deemed operable
- 30–40% of pancreatic cancers

are locally advanced, and can be classified as (i) those that are clearly inoperable, which are currently treated primarily with chemotherapy, and (ii) borderline cases, where neoadjuvant radiochemotherapy can be discussed
- a further 40% of cases are metastatic.

Focussing on borderline locally advanced pancreatic cancers, the advantages of neoadjuvant treatment are that it avoids unnecessary surgery in patients with poor prognosis who would progress anyway (25%); it treats micrometastatic disease; and can increase R0 resection, particularly in the retroperitoneal margin, which can sometimes be difficult to tackle. Radiochemotherapy is primarily useful in reducing unnecessary surgery and increasing R0 resection.

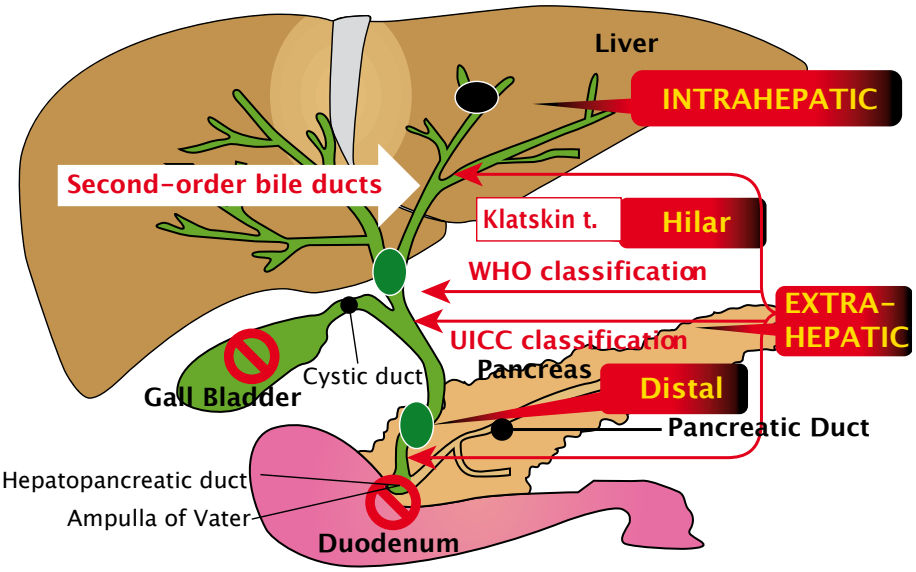
An extensive review (*PLoS Medicine* 2010, doi:10.1371/journal.pmed.1000267) showed the impact of neoadjuvant radiochemotherapy on borderline tumours includes:
- significant downstaging and downsizing
- a decrease in positive margins from 26% to 12%
- improved tolerance of treatment – there are fewer complications, notably fewer fistulas, if radiochemotherapy is given before surgery rather than afterwards, and
- 50% of cases become resectable.

I was surprised by these data. The halving in positive margins and 50% of cases becoming resectable make this approach look very promising. However, there is a problem in defining positive margins. I do not know which classification of positive margins was used in this review, but there are different classifications, with the Büchler group's criteria finding almost 75% of all operated pancreatic cancers have positive margins.

Two prospective phase II studies have investigated pre-operative radiochemotherapy in borderline resectable pancreatic cancer. One of these, from the MD Anderson Cancer Center, included 132 consecutive patients with tumours of the pancreatic head (adenocarcinoma) treated with preoperative chemoradiation followed by pancreaticoduodenectomy between 1990 and 1999 (*Ann Surg Oncol* 2001, 8:123–32).

Patients with no tumour progression before planned surgery went ahead to pancreaticoduodenectomy. Results showed the overall median survival from the time of tissue diagnosis was 21 months (95%CI 19–26 months). Survival was significantly longer for women (P=0.04) and for patients with no evidence of lymph node metastasis (P=0.03). There was no impact of age, dose of preoperative radiation therapy, delivery of intraoperative radiotherapy, tumour grade, tumour size, retroperitoneal margin status or the histologic grade of the chemoradiation treatment effect.

Cholangiocarcinoma: a heterogeneous cancer



Molecular differences between intra- and extrahepatic cholangiocarcinoma

Jean-Charles Nault (Paris, France) gave an interesting presentation on molecular differences between intra- and extrahepatic cholangiocarcinomas. Cholangiocarcinomas have a very heterogeneous pathology (see figure), with intrahepatic tumours and extrahepatic (hilar and distal) cholangiocarcinomas.

In addition, gallbladder cancers can occur in the cystic duct or the ampulla.

Genetic landscape of cholangiocarcinoma

	IHC	EHC	GB
FGFR1 Fusion protein	23% / 11%	0% / 4.4%	3%
IDH1/2	10-20%	2%	0%
SMAD4	10%		
BAP	11%	1%	
P53	10%	26%	
BRAF Substitution	5%	3%	1%
ERBB2 Amplification	4%	11%	16%
ERBB3 Mutation			11%
MET Amplification	2%	0	1%

Source: Adapted from JC Nault and PJ Ross, ASCO 2015; green figures are from John Bridgewater's presentation, which was based on the ASCO presentation by PJ Ross

Location can influence prognosis, so it is important to be clear on this in reported outcomes of studies. Cholangiocarcinomas are intrahepatic in 10–20% of cases, and extrahepatic in 80–90%, with 50–60% of these being hilar and the remainder distal type of gallbladder carcinoma.

Risk factors for cholangiocarcinoma unrelated to tumour location are liver flukes, primarily in Thailand and China, and autoimmune disease such as sclerosing cholangitis, but sporadic cases can also occur. Particular risk factors for intrahepatic cholangiocarcinoma are hepatitis B and C, diabetes and alcohol.

The link with hepatitis B and C underlines the need for rigorous diagnostic workup, because it is difficult to differentiate cholangiocarcinoma related to hepatitis C from an hepatocellular carcinoma, but it may have repercussions for outcome and choice of treatment.

I have combined the information from two presentations at the St Gallen conference, one by Jean-Charles Nault and the other one by John Bridgewater (London, UK) (see table).

It is interesting to look at some of these genetic targets and their distribution in terms of where a cholangiocarcinoma is located:

- FGFR1 fusion protein is a type of fibroblast growth factor, which can be targeted by TKIs, and occurs at a frequency of 23% in intrahepatic cholangiocarcinoma (IHC), but is much less frequent in extrahepatic and gallbladder cholangiocarcinoma.
- IDH1 mutations are also frequent in IHCs, but to a lesser degree in extrahepatic and gallbladder cholangiocarcinoma.
- HER2 amplification occurs in up to 16% of gallbladder cholangiocarcinomas, although other studies report a lower figure of 7–10%. The HER2 rate in gastric cancer is about 10% in unselected patients, so the rate of 16% in gallbladder cancer seems to be quite promising. ERB3 was reported only by Nault, with a rate of 11% mutated in gallbladder cancer. It seems that ERB2/3 signalling is quite relevant in gallbladder cancer, and may be amenable to different treatment strategies. In contrast, MET amplification does not seem to be very relevant.

Potential therapeutic targets and their respective drugs are:

- FGFR2: ponatinib
- IDH1/2: the inhibitor AGI-5198 could be promising
- BRCA1/2: a PARP inhibitor such as olaparib in combination with platinum
- PI3CA: everolimus
- BRAF: vemurafenib.

It would be interesting to screen for these mutations in a trial. However, before doing this we should see whether there is any indication from clinical data that these mutations may be influenced by ethnicity or gender. We may then be able to enrich patient groups so that every patient does not have to be screened for everything.

Question: At a rate of 16% in gallbladder cancers, is it justified to assess HER2 amplification in every gallbladder cholangiocarcinoma patient? Also, should we look for other mutations? Should we do a panel? It's a rare cancer and we don't have good options.

Answer: There is one aspect that is not highlighted here, which is whether the observations summarised in the genetic mutations table are linked to ethnic background. Given that biliary cancers have very different prevalence and origins in people from Europe, Asia or South America, the first step I think we need to take is to see how these reported frequencies correlate with where patients come from and the origin of their biliary tract cancers. I have looked at HER2 amplification in Swiss patients and, particularly in gallbladder cancer, I found that HER2 was amplified in two or three Swiss-Italian patients and treatment was extremely efficacious. In Qatar we have a Bangladeshi female patient whose gallbladder cancer is focally HER2/3 positive. The problem is that we don't have a pathway for standard pathologists

giving a reason for testing for HER2/3, so it is still an individual decision. If a pathologist is willing to perform this testing, then I think it is worthwhile, because we don't have other treatment options in second line. However, it is difficult to argue for this if someone asks for the data.

Question: Intra- and extrahepatic cholangiocarcinomas are quite different genetically. Do you design first-line chemotherapy using this information? Do you use standard cisplatin/gemcitabine or do use treatment depending on genetic data?

Answer: Personally, I use gemcitabine/cisplatin chemotherapy. I know some of my colleagues prefer gemcitabine/oxaliplatin (GEMOX), probably for historical reasons. The trial by Valle (NEJM 2010; 362:1273–81*) gave only six cycles, but I have the impression that there is a subgroup of patients who respond very well to chemotherapy and we can go beyond six cycles in these patients. However, patients may have a very benign evolution even though their cancer is metastatic, so they may not need any chemotherapy and can be managed clinically. It is difficult to know, so one would always see how chemotherapy is tolerated and continue as long as possible.*

Patterns of recurrence after surgery for extrahepatic cholangiocellular carcinoma

The pattern of recurrence after surgery is an important consideration and was reviewed by Stefan Staettner (Innsbruck, Austria). A Korean study looking at patterns of initial disease recurrence after resection of biliary tract cancer included 231 patients with hepatobiliary cancer, intrahepatic cholangiocarcinoma (IHC) or extrahepatic cholangiocarcinoma (EHC) who underwent curative resection (*Oncology* 2012, 83:83–90). Results showed recurrence in gallbladder cancer and IHC occurred after a significantly shorter time than for EHC, and location had an important impact on outcome. In the case of local diseases, recurrence occurred after 6.3 months and 6.7 months for gallbladder cancer and IHC, respectively, compared to 13.1 months for EHC. For distal disease, recurrence occurred after 5.8/6.5 months (gallbladder/IHC) versus 14.1 months (EHC). Any trial that is planned should take this into consideration.

Staettner commented that multivariate analysis showed that several factors, including distant recurrence tumour marker, lymph node status and lymphatic invasion, are correlated with poor prognosis but, surprisingly, a positive margin (R1) was not a poor prognostic factor. However, hilar and distal EHCs were combined in the Jung study, and the overall survival for these patients was 48 months, which seems an incredibly long time.

A second study covered 479 patients with biliary tract cancers from two tertiary centres in Italy (Bologna and Verona) between 1980 and 2011 (*Eur J Surg Oncol* 2015, 41:1162–9). This included 172 cases of IHC (36%); 243 cases of perihilar EHC (51%); and 64 cases of distal EHC (13%). Multivariate analysis showed that only microvascular invasion was significantly related to long-term outcomes. Staettner commented that the overall survival was only 23 months (50% less than the Korean study) and, although there was a large number of patients, the study covered a long period of time and adjuvant therapy was not reported.

In summary, the survival rate after curative resection was 20–40%, the rate of positive resection margins (R1) was high, but this did not seem to have an impact on overall survival. Staettner noted that recurrence occurs mainly within 24 months, and there are subgroups of patients who have primarily local recurrence and others who have upfront distant recurrence, and these may need to be tackled differently. Surgical morbidity is an issue that has not been studied extensively so far.

Improved outcome in extrahepatic cholangiocarcinoma with radiation therapy

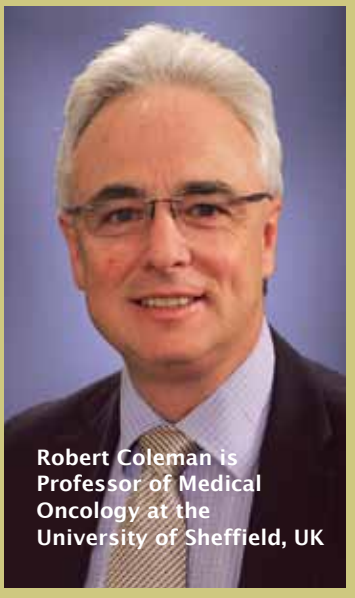
Gian Carlo Mattiucci (Rome, Italy) reviewed the impact of radiation therapy, which is a topic that attracts a lot of discussion in our tumour board. The challenges are that almost all data are retrospective, patient groups are heterogeneous, and conclusions are based on small numbers. The key publication is a comprehensive systematic review of the literature, including one randomised trial, two SEER registry analyses and 17 institutional reviews (*JCO* 30:1934–40). The sobering news was that there was no improvement with adjuvant radiochemotherapy for the study population overall, or for patient subgroups, although there was an impression of improved outcomes for margin-positive and node-positive disease. However, the benefit was seen only if the two SEER studies were excluded, with an advantage with chemotherapy for node-positive disease and with radiochemotherapy for positive margins.

Overall, there are probably no real data supporting the routine use of adjuvant chemotherapy, and specific discussions are needed for patients where surgery is insufficient or should not have been done. Adjuvant chemotherapy should not be used to cover up insufficient surgery.

"The panel recommends that bisphosphonates are considered as part of the adjuvant breast cancer treatment in postmenopausal women…"

P Hadji, R E. Coleman, C Wilson et al. (2016) Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. *Ann Oncol* 2016, 27:379–90

Bisphosphonates should be considered as part of adjuvant breast cancer treatment in postmenopausal women, or those receiving ovarian suppression therapy, and the potential benefits and risks should be discussed with relevant patients. This consensus statement, published earlier this year by a panel of 26 experts, gives new evidence-based guidance on the use of a class of drugs that could prevent one in six deaths among postmenopausal women with early stage breast cancer, and are effective against breast cancer related bone loss — but are not approved for either indication. Janet Fricker spoke to Robert Coleman, lead author of the consensus paper and meta-analysis, to ask him how the consensus statement came about and what obstacles women across Europe face in getting access to this potentially life-saving treatment.



Robert Coleman is Professor of Medical Oncology at the University of Sheffield, UK

Janet Fricker: *Research indicating a possible role for bisphosphonates in treating breast cancer has been around for more than a decade. Why did you feel now was the time for a consensus statement?*

Robert Coleman: The idea that adjuvant bisphosphonate therapy might prevent the spread of breast cancer goes back 15–20 years and encompasses both preclinical animal studies and clinical trials.

In the 1990s, two trials reported a reduction in bone recurrence and improved overall survival for the bisphosphonate clodronate (*Ann Oncol* 2008, 19: 2007–11; *Breast Cancer Res* 2006, 8:R13), while a third study suggested adverse effects for clodronate, including increases in extra-osseous metastases (*Acta Oncol* 2004; 43:650–56).

Initially, the reasons for such conflicting outcomes were unclear. When we came to design the AZURE trial [Coleman was first author], looking at the intravenous bisphosphonate zoledronic acid, we planned an exploratory subset analysis according to the women's menopausal status at the time they started treatment (*Lancet Oncol* 2014; 15: 997–1006). Since it is well known that bone metabolism changes as women age, it seemed only sensible to explore outcomes according to menopausal status.

Our results showed that while there was no overall benefit from adding zoledronic acid to standard adjuvant treatments in early breast cancer, treatment reduced the development of bone metastases in the subgroup with established menopause, delivering improved invasive-disease-free survival for women who were over five years since menopause at trial entry (HR 0.77, 95%CI 0.63–0.96).

Similarly, the NSABP-3 study investigators, who looked at the effects of the bisphosphonate clodronate used as an adjuvant treatment in operable breast cancer, included a subgroup analysis where outcomes were compared for women aged 50 years or more at study entry with those who were younger. Again, recurrence-free survival benefits were found for the older age groups (*Lancet Oncol* 2012, 13:734–42).

Together, such studies led to the theory that bisphosphonates might exert their anti-cancer benefits solely in postmenopausal women. Supporting this hypothesis, preclinical data have demonstrated improved efficacy of bisphosphonates in preventing bone metastases against the background of low levels of female and male hormones.

One study, which compared the effects of zoledronic acid (100 µg/kg weekly) on growth of disseminated MDA-231 breast cancer cells in bone between ovariectomised mice (modelling menopause) and sham operated mice (modelling premenopause), found the number of bone detectable tumours only decreased in ovariectomised mice (*Clin Cancer Res* 2014, 20:2922–32).

To clarify the issue of whether menopausal status affects bisphosphonate efficacy and to investigate available evidence in a more 'robust and precise' fashion, The Early Breast Cancer Trialists' Collaborative Group (EBCTCG), co-ordinated by the University of Oxford, undertook a meta-analysis of all unconfounded randomised trials comparing breast cancer outcomes in women who were allocated adjuvant bisphosphonates versus those who were not. The meta-analysis involved 18,766 women from 26 separate bisphosphonate trials, and was published in the *Lancet* in 2015 (vol 386, pp 1353–61).

The results showed that, among the 11,767 postmenopausal women, bisphosphonates produced highly significant reductions in recurrence (RR 0.86), distant recurrence (RR 0.82), bone recurrence (RR 0.72) and breast cancer mortality (RR 0.82).

Among premenopausal women, treatment had no apparent effect on any of these outcomes. Risk reductions for relapse and mortality in postmenopausal women treated with bisphosphonates, furthermore, were found to be similar irrespective of ER status, grade of the primary tumour, axillary lymph node involvement, and whether or not chemotherapy was used.

Overall, the results show that, for postmenopausal women, this low-cost treatment, which for zoledronic acid has been calculated to cost just a few hundred euros for the entire course of treatment, would reduce the risk of dying from breast cancer by 18% – more than one woman in six – in the first 10 years after diagnosis.

After the *Lancet* meta-analysis paper, we were left with a clear result for a group of drugs that do not have regulatory approval for the indication of preventing metastasis. We therefore felt that it would be valuable to produce a strong consensus statement giving clinicians confidence to prescribe these drugs for their patients. We also felt that the statement could be used to provide evidence to convince funding committees about the benefits of bisphosphonates in post menopausal women with early breast cancer.

While ESMO has published the Clinical Practice Guideline 'Bone Health in Cancer Patients' (*Ann Oncol* 2014, 25 Suppl 3:124–137) [Coleman was first author], this document addresses all cancers and only offers a few sentences on the use of bisphosphonates in breast cancer to prevent metastasis. We felt that it was important to develop a longer document providing more space to this important topic. We also felt that it was particularly important to publish our conclusions in an oncology journal, rather than a general medical journal, as this would help reach the wider oncology community.

JF: *What is the scientific rationale underlying this clear benefit in postmenopausal women with early breast cancer?*

RC: Even now we don't fully understand the mechanisms behind why bisphosphonates prevent bone metastases only in postmenopausal women. Our front running theory is that the postmenopausal state results in increased bone turnover, which could potentially lead to excess production of growth factors from bone, which in turn may favour survival of disseminated tumour cells or micrometastases within the bone marrow microenvironment. Through their inhibitory action on osteoclasts and slowing down of bone turnover, bisphosphonates could in theory reduce expression of these factors, and thereby prevent the establishment of micrometastatic disease.

JF: *How did you go about producing the consensus document?*

RC: For the consensus we got together an *ad hoc* group of 26 key opinion leaders, inviting representatives across the fields of both breast cancer and bone health to participate. To provide an unbiased overview, we took care to involve a number of experts who had not been involved in any of the earlier bisphosphonate breast cancer trials.

Using the nominal group methodology for consensus, a systematic review of the literature was undertaken using Pubmed and Medline databases from 1970 to 2014. Our start day took into account the fact that bisphosphonates were only recognised to have any medical uses in 1968. Conference proceedings from the San Antonio Breast Cancer Symposium, European Society for Medical Oncology and the American Society of Clinical Oncology from 2000 to 2014 were also included.

Our reasoning here was that many small studies presented at meetings do not reach the peer reviewed literature. In addition, the panel had access to the EBCTCG meta-analysis findings before publication. The literature was supported by a face-to-face meeting in October 2014. After presentations and structured discussions, participants voted on a series of questions that had been specially developed to consolidate expert opinion and address all the practical questions it was felt clinicians would want answered.

Answers to questions took the format of 'agreement' or 'disagreement', with responses graded 'strong', 'slight' or 'neutral'. We felt that it was important to develop a five-point scale, since thinking in clinical medicine is rarely black and white, and there is a need to represent the shades of grey, and highlight areas where there are still questions to be answered.

For the consensus we included additional information about preventing treatment-related bone loss, which was non-contentious, since we felt for ease of access it was important to gather all the information on breast cancer bone health together in a 'one stop shop'.

The meeting received funding from the German BANSS Charitable Foundation, who covered travel expenses for the panel and support for a medical writer.

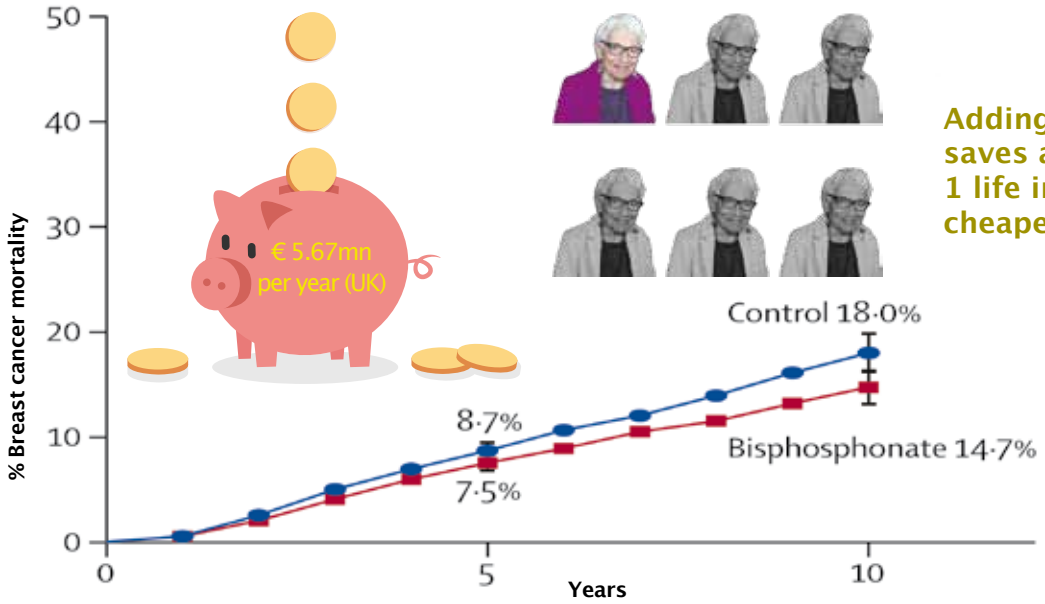
JF: *What recommendations did the panel make?*

RC: The consensus panel recommended that bisphosphonates (either intravenous zoledronic acid or oral clodronate) should be considered as part of adjuvant breast cancer treatment in postmenopausal women or those receiving ovarian suppression therapy; with some experts (58%) suggesting its use should be further restricted to those considered at intermediate or high risk of recurrence rather than across all risk groups. This view takes into account the risk–benefit ratio, where the risk of recurrence in some women is considered so low that it is not worth the possible side effects, such as osteonecrosis of the jaw.

JF: *What is the situation regarding access to bisphosphonates for use in adjuvant treatment of early breast cancer?*

RC: In Europe access to bisphosphonates to prevent metastasis in early breast cancer varies from country to

The case for bisphosphonates in postmenopausal early breast cancer



Adding bisphosphonates saves an additional 1 life in 6 and works out cheaper in the longer run

A meta-analysis involving 18,766 postmenopausal women with early breast cancer from 26 separate unconfounded randomised controlled trials (*Lancet* 2015, 386:1353–61) showed treatment with bisphosphonates lowered the mortality rate over 10 years from 18% to 14.7%, which amounts to saving an additional one in six lives – around 10,000 lives a year in Europe. A financial analysis conducted by the South Yorkshire Cancer Strategy Group showed that the savings made from reducing the number of women who need to be treated for advanced breast cancer, and from not having to perform DEXA scans to monitor bone density, outweigh the costs of using bisphosphonates as a routine part of adjuvant treatment of postmenopausal women with early breast cancer, saving the UK health service around €5.67 mn a year

country, resulting in major inequities in care. I understand that Germany and Austria introduced treatment last year, but that the treatment is not yet available in countries like Italy and France.

In the US, drugs that are not licensed are not reimbursed by insurance companies, so patients essentially have to fund these treatments out of their own pockets.

In the UK there is a postcode lottery, where clinical commissioning groups in some areas have agreed to fund bisphosphonates for this purpose, but others have not. A survey by the UK Breast Cancer Group of 125 breast cancer oncologists found that three out of four respondents had not been able to implement bisphosphonates for their early breast cancer patients.

One of the key issues determining access is that bisphosphonates used in breast cancer have been 'repurposed' and do not have licenses for the indication of preventing breast cancer recurrence. Achieving regulatory approval for a new indication for repurposed drugs would require submission of all the relevant clinical trial data in the appropriate format to the regulatory authorities and, because pharmaceutical companies do not anticipate a return on drugs that are off-patent, or soon to be off-patent, there is reluctance to fund this process.

While doctors can already prescribe 'off-label', when they consider it in the patient's best interests, in practice they may be deterred by the potential personal liability they may face in doing so. Furthermore, such 'off-label' treatments do not make it into national formularies, with the result that they are not considered by health technology assessment bodies (such as the UK's National Institute for Health and Care Excellence) who assess the clinical and cost effectiveness of treatment. This is significant, since a positive decision is often considered a prerequisite before commissioning bodies will agree to fund drugs.

In the UK the 'Off-patent drugs bill', which failed to get through parliament in November 2015 after being filibustered (the practice of delaying legislation by making long speeches), would have put into law a duty on the UK government to take steps to secure marketing authorisation for repurposed drugs when pharmaceutical companies will not, followed by a requirement for NICE to conduct technology appraisals. The

issue remains under discussion between interested ministers and advocates across a range of disease areas but does not appear to be an urgent government priority.

We want the message to get through to commissioning authorities that, irrespective of the humanitarian aspects of making these treatments widely available, use of bisphosphonates to prevent recurrent breast cancer makes good economic sense.

In Sheffield, we have recently developed a business case showing that giving bisphosphonates to patients with early breast cancer saves money in two ways. First you don't have to perform expensive bone density scans, and second, if women do not get recurrent breast cancer this saves the costs of treating advanced cancers.

Assuming the whole cohort of 35,700 postmenopausal women with invasive breast cancer are treated in the UK, we calculated that this would result in treatment costs of £16,917,783, which would be offset by savings of £6,835,122 from no longer needing to perform DEXA scans, and further savings from needing less treatment for secondary breast cancer of £15,173,500, leading to net savings of £5.09 million [€5.67 mn] per year (see http://breastcancernow.org/information-for-clinicians-about-prescribing-bisphosphonates). But, from the point of view of a commissioner trying to balance their books, that financial benefit will not be accrued for quite a few years.

JF: *What has happened since the consensus statement and what studies are ongoing or being planned?*

RC: Since the consensus there have been additional trials including the SWOG0307 trial, which addressed whether different bisphosphonates have similar efficacy. The study, presented as an abstract at ASCO 2015, randomised 6,097 postmenopausal patients with stage I–III breast cancer to receive oral clodronate (1,600 mg/day) or oral ibandronate (50 mg/day), each for three years, or intravenous zoledronic acid (4 mg/month for 6 months, then every 3 months for 2.5 years). Results showed that disease free survival and overall survival did not differ between the arms, but that there were slightly more cases of grade 3/4 adverse events with ibandronate (10.5%) than clodronate (8.3%) and zoledronic acid (8.8%).

The SUCCESS trial, comparing five versus two years of zoledronic acid in 3,800 patients, is due to report soon and should give important insight into duration of treatment. My personal bias is that bisphosphonates exert their beneficial effects early on in the disease process, and there won't be any additional advantages in giving drugs much beyond two to three years.

Interestingly, the Z0-FAST study, looking at cancer treatment induced bone loss, reported fewer recurrences in women receiving immediate zoledronic acid than in the control group, where bisphosphonate was only introduced months or years later (*Nat Rev Rheumatol* 2013, 9:365–74). To explain the upfront effect I use the analogy of grass seed where to be effective in preventing grass from germinating it is necessary to stop it taking root in the first place. Once established, however, perhaps like disseminated cancer cells, grass becomes very resilient to damage.

We will present the 10-year results of the AZURE trial in San Antonio this coming December which will give us more information on the long term benefits of treatment and may provide insights into whether women who became menopausal as a consequence of chemotherapy go on to benefit from bisphosphonate treatment.

Other trials of interest include the UK IBIS III trial (www.ibis-trials.org), run by Jack Cuzick, which will look to compare the effectiveness of metformin, zoledronic acid and aromatase inhibitors in preventing breast cancer returning in women who had their breast cancer diagnosis more than five years ago but remain at risk for recurrence of disease. We also want to continue following up patients from existing trials to see whether use of bisphosphonates has an effect beyond 10 years and influences subsequent metastases beyond bone. Ultimately we hope to build up a map showing how cancer progression is influenced long term by bisphosphonates.

The D-CARE study is exploring whether denosumab, a synthetic humanised antibody to a molecule called RANK ligand, regulating osteoclast function, can also provide benefits in early breast cancer. The big hope that Amgen have for denosumab, which is still well within patent, is that they will be the only company to get regulatory approval for the indication of preventing breast cancer recurrence.

To my mind there's a real danger that we could end up spending a factor of 50 to 100 times more on a newer agent like denosumab simply because we don't have a piece of paper that gives regulatory approval to use generic bisphosphonates, despite their extremely strong evidence base.

As the results of these trials are published, it will be important to update our consensus document with the new information. While we do not yet have any formal plans, we would very much like any future consensus to come under the umbrella of a major organisation, like ESMO, and would also like to invite representatives from North America to take part, to extend our consensus across the world. Ultimately we believe such endorsements would give us additional credibility in convincing drug funders of the urgent need to get these extraordinarily cheap life-saving drugs to patients.

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- **ESMO Advanced Course on Metastatic EGFR Mutant NSCLC**
  Seoul, Korea – 28-29 October 2016
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- **EMUC – European Multidisciplinary Meeting on Urological Cancers**
  Milan, Italy – 24-27 November 2016
- **ESO-ESMO-RCE Clinical Update on Rare Adult Solid Cancers**
  Milan, Italy – 25-27 November 2016
- **ESMO Asia 2016 Congress**
  Singapore – 16-19 December 2016
- **ESMO Summit Africa**
  Cape Town, South Africa – 10-12 February 2017
- **Advanced Ovarian Cancer Symposium**
  Valencia, Spain – 3 March 2017
- **ESMO Update for Practising Oncologists**
  Lisbon, Portugal – 3-5 March 2017
- **ICHNO – International Conference on Innovative Approaches in Head and Neck Oncology**
  Barcelona, Spain – 16-18 March 2017
- **ESMO Symposium on Signalling Pathways in Cancer**
  Sitges-Barcelona, Spain – 17-18 March 2017
- **IMPAKT - Breast Cancer Conference**
  Brussels, Belgium – 4-6 May 2017
- **ELCC - European Lung Cancer Conference**
  Geneva, Switzerland – 5-8 May 2017
- **World GI – ESMO World Congress in Gastrointestinal Cancer**
  Barcelona, Spain – 28 June - 1 July 2017
- **ESMO-ESO Course on Medical Oncology for Medical Students**
  Valencia, Spain – 13-18 July 2017 (TBC)
- **ESMO Academy**
  Oxford, UK – 4-6 August 2017
- **ESMO 2017 Congress**
  Madrid, Spain – 8-12 September 2017
- **MAP - Molecular Analysis for Personalised Therapy**
  Zurich, Switzerland – 13-14 October 2017
- **EMUC - European Meeting on Urological Cancers**
  Barcelona, Spain – 16-19 November 2017
- **ESMO Asia 2017 Congress**
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When your time is up

Conversations about dying from cancer

Cancer has traditionally been the diagnosis people fear most. But is dying from cancer so much worse than the alternatives? **Anna Wagstaff** tries to make sense of an emotive discussion that all started with a post on the BMJ blog.

"How do you want to die? You must think about it." This is the message that Richard Smith, former editor of the *British Medical Journal*, wanted to get across in a short piece he posted on the BMJ blog on New Year's Eve 2013.

By New Year's Day, his post was being reported all over the UK media, and during the following week it spread across the world, triggering an avalanche of online discussion as it went.

Why such a response? Because given a choice, Smith says he would choose to die from cancer. He titled his blogpost "Dying of cancer is the best death".

"There are … essentially four ways to die," wrote Smith. "Sudden death; the long, slow death of dementia; the up and down death of organ failure, where it's hard to identify the final going down, tempting doctors to go on treating too long; and death from cancer, where you may bang along for a long time but go down usually in weeks."

Sudden death is typically the favourite choice when the question is put to audiences, says Smith. But while it may work well for the deceased, " [it] may be very tough on those around you." Dementia may be the most awful, "as you are slowly erased". Death from organ failure – lung, heart or kidney – on the other hand, involves too much time spent in hospital "in the hands of doctors".

The advantage of death from cancer, says Smith, is that while it is possible to live with incurable disease for a long time, the dying process happens relatively fast, yet slow enough to give time for yourself and those around you to prepare for your death and say goodbye. Smith finishes with a caution to "stay away from over-ambitious oncologists" who don't know when it's time to stop active treatment and allow the disease to take its course.

Given that cancer has traditionally, across time and across cultures, been the diagnosis people fear most, the title of the piece was enough to ensure it would be widely circulated. But it was Smith's description of how those final weeks could be spent that really set the tone of the discussions that erupted on the BMJ and other websites.

Love morphine and whisky

The scenario he painted – "reflecting on life, leaving last messages, visiting special places, listening to favourite music, and preparing, according to your beliefs, to meet your makers or enjoy eternal oblivion" – was one that he himself admitted was "a romantic view of dying". But "with love, morphine and whisky", it could be achievable he suggested.

Smith's blogpost drew a barrage of comments expressing hurt, fury and indignation. People were astounded that their own terrible experiences with cancer could be described in such a glib fashion.

– "Dying a slow death from cancer is a nightmare. There is nothing to romanticize. There is no mellow philosophical self reflection during that time. Instead there is fear, extended grief, hardship, suffering, enormous financial burdens."

– "Death by cancer HURTS: tumors can gradually cut off your air supply, compress your heart so it can't beat properly, block your gut so you can't eat, erode your bones, press on nerves, or destroy bits of your brain so you can't control your body or think properly."

– "…Opiates do not control the pain, it is a constant battle between pain, constipation and laxatives and a cocktail of painkillers which do not control all pain."

– "It took my mother 15 months of ever-increasing pain and physical and mental disability to die from a transitional cell carcinoma in the sinus behind her right eye. No death could have been more cruel."

– "My father suffered two months of not being able to eat or swallow, which led to him being so weak he could not get out of bed... The cancer also affected his mind so that he was not capable of sorting out his affairs, or even of rational conversation at times. And did we enjoy having this 'extra' time seeing him in such distress? Not in the slightest."

There were many others, however, who wrote in support of Smith's overall purpose and message, including people who had watched family members die or were themselves diagnosed with incurable cancer.

– "I would take the 'sudden death' option myself, but I do understand his point of view that organ failure and dementia REALLY suck, and as an RN [registered nurse] working in long-term care facilities, I see all too many people suffering for years on end with these conditions."

– "I helped my sisters and brother at my mother's death, at 96. It was sad of course, and was a long time coming. But compared with my father in law's death 50 years ago in a car crash, I'd say the hole in our families' lives were greater following the car crash."

– "I was diagnosed with cancer and am grateful that I have cancer rather than dementia. It has increased my joy of life as I am now part of the exclusive club of people who truly know that life will end and the only possible insurance is to enjoy the moment."

– "The clarity of transition for many cancer patients to palliative care whilst clearly distressing does introduce a new if unwelcome certainty. This is what is missing from the experience of the growing population of people who are experiencing 'progressive dwindling' from degenerative diseases such as Alzheimer's."

– "Provided there are a good amount of painkillers available and, perhaps more importantly, an accepting mindset of the individual… I agree that this is indeed the best way to pass over."

The discussion triggered by Smith's blogpost prompted Charlotte Vrinten and Jane Wardle, from University College

London's Health Behaviour Research Centre, to find out how the general public rates dying from cancer. Specifically, they wanted to know whether they rate it as better or worse than dying from heart disease, on the basis of five characteristics of 'a good death' selected from the end-of-life literature (*Eur J Can* 2016, 56:172–178).

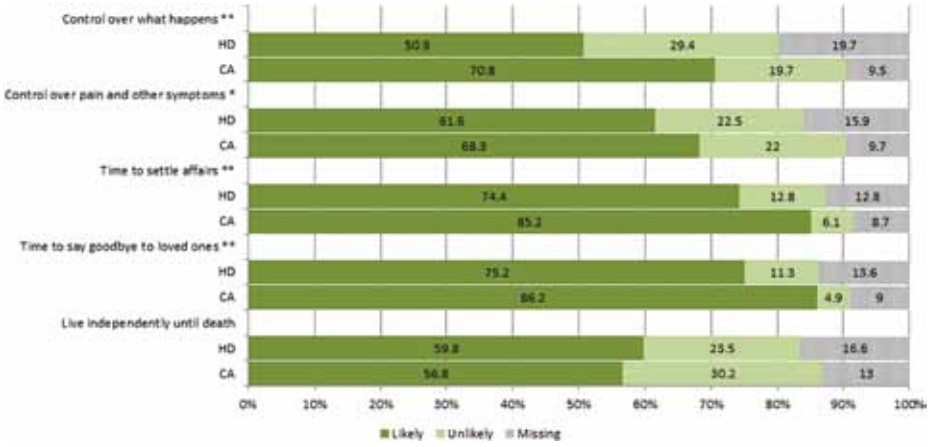
The five chosen characteristics were:

- control over what happens
- control over pain/symptoms
- time to settle affairs
- time to say goodbye and
- living independently until death.

Most respondents agreed that four out of five of these "good death" attributes would be more likely with cancer than heart disease, with the exception being living independently until death (see figure).

Their study also quoted UK evidence indicating that dying of cancer was associated with better access to palliative care services – a finding that has been reported in other countries.

'A good death': cancer vs heart disease



This survey of public attitudes among middle-aged and older people showed that dying of cancer (CA) was seen as preferable to dying from heart disease (HD) on four of the five attributes of a 'good death' they were asked about

Source: C Vrinten and J Wardle (2016) *Eur J Cancer* 56:172–178, republished under a creative commons license *P < 0.01, **P < 0.001

Why have this conversation?

Arguing the pros and cons of different ways of dying may seem a futile exercise, given that the choice of how we die is rarely ours to make. Even those opting for suicide, whether assisted or otherwise (a fifth way Smith chose not to include), cannot choose the circumstances that led them down that path.

However, as the online discussion in response to Smith's blogpost shows, it does seem to be effective at encouraging people to overcome our understandable aversion to thinking and talking about the process of dying. This could well pay off when the time comes, Smith told *Cancer World*.

"We're all going to die and I think that there is quite convincing evidence that if you at least think what sort of end would I like… where would I like to die, then probably the experience is going to be better than if you try not to think about it at all."

Referring to his "romantic" description of dying from cancer, he says that this was probably coloured by the experiences of his own parents. His father died a quick and easy death from renal cancer: "He coughed up blood in January and he had a mass on his chest X-ray… He was dead by March 4th. He had a magnificent death. Didn't have any morphine. Died at home. He was 81. He never thought he'd make it that far."

His mother, meanwhile, lives in a nursing home and has had no short-term memory for 10 years. "I'm pretty clear about which one I'd choose," says Smith.

He recognises that many deaths from cancer are more protracted and more painful than his father's, and that not everyone has reached old age when cancer strikes, or finds it easy to accept that their time has come. And he did issue an apology to the people who had been angered and upset by his post.

But he also points out that most health professionals who

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commented broadly agreed with his core argument: cancer is largely a disease of old age, and what works with cancer is the timescale. "Although everybody wants a sudden death, most people won't die that way – probably less than 10% of them. And it may be alright for you but it's certainly not good for the people around you. Whereas if you die of cancer, you can sort out things, you can say goodbye to people."

Something to aim for

Carlos Centeno is palliative care specialist based at Navarra University Hospital, in Pamplona, who is leading efforts to map and develop palliative care services across Europe, and has 20 years of experience providing symptom relief for countless patients, particularly during their final months and weeks of life.

He points out that many years before her own death, the founder of the hospice movement Dame Cicely Saunders said that if she could choose what to die of, she would choose cancer. As it turned out, that is what happened – she died of breast cancer in the hospice she had founded, St Christopher's in London.

"It is very poetic to say I want to die of cancer, but a cancer that is free of pain, suffering, deterioration. This is not a cancer"

Centeno is clear, however, that the rose-tinted death we all aspire to is the exception rather than the rule.

"I think that the idea of having time for preparation, a time to say goodbye, to receive love and give love, is the kind of death any of us would choose. We all want this time, without suffering, to do what we want to do. But the problem is we don't always have this peaceful time. It is very poetic to say I want to die of cancer, but a cancer that is free of pain, free of suffering, free of deterioration, free of complications, free of all that. This is not a cancer. This is a dream."

The physiological process of dying from advanced cancer follows no strict path, he says. "Today I have a patient with kidney cancer who is very short of breath. This is unusual for kidney cancer, but then nothing is typical for kidney cancer. Any cancer can give any symptoms in any place."

Death, he says, tends to come from multiple problems that feed into one another until it becomes impossible for the body to sustain life. Metastases to the bone, he says, eventually kill because they replace the factory of the blood. But bone metastases tend to happen at the same time as liver metastases, and deteriorating liver function also kills you. Kidney failure is another common cause of death, as the body's metabolism goes down: "The patient starts with dehydration, and that leads to kidney failure and the patient dies from renal failure. Any possibility can happen in any kind of cancer."

"Often dying of cancer is very hard," says Centeno. Nonetheless, he broadly subscribes to Richard Smith's recipe of love, morphine and whisky. Indeed he flags up the underuse of morphine across Europe as a serious cause of unnecessary suffering in dying patients. "At the end of life, morphine in expert hands is our friend. The family doctor, the general oncologist – not just palliative care specialists – have to be expert in managing this kind of medication," he says.

He emphasises, too, that despite the suffering from a failing body, sustained emotional and spiritual support can bring something positive to the experience of dying. "If you are receiving this sort of support in your physical deterioration, you can find you are a person with a life that is always preserved for those who are around you – in some way you are experiencing more as a person than ever," he says.

That's how it should be anyway.

'There are other ways to do this'

However, Centeno worries that in practice opportunities to prepare for loss and death are being lost because of our (understandable) reluctance to accept the reality of approaching death, combined with the illusion given by modern medicine that we can somehow postpone our end indefinitely – kick-start hearts, by-pass feeding routes, 'treat' terminally resistant cancers.

Like many people both within and outside the medical profession, Centeno – who works in a hospital setting – feels that something about the way we die within modern medicine is wrong, and we need to find better ways to manage our relationship with death and dying.

He contrasts Western attitudes with those he experienced on a recent trip to Uganda, where he spent some time with a community-based palliative care team. The team is part of the pioneering service that has been

running in that country for almost 35 years, and has given the country a world ranking of 35 in *The Economist's* 2015 Quality of Death Index – above several European countries, and highly impressive given that Uganda ranks 163 on the Human Development Index. The system is designed to deliver support and symptom relief – not least morphine – to people dying in their own homes.

"We have to go back to other ways to do medicine, other ways to do business with death"

"In Uganda people understand that life has a time, and at a certain time you have to go," says Centeno. "This is a natural process. In our advanced societies, the feeling is that you can buy anything, you have the right to have anything. Something is wrong. We have to go back to other ways to do medicine, other ways to do business with death."

Can we "go back"? Can countries like Uganda learn to enjoy the benefits of modern medicine without losing their accepting attitude towards death? This is an issue that Seamus O'Mahony, an Irish consultant gastroenterologist tackles in his recently published book *The way we die now: We have lost the ability to deal with death*.

Ireland, notes O'Mahony, is a country that turned from one of the most religious in Europe to one of the least in the course of a generation; that experienced the 1990's power rush of economic growth when it seemed money could buy anything, and is now going through a grim period of austerity following the 2008 financial crash.

O'Mahony argues that, having discarded the religious rituals it once relied on to "tame" dying and grieving, society has tried to hand responsibility for delivering "a good death" over to the medical profession – which cannot possibly oblige. He questions in particular the extent to which responsibility for people's spiritual/existential wellbeing is being brought within the medical sphere. He also echoes the sentiments of many of Richard Smith's harshest critics, arguing that the concept of death with dignity is itself largely a romantic illusion.

Death, he says, is "an affliction… more marked by pain, fear, boredom and absurdity than by dignity, spirituality and meaning." People who are dying, he argues, are often "too tired, too spent, to be spiritual" – a sentiment that will no doubt be appreciated by people who feel they are being

Dance of Death, by Frans Francken the Younger, ca.1635

"Having discarded religious rituals, society has tried to hand responsibility for delivering 'a good death' over to the medical profession"

blamed for not being able to die a more graceful death, or help others to do so.

O'Mahony's overall message, however, does chime with both Smith and Centeno. We're doing this wrong. We all need to learn how to deal with death as a natural part of our lives. The only way that will happen is if we overcome our natural resistance and think about it and talk about it.

The rising popularity of events like Death Cafés, where people can gather to have those conversations over tea and cake, may be an early sign of a new readiness to rehabilitate the topic of death and dying into our everyday conversations.

Can advanced-stage ovarian cancer be cured?

Treatment of advanced-stage ovarian cancer should comprise optimal debulking surgery followed by adjuvant intraperitoneal chemotherapy. **Steven Narod**, from Women's College Research Institute, Toronto, Canada, argues that widespread adoption of this model would increase cure rates for advanced ovarian cancers, from the current 20% to half of all patients.

This is an abridged version of S Narod (2016) Can advanced-stage ovarian cancer be cured? ***Nat Rev Clin Oncol*** *13:255–261. It was edited by Janet Fricker and is published with permission ©*
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In 2012, around 239,000 women worldwide were diagnosed with ovarian cancer and 152,000 died from the disease, suggesting almost 65% of all women with ovarian cancer eventually succumb to the condition (*IARC CancerBase* No 11, 2012). Around two in ten women with advanced-stage ovarian cancer survive 12 years beyond treatment, and are effectively cured (*Obstet Gynecol* 2015, 126: 491–97). Important lessons can be learnt from the experiences of these patients.

Although the main types of drugs used for ovarian cancer (taxanes and platinum-based chemotherapeutics) have not been replaced in 20 years, debate continues over the optimum timing (neoadjuvant versus adjuvant) and best routes of administration (intravenous versus intraperitoneal).

Surviving ovarian cancer

Data from the Surveillance, Epidemiology, and End Results (SEER) Program indicate 62% of ovarian cancers have serous histology, 20% endometrioid, 8% clear-cell, 5% mucinous, and 5% other histopathological subtypes, and that serous histology is responsible for 80% of all ovarian cancer deaths. The data also show 10-year survival for patients diagnosed with early-stage serous ovarian cancer is 55%, versus 15% for those with advanced-stage disease.

With studies showing almost all ovarian cancer deaths occur within 12 years of diagnosis, after which death rates approach that of women in the general population (*Gynecol Oncol* 2015, 138:741–49; *JNCI* 2013, 105:141–48), 12-year survival can be considered an indicator of (statistical) cure.

The mainstay of ovarian cancer treatment is surgery to maximally reduce tumour burden, followed by

chemotherapy to kill as many residual cancer cells as possible. In some patients, neoadjuvant chemotherapy (chemotherapy before surgery) is administered to reduce tumour volume and improve resectability.

While the National Comprehensive Cancer Network recommends neoadjuvant chemotherapy for patients with high-volume disease who are not surgical candidates due to high risk comorbidities, some institutions use it more liberally (*Nat Rev Clin Oncol* 2015, 12:239–45; *Gynecol Oncol* 2013, 131:341–46).

Molecularly targeted treatments (olaparib and bevacizumab) are aimed at impeding growth of remaining cancer cells after the first round of chemotherapy to delay disease progression, rather than achieving a cure.

Upfront chemotherapy versus surgery

In advanced-stage ovarian cancer, two randomised trials concluded survival after neoadjuvant chemotherapy was not inferior to primary debulking surgery followed by adjuvant chemotherapy, and found less morbidity in the neoadjuvant group (*NEJM* 2010, 363:943–53; *Lancet* 2015, 386:249–57). With 10-year survival universally poor (around 10%), such data suggest neoadjuvant chemotherapy improves quality of life.

Other observational studies challenge these findings, with one study showing the seven-year survival of advanced–stage ovarian cancer was 9% for neoadjuvant chemotherapy versus 41% for primary debulking surgery ($P<0.0001$) (*Gynecol Oncol* 2014, 134:462–67). One explanation might be that women offered neoadjuvant chemotherapy have more extensive disease, but even among women with no visible residual disease following neoadjuvant chemotherapy, long-term survival has been universally poor, and inferior to that of patients with no residual disease following primary surgery (*Cancer* 2009, 115:1234–44; *JCO* 2015, 33:937–43).

Many studies show that the clinical status 'no residual disease', referring to no cancer visible after surgery, is the best predictor of long-term survival (*JCO* 2015, 33:937–43; *Gynecol Oncol* 2013, 130:493–98).

For women receiving neoadjuvant chemotherapy, residual disease is assessed after completion of chemotherapy and surgery; while for women undergoing primary debulking surgery, residual disease is measured after surgery and before chemotherapy. The proportion with no residual disease is usually greater for those receiving neoadjuvant chemotherapy than those undergoing primary debulking surgery. Fifty percent or more of women with visible residual disease after primary debulking surgery will have no objective evidence of disease after adjuvant chemotherapy (*NEJM* 1996, 334:1–6; *JCO* 2003, 21:3194–200).

In an observational study of women with no visible residual disease after surgery, seven-year survival was 8% for neoadjuvant chemotherapy versus 74% for primary debulking surgery ($P<0.0001$). These results were despite 51% of patients treated with neoadjuvant therapy achieving a status of no residual disease compared with 42% of patients undergoing primary debulking surgery ($P=0.03$).

A possible explanation is that neoadjuvant chemotherapy provides a false assurance of no residual disease, with the chemosensitive cells forming the bulk of the tumour disappearing and thereby rendering chemoresistant cells invisible to the naked eye, and harder to locate and remove in subsequent surgery.

Intravenous versus intraperitoneal chemotherapy

The best ovarian cancer survival rates have been reported in women with no residual disease after primary debulking surgery who then received intraperitoneal chemotherapy .

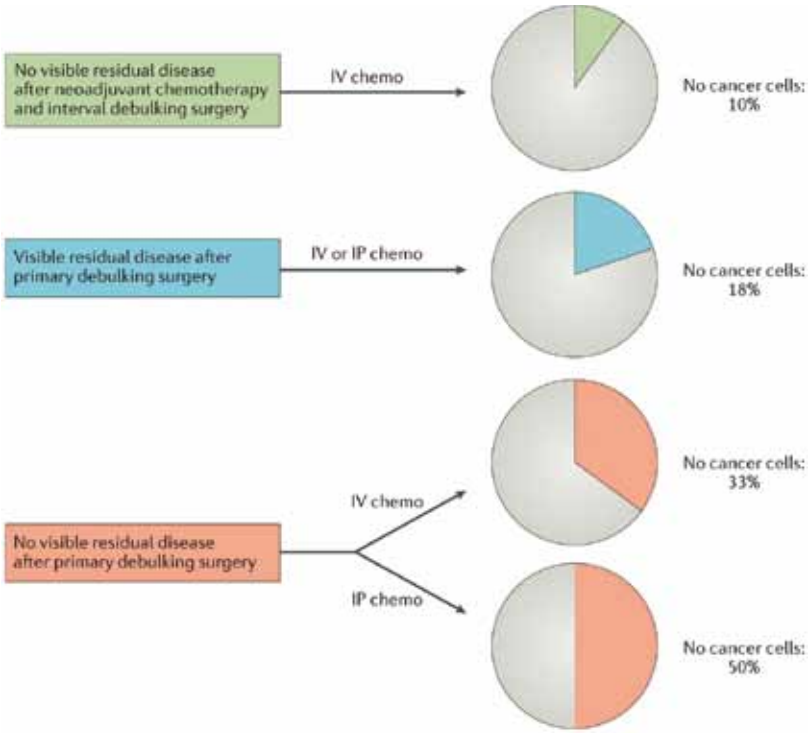
A retrospective analysis of 876 patients included in the Gynecologic Oncology Group GOG-114 and GOG-172 trials demonstrated that, among the 78 patients with no residual disease who underwent intraperitoneal chemotherapy, 10-year survival was 50% (*JCO* 2015, 33:1460–66). Data suggest that intraperitoneal chemotherapy delays recurrence in patients with minimal residual disease, but improves cure in patients with no residual disease.

While patients can have difficulty tolerating intraperitoneal chemotherapy, they should be encouraged to endure the rigours with the message that, for patients with no residual disease, the chance of curing advanced-stage ovarian cancer increases from 33% to 50% (*JCO* 2015, 33:1460–66).

One study of six US centres showed use of intraperitoneal chemotherapy ranged between 4% and 67% (*JCO* 2015, 33:2841–47). That the proportion of patients receiving intraperitoneal chemotherapy exceeded 60% in two centres demonstrates it is possible. That one centre only achieved a 4% uptake suggests that either doctors do not believe the approach works, or they give up too easily, or do not have treatment and supportive care infrastructures.

On the basis of these findings, patients with no residual disease after primary debulking surgery are ideal candidates for adjuvant intraperitoneal chemotherapy. Patients with residual disease may increase life expectancy by a year or so with intraperitoneal chemotherapy, but do not enhance their chance of cure.

A model of ovarian cancer treatment outcome



Among the women with no visible – that is, clinically detectable — residual disease after treatment of ovarian cancer (by debulking surgery, with or without prior neoadjuvant chemotherapy, and adjuvant chemotherapy), some patients have residual microscopic deposits of cancer cells that will eventually cause the disease to recur and, ultimately, lead to death. Those patients who have no residual cancer cells after such treatment are cured. Thus, the percentage of women with no cancer cells remaining post-treatment can be estimated based on the proportion of women who are alive after 12 years of follow up, because the death rate of women with ovarian cancer becomes the same as that of the general population at this time point.

The estimates in the figure are based on survival rates reported by Vergote et al., Kehoe et al., and Tewari et al (NEJM 2010, 363:943–53; Lancet 2015, 386:249–57; JCO 2015, 33:1460–66).

A model for ovarian cancer cure

When ovarian cancer cohort survival is presented graphically, curves that separate at five years invariably come together at 12 years, regardless of the treatment used.

While chemotherapy decreases recurrence and death, it does not reduce the eventual likelihood of death from ovarian cancer *per se*. Once surgery is completed, patients seem fated to survive or die, regardless of the best efforts of oncologists, who can delay recurrence, but not prevent it. Host factors, such as *BRCA1* and *BRACA2* status, predict short-term, but not long-term survival.

In a whole-genome characterisation of chemotherapy-resistant ovarian cancer, molecular markers predicted better five year survivals, but by 10 years the proportion of survivors in molecular subgroups were essentially the same.

Such observations can be reconciled under a simple model making three assumptions. First, if no residual cancer cells are present in the abdomen, recurrence or ovarian-cancer related death is impossible. Second, if residual cancer cells persist in the abdomen after surgery and chemotherapy are completed, these cells will flourish, cancer recur, and patients eventually die of the disease. Third, deaths from ovarian cancer occur within 12 years of diagnosis.

On the basis of the first two principles it can be inferred that local (intra-abdominal) recurrence is a necessary and sufficient step towards death from ovarian cancer, that women who do not have intra-abdominal recurrence rarely die from ovarian cancer and women who experience abdominal recurrence almost certainly do. Only in exceptional cases is death from ovarian cancer caused by distant metastatic spread in the absence of intra-abdominal recurrence (*Int J Gynecol Cancer* 2013, 23:1590–96). Of note, intraperitoneal chemotherapy results in higher rates of extra-abdominal recurrence (*Gynecol Oncol* 2012, 127:51–54), but lower rates of absolute recurrences (*Cancer* 2006, 106: 1624–33).

The fact that locoregional control determines survival allows the assumption that, if no viable cancer cells persist in the abdomen after treatment, the patient is cured. Pathological features of cancer are irrelevant for the fortunate in whom no cancer cells are left to proliferate. Conversely, if chemotherapy fails to eradicate all cancer cells and some remain post-treatment (even if microscopic), these ultimately flourish and lead to death within 12 years of diagnosis. Under the proposed model, the proportion of women who are alive at 12 years is precisely the proportion with no residual cancer cells after treatment.

Under the model, the chance of having no microscopic disease is highest for primary debulking surgery and intraperitoneal chemotherapy, and lowest for neoadjuvant chemotherapy (see figure).

Take home message from the author

Steven Narod is a senior scientist at Women's College Research Institute, in Toronto, and Professor at the Department of Medicine and Dalla Lana School of Public Health, at the University of Toronto, Canada.

"There is much variation in the use of intraperitoneal chemotherapy for ovarian cancer and this can be life-saving. There is a common misconception that women with advanced ovarian cancer are beyond hope and therefore the choice of therapy is not critical. This, however, is not true. Intraperitoneal chemotherapy for ovarian cancer is used sparingly in the UK, but commonly in North America, placing UK patients at a major disadvantage. The differences in treatment approach are due to methods of payment. In the UK doctors are rewarded for doing as little as possible under the NHS, while in the US doctors are rewarded for doing as much as possible in private hospitals.

Clinical implications

From the review, the clinical messages are to avoid neoadjuvant chemotherapy in ovarian cancer wherever possible, and to strive for complete debulking of the tumour with no residual disease. Then patients who have no visible residual disease following primary debulking surgery should be treated with intraperitoneal chemotherapy. The most important endpoint for ovarian cancer studies is 12-year survival; time to progression is of much less importance.

Future studies

I'd like to see studies testing the combination of neoadjuvant chemotherapy and intraperitoneal chemotherapy following debulking surgery among women with no residual disease. Following debulking surgery it would also be valuable to have studies randomising women to intraperitoneal versus intravenous chemotherapy, and finally to have data comparing differences in survival between the UK and USA."

No cancer cell left behind

The pathology and the molecular features of a cancer could possibly affect the chance of cure, either by influencing 'resectability' of the cancer to no residual disease (through primary debulking surgery), or by subsequently determining whether adjuvant chemotherapy eradicates remaining cancer cells.

One study reported ovarian cancer patients with *BRCA1* mutations were less likely to achieve no residual disease status than patients without the mutation (*Gynecol Oncol* 2015), and another that patients harbouring tumours with decreased BRCA1 levels obtain greater benefit from intraperitoneal chemotherapy (*Br J Cancer* 2013, 108:1231–37). Further work is warranted to identify interactions between molecular features, including genetic mutations and gene-expression levels, on tumour resectability, eradication, and outcome.

Synergy seems to exist between intraperitoneal chemotherapy and no residual disease, with this combination offering the highest chance of leaving no cancer cells behind.

Patients who achieve a status of no residual disease through primary debulking surgery have the best long-term survival rates (25–50%, or higher) of all patients with advanced-stage ovarian cancer, irrespective of stage at diagnosis, initial disease burden, surgical complexity, or mutation status.

While it has become a goal to avoid unnecessary morbidity by predicting patients in whom complete debulking is likely to be successful using a laparoscopic-staging or statistical index, neither approach is considered infallible. In the SCORPION trial, 45.5% of patients judged unresectable by staging laparoscopy were subsequently resected to have no residual disease (*Gynecol Oncol* 2015, 138 Suppl. 1:1–4).

In summary

Curing patients with advanced-stage ovarian cancer requires elimination of all cancer cells, with the chance of achieving this objective greatest with resection to no residual disease through maximal debulking surgery, followed by intraperitoneal chemotherapy.

Neoadjuvant chemotherapy should be limited to those for whom complete resection is judged impossible or who are not candidates for extended surgery due to comorbidities. In spite of the morbidity associated with intraperitoneal chemotherapy, data suggest this approach should be used as much as possible, and in particular in patients with no residual disease after surgery.

Overall, there is a need to readdress our thinking around ovarian cancer treatment – all women should be offered the possibility of cure.

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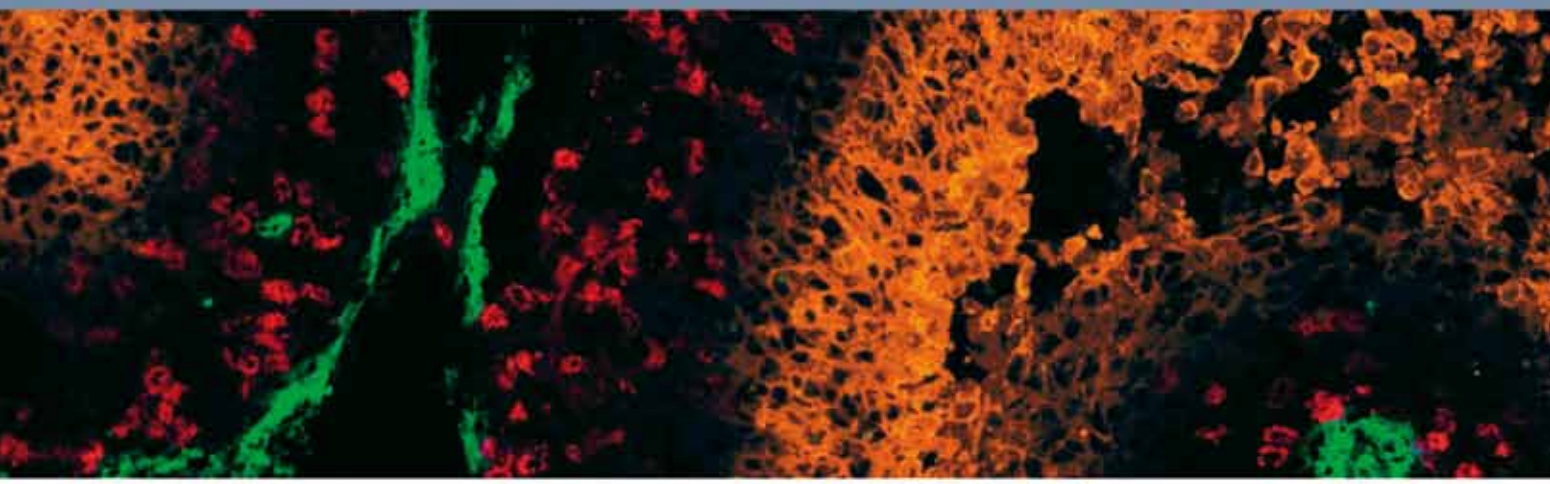

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Quantitative Methods in Radiation Oncology: Models, Trials and Clinical Outcomes
8-11 October 2017 | Maastricht, The Netherlands

Best Practice in Radiation Oncology - Train the RTT Trainers
16-18 October 2017 | Vienna, Austria

Multidisciplinary Management of Brain Tumours
22-24 October 2017 | Vienna, Austria

Image-Guided Radiotherapy and Chemotherapy in Gynaecological Cancer: Focus on MRI Based Adaptive Brachytherapy
22-26 October 2017 | Prague, Czech Republic

Image Guided Radiotherapy in Clinical Practice
29 October - 2 November 2017 | Athens, Greece

ESTRO/ESOR Multidisciplinary Approach of Cancer Imaging
2-3 November 2017 | Rome, Italy

Imaging for Physicists
5-9 November 2017 | Malaga, Spain

Paediatric Radiotherapy
30 November - 2 December 2017 | Brussels, Belgium

POSTGRADUATE COURSES OUTSIDE EUROPE

Transition from Conventional 2D to 3D Radiotherapy with a special emphasis on Brachytherapy in Cervical Cancers
8-11 March 2017 | Bengaluru, India

ESTRO-KOSRO GI: Technical and Clinical Challenges for Radiation Oncologists
2-4 June 2017 | Seoul, South Korea

Comprehensive Quality Management in Radiotherapy
5-9 July 2017 | Chengdu, China

Multidisciplinary Management of Head and Neck Oncology
9-13 December 2017 | Singapore, Republic of Singapore

PRE-MEETING COURSES

Five Pre-Meeting Courses at ESTRO 36
5 May 2017 | Vienna, Austria

UNDERGRADUATE COURSES

Medical Science Summer School Oncology for Medical Students (Vienna/ Groningen)
10-21 July 2017 | Vienna, Austria

ESO-ESSO-ESTRO Multidisciplinary Course in Oncology for Medical Students
28 August - 8 September 2017 | Antwerp, Belgium

MULTIMODAL CANCER TREATMENT
RADIOTHERAPY TREATMENT PLANNING AND DELIVERY
BIOLOGY
IMAGING
BEST PRACTICE

Getting cancer onto the global development agenda

UICC and the NCD Alliance

Despite a rapid rise in cancer cases in low- and middle-income countries, many governments have been disastrously slow to turn their attention to planning and implementing cancer services, thanks in no small part to the priorities set by the international development community.

The Millennium Development Goals, adopted in the year 2000, which set the political and funding priorities for global development efforts for the following fifteen years, notoriously lacked any reference to cancer or any other so-called non-communicable disease, thereby ensuring that the cause of cancer control was relegated to the lowest rungs of national priorities.

In an effort to redress this situation, the international cancer community mobilised to get cancer onto the agenda of the World Health Organization (WHO), succeeding in getting a Cancer Resolution passed by the World Health Assembly in 2005. Three years later this was followed with the World Cancer Declaration, a globally applicable 'road map' for developing and implementing cancer plans, which was developed and launched by the Union for International Cancer Control (UICC), the largest international organisation dedicated to helping the global health community accelerate the fight against cancer.

According to UICC's Deputy CEO, Julie Torode, while awareness and attitudes did start to change, this was slow to translate into the implementation of effective cancer control programmes. "We saw that, particularly in lower-income settings, governments expressed fear of allocating development assistance to cancer control – a topic outside of the remit of the Millennium Development Goals," she says.

It was against this background that in 2009 UICC took a bold strategic decision to throw its weight behind proposals to try to kick-start action across non-communicable diseases (NCDs), by forming an alliance with other international bodies such as the International Diabetes Federation and World Heart Federation. "In order to move the cancer agenda forward, we felt we had to shape the cancer response within the framework of NCDs," she says.

The NCD Alliance, which soon expanded to include the International Union Against Tuberculosis and Lung Disease, aimed to create momentum around the four main diseases that had previously received very little political commitment or funding – diabetes, cardiovascular and respiratory diseases, and cancer – by bringing together organisations that had global reach and long-standing relations with WHO, and the ability to translate global policy into national action through their members on the ground.

It quickly notched up some important successes, starting with the UN High-level Summit on NCDs in 2011, which finally established NCDs as a key development issue requiring the attention of heads of state and governments.

UICC's decision to focus so strongly on building the NCD Alliance was, however, greeted with some scepticism among certain sections of the cancer community, who felt that by working alongside others, the task of planning and implementing integrated cancer services across prevention, early detection, treatment and palliation could be undermined in favour of strategies focusing on the lifestyle and environmental risk factors cancer has in common with other NCDs.

Seven years on, Torode believes the UICC approach is starting to have real traction. The High-level Summit was important in debunking the myth that cancer and other NCDs are diseases of affluence. It culminated in the 2011 UN Political Declaration on the Prevention and Control of NCDs, which acknowledges that NCDs contribute to 67% of annual deaths, with the most rapidly growing burden falling in developing countries.

The NCD Alliance has since been building a growing movement, shadowing the development of the WHO Global Action Plan on the Prevention and Control of

Pooling resources. Cancer prevention, detection and care stand to benefit from an NCD action plan to provide training in non-communicable diseases to 30,000 Ethiopian health workers based at health posts like this one, located around 90 minutes' drive from Addis Ababa

NCDs 2013–2020, and pressing for targets and indicators in support of the overarching goal of reducing premature deaths from NCDs by 25% by 2025.

A strong voice for cancer

Together, the NCD Alliance and UICC were able to emphasise both the health promotional and disease management aspects of chronic diseases, taking the opportunity to open a discourse on the 'health system response'," says Torode. "When you move along the cancer journey, and look at the infrastructure required for early detection, strong referral, diagnosis, and treatment and care, using a multidisciplinary approach, a cancer-specific response is needed," she explains. "We pushed for health system response targets – and even if these are quite minimal in the Action Plan, UICC played a strong role in ensuring they were articulated."

"The Global Action Plan for NCDs," she adds, "includes a framework of indicators that start to shape a cancer plan for a country. Furthermore, when governments report back on NCDs at UN level, they have to define their cancer burden by type per 100,000 population, which implies investing in a population-based cancer registry. There are clear indications for vaccination on hepatitis B and HPV and early detection of some key cancers. And we also fought for the section recommending cost-effective interventions – so it is a live document," she says. The recent consultations on updating this appendix will bring additional strong guidance for making the right investments for cancer control, adds Torode, citing a basic package on palliative care that has been costed for cancer as a recently added feature.

As the Millenium Development Goals timeline drew to a close, a new opportunity opened up to secure a place for cancer and NCDs at the heart of global development efforts, as discussions coalesced around the Sustainable Development Goals to be agreed in 2015.

Torode stresses the important role the maturing NCD Alliance played in contributing to this agenda. "We particularly welcome the holistic approach to NCDs across all 17 of the Sustainable Development Goals, as well as the health focus on universal health coverage."

UICC is now working with its members and NCD Alliance partners to ensure effective cancer plans are set up as part of national development plans, and that expertise and civil society power that exist in the country are harnessed to achieve this end. These efforts include organising regional workshops and training sessions to provide advice and build capacity on national cancer control plan development and implementation with partners in the International Cancer Control Partnership (www.iccp-portal.org).

"The cancer plan must be right for the country and make sense against the burden and capacity to respond in that particular setting. This is why having cancer registries in place is so important," says Torode. "When countries are just getting started on national plans, it can be quite intimidating to develop

complex plans across the care continuum that are feasible and financed. That said, the number of national cancer control plans in the public domain is increasing slowly but surely."

Challenges and benefits of an NCD-wide approach

A more integrated and holistic approach to NCDs is starting to become evident in many countries. "In women's cancers we are beginning to see engagement with the child maternal health community, and the integration of cervical cancer vaccination and screening services," says Torode. "And in breast cancer we are seeing community level engagement, promoting breast health, signs and symptoms and early detection. For example, in Ghana, the Community-based Health Planning and Services (CHPS) programme, initiated in 1999, now trains its community health workers, which is an excellent example of the importance of getting the foundations of a health service in place," says Torode.

Concerns among the wider cancer community that the specific needs of cancer could get side-lined within broader national NCD action plans do seem to be shared to some extent by people active at a national level. In Ethiopia, the second largest country in Africa, with a population of more than 100 million, the government has put in place a strategic framework on NCDs, which now account for 34% of mortality and morbidity in the country.

Wondu Bekele Woldermariam, General Manager of the Mathiwos Wondu-YeEthiopia Cancer Society (MWECS – mathycancersoc.org) and Focal Person for the Consortium of Ethiopian NCD Associations, insists, however, that this broad-based framework needs to be complemented with disease-specific programmes. "Without an official cancer programme tied to government we won't be effective in tackling cancer in Ethiopia," he argues.

Wondu and his team at the cancer society were heavily involved in the launch, last October, of Ethiopia's national cancer control plan. A country-wide population-based cancer registry, and five regional registries, are included in the plan along with radiotherapy services in five regions. With support from an international foundation, MWECS recruited a technical advisor to assist in developing the plan, which was sent for review by UICC and others before being submitted to the Health Ministry and ultimately adopted by the government last year. But with only 4.7% of Ethiopia's national budget allocated to health, the amount of funding available to implement the plan will clearly be highly limited, particularly given the pressing problems of communicable diseases such as HIV, malaria, and TB.

Ethiopia has the great advantage of already having a well-developed primary healthcare system, with 15,000 health posts over the country, each with two health extension workers, and more than 3,200 health centres, which are effectively mini hospitals. "We have already agreed with government that we cannot afford a vertical programme for NCDs – what we have to do is integrate NCD prevention, detection, care and palliation into existing structures," says Wondu. We are about to launch guidelines on how NCDs can be managed at these existing facilities."

One of the main challenges, he says, will be training the 38,000 health workers in new areas. "These are high school graduates, highly trained and competent, but they are already very busy with issues of hygiene, sanitation and communicable diseases," he says. "We need to now train them in awareness and prevention of NCDs."

Wondu says he is looking forward to the publication of Ethiopia's new NCD strategic action plan, due out soon, and hopes it will recognise the need for attention to be paid to the specific diseases, and address some of the priorities for cancer.

Many countries, however, still don't have cancer control plans. One of them is Malaysia, a country with a fast-growing population of more than 30 million. Saunthari Somasundaram, President and Medical Director of the National Cancer Society of Malaysia, says that having been through a period of rapid development, the country now has the highest obesity levels in the region, and the government is very focused on trying to address this and other lifestyle risk factors.

"Malaysia has really embraced the NCD concept," she says, "and we very much follow WHO guidelines." MySihat, the Malaysian Health Promotion Board, rolls out programmes to address the risk factors of NCDs, namely tobacco, alcohol and physical inactivity, and civil society organisations are active in promoting healthy lifestyles. But Somasundaram argues that the specific issues of cancer are not getting the attention they need. "A flaw in the Malaysian NCD plan is that, even though it does refer to cancer, it does not emphasise it, and even if cancer is an NCD, and we share risk factors, it is never mentioned in the same breath as diabetes, heart disease and obesity – the problem is that it is not really seen as being a preventable disease."

Working together does, however, give all disease interests added impact on issues of common concern, such as forcing the government to turn its rhetoric on smoking into action, which it is currently resisting in the face of a powerful tobacco lobby. Plans are afoot to launch a Malaysian NCD Alliance, which is expected to be up and running by the end

The Global NCD Network. More than 50 regional and national NCD Alliances have been set up across the globe, offering a framework for pushing agendas on national cancer control plans (ncdalliance.org)

of 2016 and will be spearheaded by the National Cancer Society of Malaysia. And the global health spotlight will soon turn to Malaysia as they prepare to host the next World Cancer Congress in 2018 – hopefully showcasing progress in these areas.

Regional and national NCD Alliances

There are now more than 50 national and regional NCD alliances around the world. Katie Dain, Executive Director of the NCD Alliance says they have been emerging organically since the NCD Alliance was established in 2009. "The driver has really been the impact we have had at the global level, and the recognition that by coming together across diseases and risk factors, civil society organisations will essentially be stronger," she says.

The concept is summed up by the Sharjah Declaration, adopted at the first Global NCD Alliance Forum in 2015, which states that: *"No one sector alone will reverse the NCD epidemic, but working together we have the tremendous opportunity to chart a new course toward health and sustainable human development for a more equitable and healthier future for all."*

Whether these national alliances will be sufficiently strong to influence governments in the interests of citizens' health may, however, depend on the level of support they can call on. In addition to managing the Mathiwos Wondu-YeEthiopia Cancer Society, Wondu also runs the country's national NCD Alliance together with a colleague working in diabetes, but he doubts they can have much impact on government policies with the very limited resources at their disposal. "We have no office, we are not remunerated for our work, we have no permanent staff. We need support from our partners, the NCD Alliance and UICC, to help provide additional capacity. Being Africa's second most populous country, whatever we do here will rub off on other countries, but we need help to make real progress."

In Malaysia, a richer, more developed country, Somasundaram says that the regional NCD Alliance has already been a major driving force for civil society action against NCDs in her own country and the region. "The ASEAN [Association of Southeast Asian Nations] NCD Alliance was created off the back of the global NCD movement and we are looking forward to our very own Malaysian NCD Alliance." The Sharjah Declaration, she says, "provides a template for civil society action, and is hugely helpful for us to look to when we mobilise our existing capacity, in the absence of national guidance."

EVENTS DIRECTORY
2016 – 2017

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

EVENTS	SAVE THE DATE
EORTC NCI AACR 2016	**29 November – 2 December 2016** ***Munich, Germany*** ENA2016 28th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics
ECCO 2017	**27 – 30 January 2017** ***Amsterdam, The Netherlands*** ECCO2017 European Cancer Congress From Evidence to Practice in Multidisciplinary Cancer Care
MCCR WORKSHOP	**17 – 23 June 2017** ***Zeist, The Netherlands*** MCCRWorkshop ECCO-AACR-EORTC-ESMO Workshop on Methods in Clinical Cancer Research
2nd Special Conference EACR AACR SIC	**24 – 27 June 2017** ***Florence, Italy*** EAS2017 2nd EACR-AACR-SIC Special Conference onThe Challenges of Optimising Immuno and Targeted Therapies

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

BCC 2017

15th St.Gallen International Breast Cancer Conference 2017

Primary Therapy of Early Breast Cancer
Evidence, Controversies, Consensus

15–18 March 2017
Austria Center Vienna/Austria

Abstract Submission Deadline 15 December 2016

Information
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c/o Tumor and Breast Center ZeTuP
Rorschacherstrasse 150
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Fourth ESO-ESMO International Consensus Conference

2-4 November 2017
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Co-Chairs:
E. Senkus-Konefka, PL - E. Papadopoulos, CY

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

The ABC4 guidelines will be developed by ESO and ESMO

ESMO

The ABC4 conference and guidelines are endorsed by

and will be submitted for endorsement to

ESTRO European Society for Radiotherapy & Oncology

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