Alain Fourquet:

taking multidisciplinarity one step further

➜ Marc Beishon

Alain Fourquet will break new ground this March when he becomes the first radiation oncologist to chair Europe's major breast cancer conference, EBCC 7. He believes progress is being hampered by tunnel-vision drug trials, with protocols that are blind to the effect that the compounds, and the timing of their delivery, have on the patients' sensitivity to radiotherapy and the toxicity of the overall treatment. Delegates can expect to hear a call for radio-oncologists to be involved at an earlier stage.

The importance of a truly multidisciplinary approach to cancer care, though almost universally acknowledged, has yet to be realised in practice outside of the top cancer hospitals. Lack of resources, industry influence, fragmented hospital departments and ascendancy of certain personalities and specialisms – all these play a role in stalling progress. And all are especially apparent in Alain Fourquet's specialty, radiation oncology, which despite being one of the three central pillars of cancer treatment is often relegated to last place behind medical oncology and surgery.

As Fourquet, head of radiation oncology and a specialist in breast cancer and breast conservation at the Curie Institute in Paris notes, it is not just the shortage in many countries of equipment and specialists such as medical physicists and radiographers that accounts for poor recognition of the role of radiation oncology. "One problem is that people are understandably excited about new targeted drugs, but in some of the major trials we are seeing treatments applied without any real evidence of what order and for how long we should be doing things, such as when to give adjuvant chemotherapy and radiotherapy and how to determine efficacy and toxicity. People tend to lack knowledge and expertise in treatments outside their own specialism," he says.

"Another good example is the trend to implement partial breast irradiation in some countries, such as the US. We don't know whether it is effective – there is no proper science behind it. The history of cancer treatment and breast cancer in particular is that you cannot decide quickly on the effectiveness of new treatments – it can lead to much frustration and misleading conclusions." And failure to integrate insight and expertise across the disciplines is behind much of the rush to premature judgements, he adds.

Fourquet speaks with the authority of virtually an entire career spent in breast radiation oncology, and

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with an immense knowledge base on some of the oldest – and tried and tested – techniques. "We know that adjuvant radiotherapy cuts the risk of recurrence of breast cancer by 70%–75%. There are no drugs that do that," he says.

Certainly, if there is one place in Europe where a supportive culture of all disciplines, and radiotherapy in particular, is apparent, it is the Curie Institute – founded by one of the most famous scientists, radiation pioneer Marie Curie, and a clinician, Claudius Regaud.

"Of course, radiotherapy along with surgery were for many years the only options for treating cancer before we had chemotherapy," says Fourquet. "But the Curie and France overall has a particular heritage in using radiation in breast conserving treatment, which actually goes back to the 1950s. When I came here it was standard treatment, but unusual elsewhere. It has been routine in French centres since the early 1970s – and wasn't recommended in the US until the end of the 1980s."

Fourquet's contribution to the field can best be described as steady, if not spectacular, in line with his belief in the importance of applying research over the long term to understand properly the mechanisms involved in certain approaches. Implementing radiotherapy techniques in general has also been a major preoccupation in recent years. With colleagues at the Curie, he has been patiently building up

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optimal radiation treatment regimens for breast cancer, and now, as department head for all cancer types, he has been bringing in the new technologies that have radically changed radiotherapy – but doing so with caution and a heavy emphasis on training.

In addition to clinical work, Fourquet has been instrumental in driving clinical and translational research at the Curie, which is also France's largest cancer research institute as well as being a comprehensive cancer centre with its own hospital (in fact it has two hospitals now, following a recent merger with Centre René Huguenin, another cancer centre in Paris). "The future clearly lies in gaining a much better understanding of the biology of breast cancer and other tumours, and I think we have the tools now to identify targets not only for drugs but for radiotherapy too."

A case in point is work being carried out by one of his PhD students on genetic profiling of younger women with breast cancer – why they have a higher recurrence rate and the response to radiotherapy. "This is something I've had in mind for some time, and was started by my student with colleagues at the National Cancer Institute in Amsterdam, and is continuing here, as we have a large genomic platform. More results will be presented at the European Breast Cancer Conference [EBCC]."

Fourquet has a vested interest in publicising the

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EBCC – he is the chair of this year's event, although he is not one of Europe's great meeting attendees. He tends to pick and choose where he travels, and elected not to go to the San Antonio breast meeting last year, for example. "I agreed to take on the EBCC for two reasons. First, it is becoming an important European conference and we need to have events like this here. I don't see it competing with the US and it has a wider multidisciplinary emphasis. And second, as far as I know, there has not been a radiation oncologist in the chair until now."

With colleagues, Fourquet has shortened the conference to three and a half days – it was too long before, he says – and he is injecting more practical debate on clinical cases and controversies, along with the traditional coverage of both clinical and research topics across the breast cancer spectrum. "We have kept the format of parallel sessions and coverage of organisational and political issues as well. Of course we need to balance all interests, with the conference being jointly organised by Europa Donna [European Breast Cancer Coalition], EUSOMA [European Society of Breast Cancer Specialists] and the EORTC (European Organisation for Research and Treatment of Cancer]."

As for the profile of radiation oncology at this year's EBCC, it's no accident that among a good showing for the field the keynote Emmanuel van der Schueren lecture will be on 'Research progress and priorities in breast radiotherapy,' to be delivered by John Yarnold, a clinical oncologist at the Royal Marsden in London.

Fourquet knew he wanted to be a doctor from an early age, and went to medical school in Paris. But like many, his choice of specialism came by chance. "I was interested in oncology and haematology, and an opportunity came to work at the Curie, where the director was then Robert Calle, one of the pioneers of breast conservation." He obtained a resident's post and has never really looked back.

Although some other cancer sites formed parts of his early work, such as lymphomas and Hodgkin's disease, he moved rapidly into breast, becoming head of the radiation oncology breast cancer service by 1991, and chairman of the entire department by 2006.

"I did though spend a year on a fellowship at the Memorial Sloan-Kettering in New York, working with Samuel Hellman, who was one of the first in the US to report breast conserving treatment. I was very close to him. He is a great physician and a dedicated scientist, and was an example for many of my generation. He encouraged me to build up a long-term research programme, which we have done."

But it has not been easy to build up translational research, in particular. "It wasn't very popular with the biologists here at first, but we now have several translational programmes in my field." The Curie Institute is now the largest cancer research centre in France, working to an international level in many fields. Recent additions include a developmental biology and cancer centre, opened in 2008.

The Curie, he adds, has been rather slow to publicise its achievements and scale – most in the cancer community would cite the Gustave Roussy Institute in the Paris suburb of Villejuif as France's premier cancer centre. "They have been more active with their PR – but we will be launching a new website this year with a special breast cancer focus that will highlight our achievements and facilities much better," he says.

Apart from the main research and hospital location in central Paris, the Curie also has labs in the suburb of Orsay, and based there is one of only two proton therapy machines in France (the other is in Nice). "Then with the merger with Centre René Huguenin we will go up to 3000 breast cancer patients a year, from 1700," says Fourquet, "and we aim to have one in five patients for all tumours in clinical trials."

It is a substantial operation, and he also emphasises that the Curie has not only some of the most modern treatment technologies and research platforms, but also the databases and experience, in breast cancer in particular, going back decades, which are proving valuable for research.

One key finding has been fundamental to promoting the benefits of radiotherapy. "We have been able to demonstrate that radiation for breast cancer

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not only has an impact on local control and helps preserve the breast in good condition, but also has an impact on survival, independent of other treatments, which has come recently from statistical overviews such as that by the Oxford Group under Richard Peto. Properly doing our radiation treatment has a secondary impact on distant metastases and cuts long-term mortality."

As he adds, "We were not able to show this for a long time, because the way radiotherapy was delivered 20 to 30 years ago introduced sequelae and long-term complications, and even radiation-related mortality. That's not the case anymore – we can spare the toxicity and see the long-term impact. Here, we now offer radiotherapy to 85% of women operated on for breast cancer, which is not the case everywhere, although that's partly due to lack of access to facilities."

That radiotherapy technology has moved on recently is an understatement. As Fourquet notes, the key linear accelerator (linac) machines have not only become much smaller and more reliable, but also radically improved with techniques such as IMRT (intensity-modulated radiotherapy) and integration with sophisticated imaging. "The machines we use now can provide different photon energies for varying the dose, and the combination of imaging and IMRT means that rather than giving a homogeneous dose to one region we can adapt to the anatomy or shape of a tumour. The first big step was 3D conformational targeting and also being able to measure the actual dose in a [tumour] volume and organs at risk, which we couldn't do before."

The Curie, he adds, was one of the first in Europe to install a tomotherapy machine, which has a CT scanner and linac built into a circular head and allows modulated doses to be delivered at any angle, with the patient on a moving table. "We can really focus treatment on complicated volumes with this, such as being able to spare salivary glands almost completely when treating head and neck cancer – it's better than what is now conventional IMRT."

He stresses, though, that the aim is to have a 'one stop shop' for all radiotherapy options – simple machines are fine for some treatments, such as skin cancer – and with the proton facility and a large number of different machines at the main institute (there are seven linac suites alone), he feels this aim will be achieved with the delivery of a new proton machine, expected this April, which will replace an outdated unit. "In patients with melanoma of the eye, we can achieve about 95% local control with protons. We are aiming especially to treat more children with proton therapy, which will help to cut the long-term risk of contracting other cancers later in life."

A major problem is the sheer complexity of the new technologies. "It has been like moving from a single-seater plane to an Airbus – we have many more controls and verification systems, as sources of error are now everywhere. It's very demanding in terms of training and awareness and we have to be extremely cautious."

Fourquet has a small army of physicists, dosimetrists, radiographers and so on in his large department – the simulation and set-up involved in preparing and delivering treatment is very labour intensive and requires extensive knowledge, despite the fact that it is all done on computers. He is mindful that France, like most countries, has had disastrous failures with radiotherapy — as recently as 2007 there was a major scandal when it was revealed that a hospital in Epinal, north east France, had overdosed many patients, some of whom died.

"That was a good example of many things you should not do," says Fourquet. "The second French cancer plan, which was issued recently, addresses quality in radiotherapy with more radiation oncologists and medical physicists, and a minimum number of patients that a centre must see. It also focuses much more on multidisciplinary working and translational research. To my mind it is much better than the first plan, although that did generate investment in more modern facilities across the country."

The new criteria for radiotherapy units include a minimum of 600 patients a year, with two machines in operation to increase 'up time'. "You cannot have a centre with only one machine any more, which may cause

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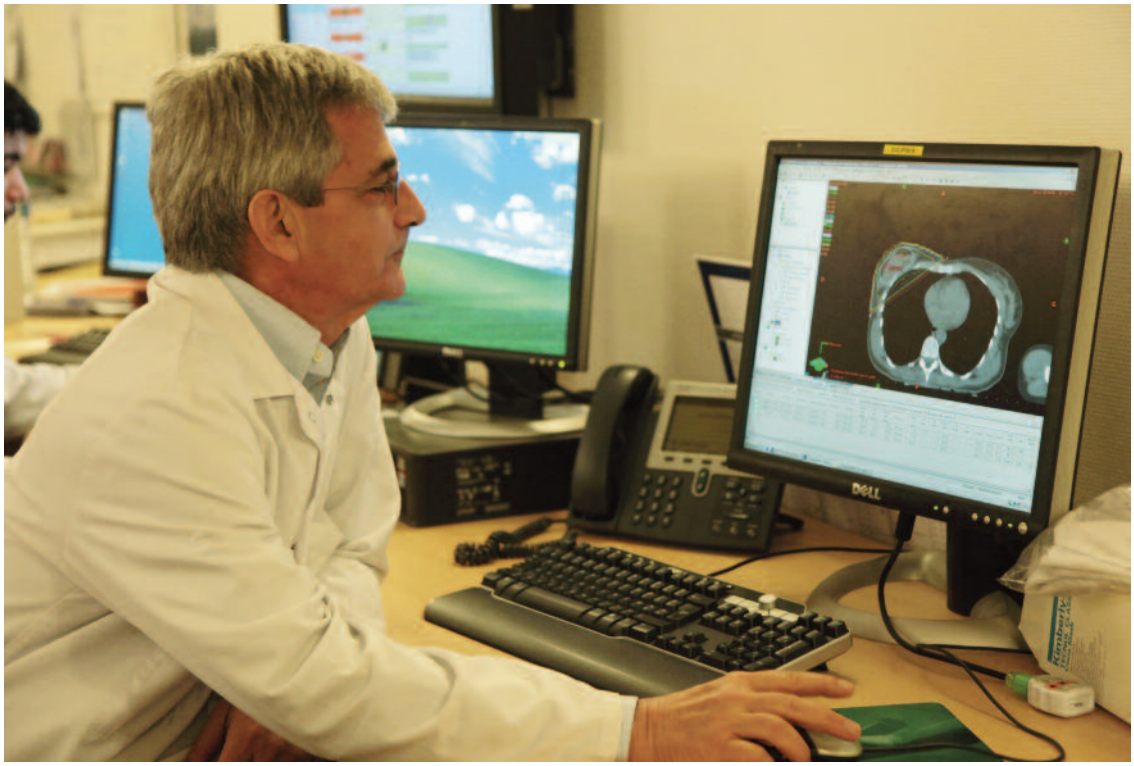

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us problems with capacity. We also have big discussions here about whether we should move to publishing outcomes of hospitals as well, as the UK is doing."

The application of radiotherapy in breast cancer has meant applying evidence-based research to counter dogma over the years, says Fourquet, so any new research focus in France's cancer plan is only to the good. The demonstration of a mortality impact after controlling for factors such as cardiac mortality has itself helped dispel the dogma that came with the chemotherapy era – that breast cancer was metastatic and local treatment could have no impact. "The quality of local treatment actually then declined until we could show its survival impact," he notes.

"We also published one of the first papers on conserving treatment for DCIS [ductal carcinoma in situ – non-invasive cancer]. Back then there was dogma that DCIS was radio-resistant so the whole breast should be removed. We started a prospective database, which now has 30,000 files, and by 1989 we were able to show that treatment with conserving surgery and radiation has a similar rate of recurrence as with invasive cancer. This triggered a lot of studies to understand DCIS."

Then there is ongoing work on younger women at high risk of cancer through the genetic *BRCA1/2* mutations. It had been thought that mastectomy is necessary because conserving surgery followed by radiation would be detrimental because of a lack of DNA repair genes, and cancer may be induced. "But we have been able to show, with others, that there are no more recurrences than in those without the mutations. The explanation seems to be that, although these aggressive tumours lack the ability to

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repair the DNA mutations, they are actually more sensitive to radiation. This is ongoing research and we need more data, but we have good clues now." Another major study, carried out by Fourquet and colleagues in the EORTC, has shown the benefit of a higher 'boost' radiation dose for younger women, and is also the subject of more ongoing trials in France and the Netherlands.

At the other end of the age spectrum, he is equally sure that older women deserve the opportunity to have a full range of treatment, including radiotherapy and chemotherapy, provided health assessments show they can tolerate it. "When the UK, for example, decided not to treat women just because they were old back in the 1970s and 80s, the outcomes were terrible. We nearly always offer radiotherapy to older women here, as we know we can also spare the heart and lung, and we have particular regimens for frail patients."

Some oncologists are suggesting now that older women do not need radiotherapy, but as Fourquet points out, "With the benefit of cutting the risk of recurrence by 70%–75%, what threshold do you decide this is useless for any group? Yes, there could be a patient for whom you estimate the risk is 1% over 10 years, so I agree, a drop to 0.3% or so is tiny. But that is not most patients – the only group I can think of are women who have surgery and endocrine treatment – and then the question is: Which is better, a few courses of non-toxic radiotherapy or five or more years of endocrine drugs with potential side-effects?"

A trend he is particularly concerned about now is partial breast irradiation. "The idea of treating only part of the breast with radiation came about for a good reason in states such as Louisiana and Texas in the US where access to health facilities can be poor and women often cannot afford to travel long distances for several radiation cycles. Rather than carrying out mastectomies, oncologists wondered if they could preserve the breast and cut the number of radiation cycles." The first studies with techniques such as brachytherapy (implanted radiation sources) were interesting, he says, and industry then stepped in with many more approaches. In Europe, countries with overstretched radiotherapy units also became interested, in particular the UK, Italy and Hungary.

"But we don't know if it is effective – there is no real science behind the idea of irradiating a smaller volume. There are trials running now that will eventually give an answer, but not after five years, as most recurrences by then are in the initial site. By ten years and beyond we will see if there are differences. What we know from trials such as that carried out by

Umberto Veronesi on conserving surgery alone against surgery and whole breast irradiation is that you have three to four times the number of recurrences if you don't do radiotherapy, and we know in the longer term we see recurrences elsewhere in the breast, even clonal recurrences – the same as the original tumour – far from the initial site."

As he adds, the trials must go on. "But the approach goes against what we have learned about breast cancer – the host, genetic predisposition and precancerous lesions make up the background for developing the disease and the effect of radiation on the whole organ is why it works. There is no logic to applying a small volume of radiation just because you can."

Where multidisciplinarity is becoming especially important now is in untangling the impact of the many combinations of treatment options opening up with targeted agents. The problem is, says Fourquet, that there is sometimes scant regard for designing trials that demonstrate the efficacy/toxicity balance. "In the conventional surgery, chemotherapy, radiotherapy sequence, there can be trials to insert more cycles of chemotherapy, each time postponing radiotherapy, despite the fact we have shown that the interval between surgery and radiotherapy may have an impact on local control. You could make a small gain by adding a chemo cycle and lose it by delaying radiotherapy, and the patients get more treatment for no benefit." Resources such as Adjuvant! Online also make no mention of radiotherapy, he notes.

Things get more complex with the addition of agents such as Herceptin (trastuzumab), which can improve adjuvant chemotherapy in 20% of patients. "In the first trials it was given differently – in Europe in the large HERA trial it was started after the end of all therapy, including radiotherapy. But in the US, it was started with chemotherapy and continued during radiotherapy – but it was not tested, just decided. Herceptin is known to improve the radiosensitive effect *in vitro*, the same type of effect we see with anthracyclines and other drugs. It also has potential cardiotoxicity, so giving it at the same time as radiotherapy raises concerns about long-term harm, but this was not tested in any trial.

"This is a typical example with new agents – angiogenesis inhibitors such as bevacizumab [Avastin] can be similarly toxic with radiotherapy. We need to be involved to test new compounds for both toxicity and efficacy by coordinating trial design with medical oncologists and industry. It's too late when the trials are running."

With breast cancer 10-year survival rates up to 85%, and local recurrence at 6% over the same time, it is of course the groups who have high recurrence rates that most concern Fourquet and colleagues, and the need to avoid unnecessary treatment to others. Like many radiation oncologists, he can see the potential to evolve the field into guiding radiation by tumour biology rather than just conventional imaging. "We need to be able to predict the radiosensitivity of tumours, knowing how various subtypes express genes involved in DNA repair. We can also expect to modulate the way we give radiation according to the structure of the tumour, where we could vary treatment depending on which part of it is growing, using functional imaging such as PET. We are already using PET to target volumes in Hodgkin's disease that spares other tissues. But we need more backing for research into radiobiology and experimental radiotherapy."

Expect many of these themes to be aired at the EBCC, and for radiation oncologists to be pretty visible, such as one of Fourquet's most well-known and closest colleagues, Harry Bartelink, long the radiation expert at the Amsterdam National Cancer Institute.

Fourquet's wife Nicole is also in medicine, working as a health geographer, and they have three children, one of whom is a biologist, and one grandchild. That no doubt sparks conversation about his main aim – to drive techniques such as gene profiling forward into everyday guidance for radiation. That's ambition enough he feels, and in any case he can see no reason to leave France's premier cancer institute. And with Marie Curie's laboratory preserved in a small museum on the site, there is certainly motivation to build on her legacy.

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