

# Jacques Bernier: keeping the faith

→ Marc Beishon

As a young medical school graduate in the '70s, Jacques Bernier ignored warnings that drugs were about to replace radiotherapy. He believed that new technology would make it safer and more effective. Today, he has faith that synergies between radiotherapy and targeted drugs can bring further benefits – and he is determined to see Europe play a full part in the research effort.

Jacques Bernier must have one of the most glorious vistas of any oncologist – from his office balcony in Genolier, Switzerland, he has a panoramic view of Lake Geneva and the mountains beyond. He's recently moved to co-head radiation oncology at the private Genolier Swiss Medical Network, having spent a long spell in Bellinzona in southern Switzerland in a similar capacity. While these centres may not be the biggest cancer operations around, Bernier has proved that this is no obstacle to scaling the heights of oncology – on more than one front.

His core work in clinical radiation oncology, in particular on head and neck cancers, has led to pioneering work on radiation dose fractionation, quality assurance and new technology, and, more recently, synergistically combining radiotherapy with chemotherapy, molecular targeted drugs or surgery. In 2000, he started the International Conference on Translational Research and Pre-Clinical Strategies in Radiation Oncology (ICTR). The third meeting, held this year in Lugano, looks to have cement-

ed this critical discussion on translational research in the packed oncology calendar.

And what better place than the traditionally neutral Switzerland for a senior, multilingual oncologist to play a part in bridging the divide between northern and southern Europe, through numerous committee and training positions, especially in the European School of Oncology (ESO) and the European Organisation for the Research and Treatment of Cancer (EORTC), where he has designed and supervised many clinical trials.

He has some good news – and not so good – about bridging the gaps in oncology and in the wider research and development community. In his own field he says the growing synergies between radiation oncology and targeted drug therapies, and the emergence of new technologies, has led to exciting progress. “Over the last decade or so radiation oncology is again in the game, which wasn't the case back in the 1980s.” The traditional isolation of radiation oncology centres has been breaking down in recent years, he adds, noting the appearance of



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more collaborative papers at his own ICTR meetings.

But in a wider context, he feels strongly that Europe has missed the boat in terms of competing with North America on the research front, in oncology and indeed in most medical and scientific disciplines. "In oncology we should have done something five to ten years ago when we saw that ASCO [the American Society of Clinical Oncology] was prevailing," he says. "Top level papers go to ASCO now for scientific and financial impact; we should have tried harder to keep them here."

That's a view shared by many, of course, but Bernier feels it's symptomatic of a fairly serious brain drain among the current generation of younger researchers, too many of whom are working in the US and not returning to Europe. It has prompted him to look closely at an issue he says is affecting much of European science. "There is no European market for research – it simply doesn't exist," he says, noting how sad it has been for him to see so many bright young researchers leave for the States. But he is not one to sound off from the sidelines. He's put pen to paper on the issue, researching and

suggesting action points – applying similar rigour to his ‘big picture’ interests as he’s known for in his clinical work.

That work currently involves rather too much administration for his liking, as he helps build the oncology department at the Genolier Swiss Medical Network, which will include a new centre in Geneva. Having spent 18 years at Bellinzona, he says he was ready for new challenges in the last part of his professional life, with the opportunity to add state-of-the-art radio-oncology equipment, which will be in place by the end of this year.

Admin is a necessary evil, he adds, to maintain a proper integration of oncology disciplines and to plan for the medium term at least. “But it’s now very difficult to have a long-term vision as things are changing so fast,” he says. “I’m not sure I can say now what radiation oncology will look like even by 2011.”

This certainly poses a challenge for radiation oncologists as they push for investment in expensive machinery and resources to staff facilities. They also face competition for resources with other departments. “Medical oncology is usually much bigger, which is not favourable to integration – there’s an imbalance of people and financial resources. Radiation oncology has been the poor relation.”

Bernier is a Belgium national and went to medical school in his own country, following in his grandfather’s footsteps. He became interested in oncology as he felt, like many in the early 1970s, that ‘something had to be done’. Taking his time over a specialism, he wasn’t put off by people telling him that radiation oncology would be finished in 10 years’ time thanks to new drug treatments. For certain, the machinery of the day could have severe side-effects, “But I was sure that new technology would improve treatment efficiency, and once the modern linac [linear accelerator] was in widespread use, we’ve seen a steady progression.”

He went on to achieve distinctions in both radiation oncology and nuclear medicine in Liège, with training also at MD Anderson and the Curie Institute, and spent his formative clinical days in hospitals in Eupen and Charleroi. Here he carried out lab research, developing

in-vitro assays for interferon, interleukin and the tumour necrosing factor – his path crossing that of Paul Franchimont, a ‘visionary’ Belgian doctor and scientist – and received awards for both his clinical and research work.

While his specialty may have taken a back seat to the rush to chemotherapy in the 1980s, he says the presence of powerful and forceful figures in radiation oncology helped him and others keep the faith. They include Jean-Pierre Bataini, from the Curie Institute in Paris, Emmanuel van der Schueren, a Belgium oncologist who died too young and who Bernier says was a great loss to European oncology, and, in the US, well-known names such as Herman Suit and Gilbert Fletcher (the latter Bernier worked with at MD Anderson). “They were either pioneering or reinforcing things, and I never had the impression that we’d reached a plateau in radiation oncology,” he says.

The history of his specialty is of more than just passing interest for Bernier. Over the last few years he has written several times on the historical context, including a paper published in 2004 in *Nature Reviews Cancer*, entitled ‘Radiation oncology: a century of achievements’, on which he was lead author. “We have to understand the lessons of the past to develop treatments that are most fruitful for the future,” he says. “For example, we have followed paths such as neutron technology that, while efficient, had severe side-effects and were too niche to be worthwhile. History has a habit of repeating itself.”

Naturally, he has a modern day example in mind – although reluctant to single out any professional colleagues, he wonders whether the interest at European level in boron-neutron capture therapy might be subject to rather too much hype. But given the huge development costs and timescales involved in creating new machinery, open debate – and patience – is surely needed. As Bernier also points out, there have been periods in the 100 plus years of radio-oncology where little outward progress was made, and much persistence and trialling with the right approaches is essential.

What is striking about his historical article is that, although the timeline for techniques such as positron-emission tomography (PET) and



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**Man and machine.** The precise images obtained through modern CT-PET scanners like this one enable Bernier to tailor the radiation dose precisely to the contours and density of each tumour, using intensity-modulated radiotherapy techniques

intensity-modulated radiotherapy (IMRT) shows that they were first developed some years ago, widespread access to affordable machinery, and new clinical techniques, are much more recent. The old cobalt-60 units, he notes, are still in use, especially in the developing world, thanks to their relatively simple operation. Meanwhile in Europe he reckons that the average age of machinery in use has not changed much since he carried out some surveys over 15 years ago.

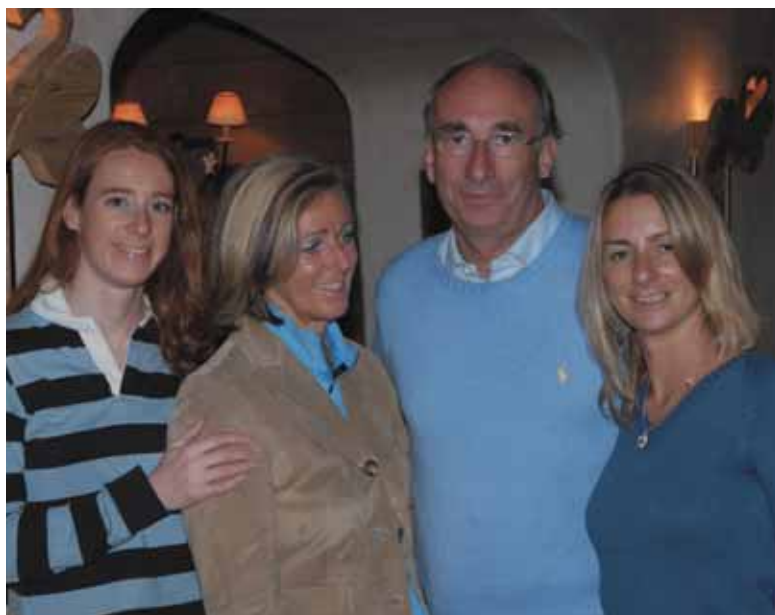
In his own history, Bernier reached deputy department head in Charleroi before, in 1988, taking a step up to be director of the radiotherapy and nuclear medicine department at the Italian Swiss Institute of Oncology, based at the San Giovanni hospital in Bellinzona, Switzerland. He took with him his earliest and most important specialism, head and neck cancer, which he'd worked on at his various place-

ments and with his main mentors. "Head and neck is a good model for clinical investigation, which is probably why I started there," he says. "Later, I have also specialised in breast irradiation – that's a key topic in my training activities with the European School of Oncology – and also lymphomas, as there are significant numbers treated at Bellinzona. But clearly head and neck is my main field."

His most significant contribution to date has been pioneering the combined use of radio- and chemotherapy in head and neck oncology. When the emphasis in the field was largely on altered fractionation techniques, which he also contributed to, Bernier was working in the early 1990s on radio/chemo combination, culminating in a paper showing the advantages of concomitant cisplatin and irradiation as an adjuvant treatment for stage III or IV head and neck cancer.

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Taking a break in the French Alps with wife Anne and daughters Caroline (left) and Géraldine (right). Bernier's love of skiing has also led him to take breaks in a more radiological sense

published side by side in the *New England Journal of Medicine* with American work that reached more or less the same conclusions. It is a good example of evidence-based medicine.”

Bernier is described by one close collaborator as a “model clinical researcher – innovative and lateral thinking with a solid grasp of clinical reality,” and he’s been a highly valuable research coordinator at the EORTC, standing down from chairing the head and neck group only recently.

“My EORTC work was extremely time consuming, but it offers an excellent platform to conduct trials and there are many top-quality people involved. But it will have to evolve to meet several challenges.”

Chief among these, he says, are the increasing administrative burdens placed on trials thanks to the “negative impact of the EU Clinical Trials Directive”, and the advent of translational research and the need to have a companion trial, say on biomarkers, alongside the main clinical trial. “We will have to change

the format of trials and it will also be important to obtain quality of life data – to calculate the therapeutic index and increase efficacy without increasing toxicity. Otherwise there is no point to the treatment.”

Another factor is a need to reverse to some extent the role of smaller centres in Europe-wide trials, as they simply will not have the resources to participate to a meaningful degree. As Bernier says of his own contribution at Bellinzona, his focus was on quality not quantity of trials – “It is better to participate with a lot of patients in 10 trials than one or two in 50, which is a nonsense,” he says.

At Bellinzona, Bernier contributed to the establishment, in 1999, of the Oncology Institute of Southern Switzerland, which marked the shift to multidisciplinary integration of specialisms, away from a general hospital model, and was one of the first such moves in the country. He notes that the geography of the region posed problems for integrating services, but modern communications such as e-mail are a great aid.

“Interdisciplinary tumour boards have the great advantage that you don’t take decisions by yourself, and they can improve the quality of treatment especially where you have many cases of one cancer type.” His model for the ideal oncology department involves what he terms the ‘magnificent five’ – training, organisation, specialism, networking and funding.

As for the status of radiation oncology in Europe, he broadly agrees with Michael Baumann, current president of the radiation oncologist body ESTRO (who was profiled in the January 2006 issue of *CancerWorld*) that radiotherapy suffers from a lack of visibility; it is dwarfed by the drugs lobby, with the result that too little money is allocated to replacing worn out and out-of-date equipment. Bernier also highlights the problem of isolation, which while

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starting to break down, still remains. “Some centres are persisting with old institutional policies, and do not integrate enough lessons from the past into their daily practice.”

He also mentions the abiding, old-fashioned image of radiotherapy in the public mind, and the shortage of professionals entering the specialty in some countries. “In Switzerland, there are few radiotherapy centres, so potential radio-oncologists and medical physicists could be concerned about their careers. Our mission is to make the case that radiotherapy is cost effective,” he adds.

“While the effectiveness arguments are well rehearsed, Bernier also notes that, as cancer patients are living longer, the number of patients needing radiotherapy is rising – quite markedly so in some countries such as the Netherlands. “It is less so in Switzerland, but the trend is still upwards.

“Radiotherapy is not Herceptin, interleukin or cetuximab – it’s much cheaper. But the message is still difficult to get across, as the magnitude of investment for new machinery and the multidisciplinary team needed to operate it is high at the start.”

The economic argument won the day at Genolier, where the latest adaptive technology will be installed at the new site in Geneva. Genolier will no doubt be a rising force in European oncology, having both Bernier and a high-profile director of the multidisciplinary team on board – the latter being Matti Aapro, another multitasking international operator.

“We are now in position to mine a rich seam of contributions from radiation oncology,” says Bernier. “I would class these essentially into technical improvement of the equipment, concomitant therapies, big-dose fractionation, and of course we can’t ignore the relationship between genomics and radio-oncology” – meaning, for instance, that a better knowledge of the tumour radiosensitivity level prior to any treatment is bound to help oncologists tailor more accurately the patient management.

He has concerns that, while satisfactory for the present, the R&D of new equipment is vested in a small handful of manufacturers, and that in any case radiation oncology is but small com-

pared with the radiology diagnostics field. New technology will certainly be needed to investigate big-dose fractionation, an area Bernier feels has not been fully explored. “We don’t know enough about the biology of large doses – we can deliver them with new techniques at higher precision without an increase in toxicity, but it will require more sophisticated machinery than we have now.”

Translational research is one of Bernier’s main interests now – in particular efforts to optimise dose distribution according to variations not just in the physical dimensions of the tumour but also biological parameters such as the metabolism or hypoxia of the tumour tissue. “One of the main breakthroughs was presented by James Bonner at ASCO in 2004 on a trial using the anti-EGFR [epidermal growth factor receptor] drug cetuximab [Erbix] in head and neck cancer, which paves the way for any cytotoxic or non-cytotoxic drug to be used in combination with radiotherapy – it is one of the main contributions in a new field.”

Bernier would like to see more attention paid to non-cytotoxic drugs, most of which are currently directed towards cell membrane receptors – either monoclonal antibodies for the outer domain of the cell membrane, or small molecules for the inner domain that trigger the signaling pathways in the cytoplasm.

“I have a mind that is rather mechanistic – I feel close to this membrane receptor, signaling pathway research field. The clinical model is not important – it’s the use of targeted therapies with radiation that appeals.”

It is the testing of drug therapies with radiotherapy that for Bernier has brought radiation oncology ‘into the game’ and into the world of clinical oncology and systemic treatment. After promoting various translational studies, into areas such as radio-resistance mechanisms and modulation, and organising several courses for the European School of Oncology, Bernier felt it was time to do things on a bigger scale, and set up in 2000 the first conference devoted to translational research strategies in radio-oncology, the ICTR. For this conference, he drew principally on his ESO, EORTC and US contacts, and as a result it initially received a somewhat cool

## A drastic reduction in permanent positions and low salaries are still driving young researchers to the US

reception from the radiation oncologist body ESTRO. However, Bernier has since invited several ESTRO people in as contributors, and the proceedings of the third meeting were published in ESTRO's journal, *Radiotherapy and Oncology*.

It's a good example of his ability to act as a bridge builder – although he points out that there is some ongoing discontentment with the 'north-south divide' in oncology in Europe, with northern countries having more senior positions in societies, and also having most of the major cancer centres. "There are clearly very large variations in the quality and quantity of centres between north and south," he says. "And I know that, despite a somewhat better balance observed recently, some colleagues in southern Europe feel frustrated about the representation on society boards – language plays a role of course."

A poverty of ambition and funds in most countries feeds into his view that Europe as whole should be worried about its overall R&D picture. "It has been a shock to me to find so many of the next generation leaving to go to the US." He has noted for example, that there has been perceivable unrest in a number of European research laboratories, especially in France and Italy, commenting that France has spent just \$3 a head on cancer research – compared with \$14 in the US.

"Overall, Europe is investing 40% less in R&D than the US and the gap is still widening. In the medium term the European Union needs to recruit 700,000 scientists to meet its needs – and what's alarming is that out of 400,000 European science and technology graduates who now work in the US, only a third intend to return home."

A toxic mix of factors is contributing to this situation, according to Bernier. Chief among them are a drastic reduction in permanent positions, low salaries – a differential of three to one between the US and the UK, for example – and "rapidly deteriorating working conditions in lab-

oratories", with "scores of dysfunctions resulting from staff shortages". Research programme fragmentation has reduced labs to 'science hotels', where each group is independent and responsible for its own funding and survival.

Bluntly: "Billions of euros and tens of thousands of jobs are at stake."

Bernier has a three-pronged prescription to reverse this decline. For researchers, more clusters of excellence for academic training should be established, he says, with a better balance of temporary and permanent posts. Further, the bureaucracy associated with applying for posts and grants should be greatly reduced. "Decision times are far too long." As a contribution, Bernier has himself set up the Foundation for the Advancement of Radiation Oncology (FARO), based in Geneva, which offers a number of training grants, and also raises funds for equipment.

For the scientific leadership, he advocates more mobility for scientists – an issue often raised in *CancerWorld* – and less fragmentation of research. The UK's National Cancer Research Institute and France's new 'cancerpoles' are steps in the right direction. "The formation of a European equivalent of the US National Cancer Institute could help exchange between these centres," he adds. For policy makers, he is backing the idea of a European research area and the concerted take up of a plan to allocate 3% of GDP to research.

While active on many bodies over the years, Bernier does not aspire to head an oncology society – and says that it is perhaps easier to communicate these big picture issues from the background. However, on the brain drain issue he is not overly pessimistic in the long run. "The problem is not as extreme as the rush to the US in the 1950s/60s, and there is excellent research and clinical work being carried out in Europe – the issue is how to develop the work and make it more visible."

Bernier has only been at Genolier a few months, so his work programme away from routine clinical work has yet to be decided. He does not feel that the switch to a private institute will affect his networking ability – he is also a professor at the University of Geneva, for example, and will continue with teaching duties there and at ESO. He adds that Genolier is not an exclusive set-up, although inevitably a lot of patients come from well-off, overseas backgrounds. Genolier also has a special relationship with Memorial Sloan-Kettering in New York for knowledge exchange, he says.

While at Bellinzona, he also became president of the Tessin League, a cancer patient organisation that interfaces with professionals, and notes that this canton in Switzerland has been a leader in such support bodies. “We developed an approach first used in France where patients could express their frustrations to medics,” he says. “It is very helpful for patients who have not so far vented their feelings and also for doctors to realise it is not a perfect world.”

With his mind back on trials – which it often is – Bernier notes that patient power could render the gold standard randomised controlled trial rather less than academic. “Patients and families are accessing a lot of information on the Internet that even insiders find difficult to interpret,” he says. “One consequence is that we are finding it harder to randomise patients into different treatment arms as they are increasingly reluctant to accept our proposals. I’m not a statistician, but methods other than randomisation may need to be found for evidence-based medicine.”

Away from work, Bernier enjoys jogging and skiing. His wife Anne, a physiotherapist, probably came in more than handy after several broken bones on the slopes. His two daughters both work in Italy, one a lawyer, the other in tourism.

On his reading list are books on geopolitics, not surprisingly, while a favourite author is



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Umberto Eco, whose ‘translational’ literary works no doubt appeal to Bernier’s mechanistic mind. Another Umberto, the Italian cancer leader Veronesi, is a close contact and Bernier is on the scientific committee of this year’s Future of Science conference in Venice, set up by Veronesi, where luminaries such as the experimental psychologist Stephen Pinker and the evolutionary biologist Richard Dawkins will be holding court.

No doubt evolution is yet another core interest for Bernier – even though he still won’t be taking bets on what his own field will look like in five years time.

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