

Marcel Verheij

Revolutionising radiotherapy

SIMON CROMPTON

Could intelligent combinations of drugs and radiation take precision radiotherapy to new levels? Marcel Verheij believes so, but may struggle to prove it without a fairer share of funding.

In the mid-80s, radiotherapy looked doomed. Chemotherapy was in the ascendant, targeted therapies were starting to appear, and in the face of new innovation radiotherapy seemed an increasingly blunt-edged approach to cancer – the equivalent, according to Marcel Verheij, of firing a cannon at an ant. “Frankly, a lot of people thought it was finished.”

Then came the digital revolution. Sophisticated imaging, planning and delivery techniques became integrated into radiotherapy so that radiation could be targeted with unprecedented accuracy. Radiation treatment became precise, measurable and lower risk. Today between 50 and 60 per cent of cancer patients receive radiotherapy. Half of those who are cured of cancer

have been treated with radiation.

But somehow the world never noticed a revolution had taken place. And Marcel Verheij, Chair of the Department of Radiotherapy at the Netherlands Cancer Institute (NKI) and professor of translational radiotherapy at the VU University Amsterdam, is one of thousands of radiation oncologists today left perplexed. Why do medical oncology and new drugs get all the attention – in the media and even in medical school – when the contribution of radiotherapy to saving lives and improving quality of life is far greater?

We meet at his office at the NKI (known as the Antoni van Leeuwenhoek Hospital) – a comprehensive cancer centre combining hospital and state-of-the art research laboratories in a modern, hotel-like complex in Amsterdam. Verheij has





JASON HARRIS

just given a talk and tour to visiting science students, and he tells me that every time he meets the students he becomes aware of how “underexposed” his specialty is at universities.

Then he shows them the equipment – software that delineates tumours and compensates for movement, CT scanning and image guidance, 3D representations of tumours and the radiation beams intersecting on them – and he knows that it can hold a special attraction to this technologically-savvy generation. “They are on the edge of their seats,” he says.

“I show the differences in what can be achieved with modern technology compared with when I started in the early 1990s, when we would delineate a tumour on a two-dimensional x-ray image with a red pencil. In those days we couldn’t envisage the high single doses of radiation we can now give with targeted techniques such as stereotactic ablative radiotherapy. If we continue at that rate of development, there’s no limit.”

His excitement centres around his own particular interest – innovative uses of radiotherapy in combination with anti-cancer drugs. As the limitations of a monotherapy culture have become increasingly apparent to the cancer world, radiotherapy has found its place in combination with other therapies. First it was chemotherapy. In the late 1980s, it was shown in lung cancer that daily cisplatin was more effective in combination with radiotherapy because it increased the local effect of radiation even when used at low, less toxic, doses. “Today there’s almost no solid tumour in a curative setting that doesn’t get a combination of chemotherapy and radiotherapy,” says Verheij.

Over 20 years, Verheij has been pushing away at the frontiers in this field. His translational research programme at the NKI is today uncovering new ways of using targeted agents at less toxic but biologically active doses to make cancer cells far more vulnerable to radiation treatment.

For example, he is hopeful that the use of synthetic alkylphospholipids in combination with radiotherapy will result in highly effective treatment strategies for patients with non-small-cell lung cancer. His work with synthetic lipids has progressed over 12 years, from cell line studies, through animal studies, into phase I and now phase II studies.

“Combining locally inflicted DNA damage with a drug that interferes with its repair creates a tumour-specific effect”

He’s also conducting preclinical studies on the similar use of death receptor ligands, small molecule inhibitors of Bcl-2 and PARP inhibitors in combination with radiation. The latter is particularly exciting: “You create DNA damage only at the site where you want it, namely the tumour and metastases. Combining this locally inflicted DNA damage with a drug that interferes with its repair, such as a PARP inhibitor, creates a tumour-specific effect, allowing an increase in therapeutic ratio. We are evaluating this concept in three different groups of patients.”

And yet for all radiotherapy’s stellar trajectory, Verheij knows that it could be moving ahead faster. It isn’t just the problem of lack of appreciation and profile. It’s the challenge of keeping research and innovation going at the same pace as medical oncology – where the research structures are clearer and better resourced.

The fact that there aren’t many professors of translational radiotherapy speaks volumes in itself. Verheij took up the professorship in 2004, and became Chair of the Department of Radiotherapy at the NKI in 2007, but long before then – since his residency started in 1993 – it was a principle at the institute to link clinicians with researchers and ensure that both understood the other’s language. Today, with Verheij at the helm, there are clearly delineated structures to twin radiotherapy clinicians with researchers, and of the 22 radiation oncologists working at the institute, seven combine their clinical activities with research. “Unless researchers know the relevance of their discoveries for individual patients, what they’re doing remains a hobby,” he says.

But even in this privileged environment, finding time and resources for radiotherapy research isn’t easy. “It is very expensive time, but if you want to do serious radiotherapy translational research, you need to invest in people to allow them to physically go to the lab, have their own desk, be part of lab discussions and not always

have the pager on. It’s easier said than done.”

Another challenge for translational radiotherapy is how long it currently takes to develop new treatments: progress from cell line studies to the clinic currently takes at least ten years. To speed up the move from pre-clinical to clinical, it’s been a priority at the NKI to invest in



genetically engineered mouse models to mimic human cancers, and develop image-guided radiation techniques specifically for animals. Verheij would also like to see greater emphasis on identifying potent biomarkers, so that new treatments are only tested on those patients who are likely to most benefit from them – so speeding up testing further.

But there is another more surprising problem facing research: lack of interest from the pharmaceutical industry. Historically, companies

have not been particularly interested in their drugs being used in combination with radiotherapy, says Verheij. So getting hold of supplies for trials has been difficult, and opportunities to develop highly effective combination therapies have been lost.

“We depend on pharmaceutical companies making their products available for trials. But the companies are mainly focused on compounds being given to patients for prolonged periods, whereas we only need the drug during relatively short periods of radiotherapy. And unlike medical oncologists, we don’t want to use the highest tolerated dose – just a lower, bio-

cial point of view, adding the drug for a limited period of time is of course less interesting, but the patient benefit may be significant.”

Fortunately, says Verheij, some pharmaceutical companies are beginning to see the light. His discussions with pharmaceutical companies such as Astra Zeneca and Merck Serono have resulted in them creating expert groups on radiotherapy which collaborate with radiation oncologists over possible trials evaluating their compounds as radiosensitisers at an earlier stage in development.

Without such initiatives, warns Verheij, some of the enormous potential of drugs such as PARP inhibitors will be missed. “Companies will test their compounds as single agents – and some of them will fail because of their toxicity. But we would never know whether at a lower dose, and used as a radiosensitiser, it might have been a wonderful drug. Once a drug has been discarded as too toxic, it’s almost impossible to get it back on the agenda.”

Such lack of understanding about radiotherapy’s potential is symptomatic of its generally low public profile compared with medical oncology. “Medical oncologists have tight relationships with the pharmaceutical companies, which they need of course because there is a pipeline of new drugs that need to be tested in the clinic. There are all these agents coming onto the market incredibly fast, which is very exciting for the media. But we, on the other hand, have one main type of treatment machine – linear accelerators (linacs). We use them for 12 years with software upgrades, and there are maybe two or three companies selling them, so the news about radiotherapy is almost by definition less. No matter how hard we try, it isn’t easy to interest journalists in new developments. It’s much easier for a medical oncologist to say ‘We have the silver bullet.’”

He is proud of meeting these challenges locally at the NKI, in particular creating the right infrastructure and staffing structures for



JASON HARRIS

logically effective dose that makes the cell more sensitive to radiation. So we have to convince both the pharmaceutical companies and medical oncologists that this is a different approach to the one they are used to. From a commer-

“Opportunities to develop highly effective combination therapies have been lost”

“If you have to make choices in health systems due to limited resources, on what do you base your choice?”

translational research – and he hopes they will have a wider impact, setting a template for others (including medical oncologists) to follow. He is in close contact with other European centres also active in translational radiotherapy, such as the Institut Gustave Roussy in Paris. He is also advising on the creation of the largest comprehensive cancer centre in the Netherlands which, pooling the expertise and resources of the Antoni van Leeuwenhoek Hospital and the oncological departments at the Utrecht Medical Centre, will reflect his unit’s multidisciplinary, research-focused approach.

“What I’ve learned throughout my career is that it’s important to invest in people around you. You can’t do the job on your own. You’ve got to motivate others to follow the same trajectory.”

None of this innovative work would have happened if three years into his residency, in 1996, Verheij hadn’t been awarded a two-year research fellowship from the Dutch Cancer Society at the Memorial Sloan-Kettering Cancer Center in New York. It was there that he researched his PhD on endothelial damage as a driver of radiation injury of the kidney, but its effect was far more profound than that.

“Interest in apoptosis (programmed cell death) was booming, and there was a group led by Zvi Fuks at Memorial doing very exciting research,” he says. “I got my chance to do fundamental research into the way the tumour cell dies on radiation, and it gave me insight into how we might exploit that knowledge – could we add agents to influence the sensitivity of cells to undergo that type of cell death? I tried to speak the same language as researchers. This was really very important for the next stage of my career.”

On his return to Amsterdam, he submitted a research grant focused in this area, and that’s where he has concentrated ever since. The lessons he learned at Memorial about translational research and about how to structure research

programmes within a hospital also shaped his plans at the NKI.

If that plotted course of his career sounds neat, Verheij’s arrival into radiation oncology in the first place was by no means straightforward. In short, he went from law, to medicine, to the army, to blood, to radiation, to cancer.

He was intellectually intrigued by what made people ill from an early age, but was unable to get into medical school on his first attempt due to a shortage of places (a lottery system decides who gets onto popular courses in the Netherlands). So he studied law for a year, until his number for medical school at Leiden University came up in 1981. The interest in medical ethics and the law has abided – for many years he was involved in the NKI’s ethical committees: “I like looking at the big picture: if you have to make choices in health systems due to limited resources, on what do you base your choice?”

He considered ophthalmology as a specialism, but his medical education was interrupted at 19 when he had compulsory military service for a year and a half. Fortunately he found work in the military blood transfusion centre – the only position where military service could be combined with research – studying blood coagulation. It meant, says Verheij, that his years in the army were not wasted. He learned about research and what it was like working in a lab. He took a lot of blood samples, saw a lot of soldiers faint – and he only had to wear a uniform once a week.

What that led to, when his military service was over, was involvement in an NKI study investigating the effect of radiation on blood vessels – they wanted a PhD student with experience in blood coagulation. And as his interest in radiation grew, that led to a job in the radiotherapy department.

Today, Verheij’s horizons continue to broaden. As a former board member of the European Society for Therapeutic Radiology and Oncology (ESTRO) he is aware of worrying international differences in radiotherapy quality and



JASON HARRIS

is determined to push forward ESTRO's work in making variations visible and stimulating improvements. ESTRO's extensive teaching programme is accessible to everyone, and he believes it is fundamental to driving up standards and spreading expertise.

In radiotherapy research, he believes there needs to be more collaboration and expertise-exchange between centres across Europe. "Practice change is hard to achieve as a single centre – you only get real progress if research is done by large consortia, combining expertise of different centres." This needs to happen before trial collaborations, so that (for example) centres specialising in preclinical models can exchange

knowledge with those specialising in proteomics or genomics and can draft trial proposals from scratch once relationships are well established. "You need to establish affinity between centres."

For such European collaboration to work, quality assurance within radiotherapy needs to be harmonised – ensuring that each centre is working according to the same protocols and terminology. National professional organisations for radiotherapy in many countries, such as the Netherlands, are already defining quality – but the effort needs to be Europe-wide. "Raising quality is not necessarily a matter of investing in centres – it's making visible the differences," he says.

“Raising quality is not necessarily a matter of investing in centres – it’s making visible the differences”

“The more experience radiation oncologists have in treating a specific type of cancer, the better the quality will be”



There are, he acknowledges, massive variations in radiotherapy equipment across Europe. But the greatest international challenge facing the specialty is creating what Verheij calls “critical mass” in radiotherapy departments – ensuring that staff have the experience and expertise to drive up quality. This inevitably involves national centralisation policies, as have been implemented in the Netherlands.

From the late 1990s onwards, a national programme of increasing radiotherapy capacity in the Netherlands has resulted in a national annual growth in equipment and personnel of 3.5–4%, but the number of radiotherapy centres has remained at 21. Verheij’s own NKI centre now treats over 5000 new patients each year. It currently has 12 linacs, seven equipped with cone beam CT scanning for image guidance (a system which his unit was instrumental in developing).

“There is a close relationship between volume and quality. In surgery, it has become common that if a hospital falls below a critical level of surgical procedures performed, it should not offer that type of operation – and I think the same has to be true in radiotherapy. The more experience radiation oncologists have in treating a specific type of cancer, the better the quality will be. It will take time to drive up quality by centralising – it has to be planned carefully so that you do not reduce patient access. But ultimately I think our profession cannot do without similar attempts to increase critical mass and demonstrate that there is a relationship between volume and quality.”

Verheij is aware that he speaks from a privileged position. When I ask him what his immediate priorities are, he talks about introducing proton beam therapy – a highly-targeted radiotherapy using protons rather than x-rays to treat cancers with a lower risk of damaging surrounding tissue. In a collaboration with the radiotherapy departments of the VU University Medical Centre and Academic Medical Centre in Amsterdam, he is planning the Netherlands’ leading proton facility – and he points out the site where it will be built, just outside his office window.

It is a world away from hospital departments struggling to meet demand with one or two ageing linacs – or drawing a red line around a blurry x-ray. But then Verheij’s belief is that progress occurs because there are leaders, innovators and centres of excellence providing models for everyone else to follow. If he hadn’t had the chance to be inspired by the integrated translational medicine structures at Memorial Sloan-Kettering when he was a junior doctor, he would never have become Chair of his state-of-the-art department in Amsterdam, setting the agenda for others.

“I call it looking in someone else’s kitchen,” he says. “I encourage all my students to do it. It’s a substantial investment in the future.” ■