Radiation that kills only tumour cells and spares healthy tissue? It sounds too good to be true. But if the promise of recent research is fulfilled, the FLASH technique of ultra high dose-rate delivery could present the greatest transformation of radiotherapy – a treatment required by half of all cancer patients – since the introduction of the linear accelerator machines in the 1950s.

For a cancer patient, FLASH could mean radiation treatment taking one or two days rather than two months, with significantly fewer side effects. For the clinician it could mean delivering improved tumour control while inflicting less damage. For the health service manager it could mean increasing the number of patients treated and lowering the overall cost of treatment.

“With FLASH radiotherapy, using electrons or protons, we are seeing something emerging that could cause a truly radical shift in radiotherapy,” says Marie Dutreix, Research Director at Institut Curie’s research centre in Orsay. “It is exciting, and potentially a big step forward,” says Alejandro Mazal, Technical Director and Head of the Medical Physics Service at the Quirónsalud Proton Therapy Centre, Madrid, Spain.

This isn’t just a pipedream. FLASH has been under serious examination in animals for the past decade, and recently the first human trials have provided indications that FLASH radiotherapy is clinically feasible and safe when used for T-cell cutaneous lymphoma and bone metastases.

Yet for all the promising data, the excitement is always hedged with conditionals. More research is needed. Much more research. Because the very fact that FLASH seems to work at all is verging on the bizarre, its mechanism currently unexplained.

In simple terms, FLASH radiotherapy revolves around delivering doses of radiation at incredibly rapid speeds of less than 500 milliseconds – around 400 to 1000 times more rapid than conventional radiotherapy – with a consequent massive increase in the dose that can be delivered within a given timeframe (the dose rate).

Delivering such ultra-high doses of radiation to living tissue sounds potentially catastrophic. But on the contrary. Ever since the 1960s, biologists have observed a surprising effect whereby, if a radiation dose is delivered to living tissue fast enough, it leaves the tissue undamaged. This discovery remained little more than a curiosity until 2014, when research led by Vincent Favaudon at the Institut Curie was published. His team, working in collaboration with another Curie team led by radiobiologist Marie-Catherine Vozenin, discovered that the effect of ultra-fast dose rate radiation on mouse tumour tissue was substantially different than the effect on healthy mouse tissue. FLASH irradiation left normal tissue relatively undamaged, but its disruptive effect on tumour tissue was equivalent to conventional radiotherapy.

The implications of this for cancer treatment were clearly enormous. Radiotherapy – in common with other treatment modalities – has always been the art of achieving a delicate balance between maximising damage to the tumour, and minimising toxicity and harm to the rest of the body. Efforts to kill the tumour are always compromised by the need to protect the rest of the body – particularly if the tumour target is close to vital organs. TheHoly Grail of radiation therapy has always been to maximise the radiation dose to the tumour, guaranteeing its destruction, whilst entirely sparing all surrounding tissue. So far, important developments such as proton therapy and intensity modulated radiation therapy (IMRT) have tried to move towards this seemingly unattainable goal by improving the targeting of the radiation dose to conform more accurately to the three-dimensional shape of the tumour, with as little toxic leakage to other tissues as possible.

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Favaudon's research seemed to indicate that this Holy Grail could be achievable by using the differential effect of ultra-high dose rate radiotherapy on healthy and cancerous tissue. The hope was not only treatment with less damage to patients: it was more effective treatment because doses could be safely raised.

"This is where the entire story shifted," says Marie-Catherine Vozenin, who went on from Orsay to set up a FLASH research laboratory at Lausanne University Hospital (CHUV) in Switzerland. "If you have sparing of the normal tissue on one side, and on the other you are improving – or at least keeping the same – tumour control, then you have enhanced what we call the therapeutic window. And this has very interesting clinical applications. It was a most unexpected type of result, and we still don't really understand how this ultra-high dose rate radiation is able to spare the normal tissue but kill the tumour."

What we know so far

In 2019 Jean Bourhis, at the Department of Radiation Oncology, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland, reported that FLASH had been used for the first time on a human (Vozenin was also a collaborator). A 75-year-old patient with multidrug-resistant T-cell cutaneous lymphoma treated with FLASH experienced only modest toxicity: transient grade 1 soft-tissue oedema and epithelitis near irradiated tumours.

Last year (2022) came a bigger step, when researchers from the University of Cincinnati and Cincinnati Children's Hospital Proton Therapy Center, in the United States, reported on a small human trial of FLASH involving 10 adults. Different research groups have used different types of particles for delivering FLASH radiotherapy. The groups of Vozenin, Favaudon, and Bourhis had all used an experimental accelerated electron beam. The Cincinnati group delivered FLASH using a proton beam.

In the Cincinnati proton therapy centre, the patients underwent palliative FLASH radiotherapy to extremity bone metastases and were followed up to at least three months post-radiation. In 8 of the 12 sites, patients reported pain relief, and in 6 there was a complete pain response (no pain). Adverse effects were mild, typically low-grade changes to skin pigmentation.

"The treatment efficacy and the profile of adverse events were comparable with those of standard-of-care radiotherapy," concluded the paper, published in *JAMA Oncology* in October 2022.

"The trial was another stepping stone to get to where we want to be eventually," says Emily Daugherty, Associate Professor at the Department of Radiation Oncology, University of Cincinnati. "It was a pivotal trial to prove we can safely treat tumours in humans using FLASH proton therapy. We are gradually upping the stakes each time, to get to where we want to be – treating primary deep-seated tumours definitively for cancer patients."

"We demonstrated that it is clinically feasible and possible – but not in every clinic right now. Our research gantry [proton therapy delivery system] was adapted and is the only one certified by the FDA [US regulators] to deliver FLASH in this way. But eventually, as we advance research, it may become widely available."

> “We are gradually upping the stakes each time, to get to where we want to be – treating primary deep-seated tumours definitively”

If all falls into place, the implications for children with cancer could be significant. “If you think about very aggressive paediatric tumours like brain stem gliomas, there are really no good curative options at the moment – we are so limited in the radiation dose we can give to these children because there’s a critical structure right next to the tumour. But imagine if we could deliver higher doses with FLASH and have some meaningful outcomes for those young patients.”

That sense of potential is shared by many. Ten years on from Favaudon’s breakthrough, there is a community of more than 1,000 physicists, radiobiologists, and clinicians in countries around the world researching the FLASH effect. Many will meet this December at the Third Flash Radiotherapy and Particle Therapy Conference in Toronto.

What we need to know

There are many pressing issues to discuss. What is the best type of particle beam to pursue? How can doses be accurately calculated given current unknowns? Will the technologies needed to deliver FLASH be affordable? How practicable will it be to convert existing radiotherapy machines? And, perhaps most fundamentally of all, how exactly does FLASH work?

As pointed out by Marie-Catherine Vozenin, many of the long-standing tenets of radiobiology have been unable to explain FLASH, and prior understanding of radiation dose rates and their relationship to tissue recovery have been challenged. She discounts earlier theories that the extremely high dose rates of FLASH deplete healthy tissues of oxygen, in the process making them more resistant to radiation. Her recent paper, Reinventing Radiobiology in the Light of FLASH Radiotherapy, published in the *Annual Review of Cancer Biology*, put forward four plausible mechanisms – preservation of stem cell niche, lipid peroxidation, protein targets, and mitochondrial reverse electron flow – together with six implausible hypotheses.

The lack of certainty that still surrounds FLASH is a source of disquiet for Alejandro Mazal, who researches high dose rate proton therapy. He is excited by the potential of FLASH to exploit the biological difference between healthy and unhealthy tissue, possibly ending the need to so accurately ‘target’ radiation beams to protect vital organs.

The cost-benefits could be considerable, he believes. FLASH could be delivered in ‘hyperfractionated’ protocols (where the total dose of radiation delivered is divided into larger doses given in one or two days, rather smaller doses given over many weeks, as in most conventional radiotherapy). “This would reduce the cost of therapy, because of the time factor,” he says. “If you reduce the number of fractions, you reduce the cost. And if FLASH has a protective effect on normal tissue, you have another saving, because you don’t have to deal with the unwanted consequences of radiation therapy. When we discuss this with health economists, the cost-benefit becomes clear.”

At the same time, he is worried about too much expectation building up around FLASH.

“There are all these different elements to radiation therapy – a chain of physics, chemistry, biology, and clinical application,” says Mazal. “And yet, in all those areas, nothing is completely understood about FLASH. So we can be excited, but we don’t want expectations to be beyond what can be achieved. There may be an effect there, but maybe not as much as people think. We don’t want to

make any errors."

Most experiments with FLASH have been conducted on small animals, and human trials have been examining practicability rather than efficacy and long-term safety, he points out. "What happens for large tumour volumes? We don't know."

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Mazal is also curious about whether irradiation of the full tumour will be necessary with FLASH. He is investigating, in a joint study with the University of Heidelberg, whether it might be effective to use ultra-high dose rates to irradiate only the part of the tumour in close proximity to a critical organ, and use conventional dose rates for the rest of the tumour. "That should simplify the technical developments of devices able to deliver FLASH," he says.

"We need to advance carefully with clinical trials in parallel with basic research, changing only one parameter at a time – for example, dose rate, or dose, or fractionation, or tumour volume – and without going beyond known limits that may cause high-level complications."

A pathway to the clinic

Vozenin agrees on the importance of small steps. For her, from a clinical point of view, the main challenge ahead is to really push the development of accelerators capable of delivering the ultra-high dose rate required for FLASH. Adapting and using existing proton therapy facilities is an obviously attractive option, says Vozenin, who has just been appointed Head of the Innovation in Radiobiology in the Oncology Department of Geneva University Hospitals (HUG).

"The main interest with a proton beam is that the dose rate is already pretty high, so using it to deliver high dose rates in the range of 100 gray per second (Gy/s) is possible. The clinical beams currently in use do not require too much modification to deliver FLASH. And it is also very interesting, because it can penetrate deep into tissue, whereas intermediate energy electrons can only treat very superficial tumours.

"So we're closest to clinical translation with protons – if, and only if, dose rates of 100 Gy/s are sufficient. And we still don't know this."

Using accelerated intermediate energy electrons – which has been explored at CHUV – has the advantage that very-high dose rates, well above 100 Gy/s, can be achieved. If a proton can deliver the dose in milliseconds (one thousandth of a second), the electron beam can deliver it in microseconds (one millionth of a second). But the machines required are unlikely to be practicable for the clinic.

Other options are being explored. A FLASH device utilising very-high energy (as opposed to intermediate energy) electron beams is being developed at CERN (the European Laboratory for Particle Physics in Switzerland) with CHUV. Similar projects are being pursued at the Institut Curie in France and at Deutsches Elektronen-Synchrotron (DESY) in Germany. A beam of very-high-energy electrons will provide both an extremely high dose rate, and the ability to reach deep-seated

tumours – but the biomedical research is so early that clinical applications are far away.

The ideal way forward, in terms of economical delivery to the clinic, would be converting conventional linear accelerators (LINACs) to deliver FLASH using photons. Unfortunately, says Vozenin, this is likely to prove difficult. “If you think about clinical workflow, it would be very nice to be able to use photon beams. But I’m not sure we will be able to do that.” The problem is that creating photons in a LINAC machine involves bouncing an electron beam off a metal target. But this has implications for the resulting dose rate. “There’s a real limitation there,” says Vozenin.

The long and the short of it is that, in the words of Vozenin “…we need a little more time.”

“It is difficult to project, in terms of how long it will take for there to be meaningful clinical applications. In terms of significant clinical trials, maybe we are talking about five years,” she says.

The next step

Emily Daugherty agrees on the need to step carefully towards larger trials, especially given the lack of understanding about how FLASH works on a cellular level. In Cincinnati, the next step is a follow-up human study examining what happens when metastases in the thorax, close to the heart and lung, are treated with FLASH. Are there any toxic effects on those vital organs? We know the answer in animals, but not in humans.

Daugherty hopes the results of that trial will be published within five years. And then maybe the first human trial of FLASH on primary, deep-seated tumours in adults will be complete within the next ten years, with a trial involving children possibly following that.

“It feels like a snail’s pace at the beginning,” she says. “But hopefully it’s going to take off exponentially as these studies are done. Then we may hope…”

The barely-spoken worry among some in the radiation therapy research community is that things will proceed too fast, mistakes will be made, and failures will bring the whole FLASH project tumbling down. Because, while the history of medicine is full of stories of courageous research groups taking leaps forward that no-one else has dared, there are also many stories of major developments being delayed for decades because of errors or indifference.

There is a balance to be achieved. Alejandro Mazal advocates care and caution, but he also knows that it is unwise to stop progress on the basis of gaps in knowledge: “If we just wait to know everything before we take the next step, we should stop research.”

The stakes with FLASH are high.

“I think the opportunity is wonderful,” says Marie-Catherine Vozenin. “If we can really enhance the therapeutic window, we will be able to cure much more, we will be able to have fewer side effects to the patient, and we will be more cost-effective – with the possibility of this being accessible not only in rich countries but every country. It would be a pity to fail.”