High radiation dose rates may improve cancer therapy

The ill-understood effect is gaining momentum and opening new avenues of research. CERN's Compact Linear Collider and other particle accelerators are contributing.

CAT PATIENTS SUFFERING from squamous cell carcinoma on their noses are treated with the standard of care—namely 10 roughly 1-minute-duration doses of 4.8 gray (Gy) each over five days (Muschti, top row)—or with FLASH radiotherapy in a single 30 Gy dose delivered in 20 ms (Lolo, bottom row). The ongoing trial is a collaboration between the Lausanne University Hospital and the Zurich Veterinary School, supported by the Swiss Cancer League. It is expected to enroll 29 cats total and be completed next year. From left to right, the cats are shown pretreatment, two weeks posttreatment, and six months posttreatment. (Photos courtesy of Carla Rohrer Bley and Marie-Catherine Vozenin.)

Dose rates hundreds to thousands of times higher than currently used in clinical treatment show promise for killing tumors while largely sparing healthy tissue. The mechanisms underlying the so-called FLASH effect are not understood, but results so far—in animals and in one human—have invigorated research into what some radiation oncologists and medical physicists say could revolutionize cancer treatment.

Scientists at medical and high-energy-physics research centers worldwide are tweaking existing accelerators to study and characterize the FLASH effect, named for the brevity of radiation exposure. The total dose is comparable to conventional therapy, but it is delivered in intense, subsecond single pulses or pulse sequences. Last month Varian launched a clinical trial that is treating bone metastases with proton FLASH therapy. Other companies are also getting involved.

In Switzerland, medical researchers at the Lausanne University Hospital (CHUV) are collaborating with physicists from the Compact Linear Collider (CLIC) project at CERN on a new accelerator to produce high-energy electrons for the first FLASH radiotherapy clinical trials on deep-seated tumors. They plan to begin the trials by 2024.

Studies are underway to better understand dose rates, why healthy tissue is spared, and more. "Think about the time response to radiation in tissue," says FLASH pioneer Marie-Catherine Vozenin, a radiation oncology professor at CHUV. "This involves novel biology questions, physics questions, chemistry questions. It's all crazy interesting." Radiation chemistry and radiation biology research were stagnant for a while, she adds. "That's not the case any more. The FLASH effect opens up work for the younger generation."

Even medical physicists who are more cautious about the potential of FLASH share a sense of excitement about the research it sparks. Daniel Low, a radiation oncology professor and vice chair of medical physics at UCLA, says the bar is high for widespread change in therapy protocols. "How hard will it be to get to parity with conventional radiotherapy? Well beyond parity?" If the FLASH effect of sparing normal tissue while damaging tumors works for cancers in humans, he says, "you can be sloppier in delivery because you can take advantage of healthy tissue. But we don't yet know the tradeoffs." And because of necessary financial investment, any new approach "needs to knock it out of the park." Although he doubts that FLASH will "step up," Low notes that radiotherapy research in the past 10 years or so has been about "dotting i's and crossing t's. This is much more exciting."

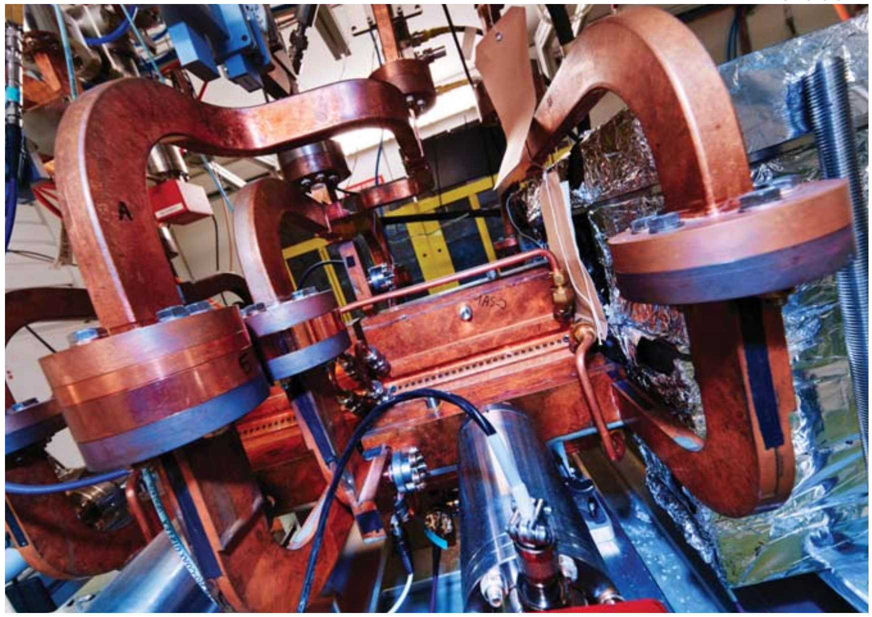
Unanswered questions

The radioprotective effect of ultrahigh dose rates was observed half a century ago on cells and bacteria in Petri dishes. Work was translated to animal studies but not to clinical ones, and research into high dose rates fizzled out. About 13 years ago, Vozenin and her colleague Vincent Favaudon used an experimental linear electron accelerator in Paris that could operate at both conventional dose rates of less than 0.03 Gy/s and at ultrahigh dose rates, in excess of 40 Gy/s. (The SI unit of ionizing radiation dose is the gray, defined as the absorption of one joule of radiation energy per kilogram of matter.)

"Out of scientific curiosity," Vozenin says, they exposed mice with lung tumors to radiation at high dose rates. "We had access to the beam, and we thought it had never been investigated." They were surprised, she says, that delivering the same integrated dose as in conventional radiotherapy retained the cure while all but eliminating the toxicity to surrounding tissue. In a 2014 paper reporting the findings, the team concluded that "FLASH radiotherapy might allow complete eradication of lung tumors and reduce the occurrence and severity of early and late complications affecting normal tissue." Subsequent studies have demonstrated the FLASH effect in pigs, rats, cats, zebrafish, and other animals.

A popular hypothesis for why FLASH radiotherapy spares healthy tissue has to do with molecular oxygen concentration. Cells are killed by mechanisms that include DNA breakage, lipid damage, and changes in cytokine cascades and inflammation signals, all of which are affected by the availability of reactive oxygen species. Solid tumors are typically hypoxic, and their response to radiation appears to be independent of dose rate. And healthy tissue appears to gain protection from radiation damage by the reduced production of free radicals in FLASH compared with conventional radiation. "FLASH exploits the difference in cell metabolism between normal and tumor tissue," Vozenin says.

But the oxygen hypothesis doesn't fully explain the FLASH effect. For example, Emil Schüler, a medical physicist at MD Anderson Cancer Center in Houston, Texas, notes that the mechanism of tumor destruction with proton radiation is less dependent than photon and electron radiation on oxygen concentration. Even so, a FLASH effect with protons still occurs. "We need to study the parameters," he says, "the mean dose rate, total time of delivery, dose per pulse, variations among organs, and more." Keeping tabs on dose delivery is also a concern. Most radiotherapy systems rely on ionization chambers for such monitoring, but they don't work properly at the subsecond time scales of FLASH. Other methods for measuring and standardizing the dose delivery are needed, he says.



A HIGH-ENERGY FLASH TEST FACILITY to study the treatment of deep tumors is planned for the Lausanne University Hospital campus. The facility, which is expected to start up by 2024, is based on CERN's Compact Linear Collider. In this prototype, the electron beam travels from left to right and gains 25 MeV over the 25 cm length of the accelerating structure (center, copper with holes). The protruding pipes with rectangular cross section are waveguides that power the accelerating structure.

There are many unanswered questions, notes Peter Maxim, vice chair of the medical physics division at Indiana University School of Medicine. "I am convinced that the FLASH effect is real based on the published preclinical studies," he says. "The million-dollar question is whether the FLASH effect is translatable to human therapy." Untangling the mechanisms of FLASH isn't necessary for its use, he adds, but it would help in designing clinical trials. And, he notes, technological advances would be needed to implement FLASH for cancer treatment.

FLASH facts

In FLASH radiotherapy studies, mean dose rates of at least 40 Gy/s are delivered in pulses in the microsecond to millisecond range; the details depend on the type of radiation and the accelerator. So far, most research has been done with electron beams, but protons and photons are also being studied, and scientists have observed the FLASH effect for all forms of ionizing radiation.

An advantage of electrons is that they can be readily produced at high fluxes. Photons are generated by bombarding electrons on a tungsten or other target, so to get high-energy photons, the electron energy has to be correspondingly higher. Protons are more expensive to accelerate, but they have advantages, one being that they can more accurately target tumor volumes. (See the article by Michael Goitein, Tony Lomax, and Eros Pedroni, in PHYSICS TODAY, September 2002, page 45, and the news story, June 2015, page 24.)

At TRIUMF, Canada's national particle accelerator center in Vancouver, researchers are gearing up to investigate FLASH with protons and photons. The most common radiation therapy at hospitals and clinics uses photons, says Cornelia Hoehr, who coleads the center's FLASH work: "There is more data, more protocols, it is mainstream, and it would be approved for clinical use faster."

Among the attractions of FLASH is that in delivering the radiation on subsecond time scales, organs and tumors are effectively motionless. In a single breath, for example, lungs can move as much as 2 cm, and movement in the bowels can push the prostate by 1 cm in a minute. On the subsecond time scale, such motions are negligible, and methods for simultaneous imaging and accurately targeting tumors are being developed. Because of the high dose rate that FLASH would deliver, the necessity for positional accuracy is enhanced, both in terms of killing cancer cells and minimizing harm to healthy ones.

Conventional radiation is typically delivered in 20–30 doses, each a few minutes in duration, over several weeks to minimize damage to healthy tissue. In FLASH, the same total dose would be delivered in a single or just a few sittings, in milliseconds instead of minutes total. Even if the tissue sparing doesn't hold for humans, reducing clinic visits would be a huge improvement in care, says Hoehr. Fewer visits would also reduce the cost of treatment.

And given that radiation therapy is in part guided by the tolerance of healthy tissue, FLASH may make it possible to give higher doses and therefore treat more types of tumors or treat them more effectively. About half of cancer patients are treated with radiation, usually in conjunction with other treatments.

Existing accelerators are limited by electron energies of 6–20 MeV to shallow tumors, down to about 4 cm. "If we can show that [FLASH] spares normal tissue, we cannot defend only using conventional dose rates anymore," says Julianne Pollard-Larkin, a medical physicist at MD Anderson. She notes that according to some models, FLASH treatment can reduce damage to healthy tissue by 70% compared to conventional radiation treatment. "FLASH looks like a win for science, for cancer patients, and for humanity."

High energies for deep tumors

For wider applicability and the potential to treat deep internal tumors, higher energies are necessary. The CERN–CHUV plan is to produce electrons in the 100–200 MeV range. "As soon as we learned of FLASH, my colleagues and I realized that CLIC technology could be relevant," says Walter Wuensch, a senior researcher at CERN. A future CLIC accelerator, if built, would use room-temperature, high-gradient technology to accelerate electrons and positrons. "The same features that make the high-energy collider not too huge or expensive also make for a good fit in a hospital campus," says Wuensch.

The building blocks adapted from CLIC for the FLASH therapy facility include high-gradient accelerating structures, suppression of beam instabilities, and a high-current photo-injector gun. Tests and simulations show that the design "will allow us to stably accelerate a lot of charge to get a high enough dose in a short time," says Wuensch. The beam will be accelerated to treatment energies in a bit more than a meter, he adds.

The Lausanne FLASH facility will use high-power microwave klystrons, which CLIC uses in tests but not in its final design. And specifications such as beam intensity, steering, and beam size are determined by the medical trial needs. The systems are similar, says Wuensch, "but to have hardware work with the reliability to treat human beings will cause some sleepless nights."

Jean Bourhis, head of CHUV radiation oncology, leads the medical side of the collaboration. He says the facility, including a building to house it, will cost around 30 million Swiss francs ($33 million). CHUV is raising funds for the facility, he says. He expects the new building and the machine to be ready by 2023 and clinical studies on deep-seated tumors to start soon thereafter. The facility is designed such that trial parameters can be varied, and it will be larger than what a future hospital machine might need. For wide adoption, a facility would have to be less variable and easier to use.

In the meantime, CHUV is conducting clinical trials on superficial tumors. "We are monitoring toxicity and tumor control and comparing FLASH to conventional radiation therapy for skin cancer," says Bourhis. In 2018 the CHUV team treated a single patient with FLASH with excellent results, he says. The patient had undergone conventional radiation therapy more than 100 times and suffered continued discomfort. A single FLASH dose cleared a lesion completely, as of five months posttherapy.

For CLIC physicists, the collaboration with CHUV is inspiring both for advancing medicine and having societal impact and for the attention it brings their accelerator project, says Wuensch. CLIC has been something of a stepchild at CERN for more than two decades, a neat project that gets ongoing research funding but no green light. In the recent European Strategy for Particle Physics (see PHYSICS TODAY, September 2020, page 26), the Future Circular Collider is a high priority, but if it proves too expensive or otherwise infeasible, plan B is CLIC.

The collaboration with CHUV, Wuensch says, could feed back into increased support for CLIC. What's more, he says, the collaboration "keeps and expands expertise in CLIC technology, and if everything goes well, clinical FLASH facilities could go into commercial production."

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