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## CANCER RADIOTHERAPY

# Radiotherapy 'flashes' to reduce side effects

**Treating hard and fast seems to be a good way to limit the side effects of radiotherapy. This is the discovery made by researchers at the Curie Institute, Inserm and the Vaud University Hospital, published in *Science Translational Medicine* on 16 July.**

**Radiotherapy remains one of the benchmark local treatments for cancer patients: increasingly accurate, it consists of irradiating cancer cells to destroy them while preserving neighbouring healthy tissues and organs as much as possible. By increasing the intensity of the irradiation 1,000 times over a very short time, the researchers have shown that the efficacy remains the same, but healthy tissues are better protected.**

"Eradicating the tumour, while limiting side effects, has always been the aim of radiotherapists", emphasises Vincent Favaudon, researcher at the Curie Institute. Radiotherapy is still one of the most effective approaches for treating cancers. It is offered to more than half of patients, combined with surgery and/or chemotherapy. For more than 20 years, developments in imaging, data processing, dosimetry and accelerators have made it possible to 'sculpt' the irradiation volume increasingly accurately, depending on the location and shape of the tumour. Despite everything, side effects due to irradiation of healthy tissues remains a crucial problem.

### An effect for each mode of administration

In collaboration with Marie-Catherine Vozenin (Inserm and Vaud University Hospital, Lausanne, Switzerland), the radiobiologist Vincent Favaudon, eminent Inserm Research Director, studied the effects of radiotherapy on healthy and tumorous tissues depending on its mode of administration. "The Curie Institute laboratories on the Orsay site has an experimental electron linear accelerator that can deliver high radiation doses in a very short time, as a flash", he explains. "To give an idea of scale, this accelerator delivers a radiation dose-rate 1,000 to 10,000 times more intense than conventional radiotherapy".

The researchers wondered if this modified the effects on the tissues. "In our tumour models, a conventionally-administered 15 Gy dose to treat a lung tumour certainly leads to the occurrence of a pulmonary fibrosis between 8 weeks and 6 months after irradiation, while when using a 'flash' irradiation no fibrosis appears below 20 Gy", explains the radiobiologist.

This protective effect was also observed on apoptosis (programmed cell death produced following unrepaired damage to the DNA), blood capillaries and skin lesions.

"On the other hand, anti-tumour efficacy remained the same on all the tumour models we tested", notes Marie-Catherine Vozenin, Inserm researcher and Head of the radiobiology laboratory in the Radio-oncology Department Vaud University Hospital. 'Flash' irradiation therefore protects healthy tissues very selectively from side effects arising.

"The equipment currently used in most radiotherapy departments, which operate using X-rays, is not efficient enough to generate the dose-rates needed for 'flash' irradiation. A major technological advance would be required to achieve it", continues Vincent Favaudon. "However, the 'Pencil Beam Scanning' system currently being installed at the Curie Institute Protontherapy Centre will be capable of such performance and the medical team, assisted by the researchers, is planning to undertake a pre-clinical trial very quickly".

**Pencil Beam soon at the Curie Institute Protontherapy Centre**

Since spring 2013, the Curie Institute Protontherapy Centre (Orsay) has been preparing to commission the technology known as 'Pencil Beam Scanning (PBS)', which will enable a proton beam to sweep over the tumour.
Installed in the treatment room with an isocentric arm - with which it is possible to orientate the beam around the patient depending on all effects - this cutting edge technology will enable the indications for protontherapy to be extended even further. "*In this way we will be able to treat new locations, particularly extra-cranial tumours with complex volumes, by ensuring very good conformation to the volume of the tumour while improving the protection of neighbouring healthy tissues and organs*", rejoices Dr Remi Dendale, the centre's medical director. "*This is what we call Intensity-Modulated Protontherapy or IMPT, which will enable us to simplify preparation of treatments, by avoiding the need to manufacture compensators (used to adjust dose distribution at depth) and some of the collimators (used to modulate the outline of energy distribution in the lateral plane)*", says physicist Nathalie Fournier-Bidoz.

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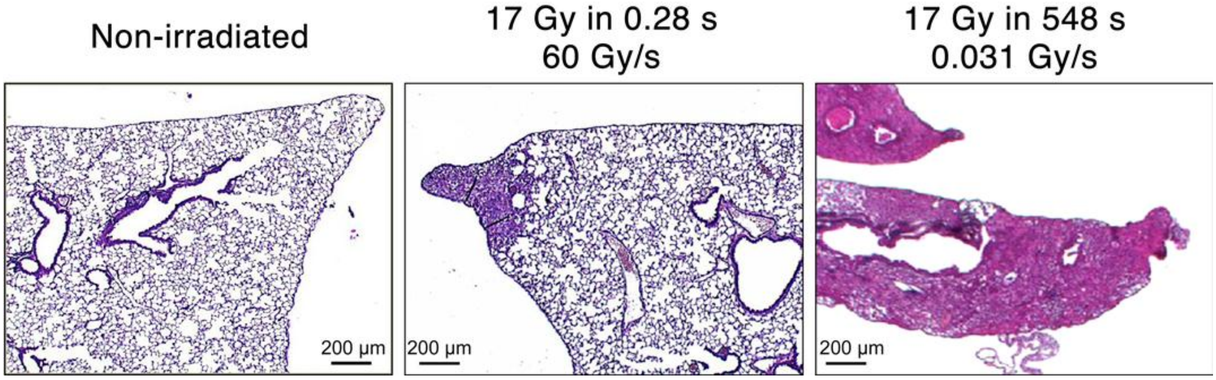
**<u>Images of tissue sections</u>**

Effect of irradiation with 17 Gy administered on 0.28 s on healthy lung tissue, equivalent to a dose-rate of 60 Gy/s (middle picture) and in 548 s, equivalent to a dose-rate of 0.031 Gy/s (right picture). Tissue irradiated with a very high dose-rate looks the same as non-irradiated tissue, while tissue irradiated at low dose-rate is completely altered.




## References

**Ultra-high dose-rate, FLASH irradiation increases the differential response between normal and tumour tissue in mice.**

Vincent Favaudon[1,2*], Laura Caplier[3], Virginie Monceau[4,5], Frédéric Pouzoulet[1,2], Mano Sayarath[1,2], Charles Fouillade[1,2], Marie-France Poupon[1,2], Isabel Brito[6,7], Philippe Hupé[6-9], Jean Bourhis[4,5,10], Janet Hall[1,2], Jean-Jacques Fontaine[3], Marie-Catherine Vozenin[4,5,10,11].

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