FLASH radiotherapy

What, how and why?

Ultra-high dose rate (FLASH) radiotherapy is a new way of treating tumours caused by cancer. Higher doses of radiotherapy are associated with trauma to the healthy tissue surrounding the tumour, whereas FLASH radiotherapy demonstrates a sparing effect of the healthy tissues without compromising the anti-tumour action. Dr Kristoffer Petersson at the Oxford Institute for Radiation Oncology, University of Oxford, along with collaborators Joseph D. Wilson, Ester M. Hammond and Geoff S. Higgins, review the available data on FLASH radiotherapy and its clinical potential in the treatment of cancer.

One in every two people in the UK born after 1960 is estimated to be diagnosed with some form of cancer during their lifetime. Radiotherapy (a non-invasive radiation treatment which damages and kills tumour cells) forms part of the treatment in 30-50% of these cases. Unfortunately, radiotherapy also damages the healthy tissue surrounding the tumour. Treatment success is dependent on delivering a high enough dose of radiation to destroy the tumour cells without causing severe trauma to the surrounding tissues. FLASH radiotherapy (FLASH-RT) is a new technique, involving treatment of tumours at ultra-high dose rates which actually reduces the trauma to normal tissue around the tumour, whilst equalling the anti-tumour effect of conventional dose rate radiotherapy (CONV-RT). However, very little is known about the mechanisms behind the FLASH effect.

Kristoffer Petersson and his colleagues at the Oxford Institute of Radiation Oncology, aim to better understand these mechanisms in the hope of bringing us closer to a successful implementation of FLASH technology in our radiotherapy clinics.

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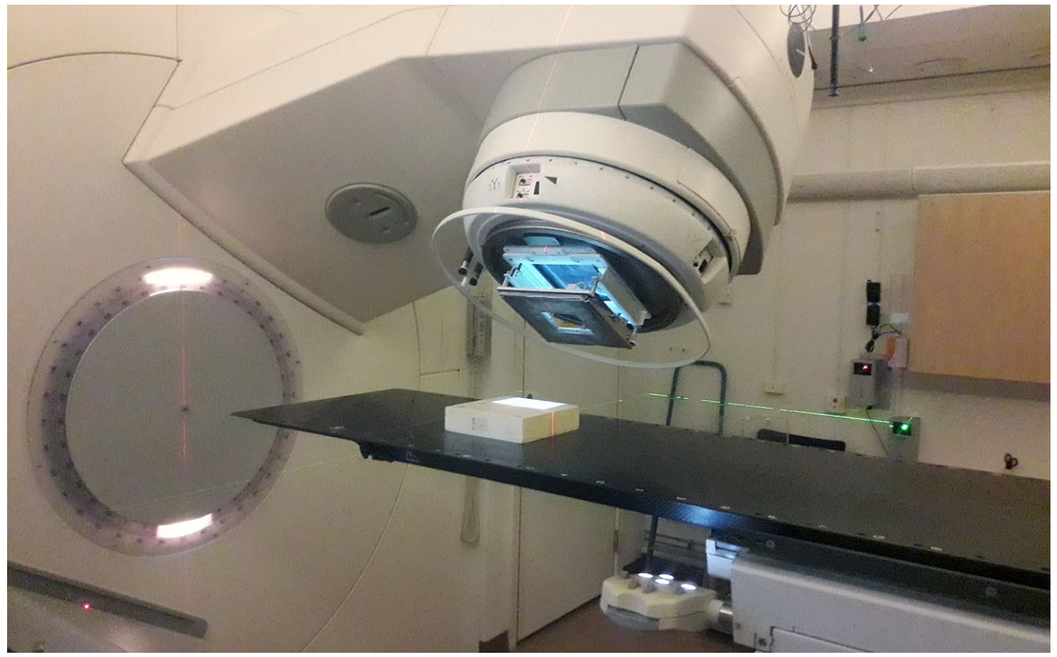
TISSUE TOXICITY

It was first noted in the 1960s that non-cancerous cells exposed to ultra-high dose rates of radiotherapy were more likely to be viable than those exposed to conventional dose rates. This has been more recently supported by studies in mice, one of which demonstrated much less lung damage in the chests of mice treated with FLASH-RT compared to those treated with CONV-RT. In another study, mice exposed to whole brain irradiation at conventional dose rates performed much worse in recognition tests compared to those treated at ultra-high dose rates. Radiation-induced skin reactions can include reddening and breakdown and have been shown to be much reduced in rodents being treated with FLASH-RT compared to CONV-RT. FLASH-RT also compared favourably in one study comparing the skin reaction of a mini-pig to different dose rates of radiotherapy. Another study involving treatment of nasal cancer in cats with FLASH-RT showed complete remission of tumours with minimal trauma to surrounding tissues.

ANTI-TUMOUR RESPONSE

Many studies demonstrate that in addition to reducing tissue toxicity, FLASH-RT also produces the same tumour response as CONV-RT. One such study compared mice with breast cancer and head and neck carcinoma grafts which had been exposed to either FLASH-RT or CONV-RT; there was no difference in treatment success between the two methods. In another study, mice were inoculated with cancer cells into their lungs, then later irradiated and CT-scanned to measure tumour size. The tumours of the mice treated with FLASH-RT were smaller than those treated with CONV-RT. There is therefore some evidence that FLASH-RT may even produce a superior anti-tumour response to CONV-RT.



Kristoffer Petersson's research lab aims to identify the mechanisms behind FLASH radiation, with a view to finding the optimum way of implementing the technique in clinical practice.

INFLUENCING FACTORS

There are multiple factors that could influence the FLASH effect, including dose rate, total dose, pulse rate, fractionation, and modality of radiation. The dose rate needed for the FLASH effect may also vary depending on the affected tissue and the delivery method. Many studies vary in the total dose of radiation used, or use doses unattainable in clinical scenarios, which complicate the findings. The source of the radiation is also a factor, as the FLASH effect has been mostly observed following the use of electron linear accelerators. More recently, the FLASH effect has also been seen following the use of proton and X-ray radiation. Pulsing the radiation at a high frequency can induce a FLASH effect, at a suitable dose-per-pulse. Further study is needed to confirm the key parameters for inducing the FLASH effect, as there are so many variables at play.

OXYGEN DEPLETION

Exactly why the FLASH effect occurs is not yet fully understood but has been hypothesised. Hypoxic tissues (tissues that are deprived of oxygen) are more resistant to radiation (and therefore less likely to become damaged) than well-oxygenated tissues. It is therefore thought that the difference in tissue toxicity between FLASH-RT and CONV-RT may be due to the level of hypoxia at ultra-high dose rates and subsequent radioresistance transferred to the irradiated tissue.

Researching the FLASH effect is of value to establish how it can be used in a clinical scenario to treat cancer patients.

IMMUNE MODIFICATION

Another proposed theory for the FLASH effect is a modified immune response – as it involves a shorter treatment time, less lymphocytes (white blood cells involved in the immune system) are affected by the radiation. One study reported less immune system activation in mice following FLASH-RT compared to CONV-RT. It should be noted that it is unclear if any immune response following FLASH-RT is contributing to the FLASH effect or caused by it. Other biological responses such as DNA damage and inflammation could also be contributing, and more studies are needed for clarification.

CLINICAL APPLICATIONS

Ultimately, researching the FLASH effect is of value to establish how it can be used in a clinical scenario to treat cancer patients. It could be used in the clinic to allow for an increase of total dose in the treatment of tumours resistant to radiation that are currently associated with worse patient outcomes, as a higher dose could be used without the associated surrounding tissue toxicity of CONV-RT. It could also be used in situations where radiotherapy offers good tumour control but is associated with tissue toxicity as the same dose

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FLASH radiotherapy demonstrates a sparing effect of the healthy tissues without compromising on anti-tumour action.

could be administered but with less toxicity than that of CONV-RT. The clinical viability of FLASH-RT in practice is complicated by inconsistencies, lack of clarity and limitations in the various studies performed. Some also do not have a control group irradiated with CONV-RT for comparison.

One human patient has been treated with FLASH-RT. He had an aggressive form of lymphoma and had previously been treated with CONV-RT which caused severe reactions to the skin surrounding the cancerous lesions and took months to heal. One lesion was successfully treated with FLASH-RT and had only mild redness and inflammation around the area treated. Although a promising outcome, this study only involved one patient and therefore allowed for limited comparison between the two methods of radiotherapy.

Electron linear accelerators have been the source of the radiation in most studies demonstrating a FLASH effect. Clinical linear accelerators can be modified to deliver FLASH-RT with electrons, which would allow for the translation into clinical trials. A limitation of this is the depth of tissue which can be treated, which is restricted to a few centimetres with these electron beams. A solution would be to use higher energy electron beams, which can have improved depth penetration. Using electromagnets, the beam can theoretically be focused to the volume of tumour, resulting in dose-to-target conformity with a single beam, comparable to that of modern X-ray techniques. A single beam delivery such as this may prove essential in producing the FLASH effect; however, these beams are currently exclusive to research accelerators which are either very great in size or associated with low pulse rate, small beam size, and stability issues.

The FLASH effect offers superior tissue protection in comparison to CONV-RT without compromising on tumour treatment.

One recent study demonstrated that X-ray tubes could potentially be used in FLASH-RT studies. These are small, relatively cheap and available in clinical practice. They are also limited by depth penetration to a few millimetres of tissue and only have a small beam size. Synchrotrons are a type of particle accelerator which are another potential source and have similar beam energies as X-ray tubes, as well as the possibility of using spatially fractionated ultra-high dose rate microbeam radiation therapy (MRT). The combination of MRT and the FLASH effect have been shown to achieve superior clinical effects in small animal models compared to conventional X-ray or CONV-RT dose rates in a range of cancers. Synchrotrons are of limited availability due to being very large and expensive.

PHASER (Pluridirectional High-energy Agile Scanning Electronic Radiotherapy) is another concept for using FLASH-RT in the clinic. Part of this is a technique involving image-guidance. Image-guidance techniques are necessary for clinical FLASH-RT treatment of deep tumours, regardless of the delivery mode used. The PHASER concept is still in development and relies on further advances in technology. A clinically available method of treating deep-seated tumours with FLASH-RT is to use proton beams, although they are both costly and sizeable. Clinical proton beams have good depth penetration and can produce accurate dose distributions with single or few beams. These are likely to be used in future clinical trials in FLASH-RT.

The FLASH effect offers superior tissue protection in comparison to CONV-RT without compromising on tumour treatment. It has been studied across various species and now a single human case has been documented. While its mechanism of action is likely to involve oxygen depletion, it is not fully understood and therefore requires further study. The doses required to achieve the FLASH effect make it unsuitable for many clinical cases. Furthermore, the availability of radiation sources capable of producing suitable beams for treatment of both superficial and deep tumours is a limiting factor in clinical trials. If further study yields more understanding of the biological mechanisms of the FLASH effect, it may be possible to achieve it at lower doses, increasing its clinical viability.

Behind the Research

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Research Objectives

Kristoffer Petersson's research lab aims to identify the mechanisms behind FLASH radiation, with a view to finding the optimum way of implementing the technique in clinical practice.

Detail

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Bio
A Medical Physicist from Helsingborg, Kristoffer Petersson completed his MSc in Sweden (2009) and PhD in Medical Radiation Physics, Lund University, Sweden (2014). Kristoffer carried out his postdoctoral research into FLASH radiation, CHUV, Switzerland (2014-2017). Following this, he led a research group in FLASH radiotherapy, Skåne University Hospital, Sweden. He has been a research group leader on FLASH radiation at the Oxford Institute for Radiation Oncology, University of Oxford since 2019.

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References

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Personal Response

What are the next steps in understanding more about the biological mechanisms of FLASH-RT?

"There are many studies that still need to be performed for us to better understand the biological mechanisms responsible for the highly beneficial FLASH sparing effect. In Oxford, we aim to perform real time oxygen concentration measurements in cells and in mice during FLASH irradiation, in order to verify (or discard) oxygen depletion as a main explanation of the effect. Most FLASH studies to date have been *in vivo* studies. For a better understanding of the biological mechanisms of FLASH-RT, several more specific *in vitro* studies are needed, for example investigating levels of DNA damage and DNA damage response."

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