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Editorial

FLASH radiotherapy International Workshop

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This issue of Radiotherapy & Oncology encloses original articles and review papers coming from presentations given at the second international workshop dedicated to FLASH radiation therapy (FLASH-RT). The meeting was organized at the CHUV University Hospital in Lausanne, Switzerland on the 12th and 13th of September 2018, in follow-up to the first workshop held at the Curie Institute, Orsay, France in 2016. Interestingly, this was the third meeting organized this year on FLASH-RT (one was held in April at the University of California – Irvine and another in August 2018 in Washington, DC by the RadioSurgery Society in conjunction with the NIH/NCI); these events show the strong interest generated by this recent exciting development in radiotherapy.

Despite major advances in high-precision treatment delivery, particle treatment, continued modality treatment and biomarker research including multimodal imaging, there is an unmet clinical need for further improvement. Still an important proportion of cancers are resistant to conventional radiation therapy warranting more effective and better tolerated treatments. However, opportunities to optimize the biological efficacy of radiation beams have probably been underexplored, and in this context, the first shared objective of the teams present at the workshop was to foster scientific knowledge to promote innovations in radiation therapy using FLASH-RT. The workshop was built around five sessions as well as round table discussions focusing on: dosimetry and medical physics, physico-chemistry, radiobiology, new accelerators, and clinical transfer.

FLASH-RT uses ultra-high dose rate irradiation produced by Linacs to deliver a single high dose of irradiation in a very short time (less than 200 milliseconds). The short duration of dose delivery was recently found to markedly modify the radiobiological response of tissues with an increase in the differential effect between tumors and normal tissues comparing single dose irradiations. In preclinical experiments, FLASH-RT is able to kill tumors while in experimental systems providing better protection for normal tissues and preventing side effects [1–7]. Biological results are reviewed in this issue of Radiotherapy & Oncology by Bourhis et al. [8]. Additional results are presented on tumor response to FLASH-RT as well as a case report describing the first treatment of a cancer patient with FLASH-RT [9]. Hypotheses regarding the possible radiochemical mechanisms respectively, namely the possible role of depletion of oxygen to organic hydroperoxides and lipid peroxidation are proposed by Spitz et al. [10]. Interestingly, the radioprotective benefit of ultra-high dose rate irradiation and its dependency on oxygen was already explored and validated in bacteria and cell models more than 40 years ago [11–15] and has been recently demonstrated in the brain of mice *in vivo* [16].

However, FLASH irradiation is still in its infancy and more work is clearly needed to narrow and understand the parameters relevant for the generation of the FLASH effect [17]. In this respect, researchers need to keep in mind that today the only relevant parameter that defines FLASH beam is the reduced toxicity at the normal tissue level at high single doses. Therefore, the physical definition of a given beam based on its ultra-high dose rate is not sufficient to characterize FLASH-beams, biological validations *in vivo* are mandatory. The so far presented studies compare mostly large single dose irradiations, whereas clinically fractionated irradiation is used to spare the normal tissue. Thorough studies comparing clinically relevant hypofractionated schemes with FLASH irradiation are necessary to determine the level of the potential therapeutic gain. Moreover, whether the physical parameters associated with a FLASH mediated sparing of healthy tissues in small volumes are the same as the ones needed for sparing healthy tissues in larger volumes remains to be studied. The ultimate goal of the teams present at the FLASH-RT Workshop is to translate this approach to the clinic. Beyond radiobiological benefits, further advantages might be associated with FLASH-RT, in particular the fact that ultra-fast irradiation is able to "freeze" organ and tumor motion, as authored by Maxim et al. in this issue [18].

To facilitate clinical translation, major physical and technological challenges remain to be solved. Issues related to dosimetry at ultra-high dose rates have been investigated and solutions have been found with passive dosimeters for accurate and reproducible dosimetry [19,20]. However, further improvements are needed to develop monitor chambers and treatment planning systems as discussed by Jorge et al. [21].

Another challenge is that very few devices can deliver ultra-high dose rate irradiation. Some have been designed for delivering ultra-high dose rates (above 40 Gy/s) and are operating on large volumes of tissue (100 cm^2 range) with electron beams (Kinetron and Oriatron Linacs, 4–6 MeV built by PMB-Alcen) [22]. Next to this, clinical Linacs can be converted into FLASH-machines as described in [23] and Petersson et al. [24] in this issue. However,

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the use of dedicated devices is currently restricted to experimental research or the treatment of very superficial tumors in a patient as reported by Bourhis et al. [9]. Therefore, optimization or development of a new generation of machines is required to readily deliver FLASH radiation to all cancer patients that may benefit.

Proton therapy beams can be modified and optimized to operate at ultra-high dose rate [25] and the main vendors are now racing to produce the first clinical Proton-FLASH device with relatively bold communication at radiation oncology meetings. However, with conventional planning and conventional spot-scanning machines FLASH dose rates were not achieved [26]. Moreover, in this issue, Beyreuther et al. [27] and Buonanno et al. [28] report contradictory data about biological evidences of a FLASH effect obtained with experimental Proton-FLASH beams. These discrepant results illustrate the need for more research and stress out the absolute necessity of defining FLASH-Beams using well defined physical parameters *combined* with their ability to produce the biological FLASH effect *in vivo*. Synchrotron facilities also operate at an ultra-high dose rate and are able to trigger the FLASH effect [4]. In this issue, Eling et al. [29] give an overview of the work performed by the teams working at the European synchrotron (ESRF) and discuss the possible dose rate limitation at synchrotrons as published earlier by Smyth et al [30]. Lastly, novel technologies of laser-plasma accelerated beams [31] as well as very high-energy electron (VHEE) and photon devices are being developed. Maxim et al. [18] provide the example of the PHASER project at Stanford University, USA, which is a treatment machine without any moving parts and pluri-directional delivery system. Other options can be proposed with a laser-plasma accelerated beam for VHEE and Proton, in which the magnetic focusing of the beam on the target might provide high conformality. These approaches are still in development and considered immature in terms of clinical transfer, but hold great promises for cancer cure in the future.

In summary, FLASH-RT appears as a promising new tool to improve differential effect between normal tissues and tumors and has potential to change the delivery of radiation therapy, with a potential significant impact on therapeutic outcome. This mandates further mechanistic inquiries and justifies promoting its rapid translation into clinical studies. However, this will necessitate tangible technological improvements for FLASH beam production and delivery.

Declaration of Competing Interest

The authors declare no conflict-of-interest.

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For the German Cancer Research Center (DKFZ, Heidelberg) Dr. Baumann is on the supervisory boards of HI-STEM gGmbH (Heidelberg).

Dr. Baumann, as former chair of OncoRay (Dresden) and present CEO and Scientific Chair of the German Cancer Research Center (DKFZ, Heidelberg), signed/signs contracts for his institute(s) and for the staff for research funding and/or collaborations with a multitude of companies worldwide.

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