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Commentary on the article: Sørensen BS et al., Pencil beam scanning proton FLASH maintains tumor control while normal tissue damage is reduced in a mouse model

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FLASH radiotherapy, in which radiation doses are delivered with ultrahigh dose rate, receives increasing attention, with the numbers of publications exponentially increasing since 2019. So far, the majority of the studies have investigated the FLASH normal tissue sparing effect. However, a solid biological [1] and physical [2] explanation is currently lacking. Furthermore, FLASH radiotherapy seems to have isotoxic effects on tumors, although based only on tumor regrowth and mouse survival data. Sørensen et al, investigated the effects of FLASH radiotherapy in C3H mouse mammary carcinoma bearing CDF1 mice, with tumor efficacy and normal tissue sparing as read-outs [3]. For the first time, the local tumor control assay as well as full dose–response curves were applied as endpoint enabling a proper comparison between FLASH and conventional dose rate effects. Results indicated similar effects on local tumor control, while preferential sparing of healthy tissue using FLASH radiotherapy [3], essentially confirming previous studies [1,4], but using clinically relevant endpoints [5]. The study has also been awarded as best abstract within the radiobiology track at ESTRO2022.

The combined assessment of tumor efficacy and early versus late radiation-induced normal tissue toxicities inherently shows the limitations of each experimental setup. Local tumor control studies require high radiation doses, which are usually too high to assess dose responses for early skin toxicities, especially for conventional dose rate experiments. Although in the current study no dose–response curves for conventional dose rate were available, the dose modifying factor for acute skin toxicity was estimated to be larger than 1.3 [3], similar as recently reported using a dedicated acute skin toxicity experimental setup [6]. Surprisingly, the dose modifying factor for late radiation-induced fibrosis, although a sparing effect of FLASH was found, was significantly smaller compared to that one for acute skin toxicity, although the majority of the animals which developed fibrosis also demonstrated acute skin toxicity. Others have shown a more prominent FLASH effect for late rather than for early endpoints [7]. A major difference between both studies is the animal model, as the C57BL/6J mouse strain has been used in the latter study, known to be prone to radiation-induced fibrosis [8].

Most data on FLASH so far have been focused on electron FLASH, although data with particle, i.e. proton and carbon ions, FLASH are emerging [9]. Particle therapy has superior dose distributions allowing higher dose escalation to the tumor, while optimally sparing adjacent normal tissues [10]. So why combining particle therapy with FLASH radiotherapy? As quoted by Prof. Durante during the ESTRO2022 Radiobiology FLASH debate: "The chance to win a horse race is larger when you do this race with a horse and its rider" [11]. Currently the majority of preclinical studies, including the current study, apply a particle shoot-through principle, i.e. carrying out the experiment in the entrance region of the beam, due to difficulties of positioning the Bragg peak inside small animals [2,7,12]. Essentially, all tissue in the beam path receive the same dose, but due to the FLASH protective effect, normal tissues will be spared from a biological point of view [2]. On the other hand, a relatively low LET is found in the entrance region of particle beams. Therefore it would be interesting to investigate to what extent LET, and therefore RBE, influences the FLASH effect. At the level of the tumor, one would expect enhanced tumor efficacy when irradiating in the spread-out Bragg Peak (SOBP) compared to the entrance region of the FLASH particle beam, due to the higher RBE. For surrounding normal tissues, FLASH is expected to preserve tissues better compared to conventional particle irradiation. A recent study did not observe differences in tumor regrowth between SOBP and entrance region irrespective of the treatment modality [13]. It would be especially interesting to investigate the extent of sparing in the distal edge, having the highest LET [14].

Overall, data show that FLASH dose rate in the entrance region results in similar tumor control compared to conventional dose rate, but resulted in reduced early and late normal tissue damage, confirming previous studies, but using clinically relevant endpoints. How an increased RBE influences the FLASH effect is yet to be established. Interestingly, a recent phase III clinical trial with cats suffering from locally advanced squamous cell carcinoma of the nasal planum had, although complete remission was achieved in the majority of the pets, to be prematurely terminated because of a grade 3 late toxicity during follow-up after single high dose

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FLASH radiotherapy [15]. In the same study, in a mini pig model of skin toxicity, late toxicity effects were found to occur in a volume dependent manner. Therefore, implementation of single high dose and larger field FLASH irradiations should be, considering the possibility of the shoot-through principle, done carefully.

Conflict of interest statement

The author declares no conflict of interest.

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