

## FLASH Radiotherapy: History and Future

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1 Radiotherapy is required by 60–70% of cancer patients during their treatment (1). Radiotherapy is the most  
2 widely used and effective anti-tumor therapy (2), but it can cause acute and late damage to healthy tissues. The  
3 dose delivered to the tumor is, hence, limited by the toxicity to nearby healthy tissue; this can mean that a tumor  
4 cannot be completely killed, and the efficacy of radiotherapy will be decreased. Thus, preventing or mitigating  
5 radiation-induced healthy tissue injury has always been a topic of particular interest in radiotherapy research.  
6 Modern radiotherapy technologies, such as intensity-modulated radiation therapy (IMRT), helical tomotherapy  
7 (HT), and proton radiotherapy can reduce radiation damage to healthy tissues. For example, IMRT reduces the  
8 incidence of grade 2–4 xerostomia in patients with head and neck cancers without compromising loco-regional  
9 control and overall survival (3). HT can also reduce the incidence of skin toxicity in breast cancer patients (4).  
10 The advantage of proton radiotherapy is that most of the energy is transferred to the position of the “Bragg  
11 peak,” and energy transfer outside of this point is very low (5). Thus, the radiation damage to healthy tissues  
12 outside the Bragg peak is relatively small, and proton therapy causes less radiation damage to healthy tissues  
13 than photon therapy when treating head and neck cancers, prostate cancer, and pediatric cancer, among others  
14 (6–8).

15  
16 FLASH radiotherapy (FLASH-RT) is a novel radiotherapy technology defined as a single ultra-high dose-rate ( $\geq 40$   
17 Gy/s) radiotherapy. Compared with conventional dose-rate irradiation, FLASH irradiation is 400-fold more rapid  
18 than conventional irradiation (Figure 1). Recent animal experiments have shown that FLASH-RT can reduce  
19 radiation-induced damage in healthy tissues (9). In the first patient with T-cell cutaneous lymphoma who  
20 received FLASH-RT, the anti-tumor effect was rapid and long-lasting; moreover, only grade 1 epithelitis and  
21 grade 1 edema occurred in the soft tissues surrounding the tumor (10). In this first clinical use of FLASH-RT, the  
22 treatment time was only 90 ms. Compared with conventional dose-rate radiotherapy, the very short  
23 radiotherapy time is another advantage of FLASH-RT. Considering that FLASH-RT can reduce the damage to  
24 healthy tissue and the advantages of the short treatment time, we have reason to predict that FLASH  
25 radiotherapy may become one of the main radiotherapy technologies in clinical practice in the future.

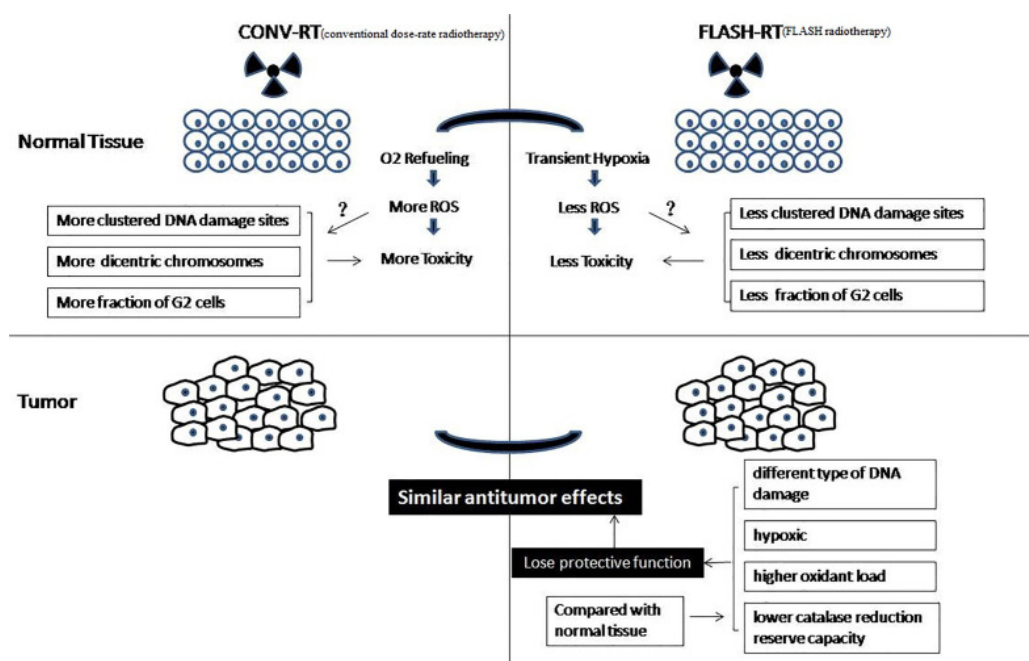
26  
27 In this paper, we summarize the history of development of FLASH-RT, its mechanism, its influence on  
28 radiotherapy, and its future.

### 30 History of FLASH-RT

31 Before 2014, FLASH-RT was referred to as the flash effect, which was first reported by Dewey and Boag in 1959.  
32 Ultra-high dose-rate 1.5-MV X-rays were used to irradiate a bacterium, *Serratia marcescens* (11). This study  
33 showed that *S. marcescens* in a nitrogen-oxygen mixture containing 1% oxygen is more radiosensitive than when  
34 in 100% nitrogen with normal dose-rate irradiation (1000 rads/min). However, when the ultra-high dose-rate  
35 (10–20 kilorads/2  $\mu$ s) was used, *S. marcescens* in the same nitrogen-oxygen mixture showed lower  
36 radiosensitivity, corresponding to anaerobic irradiation. In summary, Dewey and Boag’s study outlined that  
37 ultra-high dose-rate irradiation can protect bacteria when compared to conventional dose-rate irradiation.  
38 Similar results were observed in mammalian cells in later studies. Town reported that when mammalian cells  
39 received the same dose ultra-high dose-rate ( $3.5 \times 10^9$  rad/s) irradiation, and the dose reached up to 1000 rads,  
40 one pulse had a higher survival rate than two pulses (12). Berry et al. showed similar results in hamster cells and  
41 HeLa cells using ultra-high dose-rate (1,000 rads for the 15-ns pulse) irradiation (13). A series of experiments  
42 showed that the flash effect is related to oxygen consumption (14–18). In 2014, Favaudon reported that using  
43 FLASH-RT to treat lung tumors can lead to a complete response and reduce the early and late toxicity affecting  
44 normal lung tissue; subsequently, FLASH-RT has become a topic of particular interest in radiation research (19).  
45 A series of studies have shown that FLASH-RT delivers dramatically reduced adverse side effects in the healthy  
46 tissue of mice (20–26), and this effect was greater in mini-pig and cat (27). Finally, a T-cell cutaneous lymphoma  
47 human patient received FLASH-RT, and long-lasting complete tumor response was achieved with fewer side  
48 effects than those expected with conventional radiotherapy (10). (...)

52 **Mechanism of FLASH-RT**

53 The biological mechanism of FLASH-RT is very complex (Figure 2). Dewey and Boag first reported the effects of  
 54 ultra-high dose-rate, which showed that hypoxia<sup>1</sup> was induced following high dose-rate radiotherapy of bacteria  
 55 (11). This phenomenon can be explained by local oxygen consumption because the rapid deposition of radiation  
 56 energy occurs too fast to maintain sufficient oxygenation levels. A series of studies have shown that ultra-high  
 57 dose-rate irradiation can induce the protection of mammalian cells through transient hypoxia (including cancer  
 58 cells) (14–18). A recent study showed that hyperoxia<sup>2</sup> can eliminate flash effects in mice (33). Another theory is  
 59 that the number of DNA damage sites in FLASH-RT is less than that following conventional dose-rate irradiation.  
 60 Some authors have shown that FLASH-RT causes fewer dicentric chromosomes to be formed than conventional  
 61 dose-rate irradiation, and there was a difference in G<sub>2</sub><sup>3</sup> cell cycle arrest after FLASH-RT and conventional dose-  
 62 rate irradiation (34–37). Another study showed that radiation with short pulses leads to fewer late side effects  
 63 in healthy tissue than conventional dose-rate irradiation (38). Recently, Kim et al. showed that myosin light chain  
 64 activation plays an important role in the separation of biological effects between FLASH-RT and conventional  
 65 dose-rate irradiation (39).  
 66  
 67



68 However, those studies did not demonstrate the same protective effect between healthy and tumor tissues *in*  
 69 *vivo*. In *vivo*, FLASH-RT leads to differential responses between healthy and tumor tissues. Compared with  
 70 conventional dose-rate irradiation, FLASH-RT can reduce radiation-induced lung fibrosis and has the same  
 71 antitumor effectiveness in mice (19). Why are there differential responses between healthy and tumor tissues *in*  
 72 *vivo*? A theory is that the different types of DNA damage caused by FLASH-RT and conventional dose-rate  
 73 irradiation result in the differential responses of healthy and tumor tissue (33, 40, 41). Another theory is that  
 74 solid tumors are hypoxic<sup>4</sup>, so they will not be protected from the transient hypoxia caused by FLASH-RT, while  
 75 healthy tissues will be, resulting in the differential effect (23, 33). In addition, some authors believe that cancer  
 76 cells and normal cells have different abilities to scavenge hydrogen peroxide products. FLASH-RT instantaneously  
 77

<sup>1</sup> **Hypoxia** is a condition in which the body or a region of the body is deprived of adequate oxygen supply at the tissue level.

<sup>2</sup> **Hyperoxia** occurs when cells, tissues and organs are exposed to an excess supply of oxygen (O<sub>2</sub>) or higher than normal partial pressure of oxygen.

<sup>3</sup> **G<sub>2</sub> phase, Gap 2 phase, or Growth 2 phase**, is the third subphase of interphase in the cell cycle directly preceding mitosis. It follows the successful completion of S phase, during which the cell's DNA is replicated. G<sub>2</sub> phase ends with the onset of prophase, the first phase of mitosis in which the cell's chromatin condenses into chromosomes.

<sup>4</sup> **Hypoxic:** caused by not enough oxygen being available to the blood and body tissues. **Nota:** *Hipóxia tumoral é a situação em que as células tumorais foram privadas de oxigênio. À medida que um tumor cresce, ele rapidamente supera seu suprimento sanguíneo, deixando porções do tumor com regiões onde a concentração de oxigênio é significativamente menor do que em tecidos saudáveis.*

78 consumes oxygen in all local tissues and produces hydrogen peroxide products. Healthy tissue cells have a lower  
79 oxidant load and higher catalase reduction reserve capacity; therefore, healthy tissue can remove hydrogen  
80 peroxide products more easily than tumor tissue (42).

81 In general, previous studies have agreed that FLASH-RT leads to local oxygen consumption that is much faster  
82 than tissue oxygenation, which results in transient radiation-induced hypoxia. Interestingly, some researchers  
83 believed that FLASH-RT using carbon ions would improve therapeutic ratio with greater toxicity in the tumor  
84 due to the generation of oxygen at the spread-out Bragg peak (43). Hence, the mechanism behind the  
85 differential responses of healthy and tumor tissues remains unclear and the various explanatory hypotheses  
86 require more experimental verification (44).

87

### 88 **Influence on Radiotherapy**

89 FLASH-RT might potentially change the theories of radiobiology as follows. The first change may be in the five  
90 Rs of radiobiology: DNA repair, reoxygenation, repopulation, redistribution, and intrinsic radiosensitivity (45).

91 The delivery time of FLASH-RT is too short for reoxygenation, repopulation, and redistribution to occur, or  
92 reoxygenation, repopulation, and redistribution may occur but cannot influence the effect of radiotherapy

93 because FLASH-RT is performed only once. Therefore, FLASH-RT may be related to two Rs: DNA repair and  
94 intrinsic radiosensitivity. The second change may be the limit dose of healthy tissue because preclinical studies

95 have confirmed that compared with conventional dose-rate irradiation, FLASH-RT needs a higher dose to cause  
96 the same degree of toxicity. As a result, when healthy tissue is irradiated in FLASH-RT, its  $\alpha/\beta$  value will change.

97 Conventional dose-rate irradiation (15 Gy) triggers lung fibrosis, but higher dose FLASH-RT (20 Gy) does not  
98 cause lung fibrosis after 36 weeks. Regarding skin toxicity, both 20 Gy and 15 Gy FLASH-RT do not exhibit

99 macroscopic signs of cutaneous lesions, but 17-Gy conventional dose-rate irradiation can lead to severe  
100 cutaneous lesions within the irradiated field (19). Compared with conventional dose-rate radiotherapy, FLASH-

101 RT also shows protective effects in other healthy tissues, including the brain and digestive tract  
102 (9, 16, 20, 21, 27, 46, 47). A series of animal experiments have shown that the tolerance of healthy tissues is

103 increased; thus, when FLASH-RT is used, the  $\alpha/\beta$  value of healthy tissues will differ from the current value using  
104 in conventional dose-rate irradiation. The third potential change is the comprehensive treatment strategy. For

105 example, how can radiotherapy be combined with chemotherapy? Because FLASH-RT is performed only once  
106 for a very short time, concurrent chemoradiotherapy is not possible; only neoadjuvant and adjuvant

107 chemotherapy can be administered. The fourth change may be the fraction of radiotherapy. If FLASH-RT  
108 technology is used in clinical practice and gradually develops, single fraction radiotherapy will be widely used to

109 replace the current multiple fractions of radiotherapy.

110 (...)

**1. Mark True or False. According to the author, as stated in the text (lines 1 – 14):**

- ( ) Tumors cannot be killed completely because they are intrinsically radioresistant.
- ( ) 60-70% of radiotherapy cancer patients will exhibit acute dose toxicity.
- ( ) The efficacy of the tumor control is limited by the damage to adjacent healthy tissue.
- ( ) Modern technologies such as IMRT are more efficient because they use higher energy.
- ( ) In FLASH, no tumor cannot be completely killed due to the timescale of the treatment.

FFVFF

**2. Mark True or False. The FLASH technology is:**

- ( ) A novel technology that delivers a very high dose in a very short time.
- ( ) A technology that delivers the same dose 400 times faster to the tumor.
- ( ) A standard technology used commercially since 2014.
- ( ) A technology where no radiation-toxic side-effects occur.
- ( ) A technology where the energy is the key difference to other techniques.

VVFFF

**3. Analyze the statements and mark the correct option. It is correct to say, according to the author (lines 31-48), that:**

- I. The FLASH effect was observed by Dewey and Boag bacteria irradiated with the same dose at very high dose rates are less radiation-sensitive when compared to normal dose rate irradiations (1000 rads/min).
  - II. When mammalian cells are irradiated, a lower irradiation time used to deliver the same dose results in a higher survival rate.
  - III. The flash effect has a relation to the consumption of oxygen.
- a) Only I is True.
  - b) Only I and II are True.
  - c) Only III is True.
  - d) All affirmatives are True.

**4. It is correct to say, according to the author (lines 52-65), that:**

- a) Dewey and Boag showed that the FLASH effect is characterized by the consumption of oxygen that reduces the radiation damage to normal cells.
- b) Both hypoxia and radiation effects combine to enhance the damage to cells.
- c) By exposing mice to excess oxygen and high dose rates, the flash effect will be enhanced.
- d) FLASH has a disadvantage of higher late side effects.

**5. It is CORRECT to say, according to the theories discussed by the author (lines 69-86), that, in-vivo FLASH-RT results in higher differences between healthy and tumor tissue, when compared to conventional radiotherapy (RT) because:**

- a) Solid tumors are already naturally deprived of oxygen, therefore the hypoxia produced by FLASH will have no effect on these cells.
- b) The DNA of tumor and healthy cells are different.
- c) Cell cycles have different rates for tumor and healthy cells.
- d) tumor tissue can consume hydrogen peroxide products more easily than healthy tissue.

**6. In Lines 81-86 the author show that the mechanism behind FLASH-RT is:**

- a) well established and understood.
- b) related to the consumption of oxygen that results in hypoxia to the cells.
- c) related to the production of free oxygen at a higher rate than cell production.
- d) related to radiation interaction with carbon in cells.

**7. According to Section "Influence on Radiotherapy" lines 88-109:**

- a) Radiation biology is currently sufficient to understand the mechanism behind FLASH-RT.
- b) There is evidence that DNA repair, reoxygenation, repopulation, redistribution, and intrinsic radiosensitivity does not apply to pulses in the FLASH timescale.
- c) Doses in FLASH must be higher to achieve the same level of radiation damage.
- d) DNA repair and intrinsic radiosensitivity do not apply for FLASH.

8. In “The second change may be the limit dose of healthy tissue because preclinical studies have confirmed that compared with conventional dose-rate irradiation, FLASH-RT needs a higher dose to cause the same degree of toxicity.”, the “limit dose” is:
- a) The minimum dose required for tumor control.
  - b) The maximum dose that occurs in a planned treatment.
  - c) The dose above which undesired effects occurs in healthy tissues.
  - d) The treatment dose.
9. Compared with conventional dose-rate radiotherapy (RT), FLASH-RT shows:
- a) Better protective effects for healthy tissue.
  - b) Higher toxicity for healthy tissue.
  - c) A lower tolerance dose for brain and digestive cells.
  - d) The need of using higher energies to achieve an appropriate therapeutic ratio.
10. According to the author, how probable is that FLASH-RT will become a reality?
- a) Totally possible, with all technological difficulties already addressed.
  - b) Highly possible, with various experts working together to overcome various difficulties.
  - c) Improbable, because costs are too high.
  - d) Highly improbable because the issues needed to be overcome require physics not yet available.