Radiation Oncology at Light Speed: The Rise of FLASH Radiotherapy

In a darkened lab in 1895, Wilhelm Röntgen captured the first image of human bone using invisible rays, effectively discovering the x-ray.[1] Soon after, scientists realized that x-rays could damage live tissue and within three short years, radiation was being used to treat cancer.[1,2] This marked the beginning of radiation therapy and changed the trajectory of cancer treatment forever. Today, there are 20 million new cancer cases annually and radiation therapy plays an integral role in the treatment of 60% of patients.[3,4] Its role is often curative for localized cancers of the blood (lymphoma), brain, head and neck, lung, breast, cervix and prostate, among others.[5,6] Radiation therapy is also critical in palliative care, helping to relieve symptoms of metastatic disease including painful bone metastases, compression of structures and bleeding control.[7] By examining the progression of radiotherapy techniques, this essay highlights FLASH radiotherapy as a transformative technique that could redefine cancer treatment through its unique biological effects and clinical potential.

Today, conventional radiotherapy methods include external beam radiation therapy (EBRT), a non-invasive approach that delivers beams of radiation from an external source, typically a linear accelerator, to treat cancers inside the body.[6] Historical advances within EBRT include three-dimensional conformal radiation therapy, which integrates computed tomography imaging to shape radiation beams to the contours of the tumor, improving dose delivery while sparing healthy tissue.[7] Intensity-modulated radiation therapy marked another major step forward by enabling the modulation of radiation beam intensity across different areas of the treatment field, allowing for even more precise targeting of tumors and improved sparing of nearby organs at risk.[4,7,8] Stereotactic body radiation therapy delivers very high doses of radiation over a small number of treatment sessions (hypofractionation), offering high local tumor control for selected tumors with minimal exposure to surrounding tissues.[7] Proton therapy represents another significant advance by taking advantage of the Bragg peak phenomenon, which allows protons to deposit the majority of their energy at a specific depth, minimizing exit dose and reducing toxicity to healthy tissues beyond the tumor.[4] These modern approaches reflect the ongoing goal in radiation oncology, to maximize tumor control while minimizing damage to healthy tissue.[4] Despite these advances, achieving this balance remains a central challenge in the field today.[4]

Enter FLASH radiotherapy, a promising new approach aimed at overcoming some of the biggest challenges in radiation therapy, particularly minimizing damage to healthy tissue. FLASH radiotherapy is defined as irradiation at an ultra-high dose rate of ≥40 gray (Gy) per second, where 1 Gy represents 1 joule of radiation energy absorbed per kilogram of tissue.[4] In comparison, conventional radiotherapy typically delivers radiation at 1 to 6 Gy per minute, making FLASH radiotherapy an average of 600 times faster in dose delivery.[9] When radiation is delivered this rapidly, a biological phenomenon known as the FLASH effect has been observed.[4] This is a differential tissue response in which healthy tissue appears to be spared, while tumor control is maintained.[4,10] The earliest observation of this effect dates back over 50 years to a

study by Dewey and Boag, who found decreased radiosensitivity and possible protective effect in *Serratia marcescens* bacteria irradiated with high-dose-rate compared to lower-dose-rate X-rays.[11] The first modern preclinical demonstration of FLASH radiotherapy was in 2014 by Favaudon et al., who treated mice with lung tumors using ultra-high dose rate radiotherapy.[12] This study showed complete tumor control while preventing pneumonitis and fibrosis in FLASH treated mice, whereas these adverse effects were seen in all mice treated with conventional radiotherapy. Since then, additional studies on mouse brain, intestine, skin, and limbs, as well as cat and mini-pig skin have been conducted with favorable outcomes.[13,14,15,16] The mechanisms behind how the FLASH effect occurs is not fully understood. One leading hypothesis is that FLASH irradiation rapidly consumes local oxygen, creating transient hypoxia.[4,9] In healthy, well-oxygenated tissue, this limits the oxygen fixation of DNA damage, meaning there is less oxygen available to bind to radiation-induced DNA radicals and make permanent DNA damage.[17] As a result, DNA damage is less severe and more repairable, leading to reduced toxicity.[17] However, because solid tumors are often already hypoxic, they may not gain the same benefit from transient hypoxia.[4]

In 2019, the first-in-human demonstration of technical feasibility and early clinical safety of FLASH radiotherapy was performed.[9] A 75-year-old man with treatment-resistant CD30+ cutaneous T-cell lymphoma and widespread skin involvement was treated with 15 Gy in 90 milliseconds using electron FLASH radiotherapy.[9] The results were promising as he developed only grade 1 epithelitis and transient edema, with no high-grade toxicity, while achieving a complete tumor response, durable for the 6 months follow-up period.[9] In 2022, the first formal clinical trial of proton FLASH radiotherapy was published.[18] The FAST-01 non-randomized trial enrolled 10 patients with painful bone metastases in the extremities, delivering 8 Gy in a single fraction at a nominal dose rate of 60 Gy/s.[18] Across 12 treatment sites, no serious adverse events were reported.[18] Only mild side effects occurred, including mild hyperpigmentation and pruritus.[18] Importantly, no fibrosis, vascular changes, or late toxicities were observed.[18] Complete or partial pain relief was reported at 8 of 12 sites, with an overall response rate of 66.7%, comparable to conventional radiotherapy.[18,19] These early results are exciting for the prospects of FLASH radiotherapy, demonstrating initial clinical feasibility and short-term safety.[18] However, limitations of this study include small sample size, restriction to extremity sites, and short follow-up (median 4.8 months). This means long-term safety and safety in treating tumors near critical organ sites remain unknown. Furthermore, there were no comparator groups, making it difficult to contextualize the outcomes against those of established radiotherapy treatments. Importantly, the study utilized proton FLASH radiotherapy without capitalizing on the Bragg peak, raising the question of whether the FLASH effect alone outweighs the loss of Bragg peak precision. If technologies can successfully integrate the Bragg peak into FLASH delivery, it may unlock the full therapeutic potential of proton FLASH radiotherapy.

Flash forward to today, the mechanism behind the FLASH effect remains complex and not yet fully understood. Thus, there is a need for further basic science research. Since the FLASH effect is highly tissue-dependent, further research should prioritize in vivo studies using animal models or advanced ex-vivo systems like human organoids.[20,21] A key gap in current knowledge is whether FLASH causes differential DNA damage compared to conventional radiation, specifically with regards to double-stranded DNA damage.[20,21] Investigating molecular markers like γ-H2AX, 53BP1 and Rad51 could provide critical insight into mechanisms of DNA damage and repair that are unique to FLASH radiotherapy. More large-scale human clinical trials are also essential for confirming the FLASH effect in patients, establishing the dose thresholds needed for effective tumor control with minimal side effects, and assessing both acute and long-term toxicities across different cancer types and treatment sites. Furthermore, it remains unclear whether fractionation can be effectively integrated into FLASH radiotherapy. A preclinical study investigating hypofractionated FLASH radiotherapy in glioblastoma-bearing mice has shown promising results that demonstrate comparable overall survival and tumor control to conventional radiotherapy.[22] However, clinical trials in humans are still needed to confirm whether the FLASH effect can be preserved across fractionated treatment regimens. Finally, despite current technological limitations, future comparative studies should aim to standardize variables such as particle type (electrons, photons, or protons) and field geometry to enable accurate comparisons. FLASH radiotherapy remains in the very early stages of clinical development, but it represents a promising frontier in radiation oncology.

Just as Röntgen's chance discovery of invisible rays in a darkened lab sparked a new era in medicine, today's researchers are once again reshaping the landscape of cancer care. As science continues to push the limits, the future of radiation oncology holds exciting and hopeful possibilities for safer and more effective therapies.

Citations

1. Tubiana M. Wilhelm Conrad Röntgen and the discovery of X-rays. Bull Acad Natl Med 1996;180:97–108.
2. History of cancer treatments: radiation therapy. N.d. https://www.cancer.org/cancer/understanding-cancer/history-of-cancer/cancer-treatment-radiation.html (accessed April 12, 2025).
3. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clinicians 2024;74:229–63. https://doi.org/10.3322/caac.21834.
4. Lin B, Gao F, Yang Y, Wu D, Zhang Y, Feng G, et al. FLASH radiotherapy: history and future. Front Oncol 2021;11. https://doi.org/10.3389/fonc.2021.644400.
5. Baskar R, Lee KA, Yeo R, Yeoh K-W. Cancer and radiation therapy: current advances and future directions. Int J Med Sci 2012;9:193–9. https://doi.org/10.7150/ijms.3635.

6. Jaffray DA, Gospodarowicz MK. Radiation therapy for cancer. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Cancer: Disease Control Priorities, Third Edition (Volume 3), Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2015.
7. Abshire D, Lang MK. The evolution of radiation therapy in treating cancer. Seminars in Oncology Nursing 2018;34:151–7. https://doi.org/10.1016/j.soncn.2018.03.006.
8. Taylor A, Powell MEB. Intensity-modulated radiotherapy—what is it? Cancer Imaging 2004;4:68–73. https://doi.org/10.1102/1470-7330.2004.0003.
9. Bourhis J, Sozzi WJ, Jorge PG, Gaide O, Bailat C, Duclos F, et al. Treatment of a first patient with FLASH-radiotherapy. Radiotherapy and Oncology 2019;139:18–22. https://doi.org/10.1016/j.radonc.2019.06.019.
10. Montay-Gruel P, Acharya MM, Petersson K, Alikhani L, Yakkala C, Allen BD, et al. Long-term neurocognitive benefits of FLASH radiotherapy driven by reduced reactive oxygen species. Proc Natl Acad Sci USA 2019;116:10943–51. https://doi.org/10.1073/pnas.1901777116.
11. Dewey DL, Boag JW. Modification of the oxygen effect when bacteria are given large pulses of radiation. Nature 1959;183:1450–1. https://doi.org/10.1038/1831450a0.
12. Favaudon V, Caplier L, Monceau V, Pouzoulet F, Sayarath M, Fouillade C, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med 2014;6:245ra93. https://doi.org/10.1126/scitranslmed.3008973.
13. Montay-Gruel P, Petersson K, Jaccard M, Boivin G, Germond J-F, Petit B, et al. Irradiation in a flash: unique sparing of memory in mice after whole brain irradiation with dose rates above 100Gy/s. Radiother Oncol 2017;124:365–9. https://doi.org/10.1016/j.radonc.2017.05.003.
14. Loo BW, Schuler E, Lartey FM, Rafat M, King GJ, Trovati S, et al. (P003) Delivery of ultra-rapid flash radiation therapy and demonstration of normal tissue sparing after abdominal irradiation of mice. Int J Radiat Oncol Biol Phys. 2017;98:E16. https://doi.org/10.1016/j.ijrobp.2017.02.101.
15. Cunningham S, McCauley S, Vairamani K, Speth J, Girdhani S, Abel E, et al. FLASH proton pencil beam scanning irradiation minimizes radiation-induced leg contracture and skin toxicity in mice. Cancers (Basel) 2021;13:1012. https://doi.org/10.3390/cancers13051012.
16. Vozenin M-C, De Fornel P, Petersson K, Favaudon V, Jaccard M, Germond J-F, et al. The advantage of FLASH radiotherapy confirmed in mini-pig and cat-cancer patients. Clin Cancer Res 2019;25:35–42. https://doi.org/10.1158/1078-0432.CCR-17-3375.
17. Grimes DR, Partridge M. A mechanistic investigation of the oxygen fixation hypothesis and oxygen enhancement ratio. Biomed Phys Eng Express 2015;1:045209. https://doi.org/10.1088/2057-1976/1/4/045209.

18. Mascia AE, Daugherty EC, Zhang Y, Lee E, Xiao Z, Sertorio M, et al. Proton FLASH radiotherapy for the treatment of symptomatic bone metastases: The FAST-01 Nonrandomized Trial. JAMA Oncol 2023;9:62–9. https://doi.org/10.1001/jamaoncol.2022.5843.
19. Hartsell WF, Scott CB, Bruner DW, Scarantino CW, Ivker RA, Roach M, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst 2005;97:798–804. https://doi.org/10.1093/jnci/dji139.
20. Hughes JR, Parsons JL. FLASH radiotherapy: current knowledge and future insights using proton-beam therapy. Int J Mol Sci 2020;21:6492. https://doi.org/10.3390/ijms21186492
21. Borghini A, Labate L, Piccinini S, Panaino CMV, Andreassi MG, Gizzi LA. FLASH radiotherapy: expectations, challenges, and current knowledge. Int J Mol Sci 2024;25: 2546. https://doi.org/10.3390/ijms25052546
22. Montay-Gruel P, Acharya MM, Jorge PG, Petit B, Petridis IG, Fuchs P, et al. Hypofractionated FLASH-RT as an effective treatment against glioblastoma that reduces neurocognitive side effects in mice. Clin Cancer Res 2021;27:775-784. https://doi.org/10.1158/1078-0432.CCR-20-0894