FLASH Radiotherapy:
Workflow, Safety, and Future Readiness

11th International & 30th Annual Conference of Association of Radiation Therapists and Technologists of India
(ARTTICON - 2026)

Prakash Umbarkar

M.Sc. (Physics), PGDRTT

Scientific Officer – Sr. Radiation Therapist

P. D. Hinduja Hospital and Medical Research Centre Mumbai-India

Email: umbarkarprakash@gmail.com

HINDUJA HOSPITAL

LIVE TO GIVE HOPE

Introduction.....

- The goal of radiotherapy is to deliver **high doses to the tumour** while **minimising damage to normal tissues.**

- Over the last decade, advances in **IMRT, IGRT, ART, and proton therapy** have improved **patient outcomes** and **reduced toxicity**.

- However, some tumours remain **resistant to radiotherapy**, while **normal-tissue tolerance** limits further dose escalation—creating a **major clinical need.**

- Therefore, **novel approaches** are needed to further **optimise radiotherapy**.

"What novel approach?"

*Need for novel approaches to widen the therapeutic window—such as **FLASH Radiotherapy***

Introduction

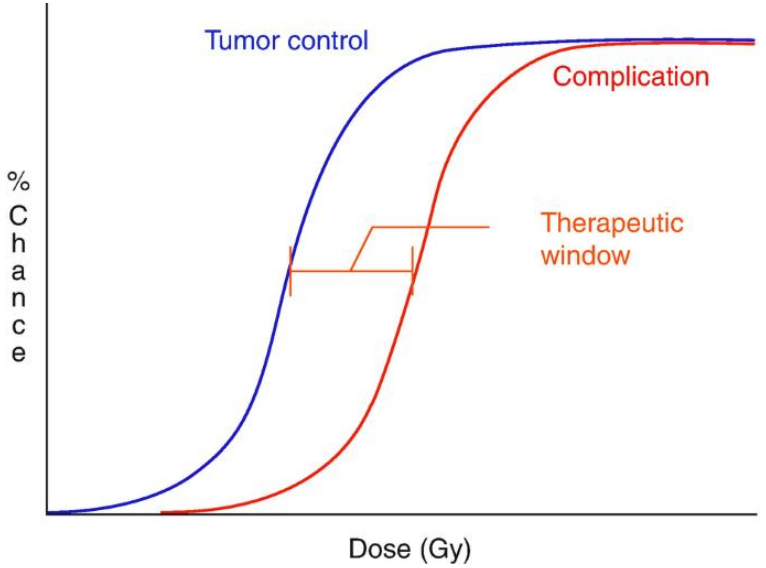
FLASH Radiotherapy: A New Era in Radiation Therapy

- FLASH delivers radiation at **ultra-high dose rates** in a very short time.
- Potential to **reduce normal-tissue toxicity** while maintaining tumour control — the **"FLASH effect."**
- Moving from **preclinical research toward clinical application**.
- Clinical implementation requires **new workflows, safety systems, QA, and team readiness**.
- **Treatment delivery and patient safety** present new challenges for clinical translation

"If FLASH is the future of radiotherapy, are we ready to deliver it safely?"

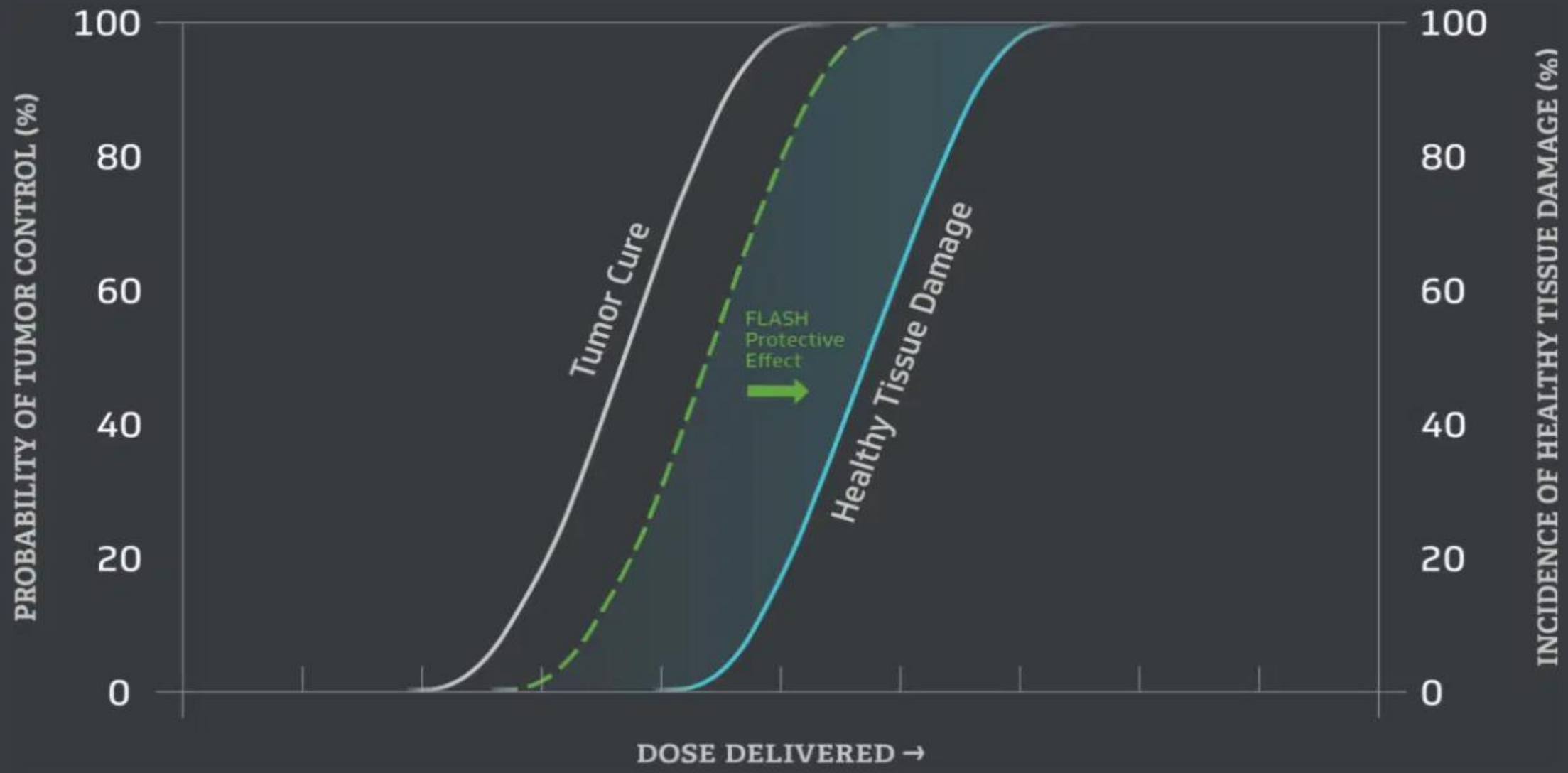
FLASH Radiotherapy: Background & Concept

What is FLASH effect?



- FLASH-RT delivers radiation at **ultra-high dose rates (UHDR)**.
  - **Several thousand times higher** than conventional RT.
- FLASH-RT can **significantly reduce normal-tissue toxicity** compared with conventional RT.
- It **maintains antitumor efficacy** with similar levels of **tumor control**.

The FLASH Effect Significantly Improves the Therapeutic Ratio for Curing Cancer



The Earliest Observations (1950s - 1980s)

❑ The three historical observations:

- **1959 – Dewey & Boag:** Reduced **bacterial sensitivity** at very high dose rates.
- **1967 – Town et al.:** Similar sparing effect observed in **mammalian cells**.
- **1982 – Hendry et al.:** Reduced **radiation-induced necrosis in mouse** tails.

❑ Why did research slow down?

- **Mixed results –** Some studies found no significant effect.
- **High dose requirements –** The effect appeared to require very high doses.
- **Limited technology –** Suitable clinical UHDR sources were not widely available

References: *Dewey & Boag (1959); Town (1967); Hendry et al. (1982); Held (2024); Wardman (2020); Ronga et al. (2021); Lowe (2022).*

The "Rediscovery"

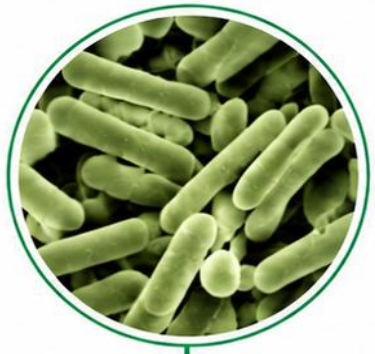
FLASH Effect (2014-2017)

FLASH reopened *interest in UHDR radiotherapy and demonstrated its potential to protect* ***normal tissue while maintaining tumour control.***

References: *Favaudon et al. (Sci. Transl. Med., 2014); Gesualdi et al. (Cancer/Radiothérapie, 2024); Lokody (Nat. Rev. Cancer, 2014); Montay-Gruel et al. (PNAS, 2017).*

Timeline of FLASH Radiotherapy

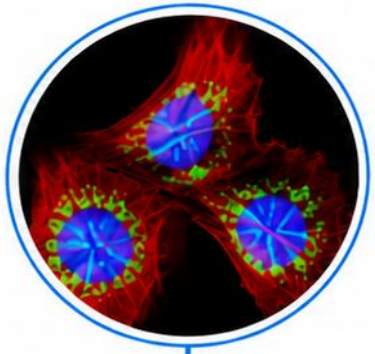
From discovery to clinical reality



1959

First discovery in bacteria

- Very high dose-rates reduced radiation sensitivity
- Higher survival rate



1967

Mammalian cells and dose-rates

- With increasing dose-rate:
  - ↑ RT resistance
  - ↑ Survival rate

2014

First discovery in vivo

- First clear definition of FLASH: dose rate ≥ 40 Gy/s
- Normal tissue sparing while maintaining tumour control in animal models

2019

First treatment in cancer patient

- Proton FLASH for bone metastases (FAST-01)
- Complete and durable response
- Low toxicity

2023

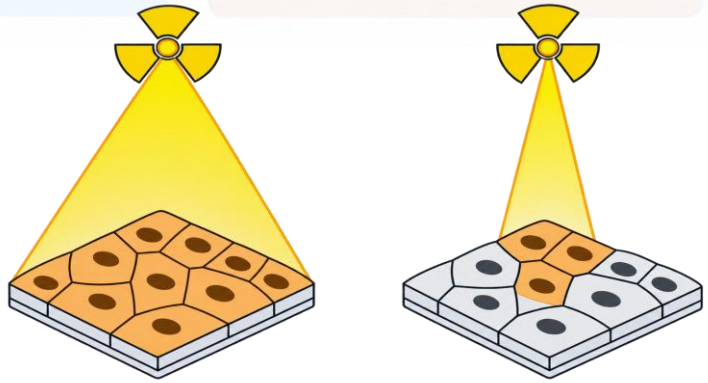
First clinical trial of FLASH

- Therapy for bone metastases: good efficacy and low toxicity
- Moves FLASH towards broader clinical applications

CONV-RT

Features

- Average dose rate ≤ 0.03 Gy/s
- High number of fractions
- Relatively low dose per fraction
- Long total treatment time



FLASH RT

Features

- Average dose rate ≥ 40 Gy/s
- Relatively low number of fractions
- Large dose per fraction
- Shorter total treatment time

R. Tang et al.) Cancer Letters 587 (2024

ESTRO meets ASIA 2026

Electron FLASH Trial: The Zurich experience

Matthias Guckenberger

FLASH effect

FLASH radiotherapy

VHEBT | Protons | Electrons 4.5–5.5 MeV | Soft X-rays | Carbon ions

FLASH effect in mouse models

Sparing of late responding organs (DMF >1.4)

- Long-term sparing of cognition
- Acute and late sparing of the vasculature
- Reduced neuroinflammation

- Reduced inflammation
- No pneumonitis
- No fibrosis

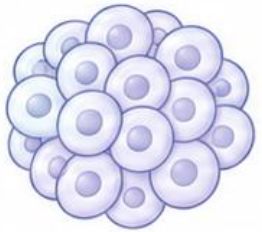
- Reduced inflammation
- No acute ulceration
- No fibrosis

Sparing of acute responding organs (DMF >1.1)

- Sparing of intestinal function
- Sparing of intestinal crypts
- Reduced inflammation

- Sparing of morphogenesis

Other effects



- Isoefficient tumour eradication
- Inhibition of metastasis (heavy ions)

“FLASH protects normal tissues across different organs.”

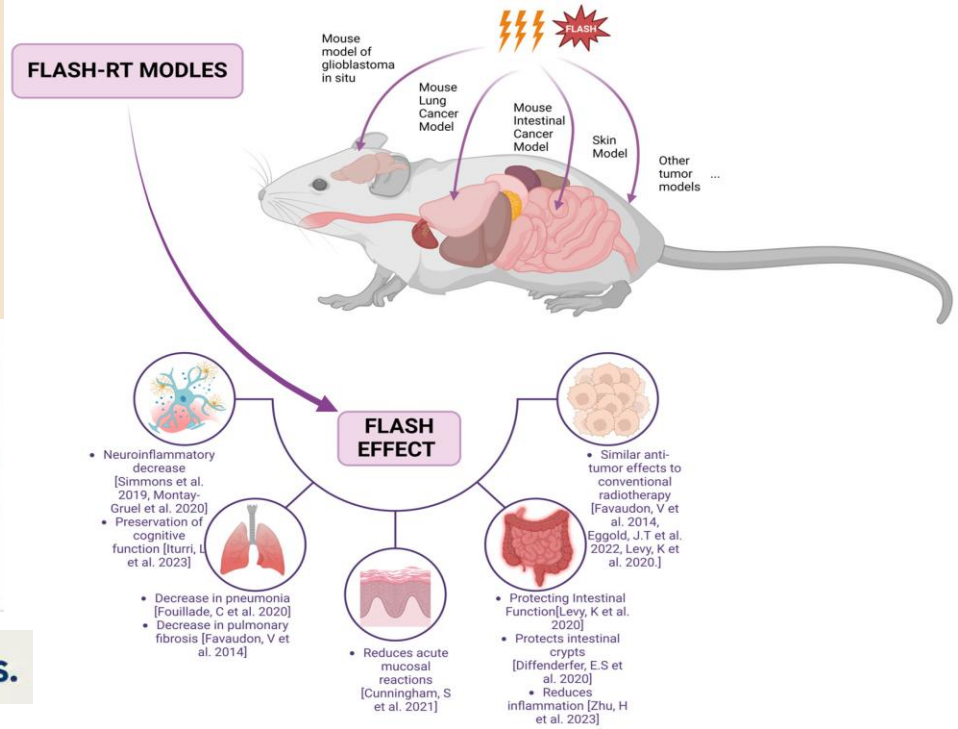
REFERENCES: Favaudon et al., Radiotherapy and Oncology 2022

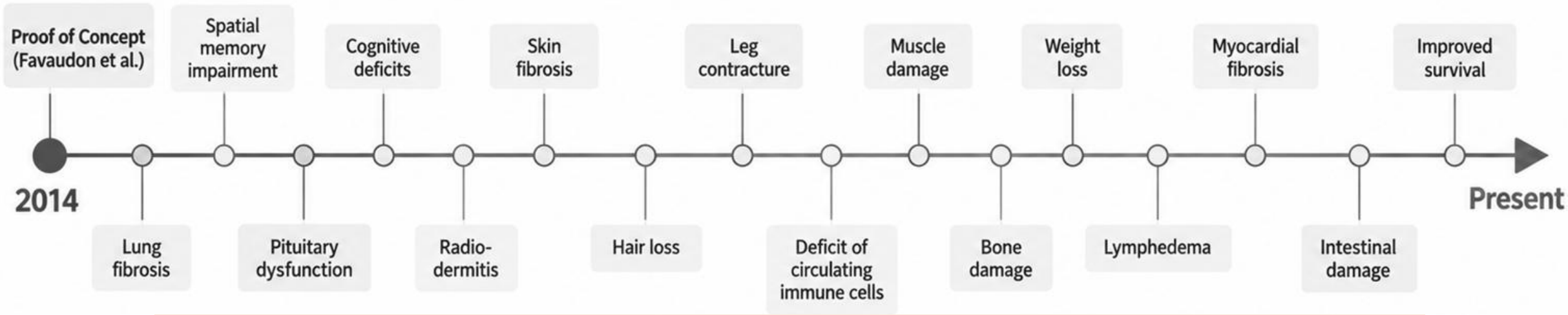
In vivo studies on FLASH radiotherapy

Protective normal tissue FLASH effect

FLASH compared to cRT prevented/decreased:

Protective FLASH effects on lung, brain, skin, bone, muscle, immune, lymphatic, bowel tissues.

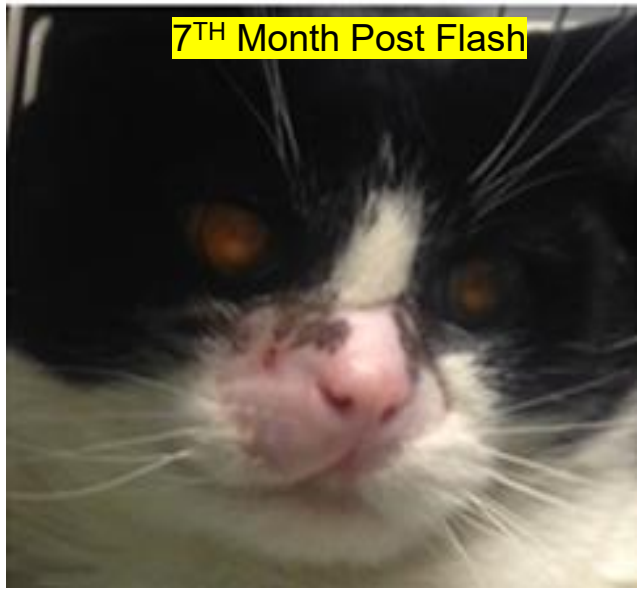


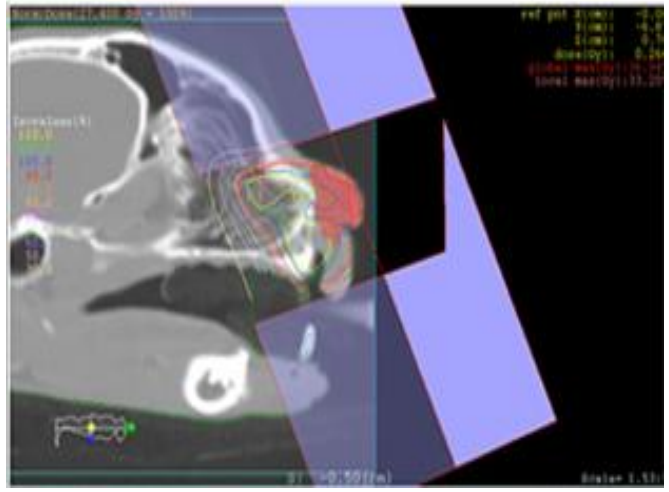


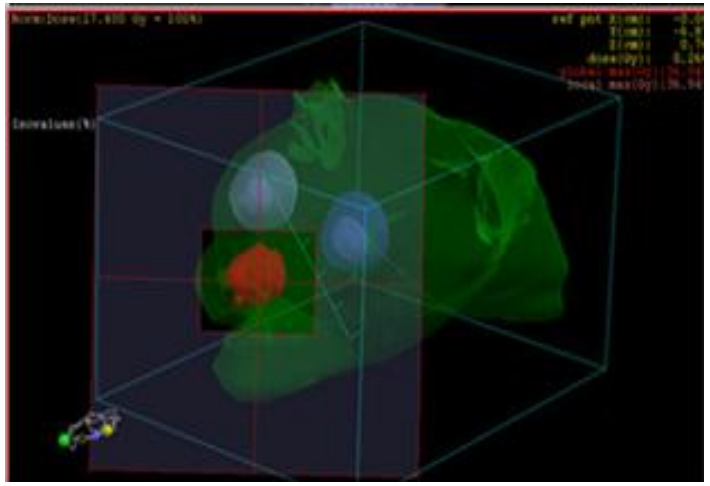
"Compared with conventional radiotherapy, FLASH showed a lower risk of mortality and improved survival."

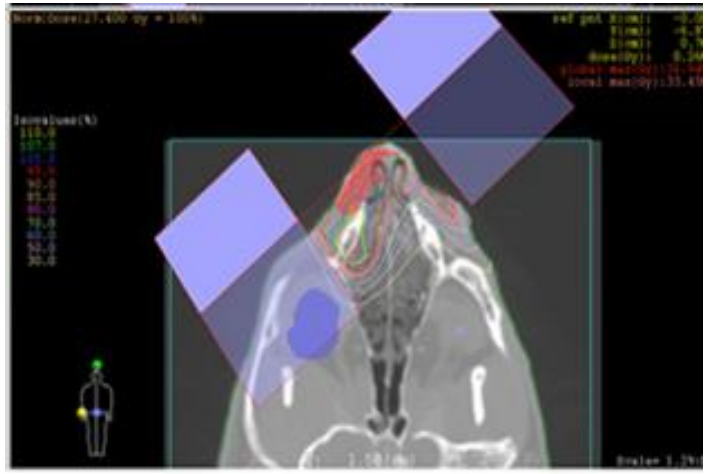
Ouying Yan et al.-FLASH Radiotherapy-2024-FLASH Radiotherapy: Mechanisms of Biological Effects and the Therapeutic Potential in Cancer

Clinical Response to FLASH Radiotherapy in a Cat









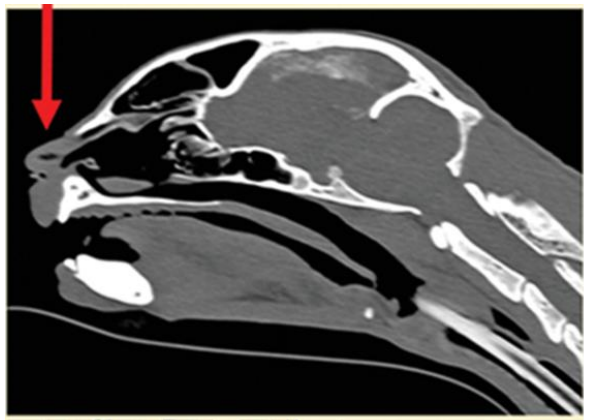
Vozenin et al-2019

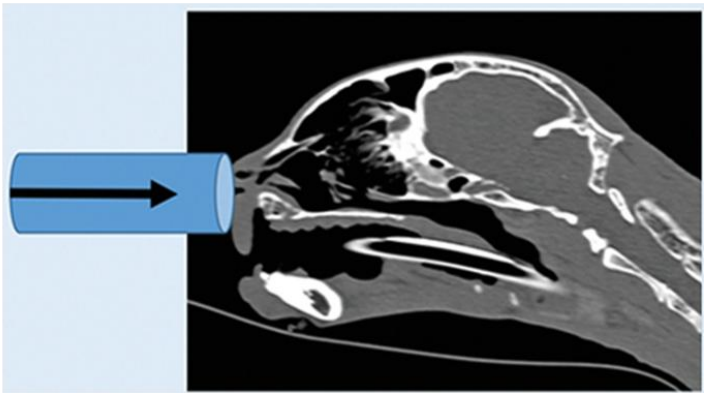
Randomized Clinical Evidence: FLASH-RT vs Conventional RT in Cats

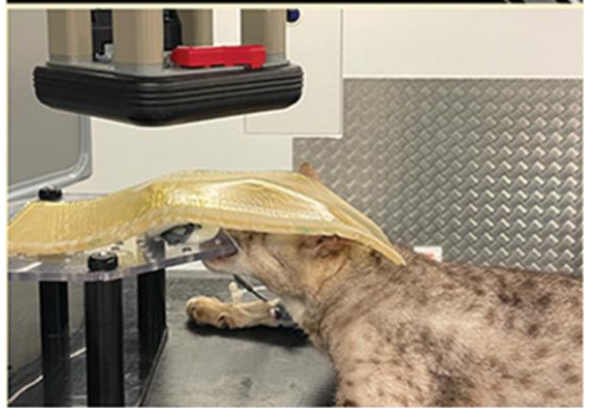
Conventional RT:
vertical beam with the **cone/applicator above the nose**

Cat treatment set-up and positioning

FLASH RT:
horizontal beam with the **cone/applicator directly at the nose**







10 × 4.8 Gy

LC @ 1y: 100%

Bone necrosis: 0%

1 × 30 Gy

LC @ 1y: 100%

Bone necrosis: 43%

Randomized study in cats with nasal planum carcinoma (n = 16)

Rohrer Bley et al. Exploring the Limits of FLASH Radiotherapy: Late Toxicity Clin Cancer Res; 28(17) 2022

Clinical Trial Brief Report

Clinical Cancer Research

The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients

Marie-Catherine Vozenin[1], Pauline De Fornel[2], Kristoffer Petersson[1,3], Vincent Favaudon[4], Maud Jaccard[1,3], Jean-François Germond[3], Benoit Petit[1], Marco Burki[5], Gisèle Ferrand[6], David Patin[3], Hanan Bouchaab[1], Mahmut Ozsahin[1,6], François Bochud[3], Claude Bailat[3], Patrick Devauchelle[2], and Jean Bourhis[1,6]

Abstract

Purpose: Previous studies using FLASH radiotherapy (RT) in mice showed a marked increase of the differential effect between normal tissue and tumors. To stimulate clinical transfer, we evaluated whether this effect could also occur in higher mammals.

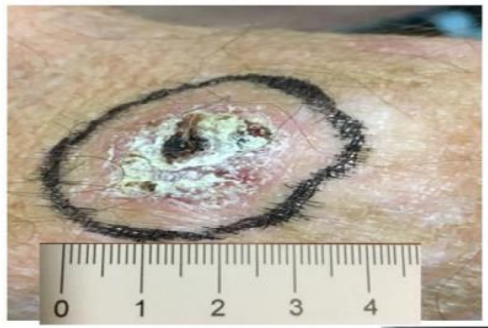
Experimental Design: Pig skin was used to investigate a potential difference in toxicity between irradiation delivered at an ultrahigh dose rate called "FLASH-RT" and irradiation delivered at a conventional dose rate called "Conv-RT." A clinical, phase I, single-dose escalation trial (25–41 Gy) was performed in 6 cat patients with locally advanced T2/T3N0M0 squamous cell carcinoma of the nasal planum to determine the maximal tolerated dose and progression-free survival (PFS) of single-dose FLASH-RT.

Results: Using, respectively, depilation and fibronetosis as acute and late endpoints, **a protective effect of FLASH-RT was observed (≥20% dose-equivalent difference vs. Conv-RT).** Three cats experienced no acute toxicity, whereas 3 exhibited moderate/mild transient mucositis, and all cats had depilation. With a median follow-up of 13.5 months, **the PFS at 16 months was 84%.**

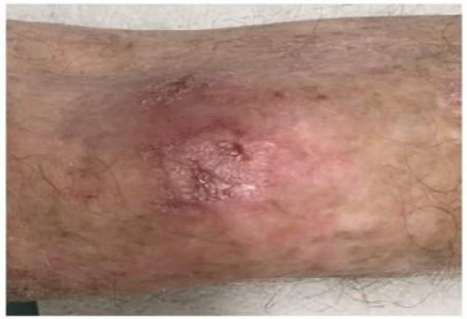
Conclusions: **Our results confirmed the potential advantage of FLASH-RT and provide a strong rationale for further evaluating FLASH-RT in human patients.**

See related commentary by Harrington, p. 3

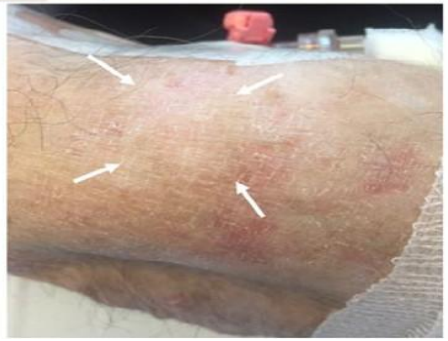
From the Lab to the Clinic (2019-Present)



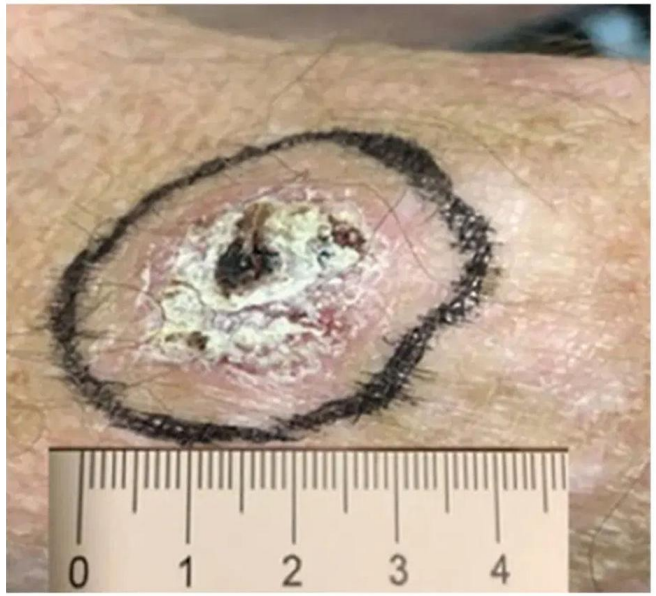
1a : Day 0



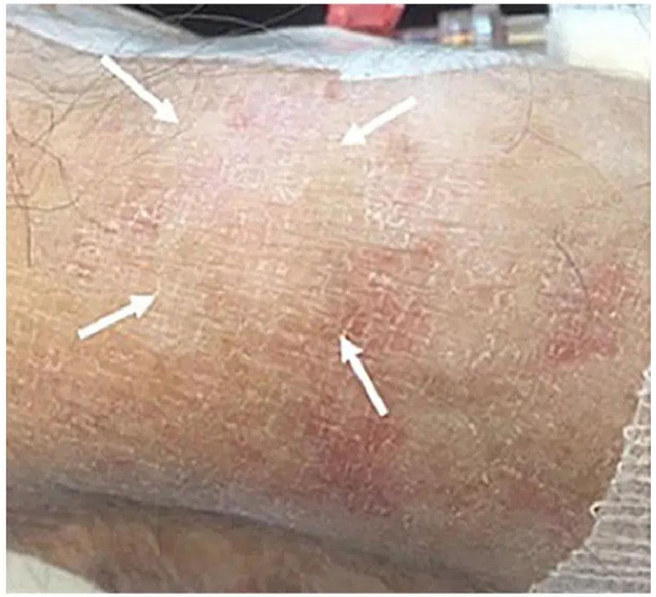
1b : 3 weeks



1c : 5 months



Before **Flash** treatment



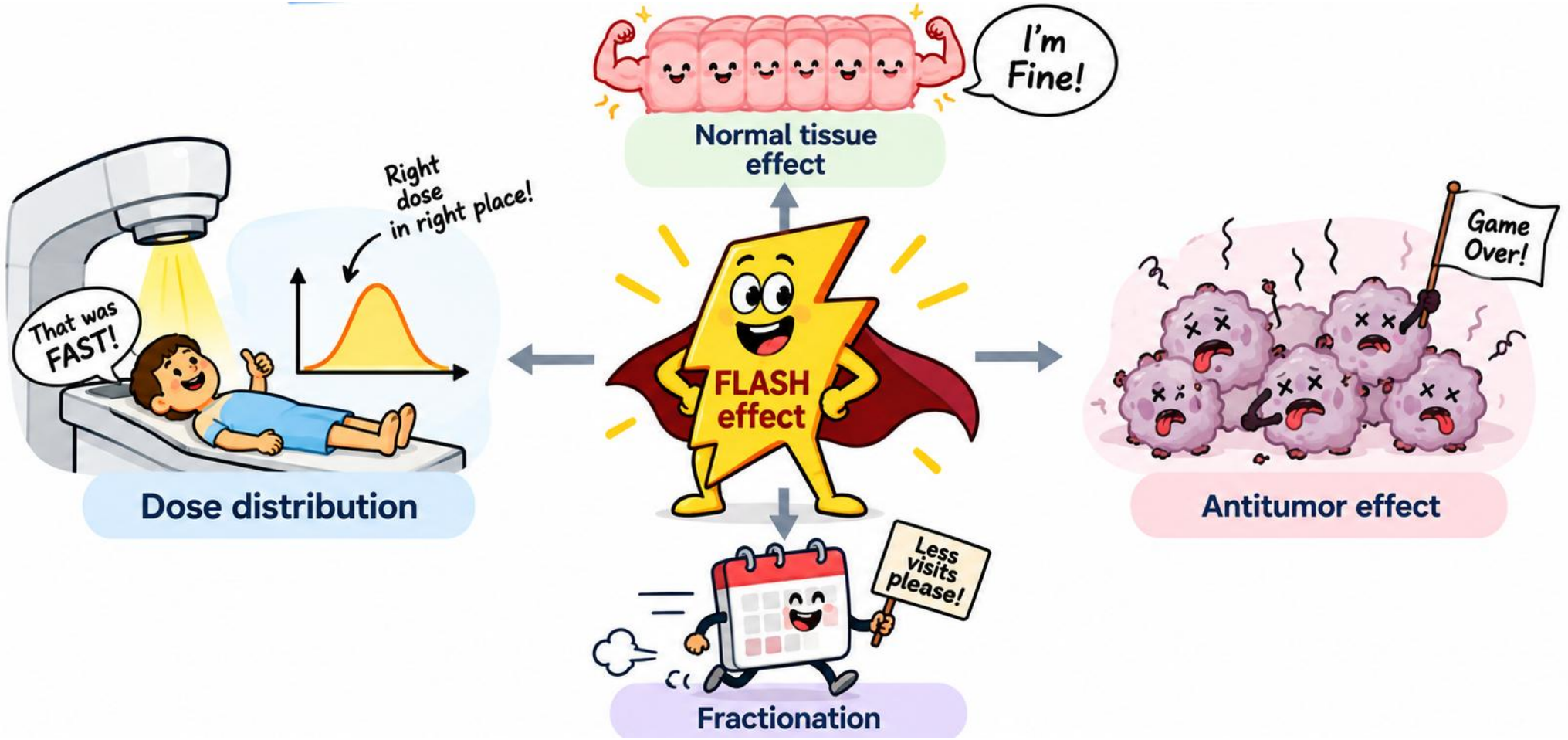
After **Flash** treatment

First Patient – 2019

- **Bourhis et al.** reported the **first human FLASH-RT treatment** in a 75-year-old man with recurrent cutaneous T-cell lymphoma .
- After **100+ previous radiation treatments**, he received **15 Gy in a single fraction in just 90 ms**.
- **Complete tumour response** with substantially reduced skin toxicity was reported

References: Bourhis et al. (*Radiother. Oncol.*, 2019); Gaide et al. (*Radiother. Oncol.*, 2022).

Challenge: Clinical Trial Design



Many variables to consider in clinical trial design

Reference: Dal Bello et al., Radiother Oncol 2023;187:109822.

Ultra-High Dose Rate (FLASH) Radiotherapy: Silver Bullet or Fool's Gold?

Joseph D. Wilson[1†], Ester M. Hammond[1†], Geoff S. Higgins[1†] and Kristoffer Petersson[1,2†]*

[1] *Department of Oncology, The Oxford Institute for Radiation Oncology, University of Oxford, Oxford, United Kingdom,*
[2] *Radiation Physics, Department of Haematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, Sweden*

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Edited by:
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Marie-Catherine Vozenin,
Lausanne University Hospital (CHUV), Switzerland

***Correspondence:**
Kristoffer Petersson
kristoffer.petersson@oncology.ox.ac.uk

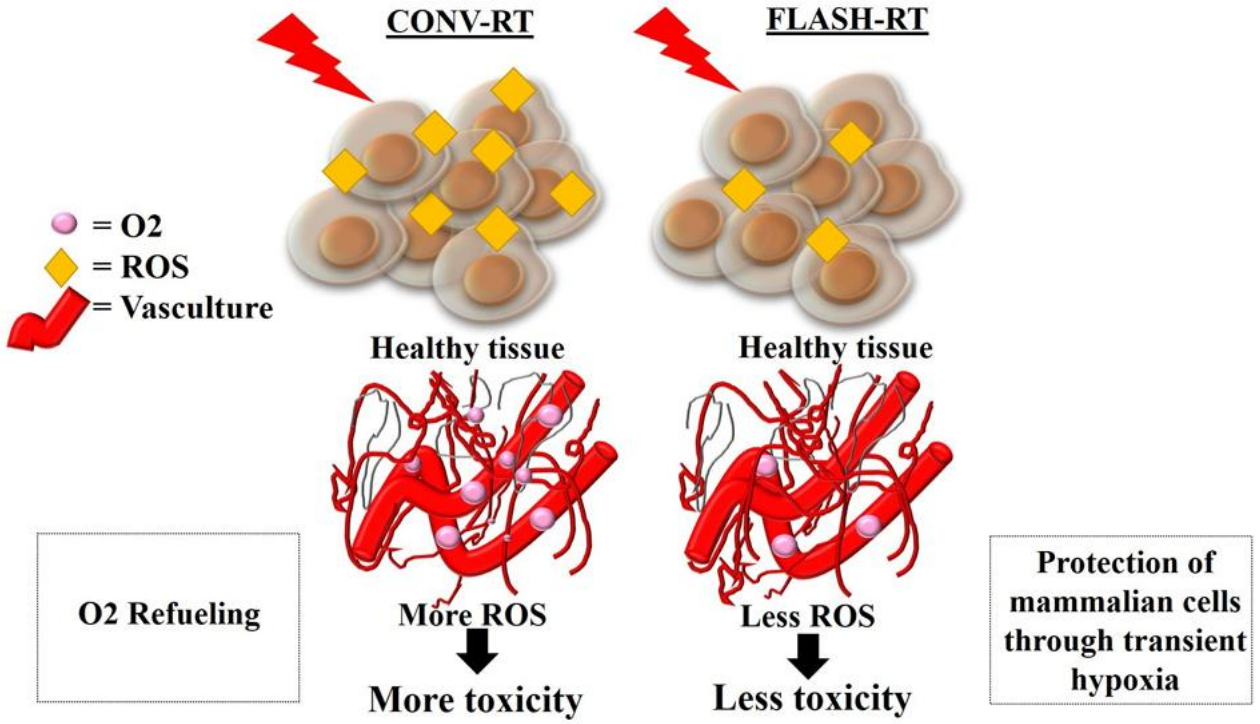
Radiotherapy is a cornerstone of both curative and palliative cancer care. However, radiotherapy is severely limited by radiation-induced toxicities. If these toxicities could be reduced, a greater dose of radiation could be given therefore facilitating a better tumor response. Initial pre-clinical studies have shown that irradiation at dose rates far exceeding those currently used in clinical contexts reduce radiation-induced toxicities whilst maintaining an equivalent tumor response. This is known as the FLASH effect. To date, a single patient has been subjected to FLASH radiotherapy for the treatment of subcutaneous T-cell lymphoma resulting in complete response and minimal toxicities. The mechanism responsible for reduced tissue toxicity following FLASH radiotherapy is yet to be elucidated, but the most prominent hypothesis so far proposed is that acute oxygen depletion occurs within the irradiated tissue. This review examines the tissue response to FLASH radiotherapy, critically evaluates the evidence supporting hypotheses surrounding the biological basis of the FLASH effect, and considers the potential for

Biological Mechanisms Behind FLASH RT

Proposed Biological Hypotheses Behind the FLASH Effect

❑ **Four key biological mechanisms proposed:**

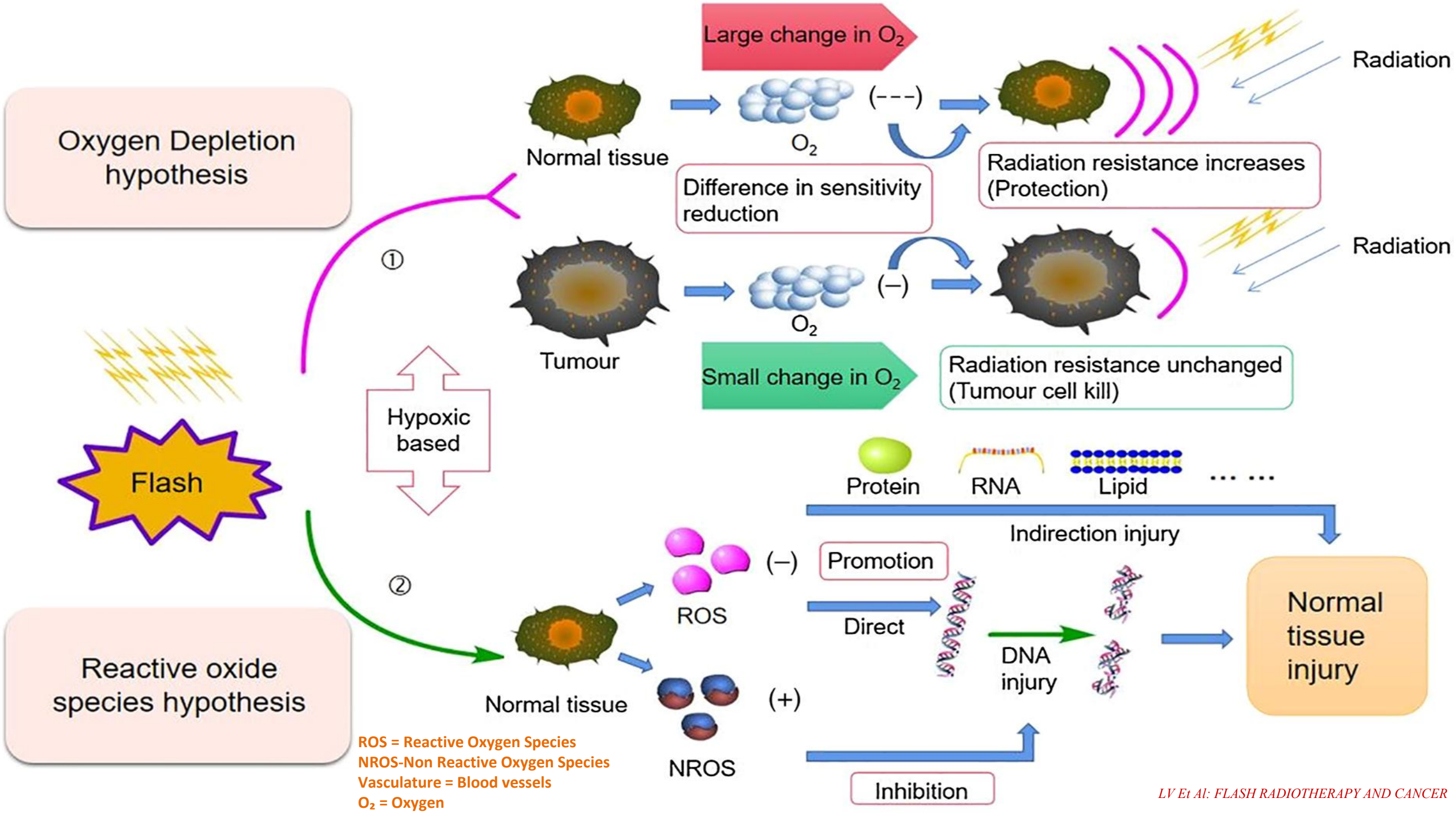
1. Oxygen depletion
2. Free radical interaction
3. DNA damage
4. Immune/inflammatory response



- These mechanisms are still hypotheses and are not fully established.
- Each mechanism has its own limitations and is still being investigated.

ROS = Reactive Oxygen Species
Vasculature = Blood vessels
O_2 = Oxygen

Alhaddad L, Osipov A, Andreyan A, Leonov S. FLASH Radiotherapy: Benefits, Mechanisms, and Obstacles to Clinical Translation. ***IJMS. 2024;25.***


Oxygen Depletion hypothesis
Large change in O_2
Normal tissue
O_2
(---)
Radiation
Radiation resistance increases (Protection)
Difference in sensitivity reduction
①
Tumour
O_2
(–)
Radiation
Small change in O_2
Radiation resistance unchanged (Tumour cell kill)
Hypoxic based
Flash
Protein
RNA
Lipid
… …
Indirection injury
②
ROS
(–)
Promotion
Direct
DNA injury
Normal tissue injury
Normal tissue
NROS
(+)
Inhibition
Reactive oxide species hypothesis
ROS = Reactive Oxygen Species
NROS-Non Reactive Oxygen Species
Vasculature = Blood vessels
O_2 = Oxygen

What Is Role Of Oxygen In FLASH RT??

FLASH Workshop 2025: The Role of Oxygen in FLASH Radiation Therapy

FLASH Workshop 2024: The Role of Oxygen in FLASH Radiation Therapy

- The FLASH effect has been shown to be influenced by the amount of oxygen presence in the medium within the tissue.
- Increased tissue oxygen has been shown to reduce the protective nature of FLASH in healthy tissue.
- The underlying mechanism by which oxygen influences the FLASH effect is still unknown.

Influence On Radiotherapy

Risk of Radiobiology

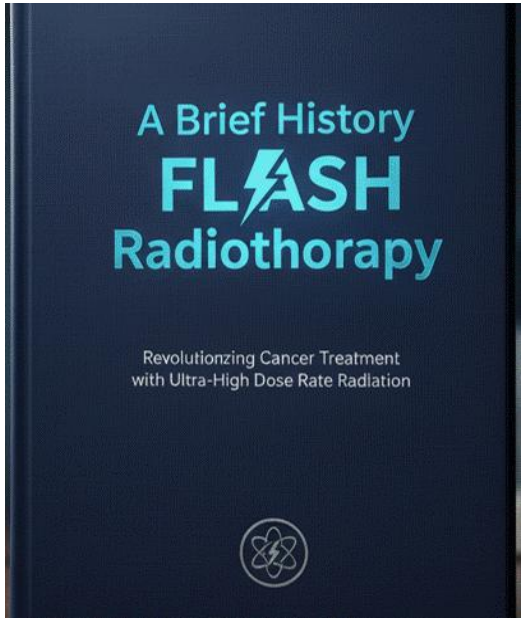
- FLASH-RT challenges the **Five R's** due to its ultra-short treatment time.
- May reduce the impact of **repair, repopulation, redistribution, and reoxygenation**.
- The FLASH effect may depend on **dose rate, dose per pulse, and irradiation time**.

Dose–Response

- **Higher doses** may be possible with FLASH-RT while maintaining **normal-tissue protection**.
- Tumor control may be **maintained or improved**.

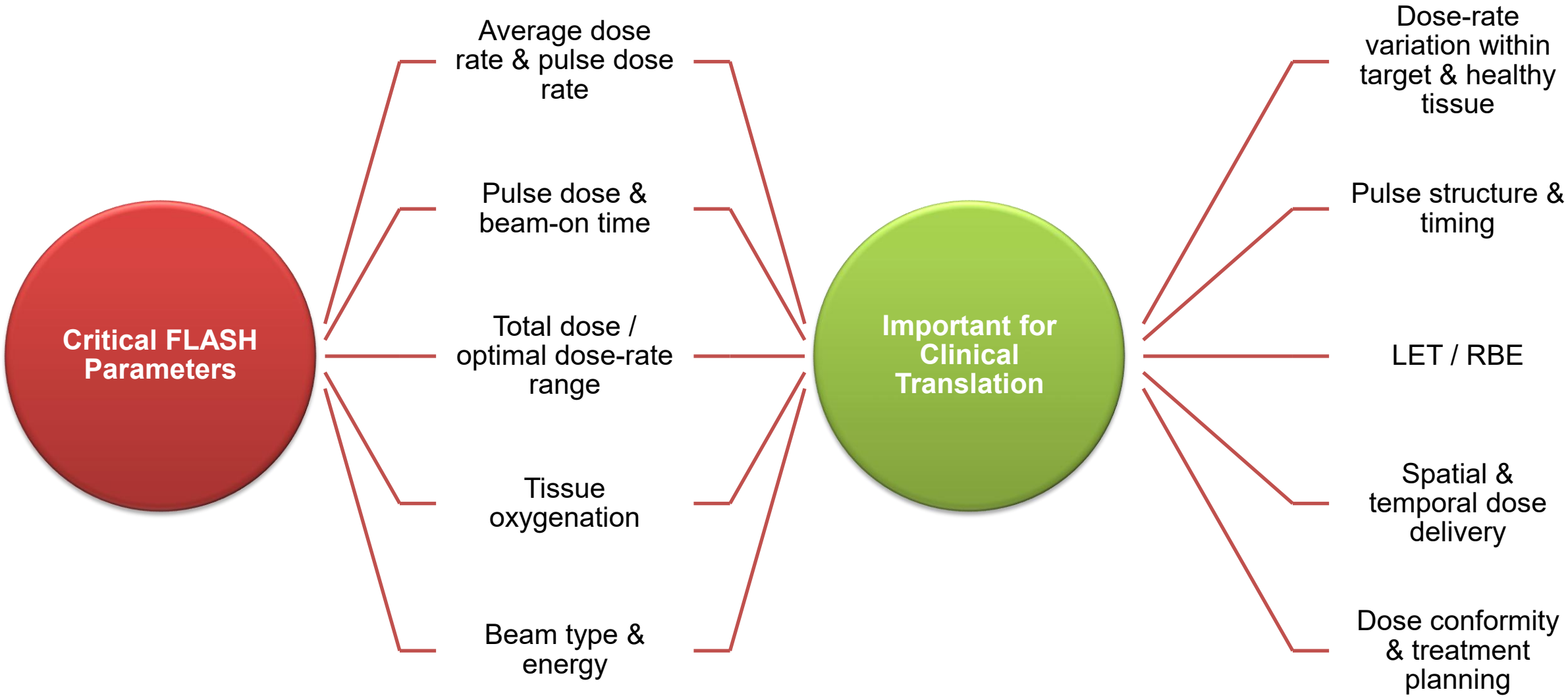
Normal-Tissue Protection

- FLASH-RT shows **reduced normal-tissue toxicity** in several preclinical studies.
- This may help widen the **therapeutic window**.



FLASH-RT may introduce *dose rate as a new factor* in radiobiological response.

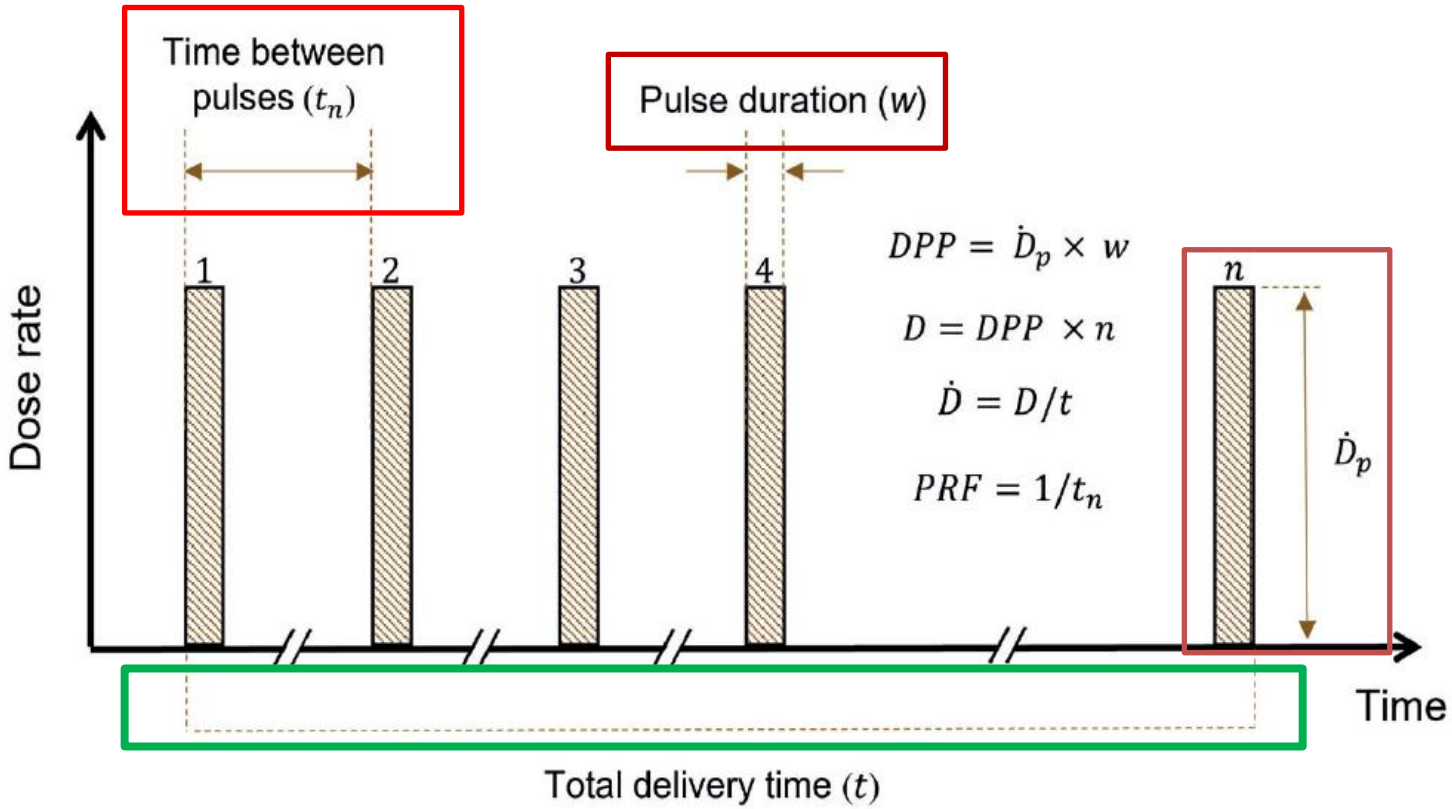
Factors That Matter in FLASH



Which factors influence the FLASH effect?

Key beam parameters for FLASH electron radiotherapy using a linear accelerator

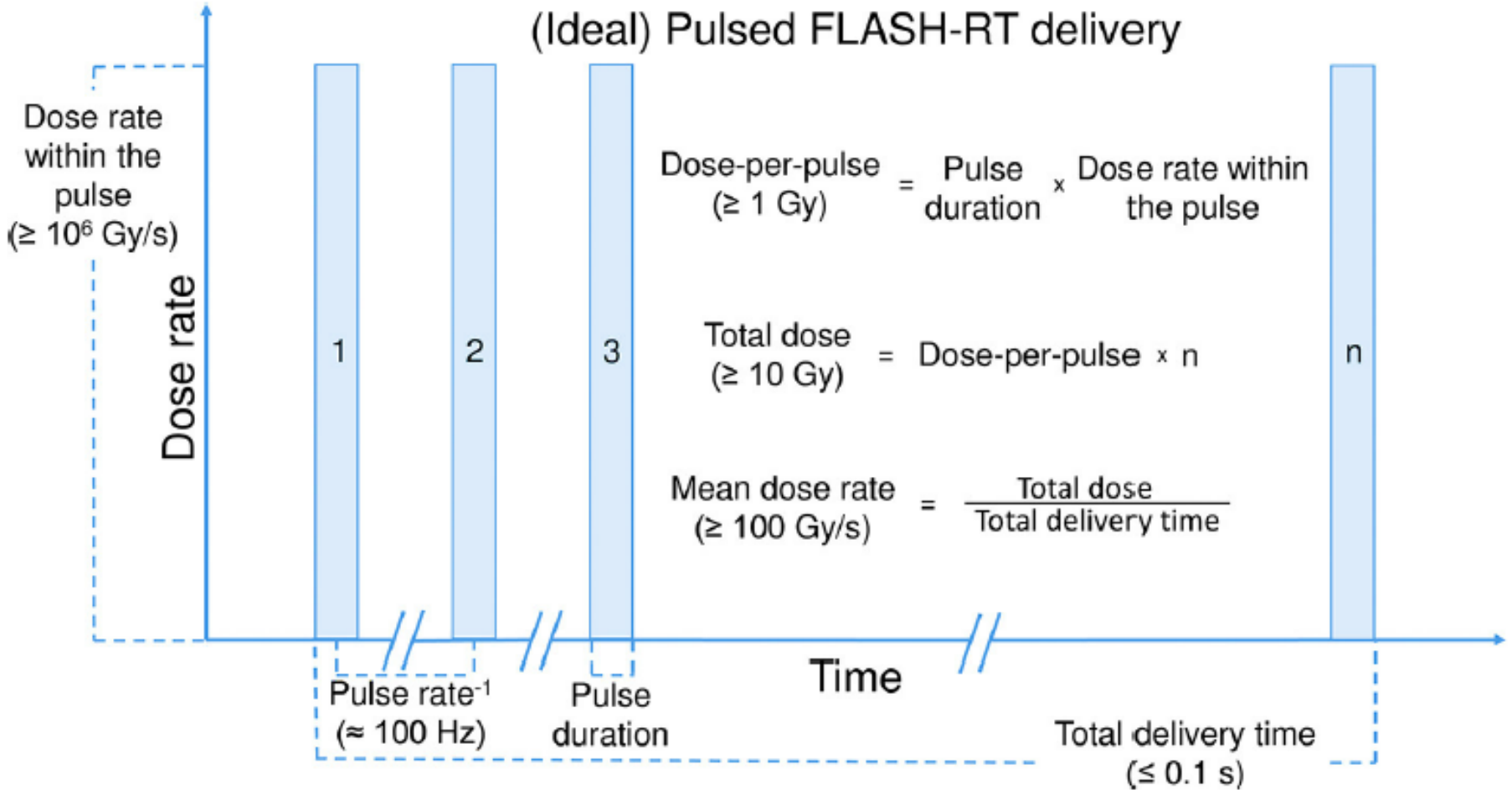
Beam parameter	Description
Average dose rate ($\dot{D}$)	Mean dose-rate for multi-pulse delivery
Pulse dose rate ($\dot{D}_p$)	Dose-rate within a single pulse
Dose-per-pulse (DPP)	Dose delivered in a single pulse
Pulse repetition frequency (PRF)	Number of pulses delivered per unit time
Pulse duration (w)	Time for delivery of a single pulse
Number of pulses (n)	Number of pulses delivered during one fraction
Total delivery time (t)	Irradiation time from start of first pulse to the end of the last pulse
Time between pulses (t_n)	Time from end of one pulse to start of next pulse
Fraction dose (D)	Total dose for a single fraction



Terminology and pulse structure of a pulsed electron beam

Author(s): Elise Konradsson, Radiotherapy in a FLASH: Towards clinical translation of ultra-high dose rate electron therapy:2023

Pulsed FLASH-RT delivery



A schematic view of a pulsed beam delivery, specifying some parameters which seems to be important for inducing the FLASH effect.

Immobilization In The Light Of Future Developments

Radiotherapy and Oncology 139 (2019) 18–22

Contents lists available at ScienceDirect

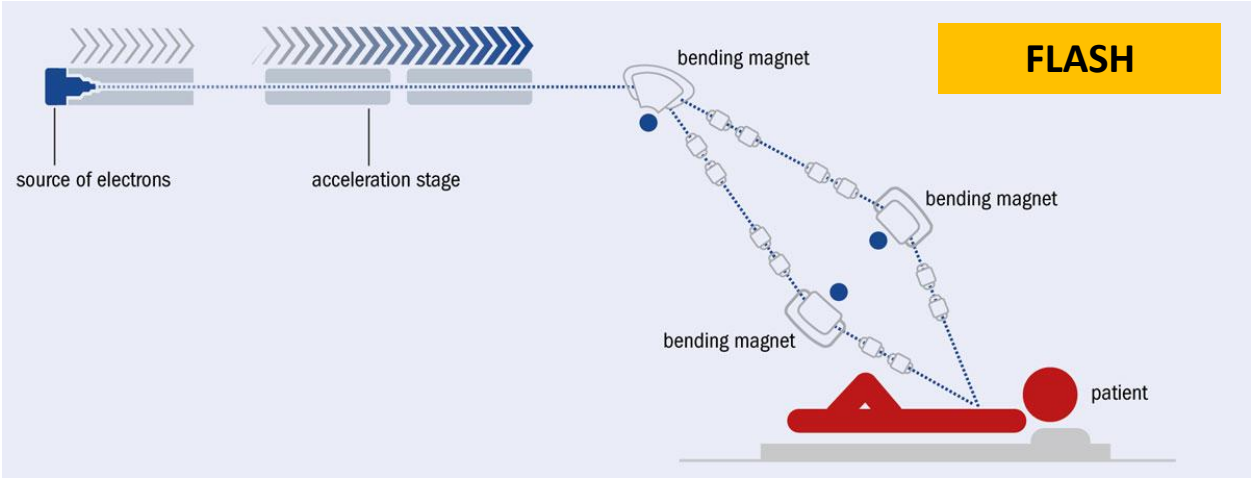
Radiotherapy and Oncology

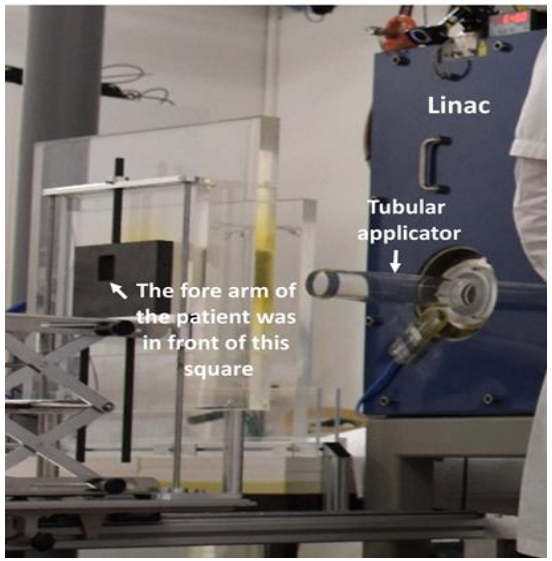
journal homepage: www.thegreenjournal.com

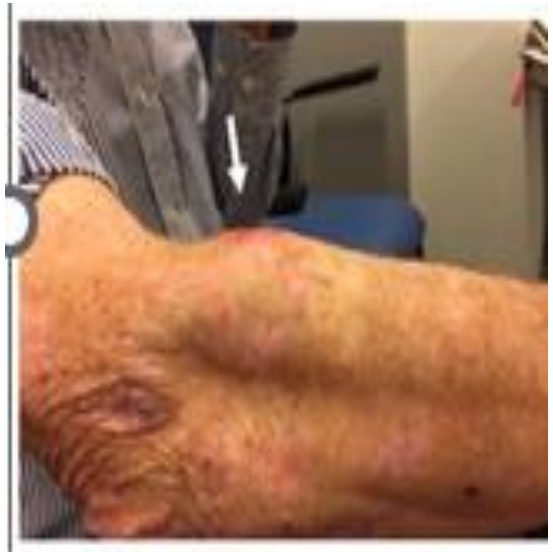
First in Human

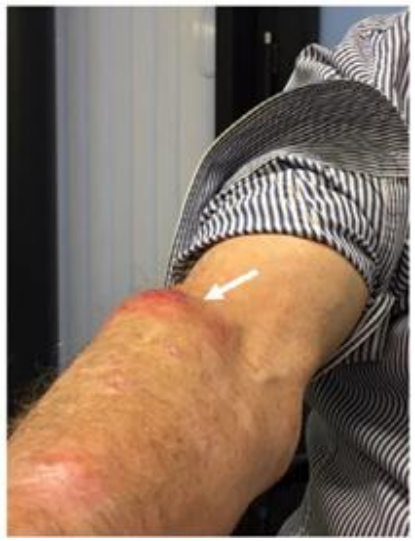
Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]









First clinical treatment: 15 Gy in 90 ms

- Ultra high dose rate = All dose delivered in a flash.
- Very strict PPD and fixation.
- Dose delivered in a flash, so less opportunities to move
- **Role for SGRT (and triggered beam) and less need for rigidness?**

Comfortable and stable

Flash RT Radiotherapy Workflow

Conventional Radiotherapy Workflow

Common clinical workflow — modality-specific parameters may vary

1. Patient Selection	2. Simulation	3. Contouring	4. Treatment Planning	5. Plan Evaluation	6. Quality Assurance	7. Patient Setup & Image Guidance	8. Treatment Delivery	9. Follow-up
Clinical indication Performance status	CT (± 4DCT) Immobilization	GTV / CTV / PTV OARs	Optimize dose distribution	Target coverage OAR constraints	Machine QA Patient-specific QA	Immobilization Image verification	Dose per fraction Multiple fractions	Treatment records Clinical outcomes

FLASH Radiotherapy Workflow (Electron / Photon / Proton)

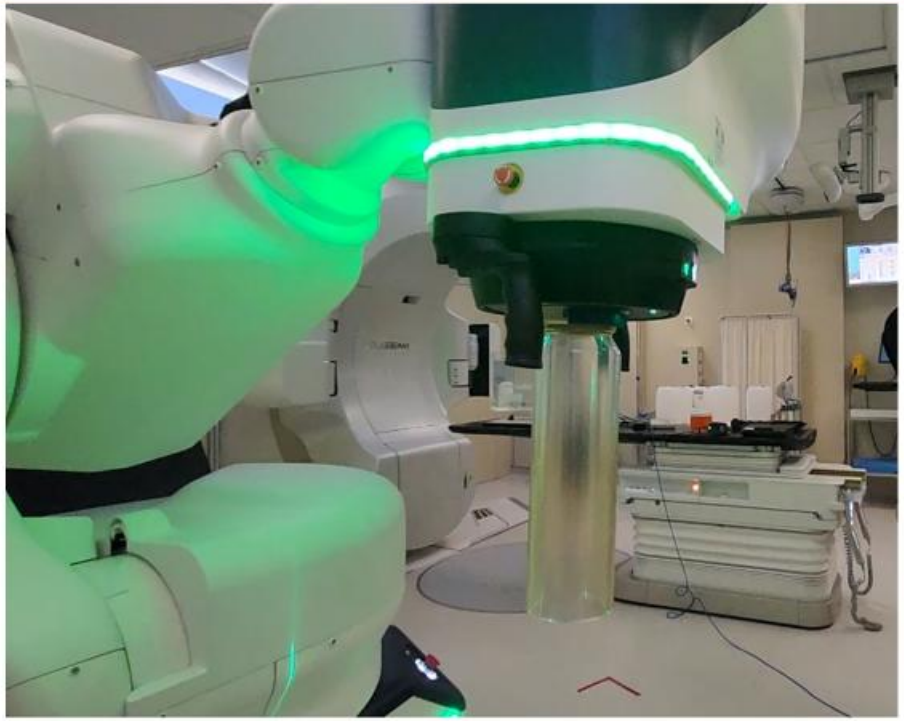
1. Patient Selection	2. Simulation	3. Contouring	4. FLASH Treatment Planning	5. FLASH Feasibility Check	6. FLASH-Specific QA	7. Patient Setup & Image Guidance	8. FLASH Delivery	9. Delivery Verification	10. Follow-up
Clinical indication FLASH eligibility OAR assessment	CT / 4DCT Immobilization Motion assessment	GTV / CTV / ITV / PTV OARs	Modality selection Dose + Dose rate Beam geometry Irradiation time	Target coverage OAR constraints Required dose rate Delivery feasibility Motion / robustness	Machine QA Dosimetry QA Dose-rate QA Patient-specific QA	Immobilization Position verification Final safety check (Time-out)	Ultra-high dose rate Very short irradiation (often single fraction in current studies)	Delivered dose Dose-rate verification Treatment records	Acute toxicity Tumor response Long-term outcome

Additional / Modified Steps in FLASH RT

- FLASH eligibility / feasibility assessment
- Motion management
- Planning with dose-rate optimization
- FLASH-specific QA (including dose-rate)
- Final safety checks for UHDR delivery
- Verification of delivered dose and dose rate

Daugherty et al., Radiother Oncol. 2026;222:111671. Zou et al., IJROBP. 2023;116(5):1202–1217.

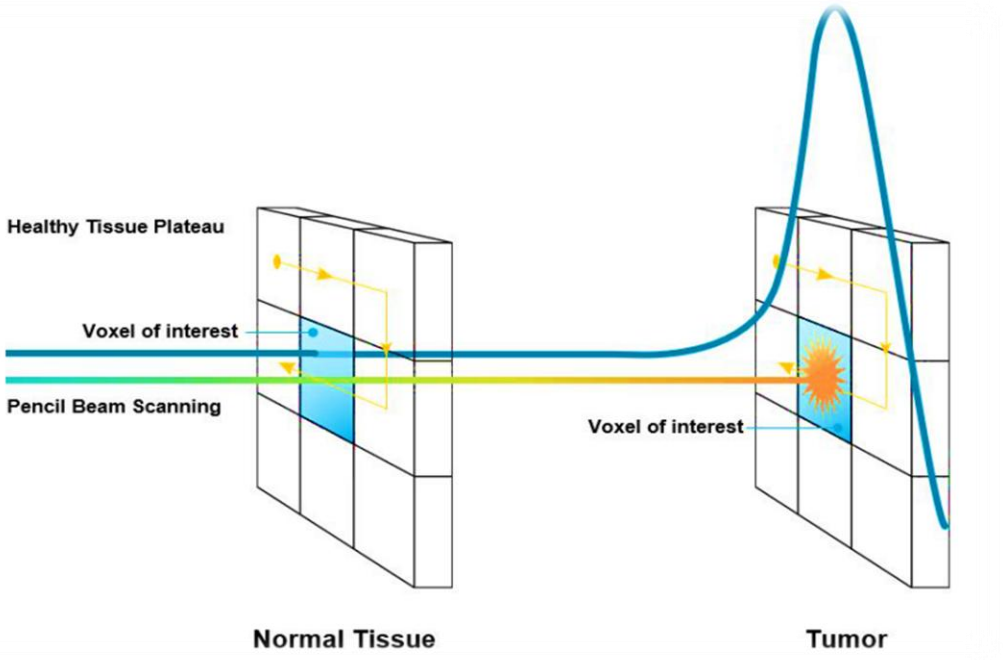
FLASHKNiFE (THERYQ) – Technical Features

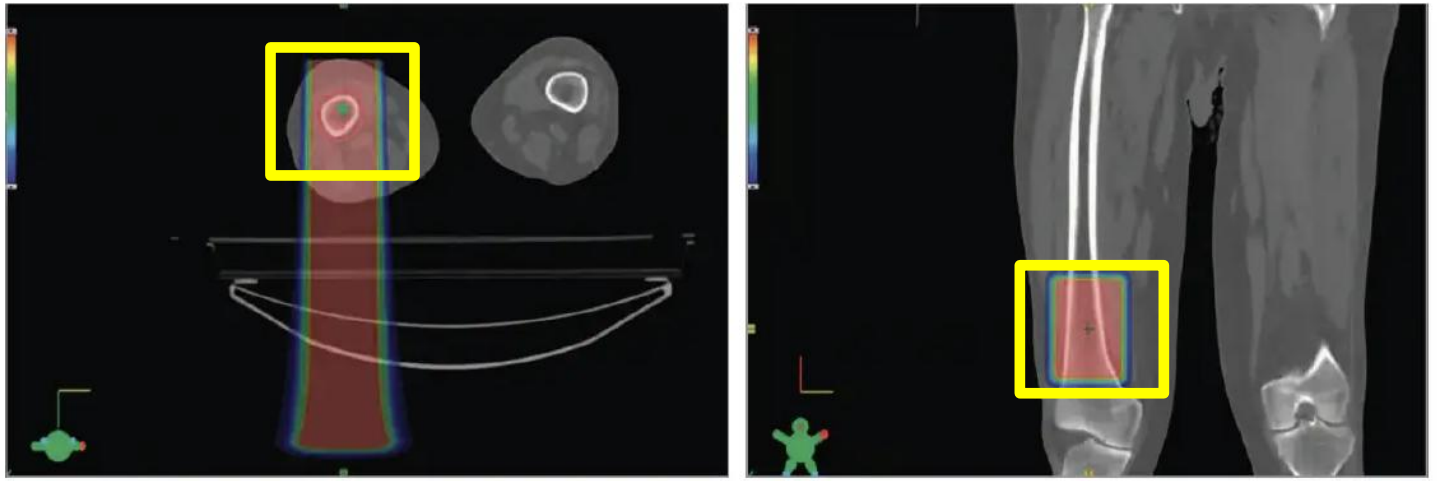


- **6 & 9 MeV electron beams**
- **FLASH dose rate:** >40 Gy/s for ultra-short irradiation
- **Dedicated FLASH modes:** Optimized beam and pulse parameters
- **Simple beam shaping:** Customizable collimation for FLASH fields
- **Compact design:** Suitable for clinical and research environments

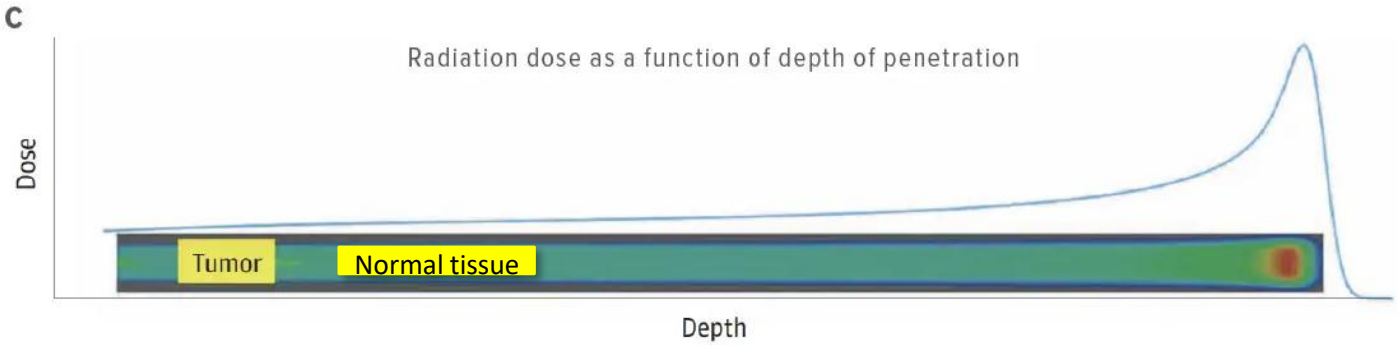
UZ Brussel (Brussels University Hospital)

FLASH Treatment Plan and Bragg Curve Showing Radiation Dose in Color Wash





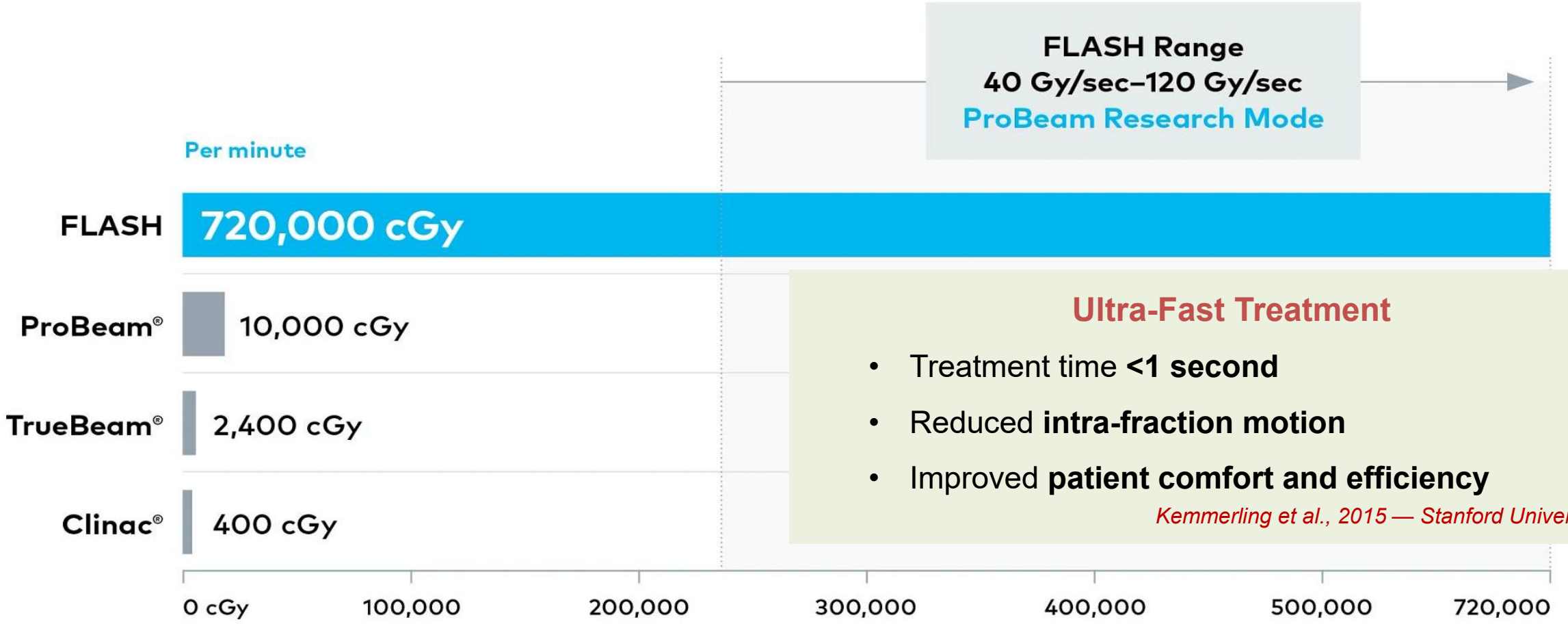
Target volume was placed in the **entrance region** or the **plateau region**



- A **single energy ONLY** was used and **there was no SOBP!**
- Full dose (8 Gy) **through** and **through** the cross-section
- Tumor entirely in the **entrance dose region, not in Bragg peak!**
- Bragg peak **'escaped'** from the body!....

AnthonyE,et al-JAMA Oncol.2023;9(1):62-69

FLASH vs Conventional Radiotherapy: Dose Rate



Ultra-Fast Treatment

- Treatment time **<1 second**
- Reduced **intra-fraction motion**
- Improved **patient comfort and efficiency**

Kemmerling et al., 2015 — Stanford University, USA

"FLASH delivers radiation at ultra-high dose rates, enabling the prescribed dose to be delivered in a fraction of a second."

Source: Varian Medical Systems. ProBeam 360° brochure. "FLASH therapy."

Current Challenges and Limitations

- **Advanced Technology Required**
  - Specialized systems are needed to deliver and control ultra-high dose rates safely.
- **Precise Beam Control**
  - Accurate beam monitoring, control and delivery are essential for safe FLASH treatment.
- **New Dosimetry & QA**
  - Conventional methods may not be adequate; standardized dosimetry and QA approaches are still developing.
- **Unclear Biological Mechanisms**
  - The exact FLASH mechanism, including the role of oxygen and biological responses, is not fully understood.
- **Limited Clinical Evidence**
  - Clinical experience is still limited; further studies are needed to confirm long-term safety and effectiveness.

Current Status and Future Readiness

- **Still in Development:**
  - FLASH is currently an active area of research and is not yet a routine clinical treatment.
- **Growing Global Research:**
  - Research teams worldwide are conducting preclinical studies and early clinical trials.
- **Promising Early Results:**
  - Early studies suggest reduced normal-tissue damage while maintaining tumor treatment effectiveness.
- **Path to Clinical Practice:**
  - Standardized technology, dosimetry, quality assurance, safety protocols, and clinical evidence are needed for wider clinical use.

Future Readiness& Path to Clinical Practice:

Radiation therapists and the multidisciplinary team need to understand the technology, workflow, safety, and treatment process to prepare for future clinical implementation.

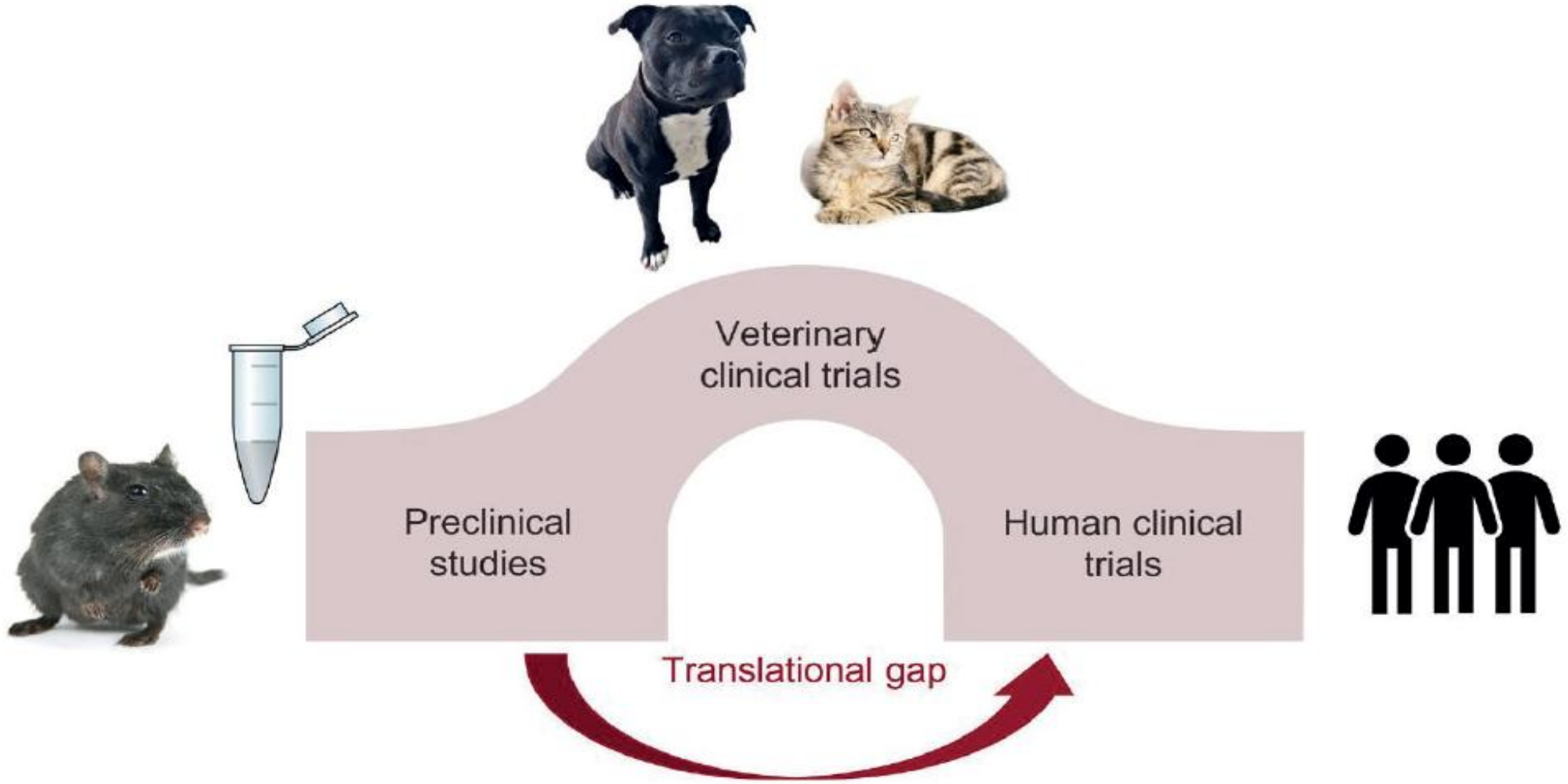


Figure 12: Veterinary clinical studies can help bridge the translational gap between the laboratory setting and human clinical trials.

Konradsson, E. (2023). Radiotherapy in a FLASH: Towards clinical translation of ultra-high dose rate electron therapy. [Doctoral Thesis (compilation Lund University.

Transformative innovation through partnership

2–6 May 2025 | Vienna, Austria

ESTRO 2025

From Bench to Bedside: The Evolving Future of FLASH Radiotherapy

ESTRO 2025 Congress Report

Technology & Dosimetry

- UHDR dosimetry is advancing, but standards are still evolving.
- New detectors and QA tools support safe FLASH delivery.

Member of the ESTRO FLASH focus group

Biology & Mechanisms

- FLASH shows normal-tissue sparing and immune effects.
- Oxygen, beam pauses and fractionation influence the FLASH effect.
- Mechanisms remain **not fully understood.**

Treatment Development

- **Proton FLASH** shows promising tissue-sparing effects.
- **VHEE** may enable treatment of deep tumours.
- Advanced planning and QA technologies are emerging.

Clinical Translation

- Early **Phase I trials** show encouraging safety.
- **Veterinary studies** may help bridge preclinical to human trials.
- Clinical trials are now feasible and essential.

FLASH has evolved from experimental research into a major clinical innovation.

The field is moving toward clinical trials, but safety, dosimetry and biological mechanisms still need further validation.

ESTRO 2022 | 6-10 May 2022 Copenhagen, Denmark

A matter of debate: FLASH and particle therapy go head-to-head

ESTRO 2022 – Radiobiology Corner

Laure Marignol, Trinity College Dublin, Ireland

FLASH Radiotherapy

- Spares normal tissue
- Similar tumour control
- Very short treatment time
- Reduced inflammation
- Technical & biological questions remain

DEBATE

Particle Therapy

- High dose precision (Bragg peak)
- Lower dose to normal tissue
- Shorter treatment time
- Evolving clinical use
- Questions on biological effectiveness

Audience Vote Results (N = 109)

Before the debate	55%	favoured FLASH
After the debate	65%	favoured particle therapy

- Both FLASH and particle therapy are promising.
- Particle therapy currently has stronger clinical support.
- Future depends on research and patient selection.

After the debate:

65% of the audience favoured particle therapy, showing a shift towards its current clinical maturity.

Take-Home Message

FLASH RT is promising, but more research and preparation are needed.

- **Radiobiology:** Better understanding of the **FLASH effect** and its mechanisms.
- **Physics & Technology:** Develop stronger technical knowledge of **ultra-high dose-rate physics, dosimetry and QA**.
- **Treatment Workflow:** Learn and standardize the complete **planning → verification → delivery** process.
- **Learning Curve:** Build knowledge and **practical experience** before clinical implementation.
- **Multidisciplinary Team:** Close collaboration between **radiation oncologists, physicists, RTTs, biologists and engineers**.
- **Future Readiness: Prepare our teams and infrastructure in India before wider adoption of FLASH technology.**

“Learn today, prepare today, and be ready for FLASH tomorrow.”

Thank you.....

Prakash Umbarkar

P.D Hinduja National Hospital Mumbai-India

Email: umbarkarprakash@gmail.com

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