Dose-Rate Effect

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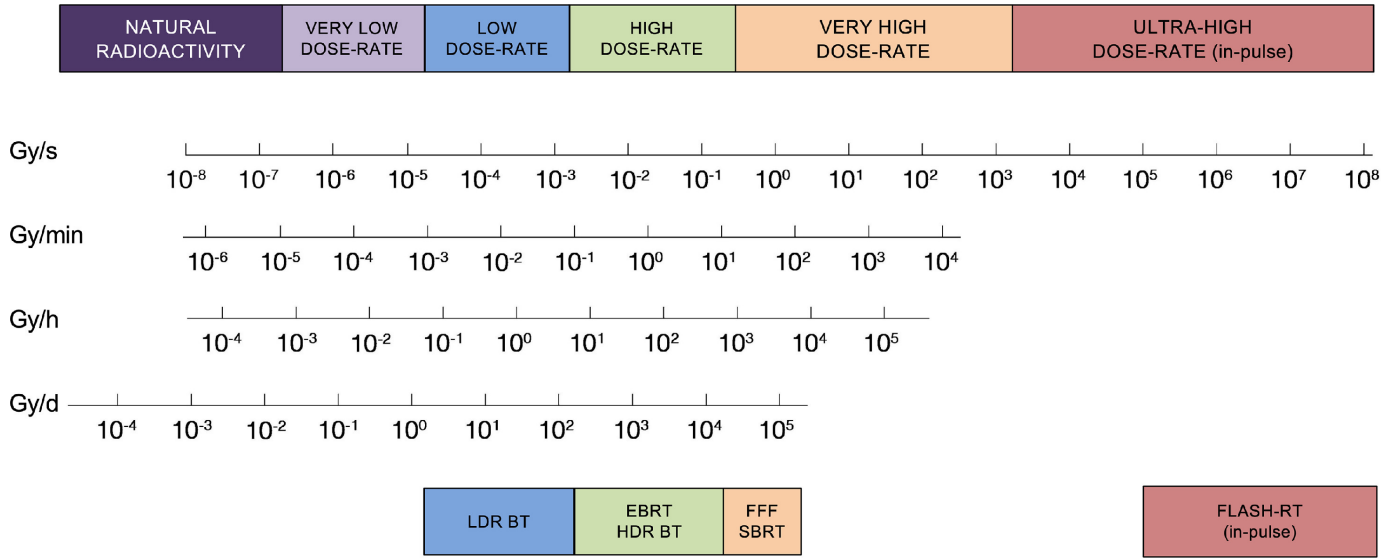
Disclosures

No conflicts to disclose

Learning Objectives

- Understand the concept of dose-rate effect
- Understand the mechanism of dose-rate effect and its key components
- Identify clinical significance of dose-rate in conventional radiotherapy
- Understand the potential for ultrahigh dose-rates

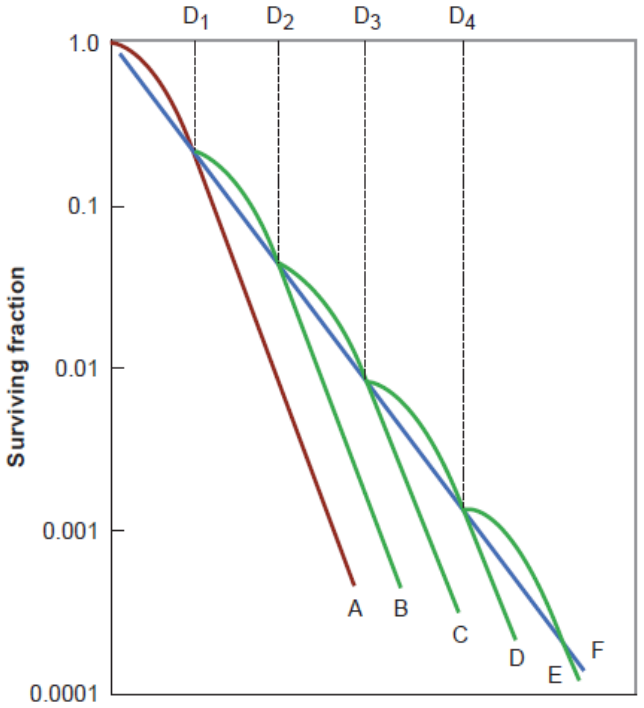
Classification if dose-rates



- **Clinical dose-rates:**
  - **0.001-0.1 Gy/min (LDR)**
  - **0.1-10 Gy/min (HDR and EBRT)**

Dose-rate effect

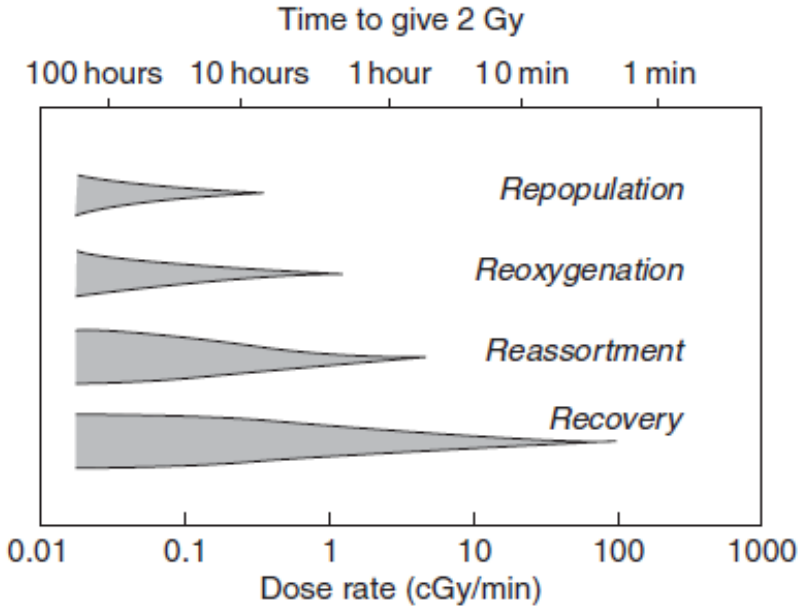
- For X-rays, dose-rate is one of the factors in biological consequence
- Lower dose-rate and prolonged exposure -> reduced biological effect (typically)
- Repair of sublethal damage (SLD)
- The ultimate form of fractionation.



Radiobiology for the Radiologist, 7th ed. Eric J. Hall

Mechanisms of dose-rate effect

- **At clinical doses and dose-rates: chemical processes occur but no DNA repair or any other procss (2 Gy @ 1-5 Gy/min)**
- **Lower dose-rate for a given dose allows for other biological processes to happen (4Rs or radiobiology)**
- **Cellular repair is fastest (half-time <1 hr)- Dose-rate range: 1 Gy/min-0.1 cGy/min**
- **Repopulation is slow (half-time > 1day)- Dose-rate < 2 cGy**
- **Redistribution and reoxygenation: intermediate dose-rate range**

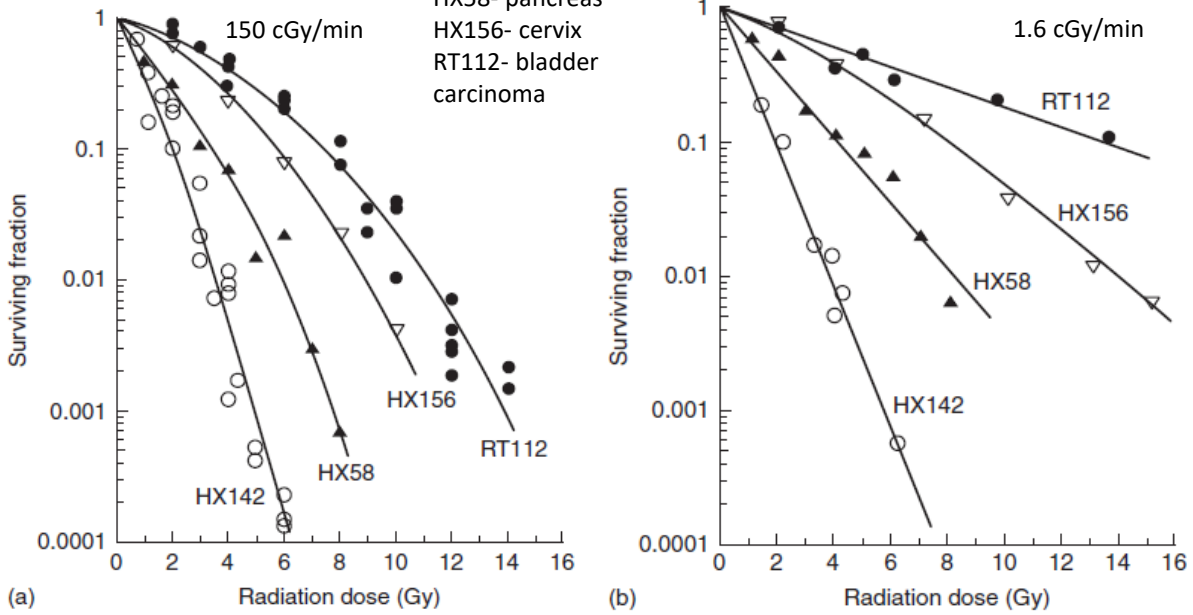


Basic Clinical Radiobiology, 4th edition

Dose-rate and cell survival

- **Dose-rate effect varies for different cell types**
- **Wide range of sensitivity among cell lines**
- **~ factor of 3 in the doses to provide the same effect for high dose-rate**
- **~ factor of 7 in the doses to provide the same effect for low dose-rate**
- **Low dose-rate -> better separation between cells witl different radiosensitivities**

HX142- neuroblastoma
HX58- pancreas
HX156- cervix
RT112- bladder carcinoma



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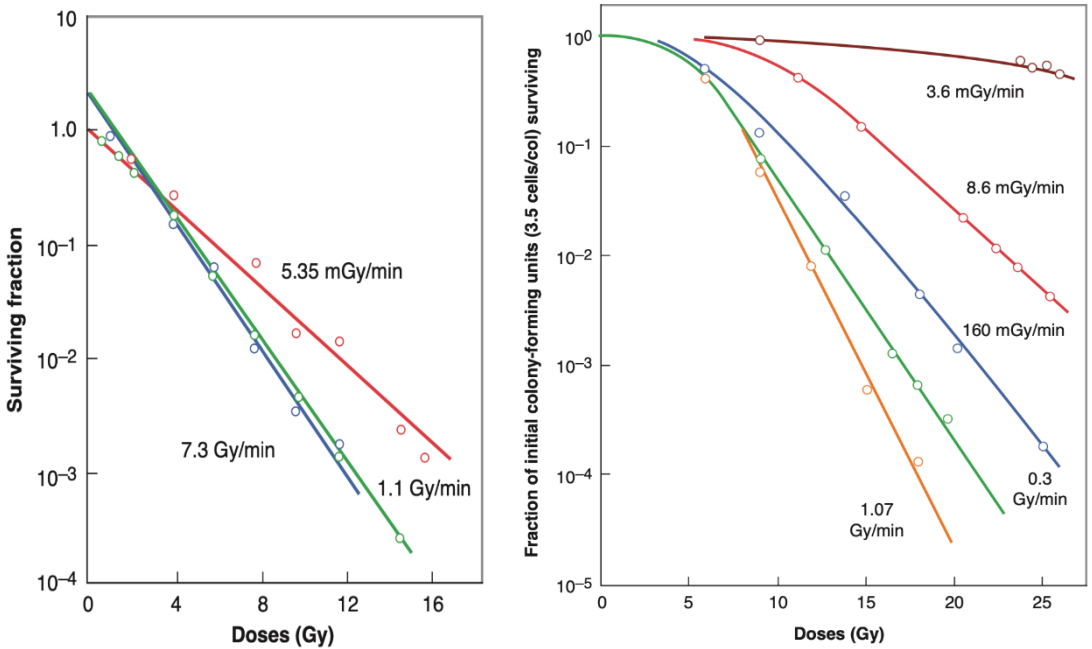
Dependence on cell type

- **HeLa cells have a small shoulder for acute exposure and small dose-rate effect (left)**
- **Chinese hamster cells have a broad shoulder and large dose-rate effect (right)**



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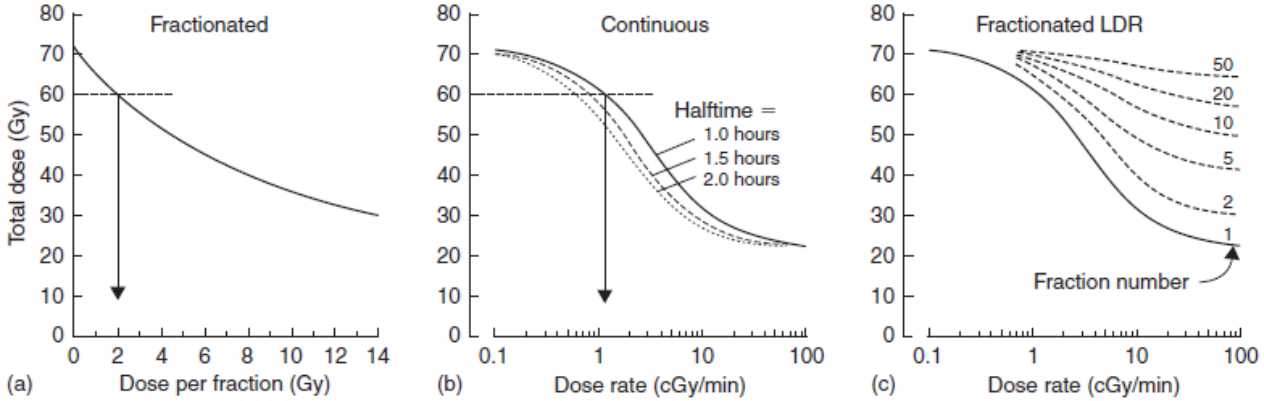
Isoeffect relationships



- **Incomplete repair model for continuous irradiation:**
  - **E: level of effect**
  - **D: total dose**
  - **g: function of duration of continuous exposure**
  - **T1/2: recovery halftime**

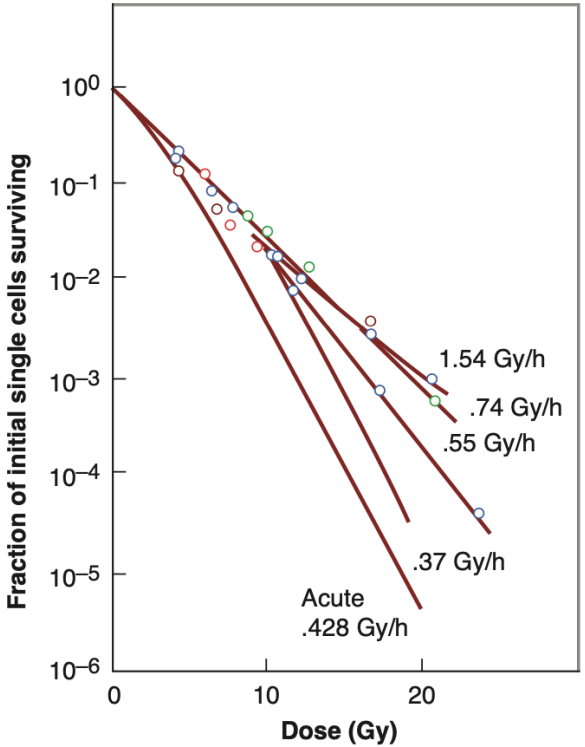
$$E = \alpha D + \beta D^2 g$$

$$g = 2[\mu t - 1 + \exp(-\mu t)]/(\mu t)^2$$

$$\mu = 0.693/T_{1/2}$$

Inverse Dose-rate Effect

- Occurs in certain cell lines
- Dose-rates < 1.5 cGy/min
- Increased cell killing
- Cells progress through the cell cycle into more sensitive phases
- May be a factor ineffectiveness of low-dose permanent implants



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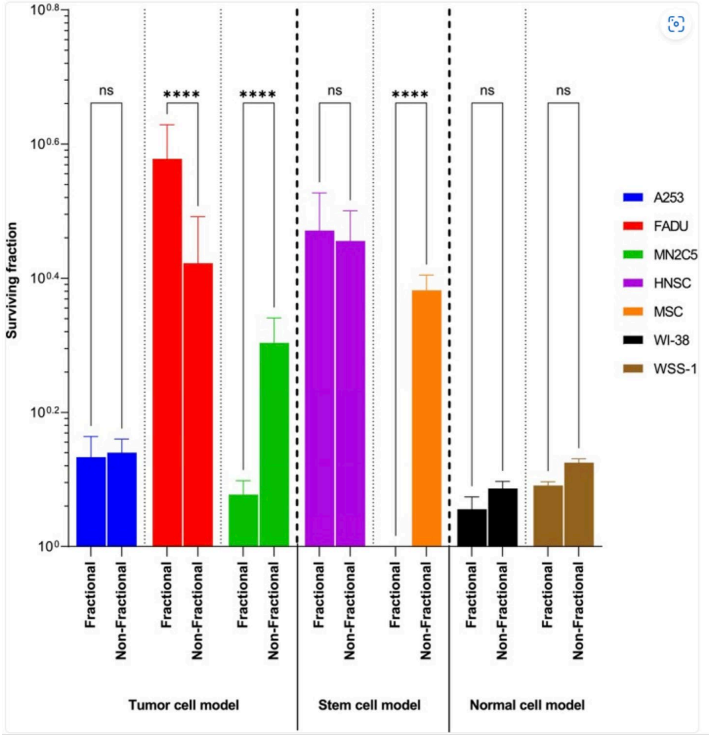
IMRT and Dose-rate

- IMRT/VMAT: higher number of segments to deliver conformal treatment
- Results in longer treatment times
- Up to 20% decreases in cell kill effectiveness for 20-30 min treatment
- More recent studies show cell type dependence

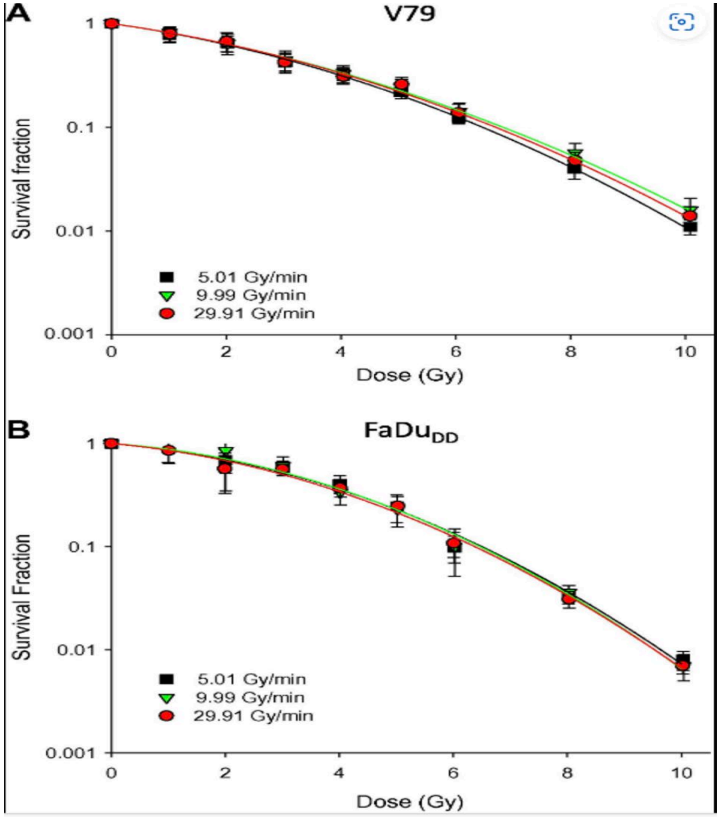


Kamer et al, Cancer Med. 2023 Sep 27;12(19):19874–19888

FFF beams and Dose-rate

- **Flattening filter-free (FFF) beams -> instantaneous dose rate increase by approximately a factor 4**

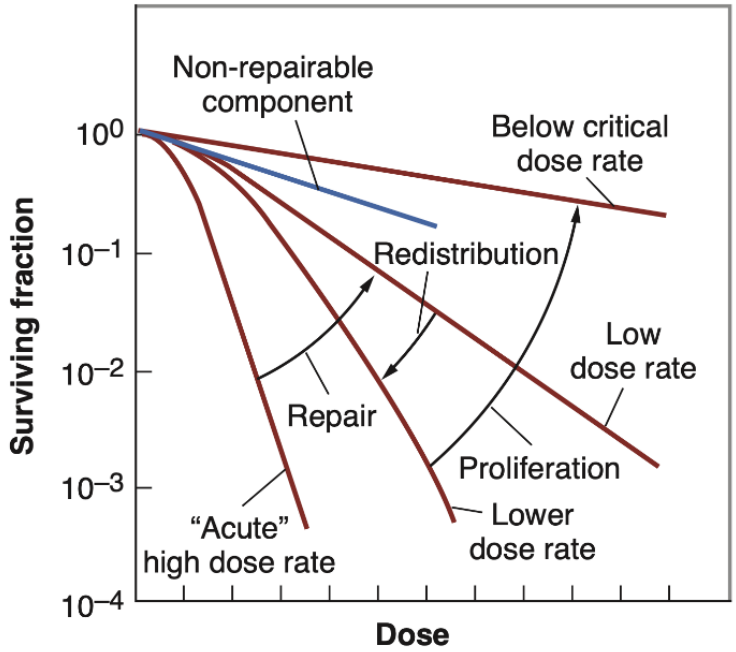
- **The *in vitro* cell survival studies showed no difference when increasing the dose rate to 30 Gy/min**



Sorensen et al, radonc.2011.06.018

Summary of dose-rate effect

- Acute exposure -> initial shoulder
- Lowered dose-rate -> SLD repair with protracted exposure -> no shoulder
- Further lowered dose-rate -> redistribution
- Further reduction -> proliferation

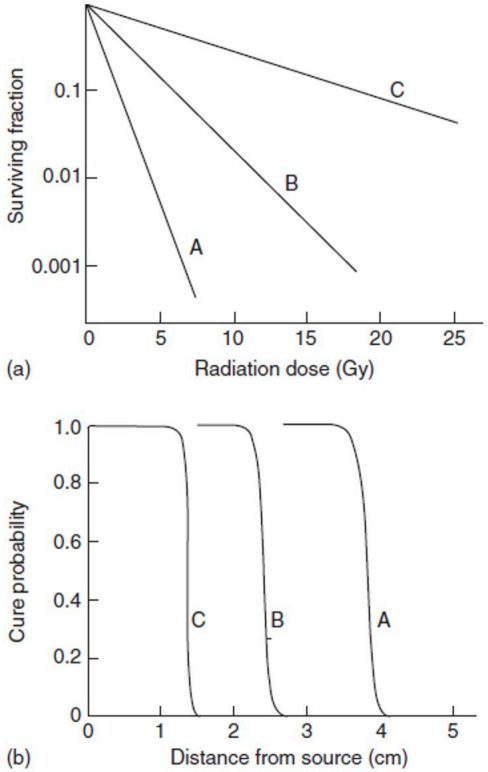


Radiobiology for the Radiologist, 7th ed. Eric J. Hall

Dose rate and brachytherapy

- **Choice of BT not related to radiobiology**

- **Dose-rate dependence based on distance from the source**



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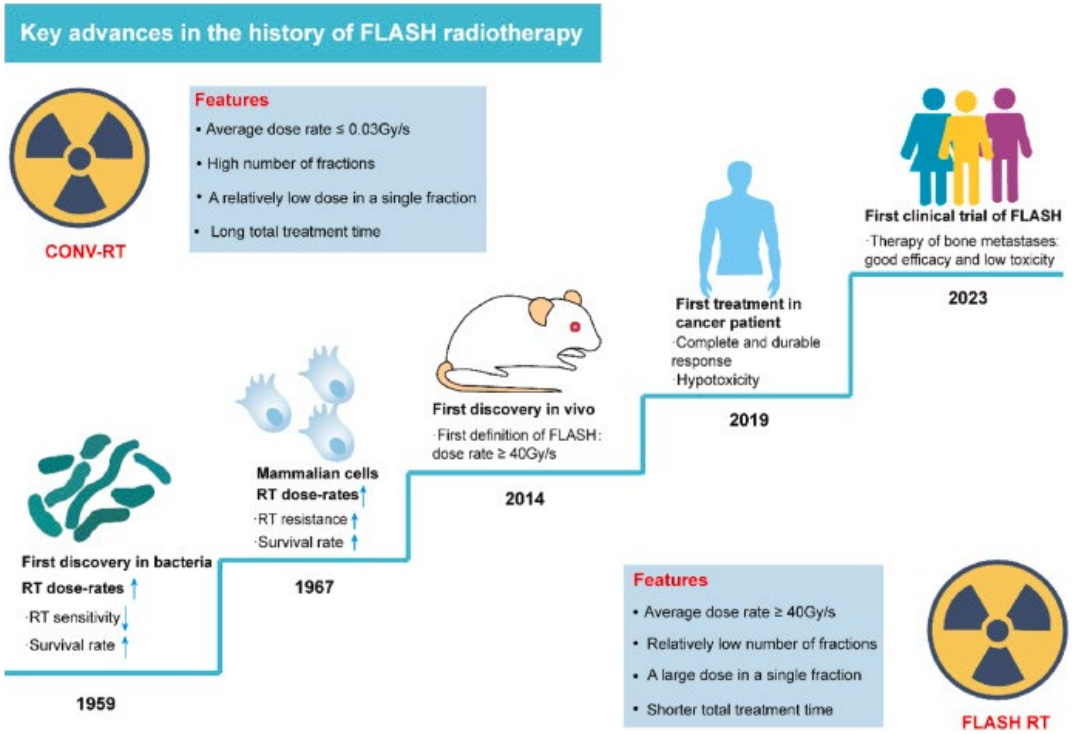
The Flash effect

	FLASH-RT	CONV-RT
Mean dose rate	≥40Gy/s	≤1Gy/min
Delivery time	<200ms	> 1min
Dose delivery	High dose in a single fraction	Low dose in a single fraction
Tumor control	A similar antitumor effect as CONV-RT	Effective tumor killing
Normal tissue sparing	Reduce the damage to healthy tissues	Acute and late damage to healthy tissues
Defects	Few accessible irradiation facilities	Radiation injury and limited treatment window

FLASH-radiotherapy (FLASH-RT), Conventional dose rate radiotherapy (CONV-RT).

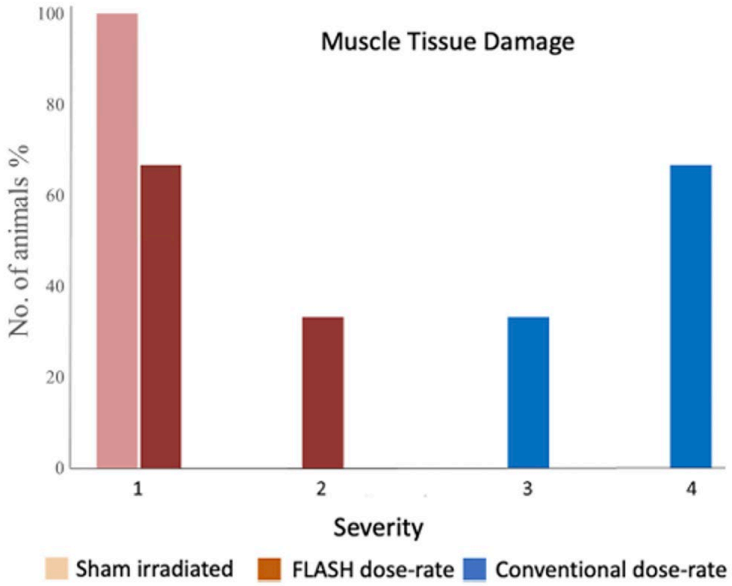
The FLASH effect

- Decreased radiosensitivity in Salmonella bacteria increased survival rate with increasing dose-rate (1959)
- Increased radioresistance due to oxygen depletion in mammalian cells with increased dose-rate (1967-69)
- In vivo FLASH showed suppressed pneumonia and pulmonary fibrosis after a single dose of 17 Gy with no loss in antitumor effect.



Biological mechanism of FLASH

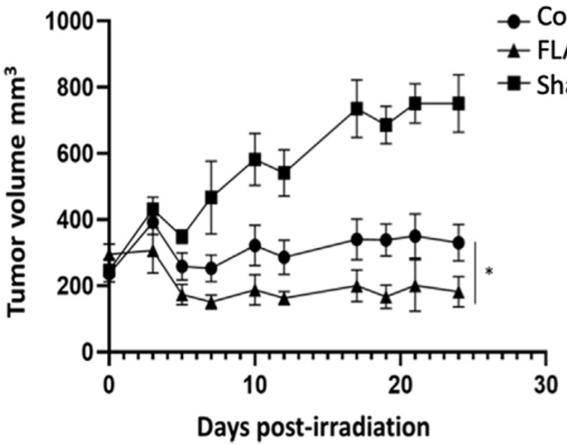
- **Protective effect of FLASH on normal tissue has been shown for a variety of tissues in animal models (brain, lung, intestines, etc.)**
- **Oxygen depletion hypothesis**
- **FLASH-RT induces fewer DNA single-strand breaks (SSBs) than CONV-RT by reducing the production of perhydroxyl radicals**
- **Decreases normal tissue injury by diminishing the stress response and inflammatory response**

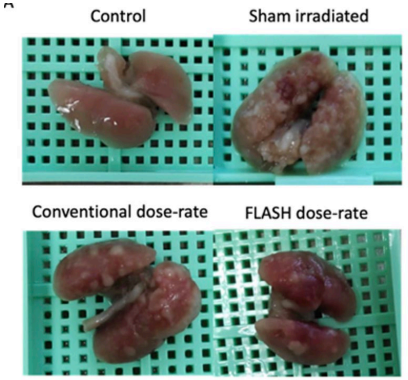


Tinganelli et al, Radiotherapy and Oncology 175 (2022) 185–190

Biological mechanism of FLASH

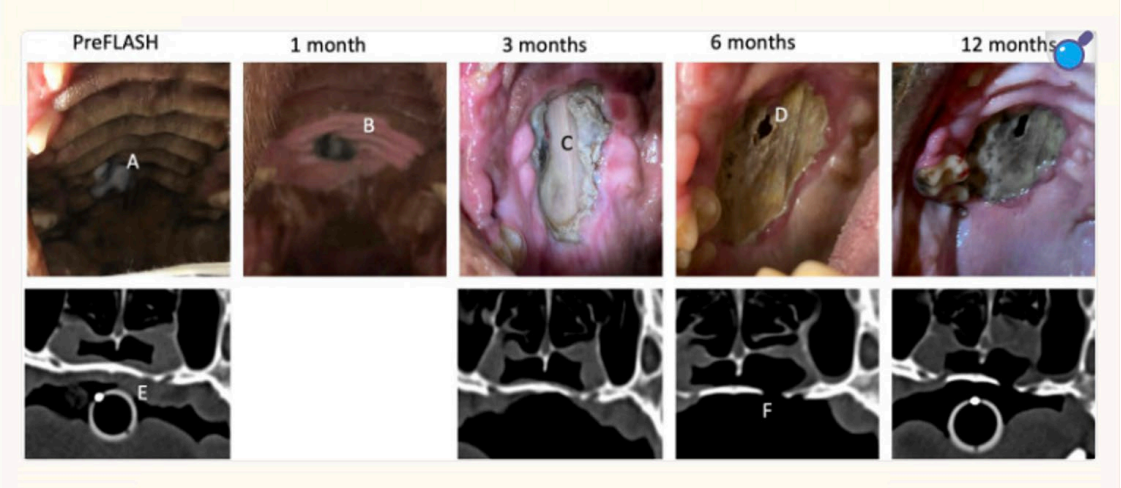
- **Tumour killing:**
  - **Creating more reactive oxygen species, mediating DSBs in tumours**
  - **Promote tumour killing by increased recruitment of T lymphocytes**
  - **Increasing the size of intratumou iron pools magnifying organic hydroperoxide and oxidative damage**





Tinganelli et al, Radiotherapy and Oncology 175 (2022) 185–190

The Flash effect-preclinical results

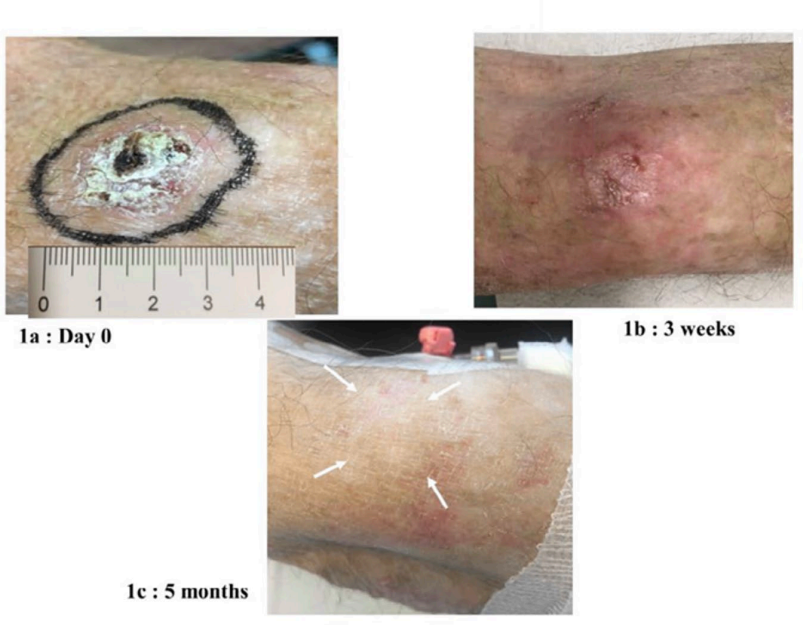


- Canine study with 10 MeV electron FLASH beam, average 115 Gy/sec, treatment time < 305 msec
- 11 dogs with oral cancers
- Generally effective treatment (8 complete response, 3 partial response)
- Increased grade 3 late normal tissue toxicity (oral radionecrosis)
- Single fraction of >30 Gy exceeded bone tolerance

Borreson et all, Front Oncol, 2023, Sep 11;13:1256760

The Flash effect-clinical results

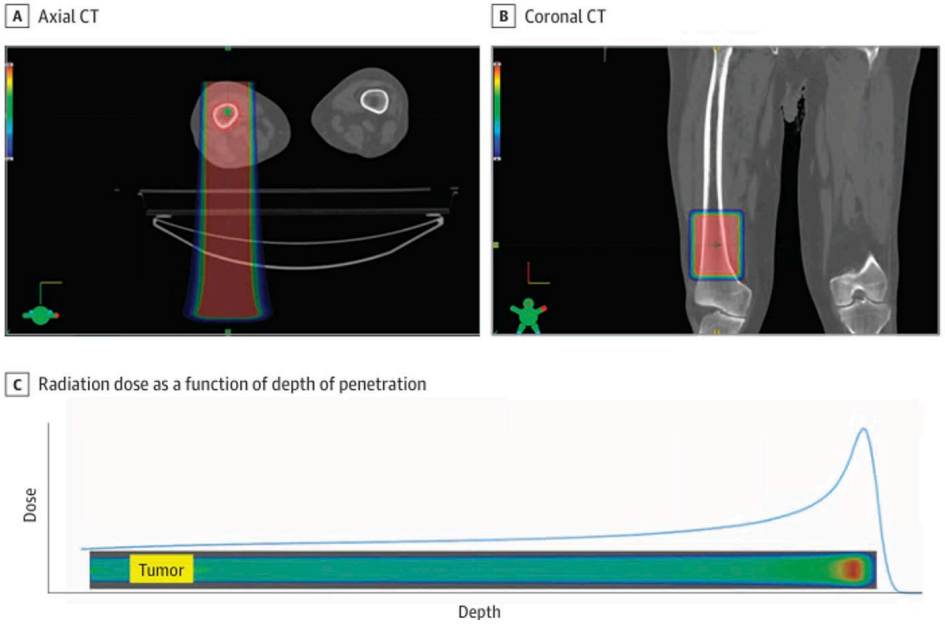
- 75-year-old patient with a multiresistant T-cell cutaneous lymphoma disseminated throughout the whole skin surface
- 15 Gy in single fraction, treamtent time 90 sec
- 110 previous RT treatments
- Only grade 1 toxicity at 3 weeks
- Complete and durable tumour response at 5 months



J. Bourhis et al./Radiotherapy and Oncology 139 (2019) 18–22

The Flash effect-clinical results

- First FLASH clinical trial in humans
- FLASH with proton beam
- 10 patients with extremity bone metastases
- 8 Gy in single fraction at 60 Gy/sec
- Endpoint: feasibility, pain score, side effects
- Adverse events were mild and consistent with conventional radiotherapy
- Transient pain flares: 4 of the 12 treated sites, pain relief: 8 out 12 sites, complete response (no pain): 6 of the 12 sites .



Mascia et al. JAMAOncol. 2023;9(1):62-69

Summary

- Dose-rate effect is the ultimate form of fractionation
- Mechanisms depend on dose-rate and duration of exposure
- Dose-rate effect is cell type dependent
- IMRT and VMAT techiques may lead to reduced cell killing. The effect depends on cell type
- Higher dose-rates of flattening filter free beams don’t impact cell survival
- FLASH RT may offer normal tissue protection with isoeffect tumour control but more long studies with long term follow up are needed.

Questions?

Thank you!

Hedi Mohseni