Nuevas avenidas en radioterapia: moldeando la respuesta biológica

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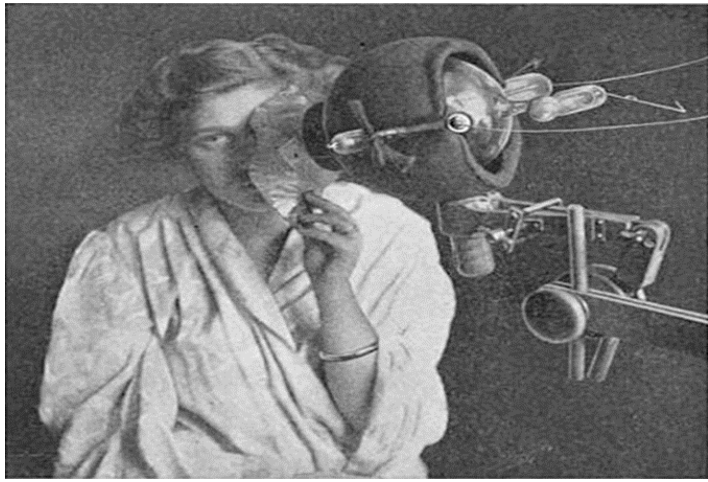
Radiotherapy

- One of the most important methods of cancer treatment. At least 50 % of all cancer patients will receive radiotherapy at some stage during the course of their illness

- The classical paradigm in RT is changing



From direct cell death (DNA double strand breaks) …

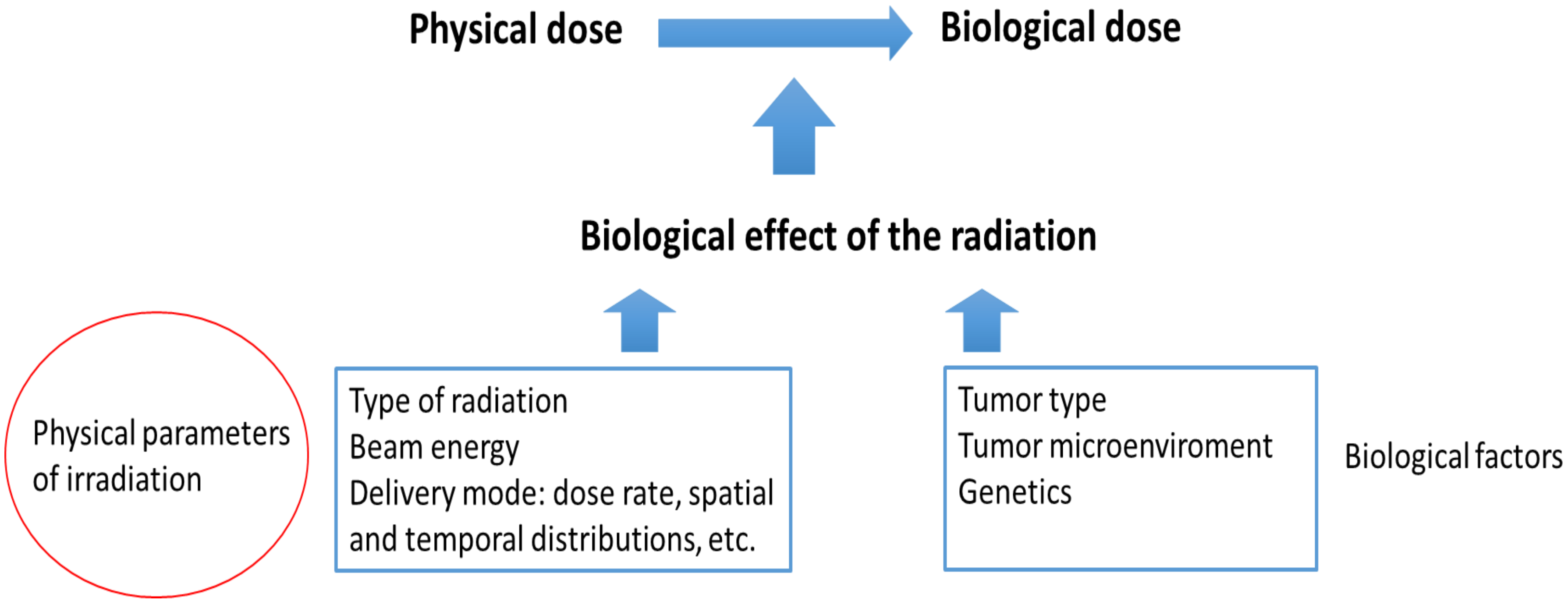
… *to non-(DNA) targeted effects*

emerging evidence of the importance of cell signaling, role of vascular and immune system, among others, in biological response.

Radiotherapy

- Treatment of some **radio resistant tumors, paediatric cancers** and tumors close to a delicate structure (i.e. spinal cord) is currently **limited**

- The main challenge in RT is to find **novel** approaches leading to an increase of the normal tissue resistance

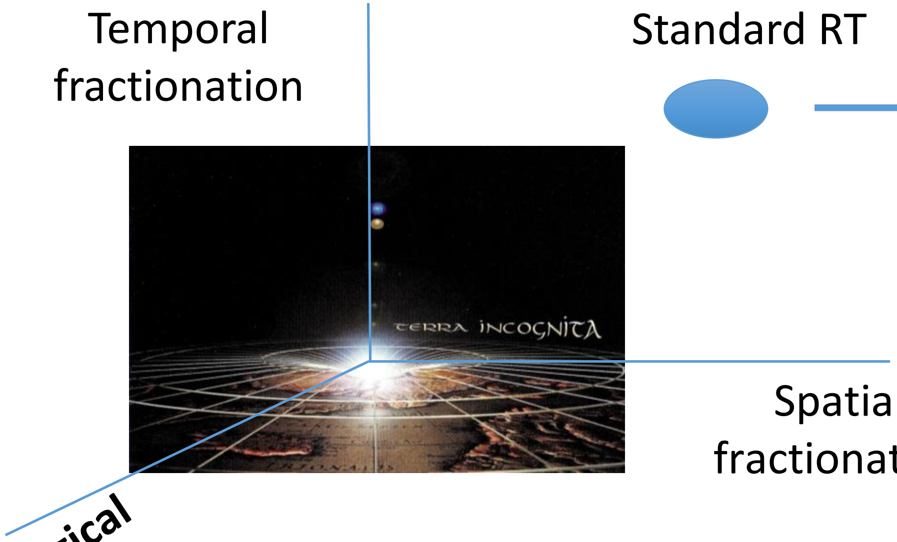


Radiotherapy: modeling biological response

- Standard RT is **restricted** to the same few temporal and spatial schemes, dose rates, broad field sizes

Temporal fractionation

Standard RT



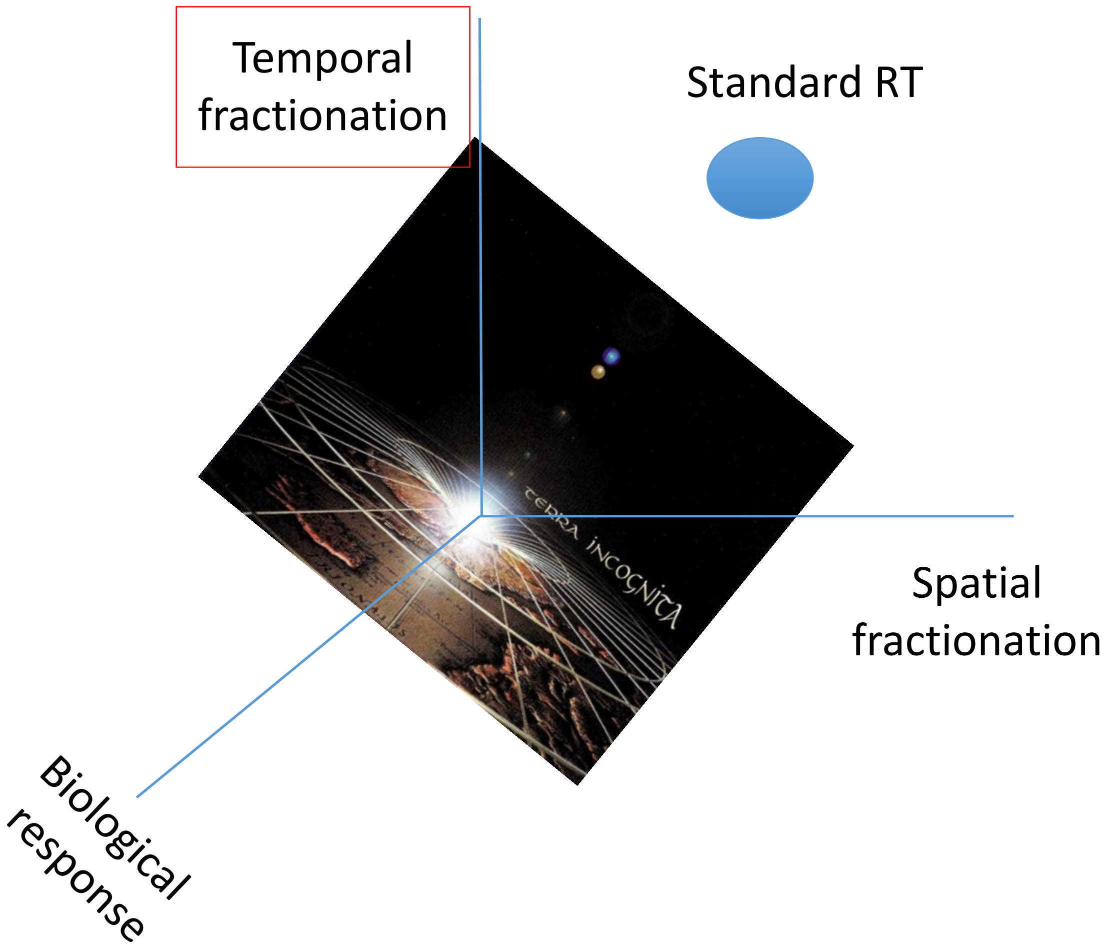
Spatial fractionation

Biological response

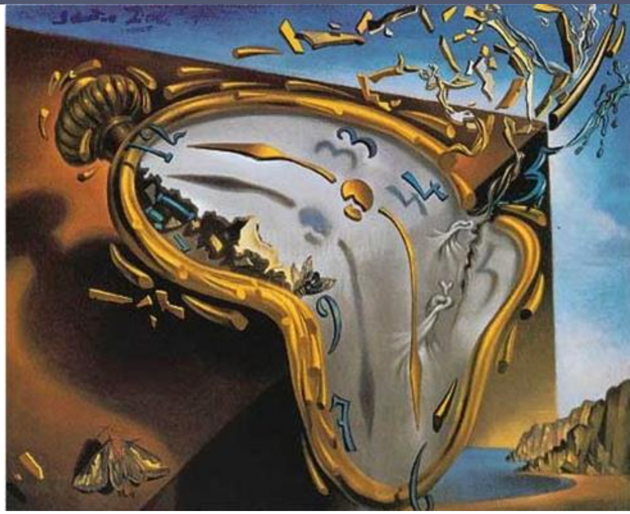
- *Mainly photons*
- *2 Gy/session, 1 session per day, 5 days/week*
- *Dose rate~ 2 Gy/min*
- *Field sizes > cm^2*
- *Homogeneous dose distributions*

Large "terra incognita" on how radiation physical parameters impact on biological response

Radiotherapy: modeling biological response

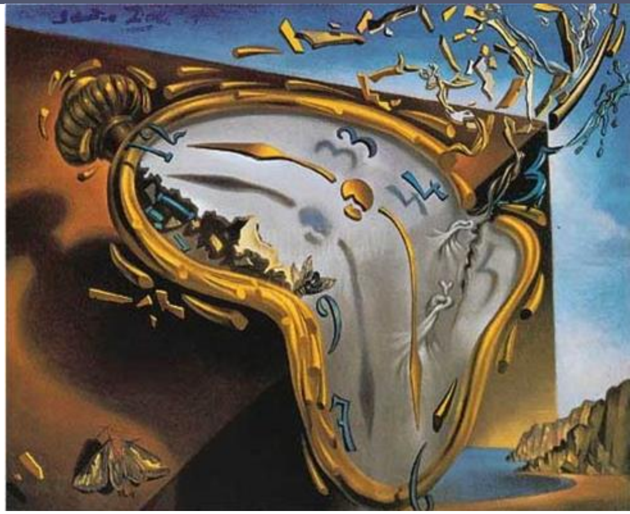


Temporal fractionation of the dose



- Dividing a dose into several fractions spares normal tissues
  - Repair of sublethal damage between dose fractions
  - Repopulation of cells
- Dividing a dose into several fractions increases damage to the tumor
  - Reoxygenation of tumor environment
  - Reassortment of cells into radiosensitive phases of the cell cycle
- Prolongation of treatment reduces early reactions
- However, excessive prolongation allows surviving tumor cells to proliferate

Temporal fractionation of the dose



Common scheme 2 Gy/session, 1 session/days, 5 days week, 5-6 weeks

Other schemes explored

- Hypofractionation (higher doses-less days)

  benefit for some prostate, breast, lung cancers

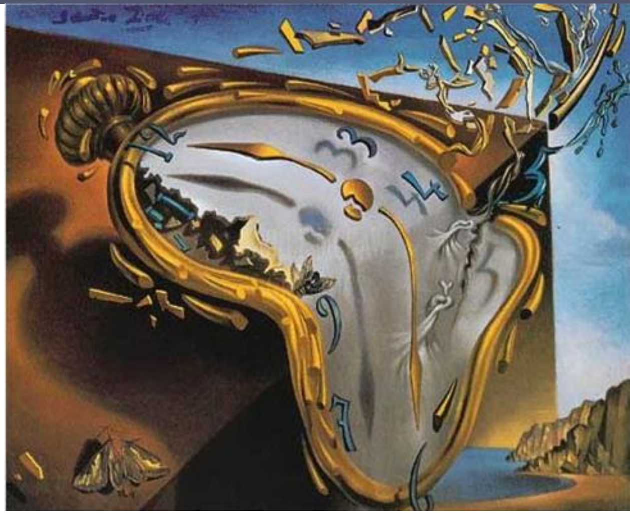
- Hyperfractionation (lower doses, twice per day, more days)

  advantageous for some head-and-neck and cervical squamous cell cancers

- Continuous hyperfractionated accelerated radiation therapy (three small sessions per day)

  used to treat lung cancer

Temporal fractionation of the dose



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TIME MATTERS

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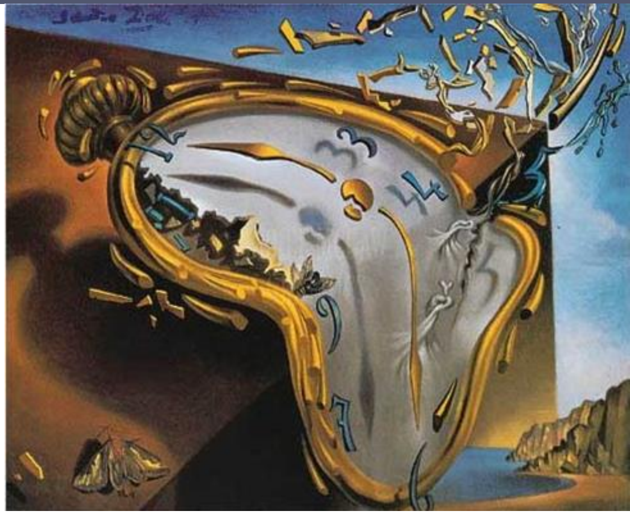

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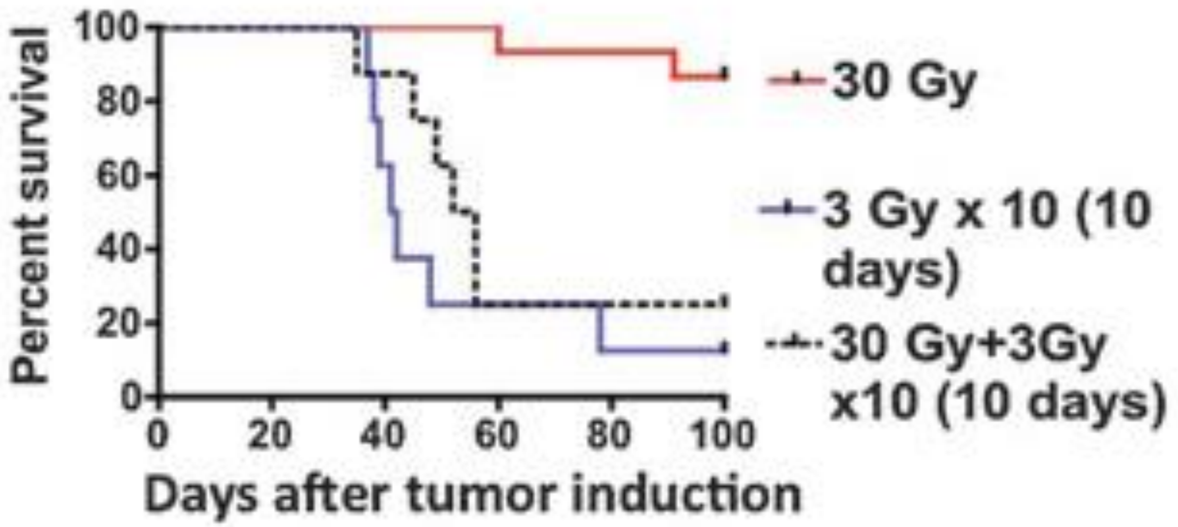
High single dose can estimulate immune system

High single dose radiation (30 Gy) increases CD8$^+$ T cells in the stroma of tumors with induced remissions



BALB/c mice. CT26 & MC38 colon tumors

Baker et al, Clin. Cancer research 2015

Radiotherapy: modeling biological response

Tumor control probability

Normal tissue complication probability

Physical dose → **Biological dose**

Biological effect of the radiation

Physical parameters of irradiation

Type of radiation
Beam energy
Delivery mode: **dose rate**, spatial and temporal distributions, etc.

Tumor type
Tumor microenviroment
Genetics

Biological factors

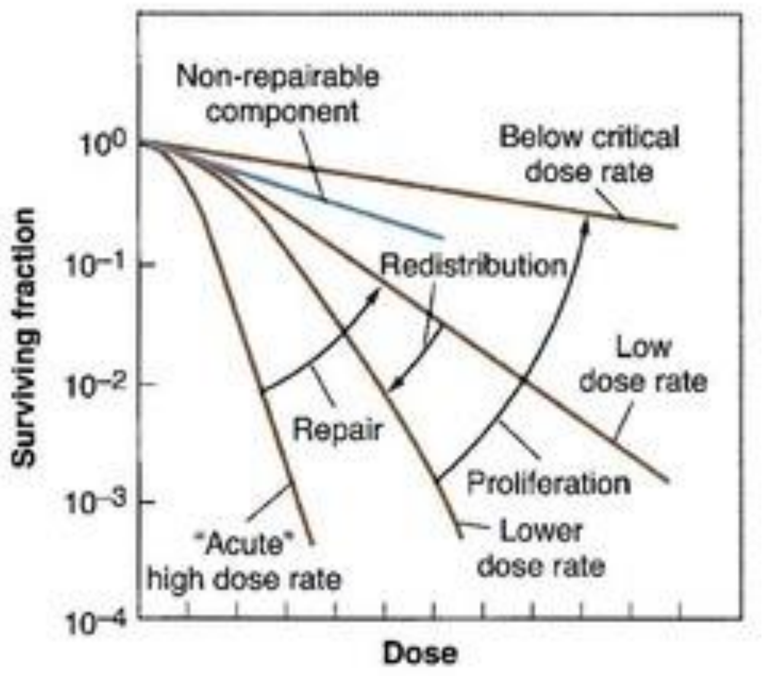
Dose rate

Common dose rates in external RT 2 Gy/min -- Most modern machines 18 Gy/min

In general ↓dose rate ⇨ ↓ cells killing (time to repair)

However, in some cases (low dose rates) there is an inverse dose rate effect, which is thought to be due to redistribution and cells piling up in the radiosensitive G2 cell cycle check point.

No evaluations performed at very high dose rates.



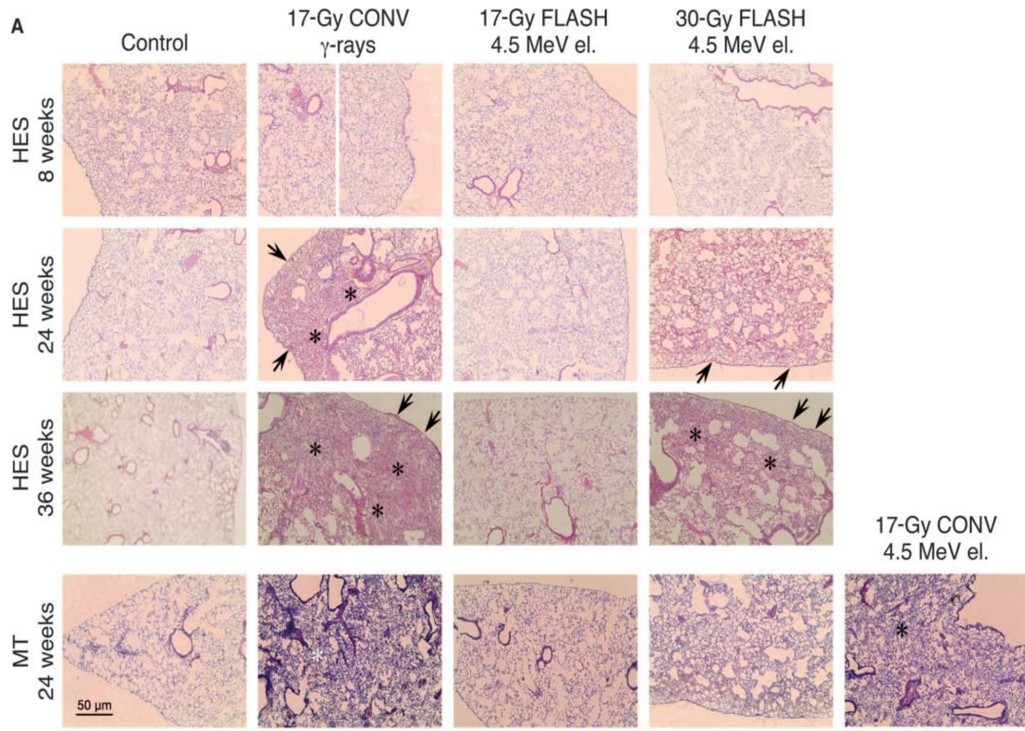
Dose rate

FLASH irradiation ⇨ the dose is given in short pulses (< 500 ms) at ultrahigh dose rate (> 40 Gy/s)

Differential effect tumor-healthy tissues

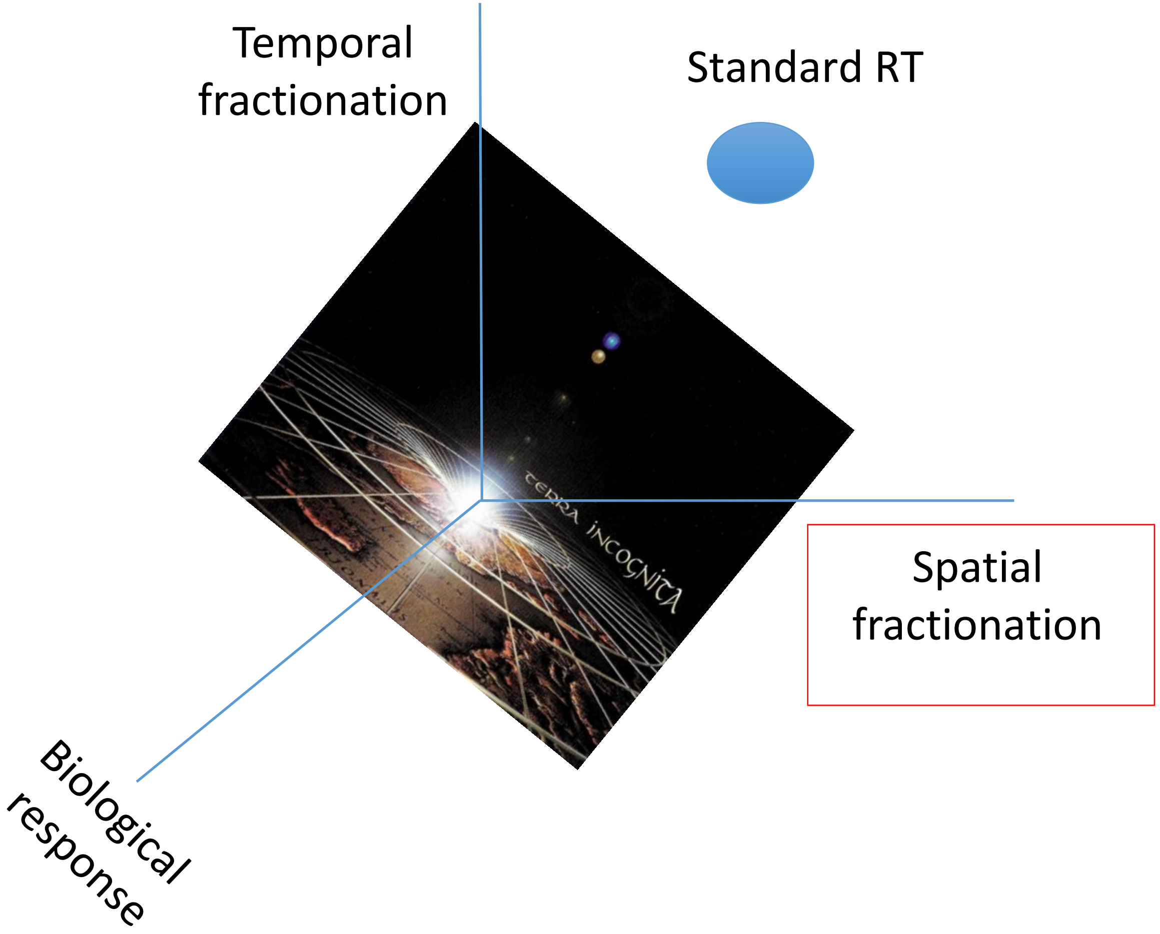
- *Tumor control equivalent to conventional RT*
- *Significantly reduces side effects in normal tissues*

Ex. complete lack of acute pneumonitis and late lung fibrosis after bilateral thorax irradiation of C57BL/6J mice with FLASH at doses known to trigger the development of fibrosis in 100% of animals after conventional RT.

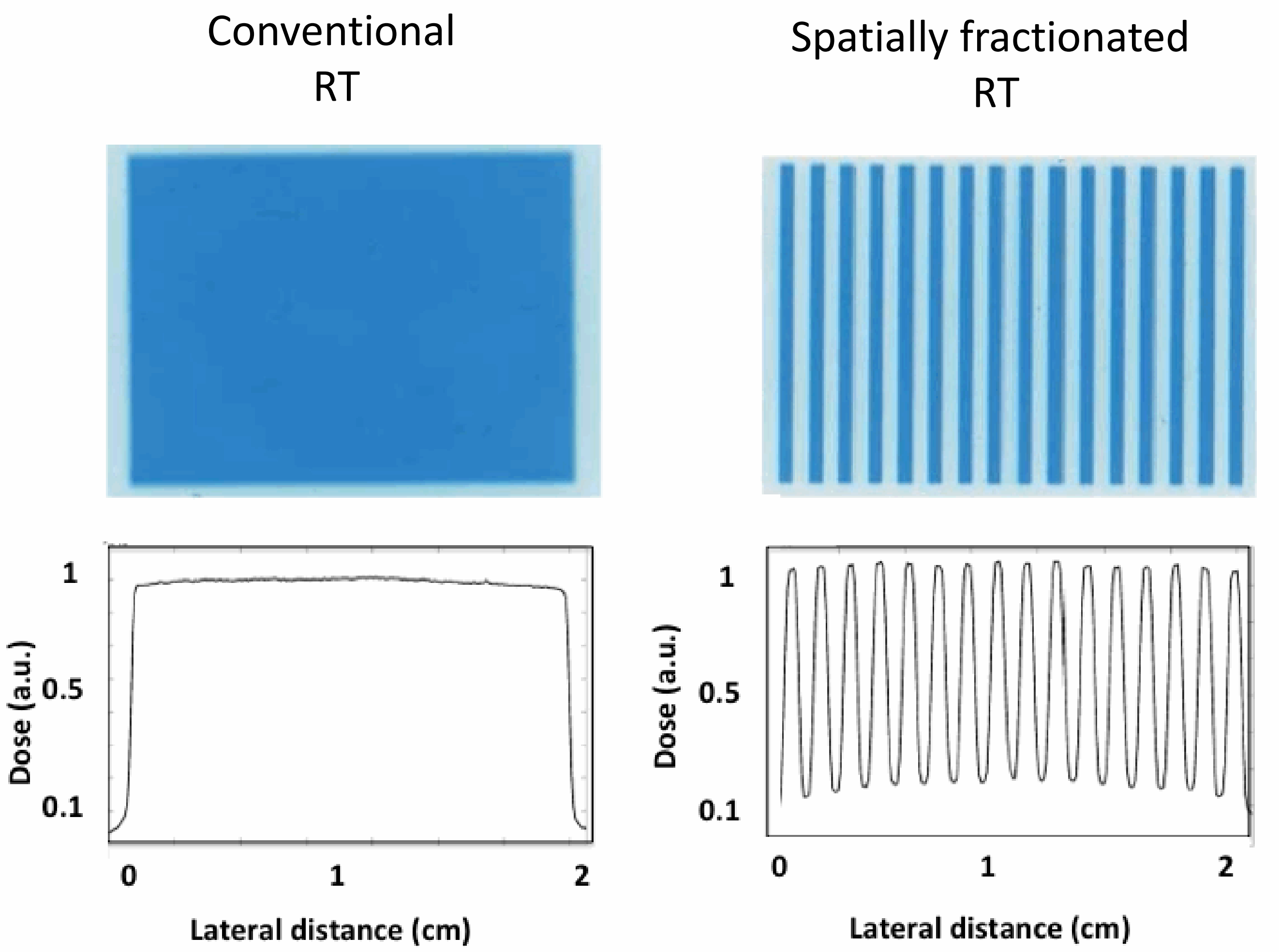


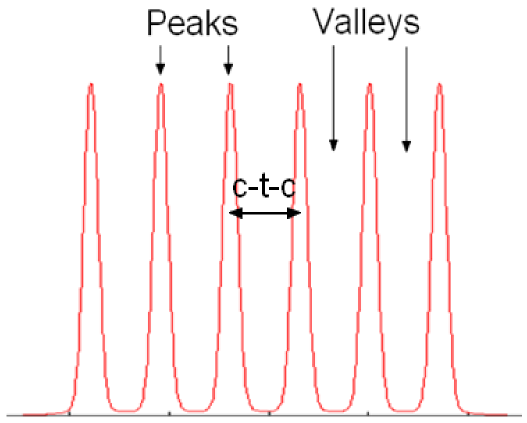
Favaudon et al. 2014

Radiotherapy: modeling biological response



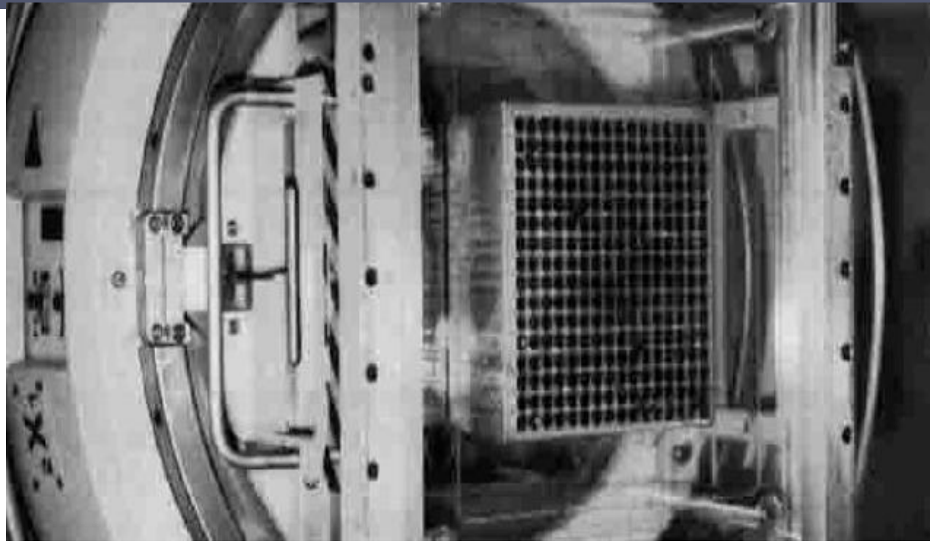
Spatial fractionation of the dose





$$PVDR = \frac{D_{\text{peak}}}{D_{\text{valley}}}$$

RT techniques based on a spatial fractionation of the dose



GRID Therapy (few hospitals in the world)

1909 Alban Kohler used a “perforated screen” (grid)→ effect similar to treatment with small pencil beams.

Widely used in the 1950s as a way to reach tumors deep in the body with kilovoltage beams.

From the 70s GRID therapy with megavoltage radiation beams → palliation of selected, massive and bulky tumors

Improved response to RT and may possibly have cell killing effects outside the directly irradiated area

Beam sizes > 1 cm^2

PVDR from 2 to 5

Radiotherapy: modeling biological response

Tumor control probability

Normal tissue complication probability

Physical dose → **Biological dose**

Biological effect of the radiation

Physical parameters of irradiation

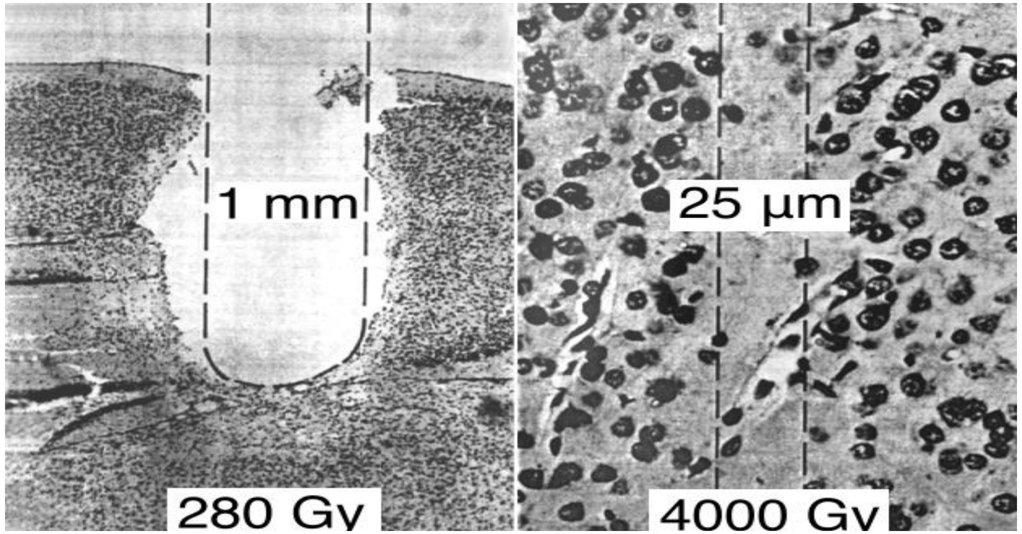
Type of radiation
Beam energy
Delivery mode: dose rate, spatial and temporal distributions, field size, etc.

Tumor type
Tumor microenviroment
Genetics

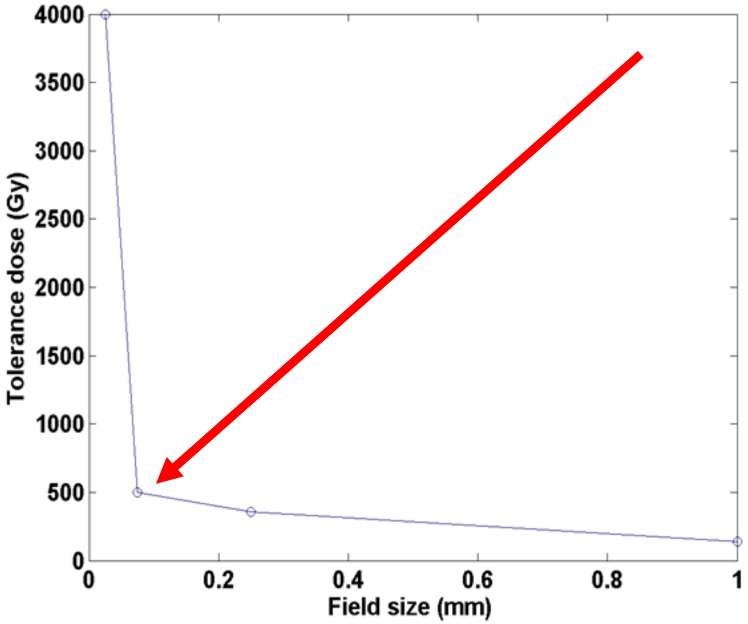
Biological factors

Field size

Dose-volume effect: the smaller the field size is, the higher the tolerance

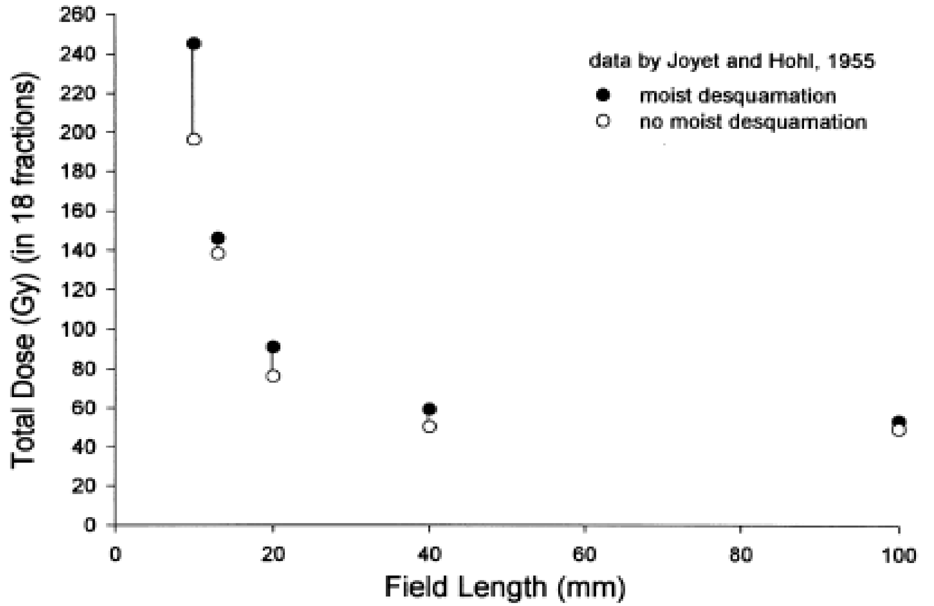


Zeman et al., Science (1959)

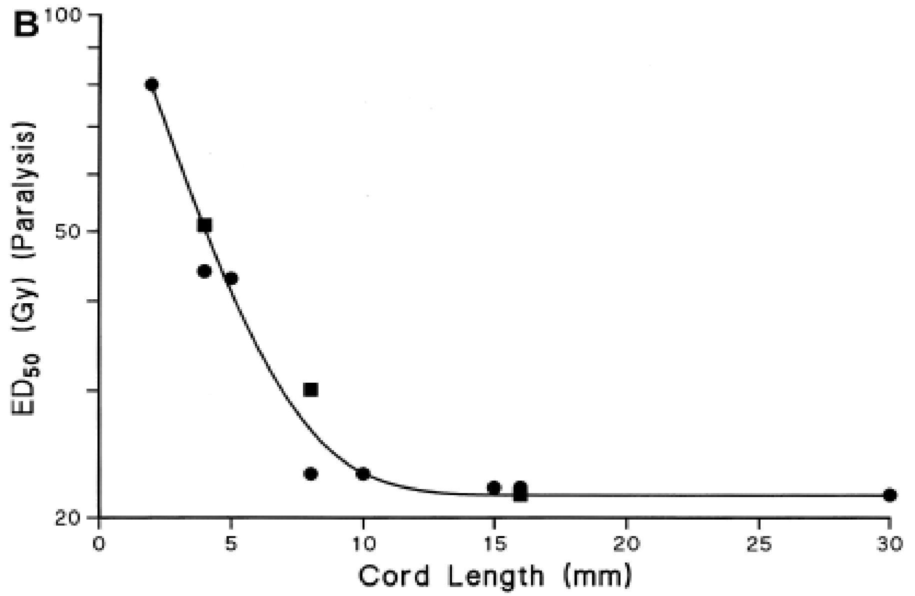


More recent examples with high energy photons

SKIN



SPINAL CORD



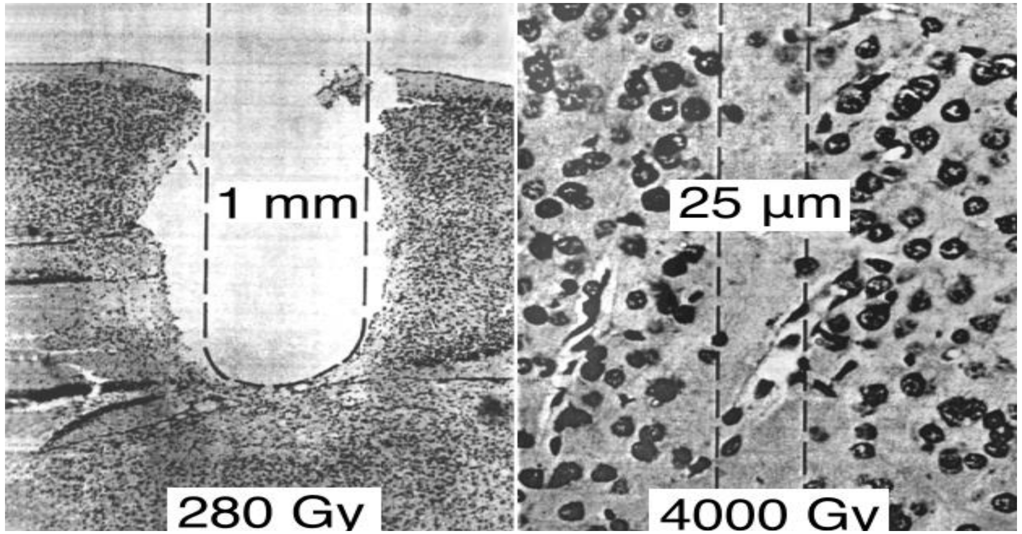
J.W. Hopewell, K.R. Trott / Radiotherapy and Oncology 56 (2000) 283-288

Novel RT techniques based on “different” delivery modes

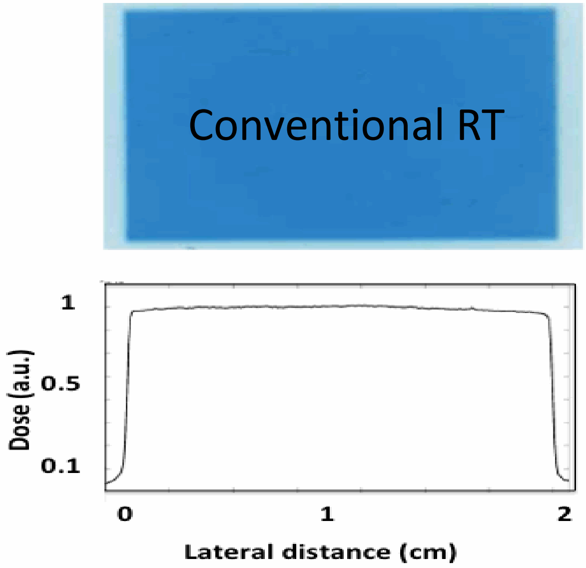
Combination

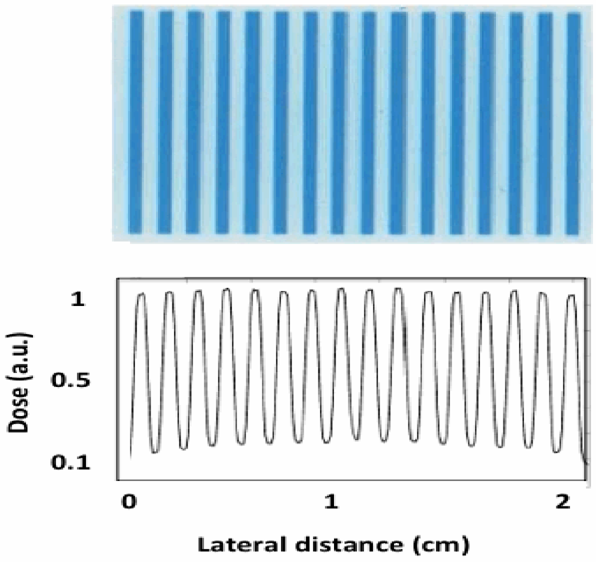
very small field sizes (< $1mm^2$) + Spatial fractionation of the dose

Dose-volume effects



Zeman et al., Science (1959)



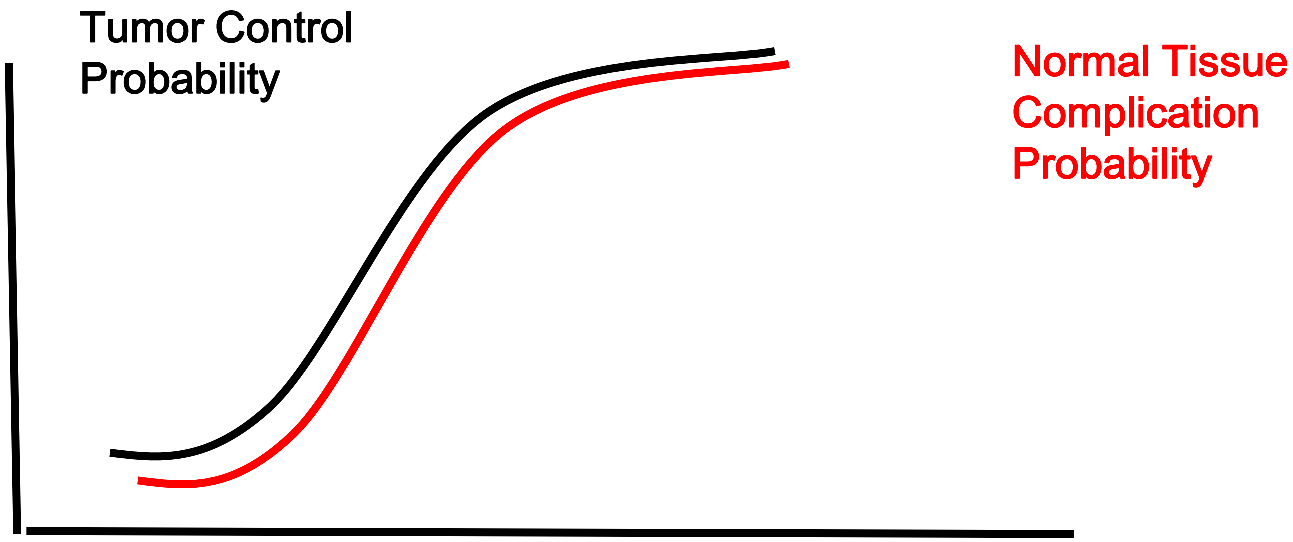


Novel RT techniques based on “different’’ dose delivery methods

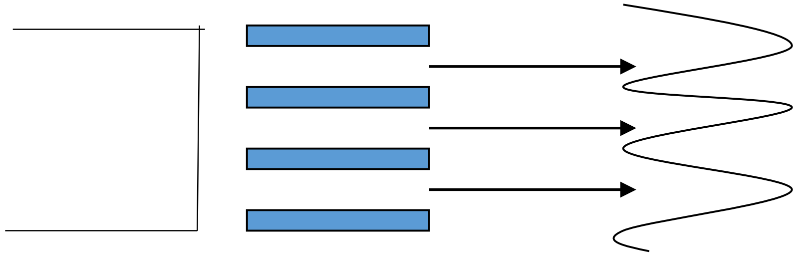
Dose-volume effects→ exponential increase of healthy tissue tolerances

+

Spatial fractionation→ gain in healthy tissue recovery →increase of healthy tissue tolerances



Synchrotron micro and minibeam radiation therapy



Submillimetric field sizes (25 to 700 µm)
Interbeam separation (400 to 3500 µm)

Dose profiles consist of a pattern of peaks and valleys

Kilovoltage beams

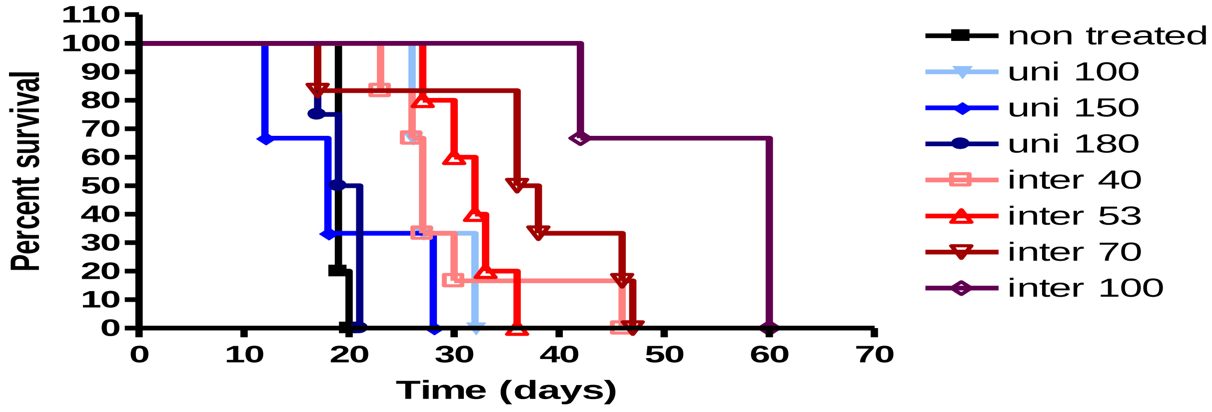
Minibeam Radiation therapy

High resistance of normal tissues (whole rat brain)

Doses as high as 100 Gy/session are still well-tolerated by the rat brain in comparison to 22 Gy in RT conventional

Prezado et al, Rad. Reseach 2015

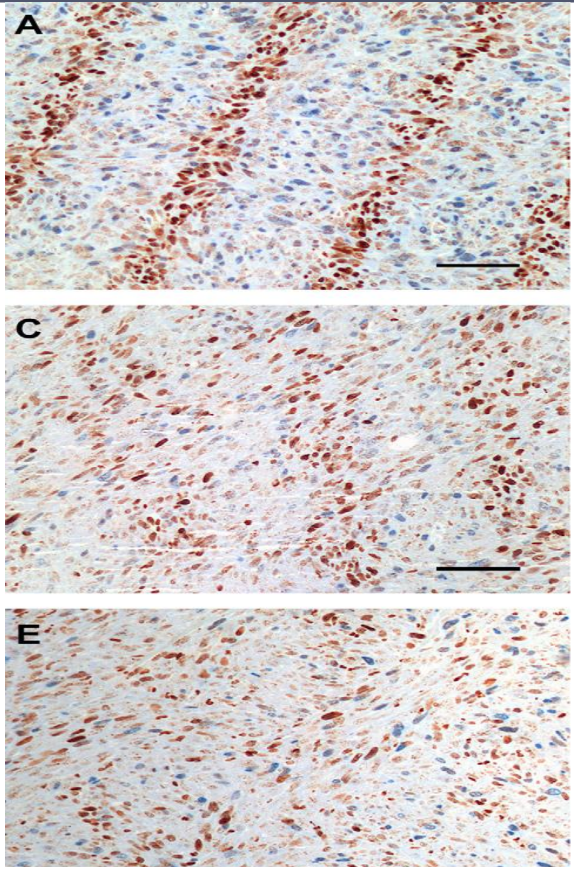
A factor 3 increase in lifespan of glioma bearing rats



Prezado et al., J. Synchr. Rad. 2012

Transfer from synchrotrons to cost-effective equipment: feasible

Biological effects not well understood



<u>Possible participants in normal tissue sparing</u>

- Dose-volume effects
- Cell migration from valleys to peaks
- Non-targeted effects

    -cell signalling effects like cohort effects

    -abscopal effects

- Microscopic prompt endothelial-repair effect, leading to a fast repair of vascular damage.

Radiotherapy: modeling biological response

Tumor control probability

Normal tissue complication probability

Physical dose → **Biological dose**

↑

Biological effect of the radiation

Physical parameters of irradiation

Type of radiation
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Delivery mode: dose rate, spatial and temporal distributions, field size, etc.

Tumor type
Tumor microenviroment
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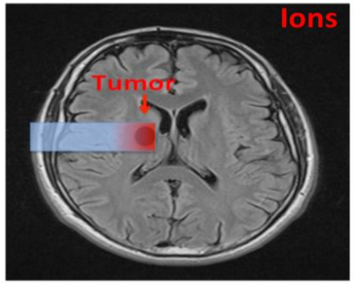
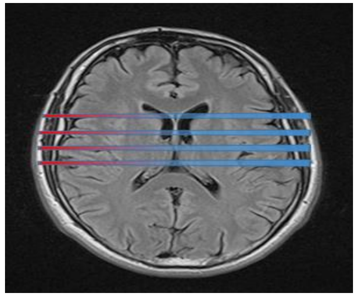
Biological factors

Different particle type

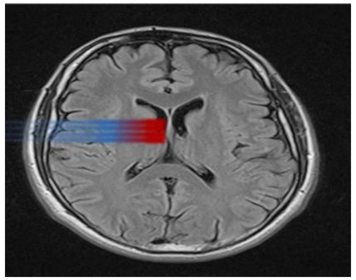


Different particle types
(charged ions)

+



Minibeam radiation therapy
(MBRT)

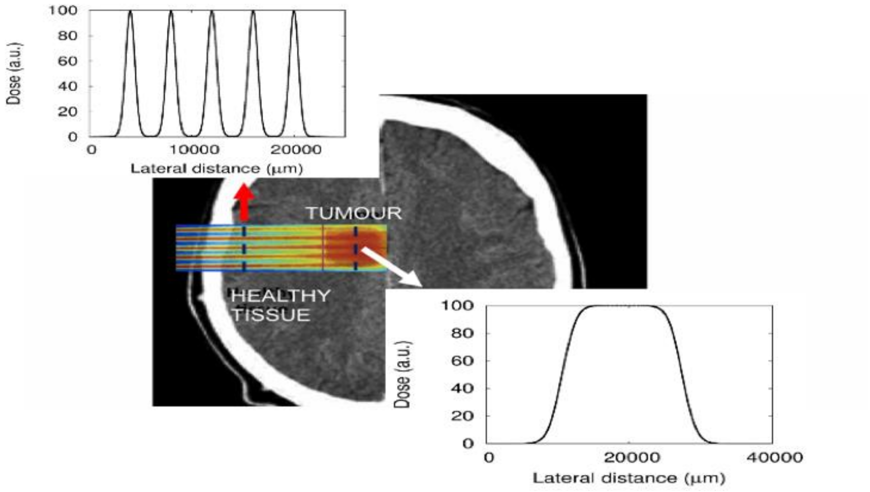


Hadron minibeam radiation therapy (*HADRON*MBRT)

I) Proton MBRT
II) Heavy ions MBRT

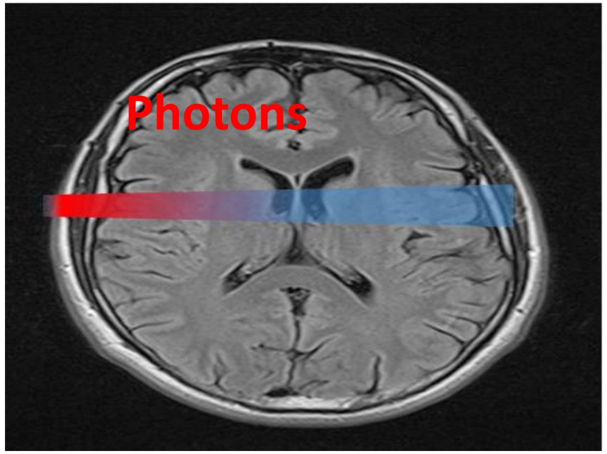
Novel approaches in disrupture with standard RT

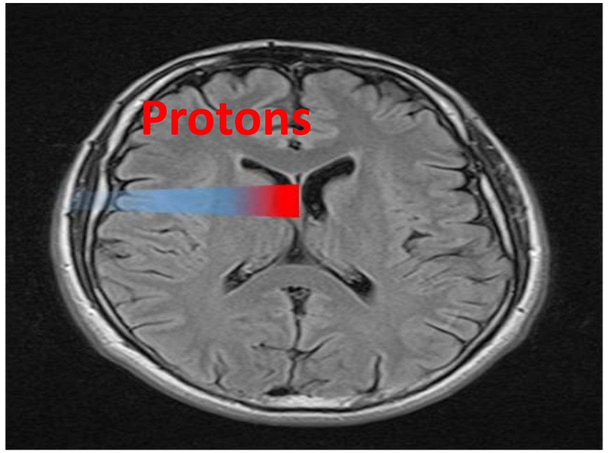
Proton minibeam radiation therapy

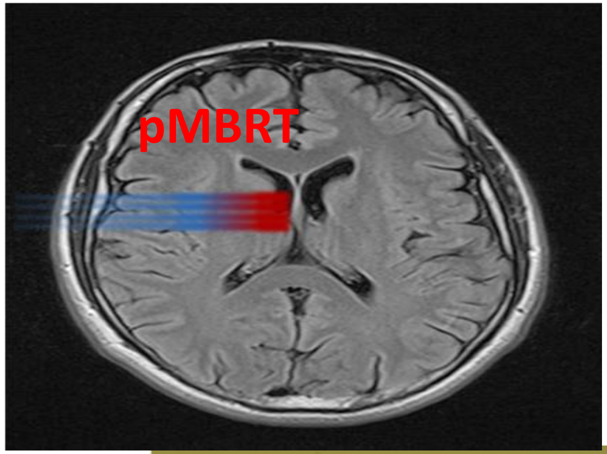


Homogeneous dose distribution in the tumour & spatial fractionation (peaks and valleys) in normal tissue

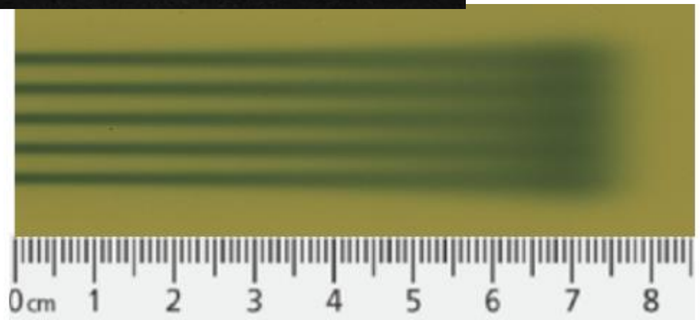
Prezado et al Med. Phys 2013







First experimental implementation in the world at the Orsay proton therapy center (ICPO) in 2014 (Med. Phys. 2015)



Scoop: first in vivo experiment

<u>Whole rat brain irradiations, 7 weeks old healthy Fischer 344 rats</u>

-Irradiations with broad beam (conventional proton therapy)

- pMBRT technique

Single fraction,
same average dose (25 Gy)

Long term study: histological and MRI studies at 6 and 12months after irradiations

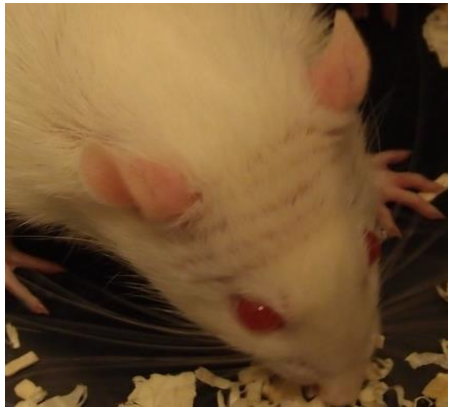
<u>Observations up to date (4 months after irradiation)</u>

Broad beam: severe moist desquamation (grade 3)

pMBRT: no skin damage, reversible epilation, no behavioural changes or clinical symptoms

Broad beam (25 Gy)

pMBRT (58 Gy peak dose)



Conclusions

- We are still far away from having found the optimum way to use ionizing radiation for therapy
- Some relevant radiobiological effects/mechanisms only recently explored
- Physics paramaters of the irradiation can be used to model the biological response – to improve treatment outcome
- **Advancements in radiotherapy require a multidisciplinary approach**

Thank you for your attention

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