Physical Dose and Biological Effects in Radiotherapy

A Biologist's Perspective

From Cellular Mechanisms to Clinical Outcomes

Samuel Valable, ISTCT Lab, Caen FRANCE

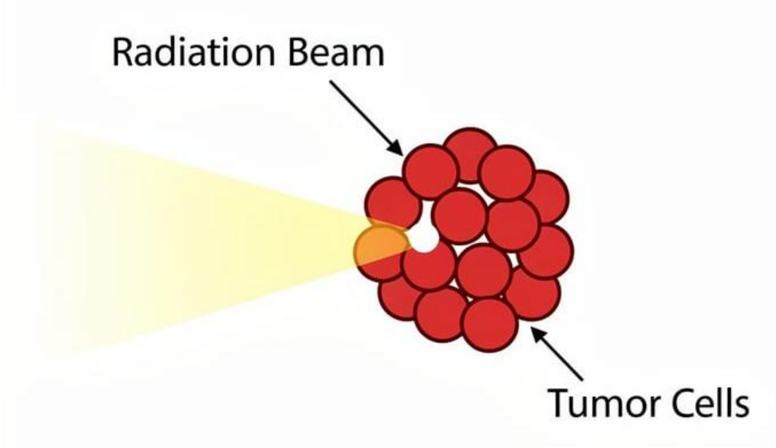
Introduction

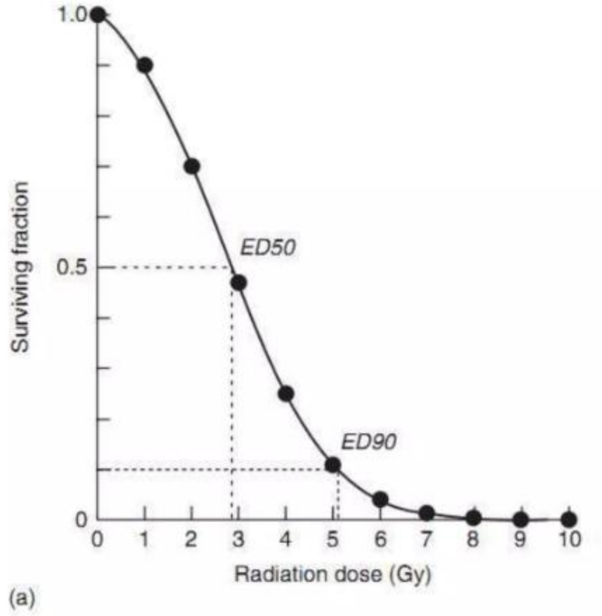
Why it matters: Understanding how physical dose translates to biological effects to improve cancer treatment and minimize side effects.

Key Questions:
How do cells and tissues respond to radiation at the molecular, cellular, and **systemic levels**?

How does energy deposition at the microscopic level lead to **macroscopic outcomes** ?

Biological Effects: From Physics to Biology





Cellular Targets

DNA: Single/ Double-strand breaks (DSBs).

Membranes/Organelles: Lipid peroxidation, mitochondrial dysfunction.

Energy Deposition Mechanisms

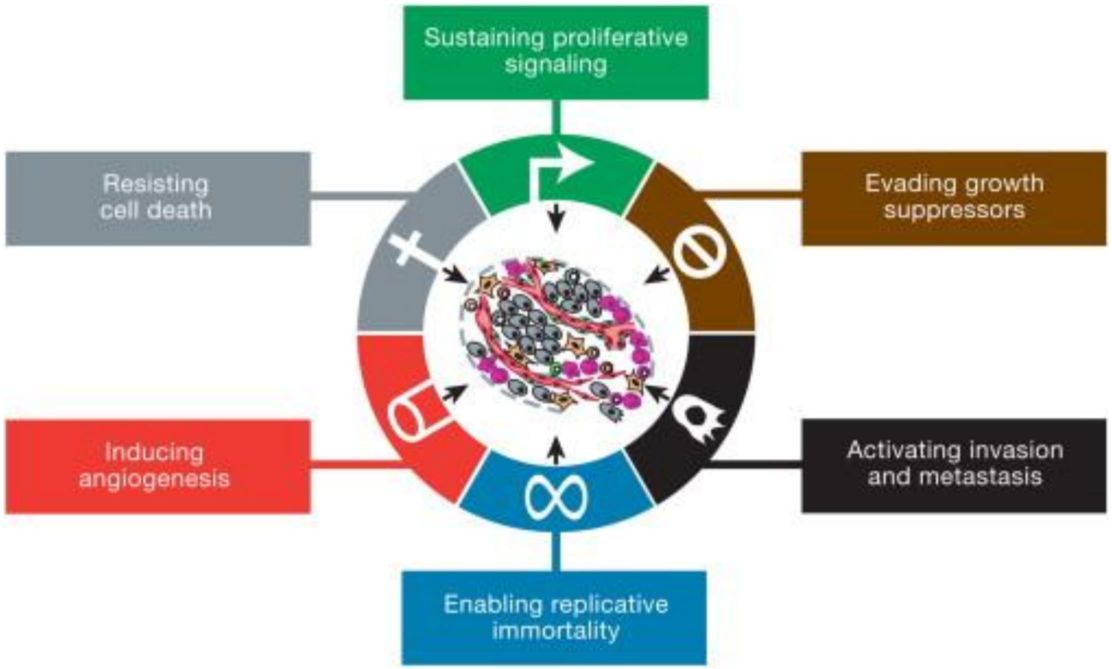
1. **Direct Ionization**: DNA damage from direct energy deposition.
2. **Indirect Effects**: Free radicals (e.g., •OH) from water radiolysis

In some situations, we do not observe a similar biological effects while using a similar physical dose?

1. Hypoxia
2. Abscopal Effect

Hallmarks in cancer 2000

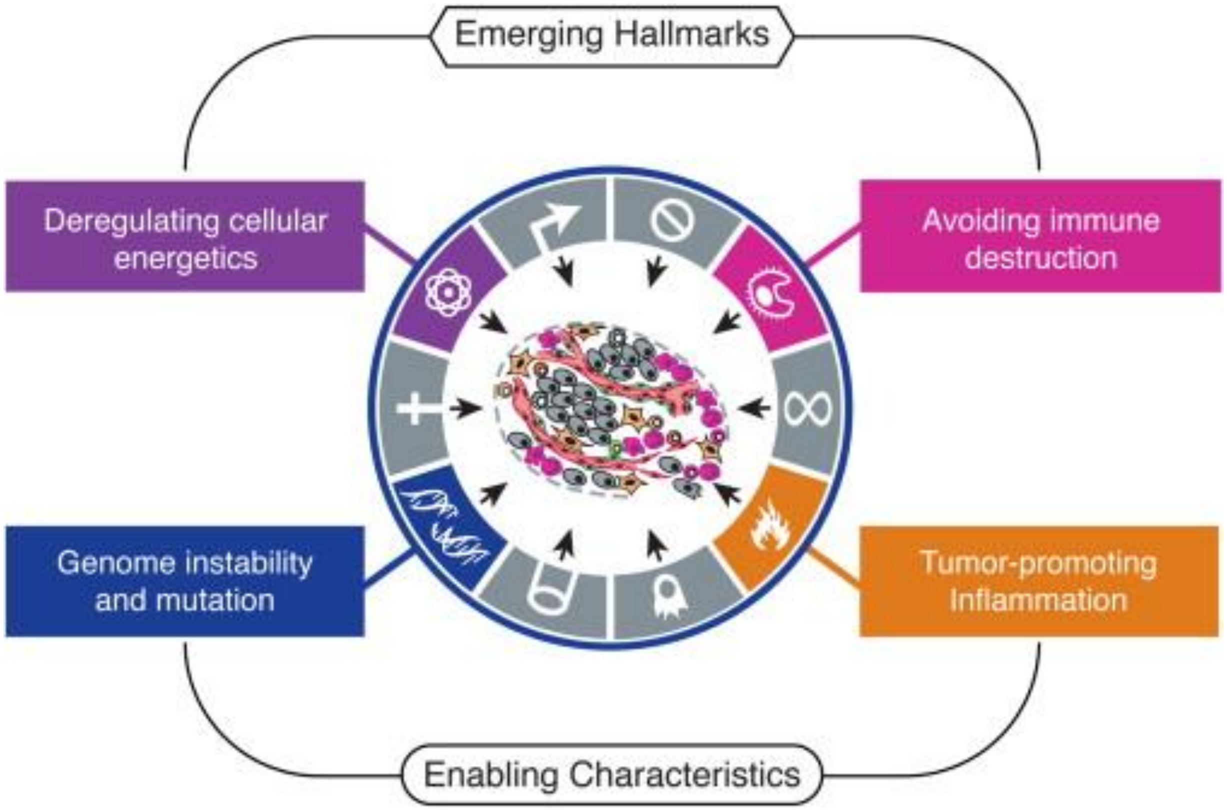
« 6 »



Hanahan and Weinberg 2000, Cell

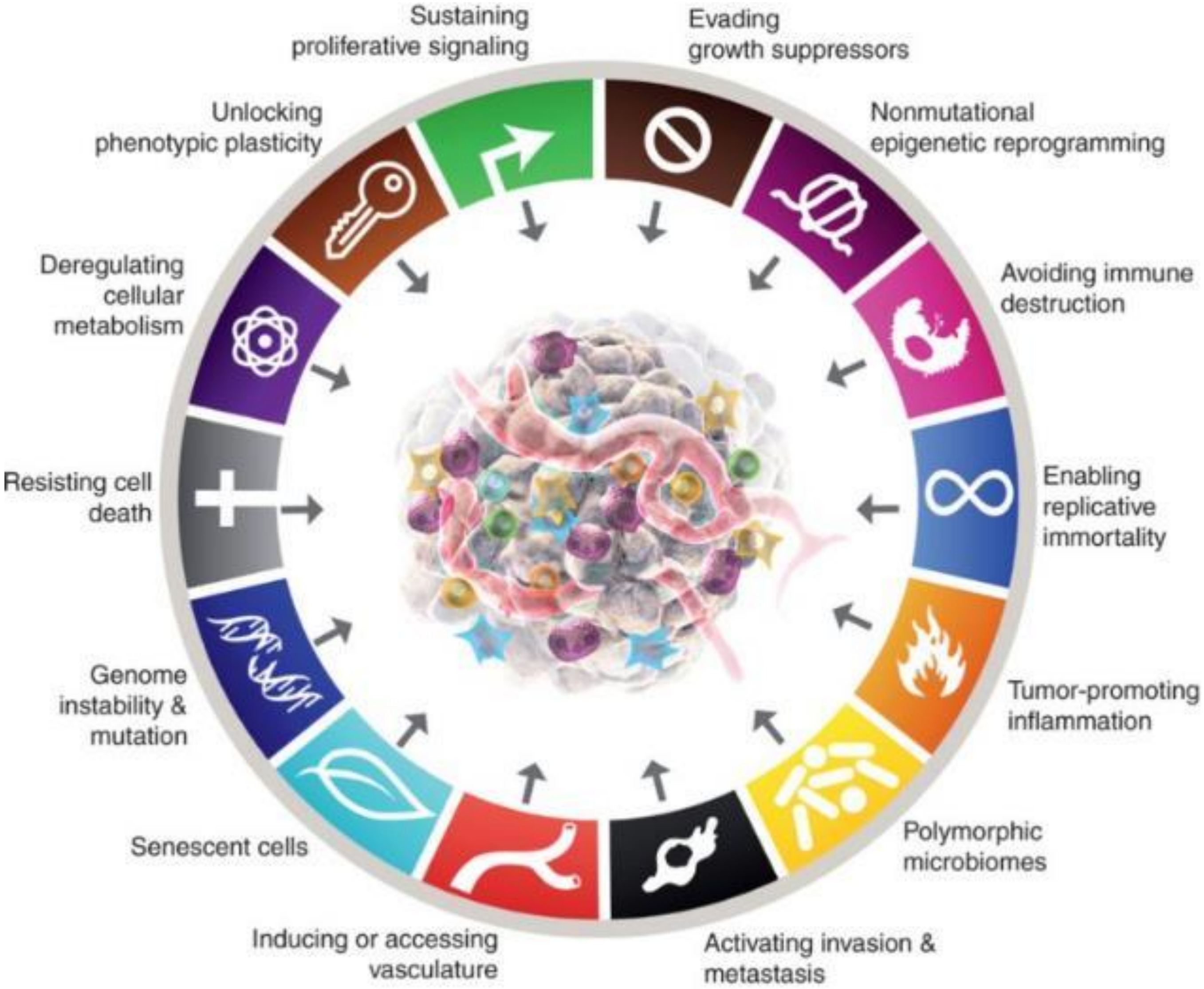
Hallmarks in cancer 2011

« 10 »



Hanahan and Weinberg 2011 Cell

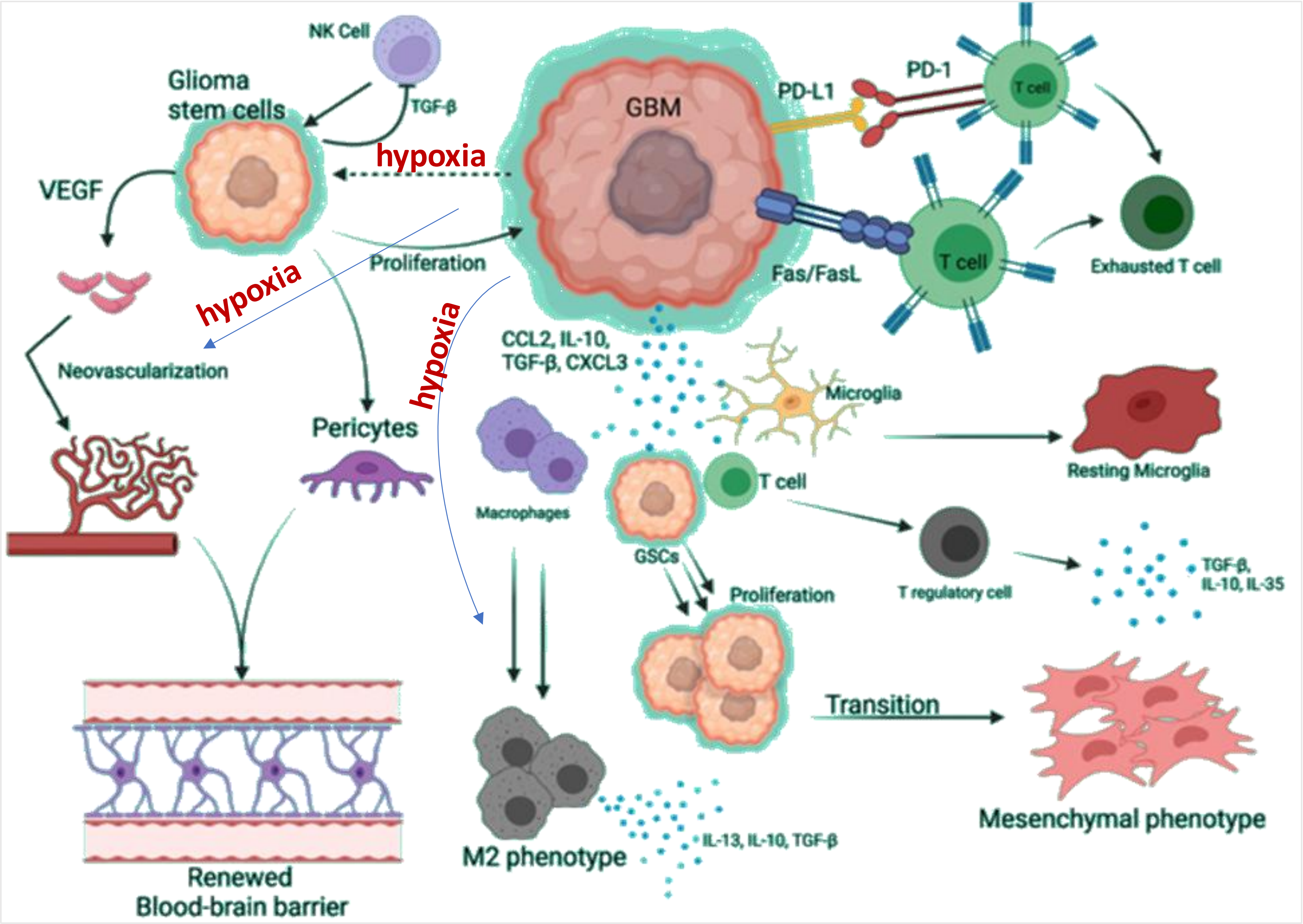
Hallmarks in cancer 2022
14



« …highly complex environment »

Hanahan 2022 Cancer Discovery

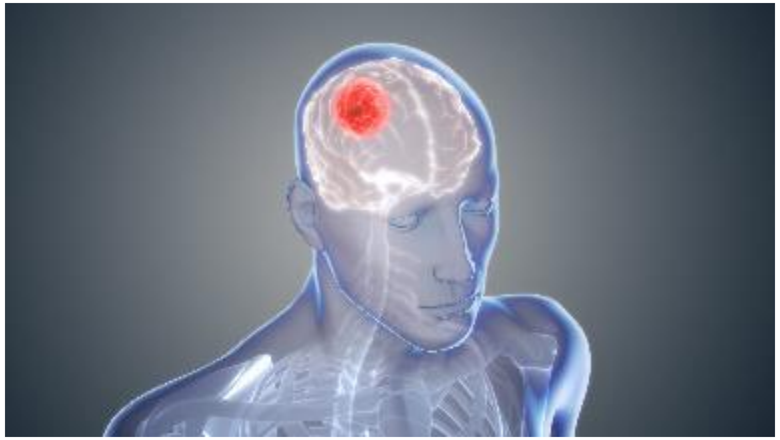
The example of Glioblastoma



« Need to target not only tumor cells but also to address the tumor microenvironment »

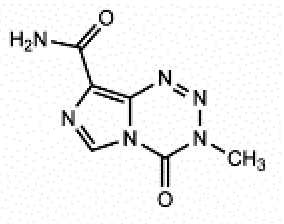
Kreatsoulas D, 2022J Hematol, Oncol.

The example of Glioblastoma

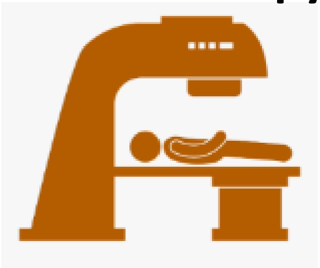


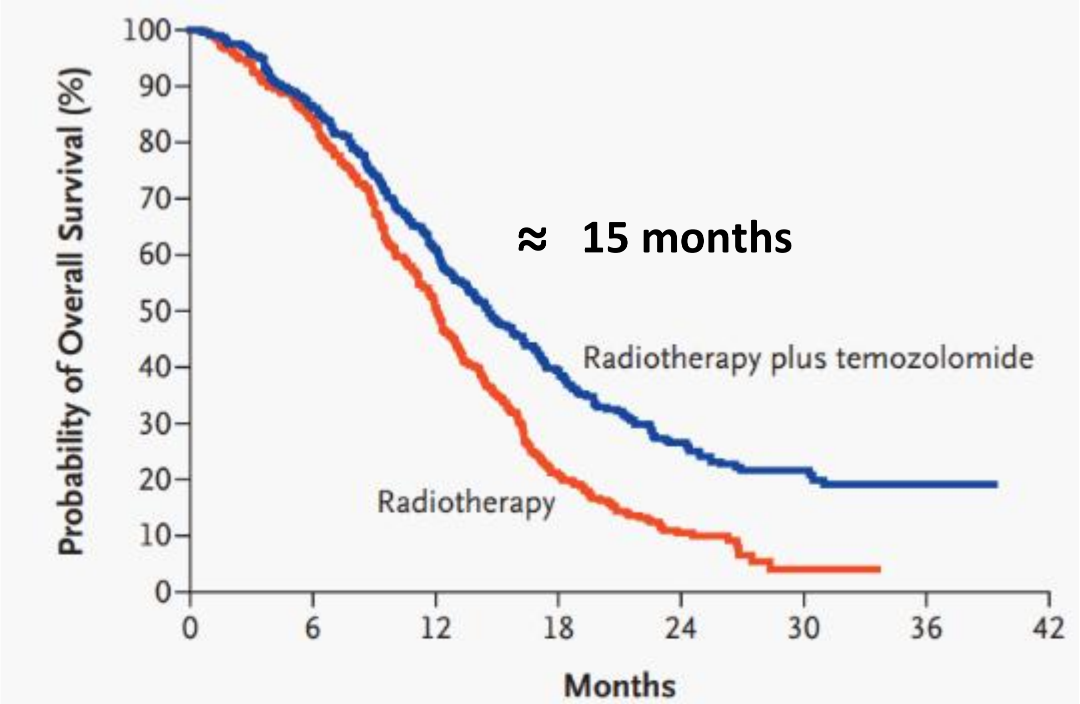
Surgery

Chemotherapy



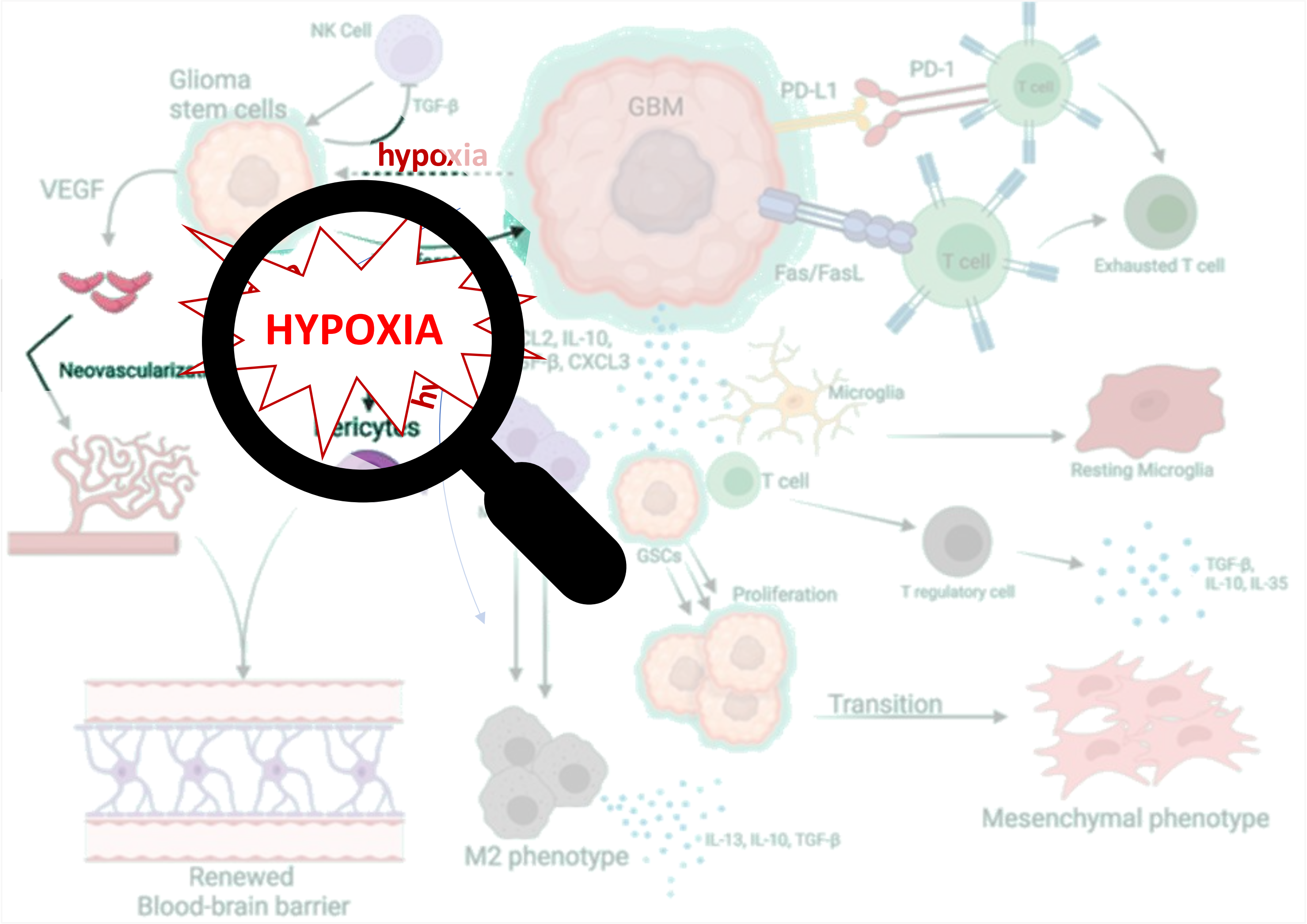
Radiation therapy





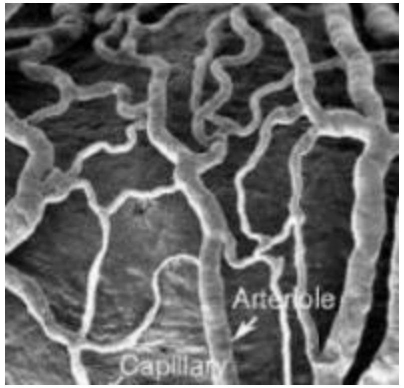
High resistance to conventional treatments

Origin of resistance: HYPOXIA



Hypoxia and tumors

Normal situation



Nutrients

Oxygen

Oxygen pressure = 30-40 mmHg

Tumor

Nutrients

Oxygen

Oxygen pressure < 5 mmHg

➔ **Severe hypoxia**

Hypoxia and tumors

➔ Use of needles and electrodes

Median ptO2 in low grade glioma = 33,1 mmHg

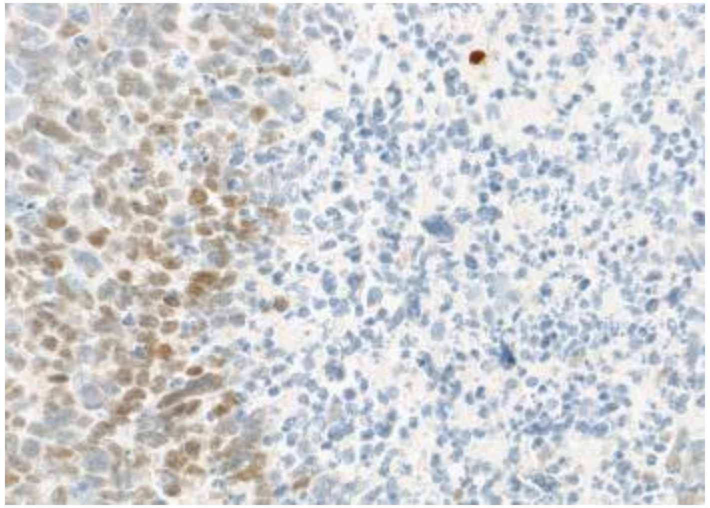
Collingridge *et al.* 1999

Median ptO2 in GBM = 7,25 mmHg

Patient no.	Tumor pathology	Median pO_2† (mmHg)
1	Glioblastoma	24.3
2	Glioblastoma	3.2
3	Glioblastoma	19.3
4	Glioblastoma	5.4
5	Glioblastoma	2.5
6	Glioblastoma	4.5
7	Glioblastoma	0.1
8	Glioblastoma	5.4
9	Glioblastoma	7.7
10	Glioblastoma	0.1

Rampling *et al.* 1994

➔ Immunohistochemistry HIF 1a



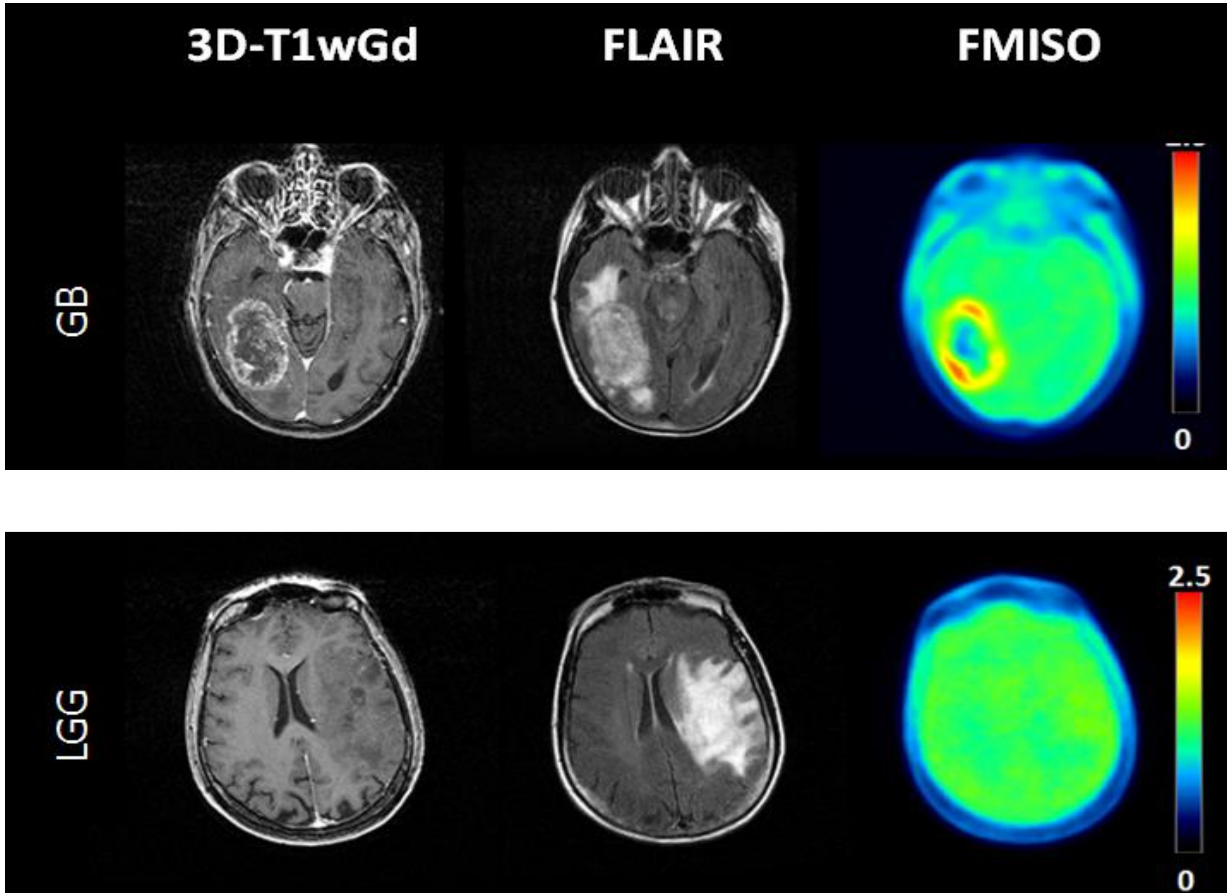
positive negative

Marked heterogeneity among patients

Marked heterogeneity within a single tumor mass

Non invasive detection of hypoxia using imaging

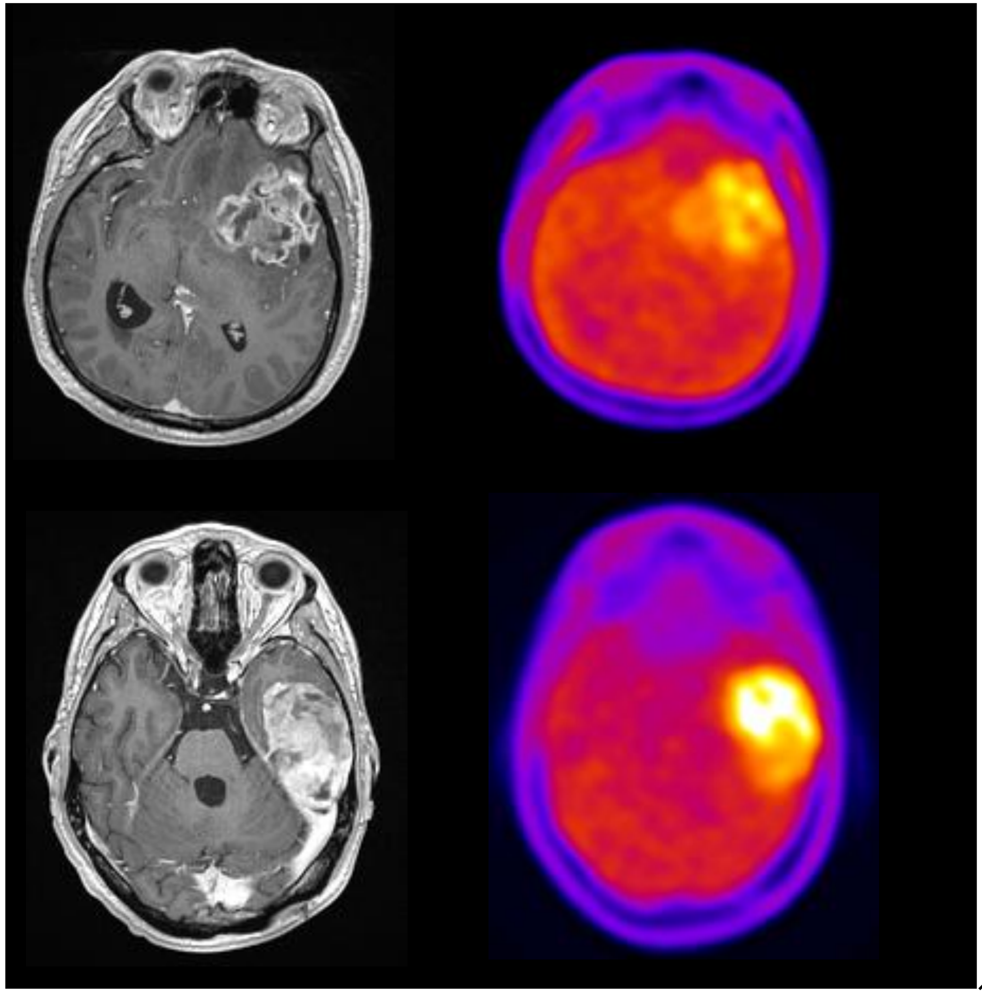
Investigator: Pr JS Guillamo, CHU of Caen



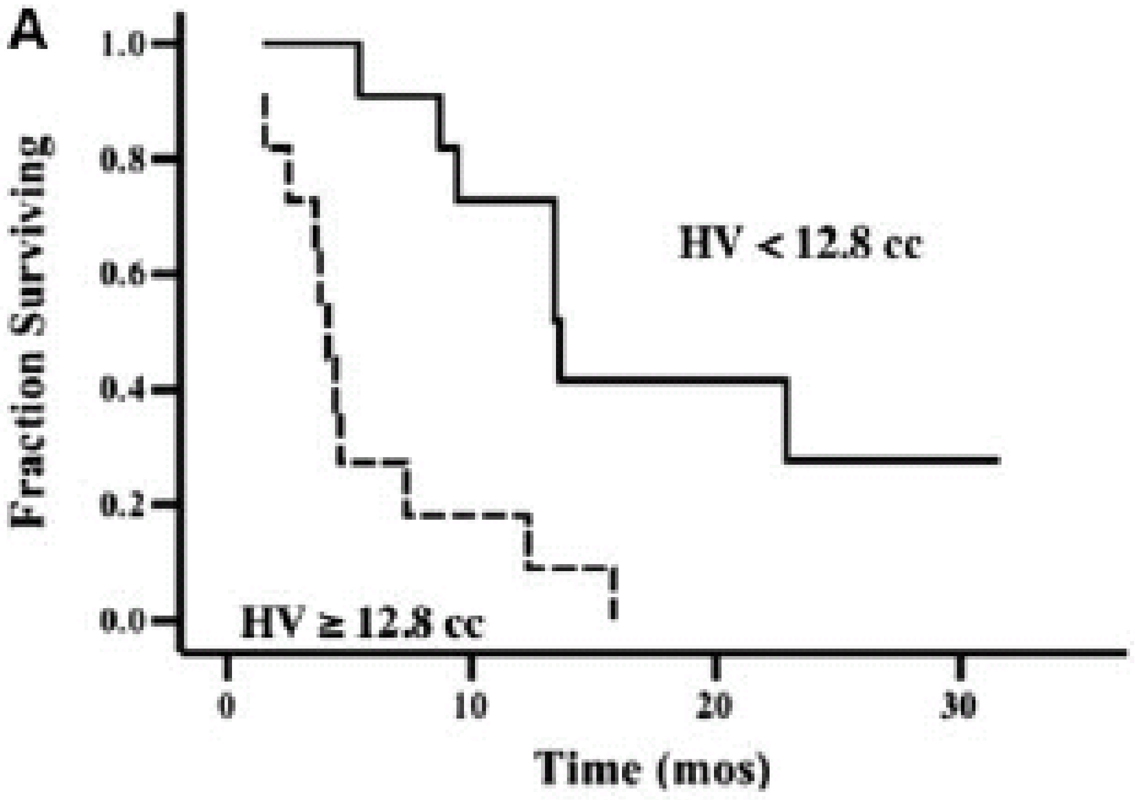
Bekaert L et al., 2017

Da Ponte K et al., 2017

High Grade Brain Tumors



Hypoxia and tumors



	Log hazard ratio coefficient (SE)	P
Survival		
HV	0.024 (0.01)	0.001
T/B_{max}	1.46 (0.400)	0.0002
T0	0.042 (0.064)	0.51
T1Gd	0.03 (0.02)	0.04
T2	0.007 (0.01)	0.44
T2-T0	0.008 (0.01)	0.45
Age	0.056 (0.03)	0.03
KPS	-0.03 (0.02)	0.09
Extent of resection		
GT vs Bx	-0.76 (0.69)	0.27
ST vs Bx	0.07 (0.52)	0.90

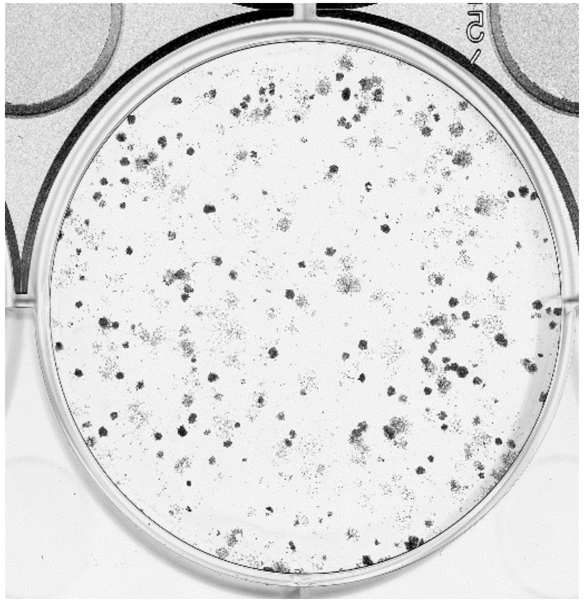
Spence et al., 2008

Hypoxia ↗ : prognosis ↘

Radiotherapy and hypoxia

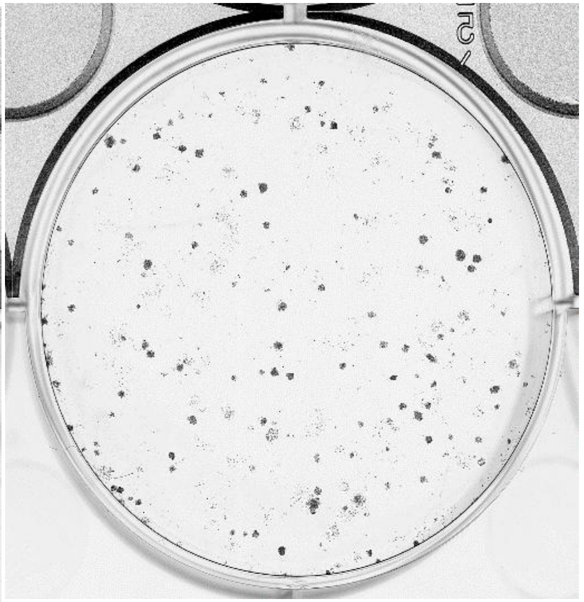
Low LET Particles (x-rays)

No RT



4 Gy
with oxygen

4 Gy
w/o oxygen (0.1% O2)



THE CONCENTRATION OF OXYGEN DISSOLVED IN TISSUES AT THE TIME OF IRRADIATION AS A FACTOR IN RADIOTHERAPY

By L. H. Gray, M.A., Ph.D., A. D. Conger, Ph.D., M. Ebert, Dr. Rer. Nat., S. Hornsey, B.Sc., and O. C. A. Scott, M.B., B.Ch.

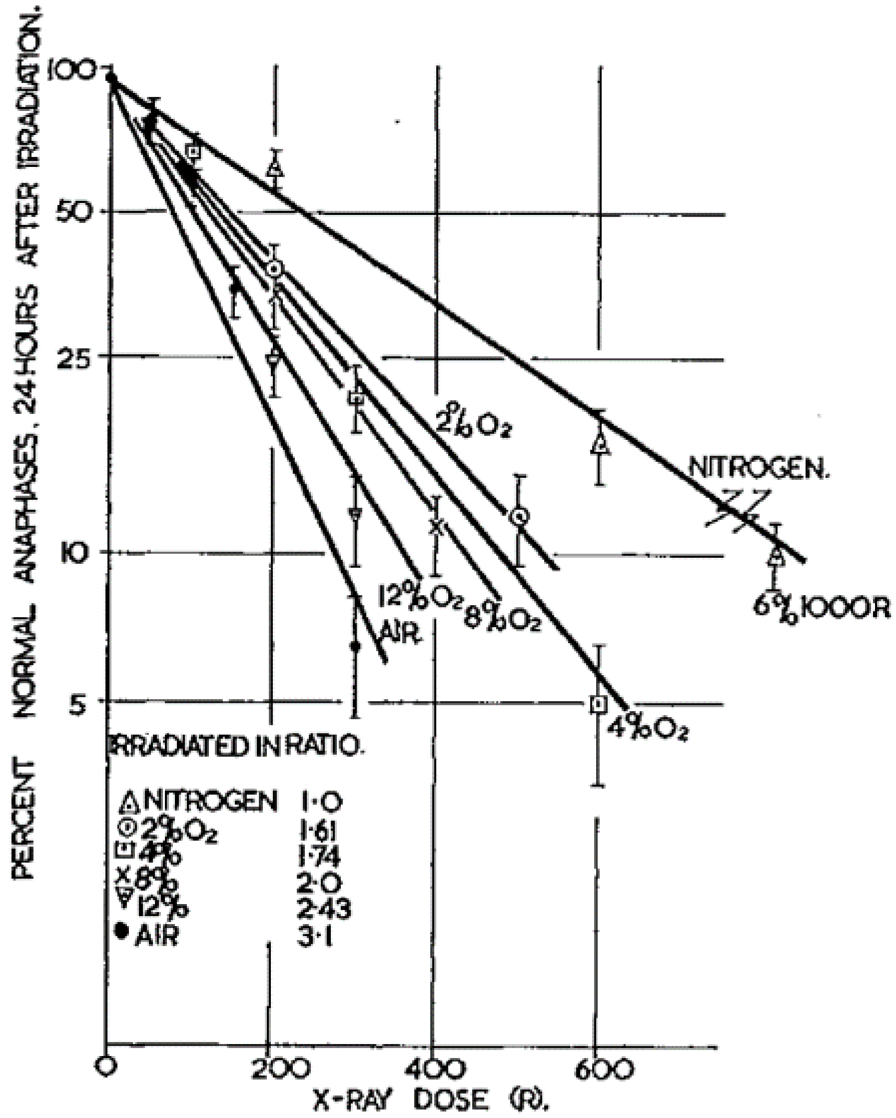
Radiotherapeutic Research Unit, Hammersmith Hospital, London

(Accepted for publication September, 1953)

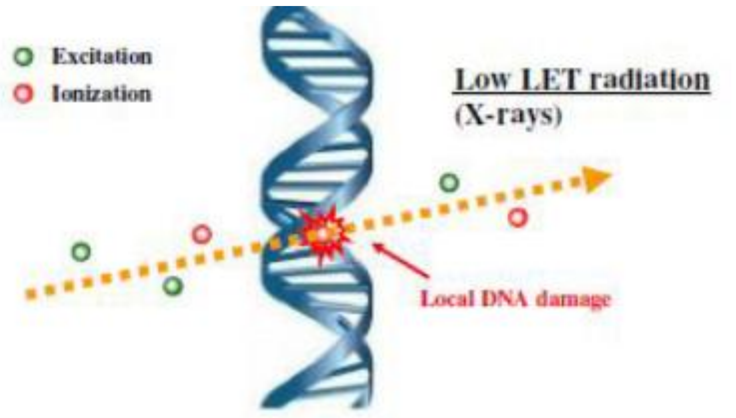
Cytological damage suffered by mouse ascites tumour cells when exposed to X rays *in vitro* at different oxygen tensions.

Abscissae: X-ray dose in röntgens.

Ordinates: Percentage of normal anaphase figures seen in cells dividing 24 hours after irradiation. The fluid containing the cells was in equilibrium either with pure oxygen or pure nitrogen as indicated in the figure.

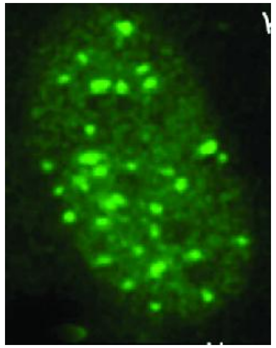


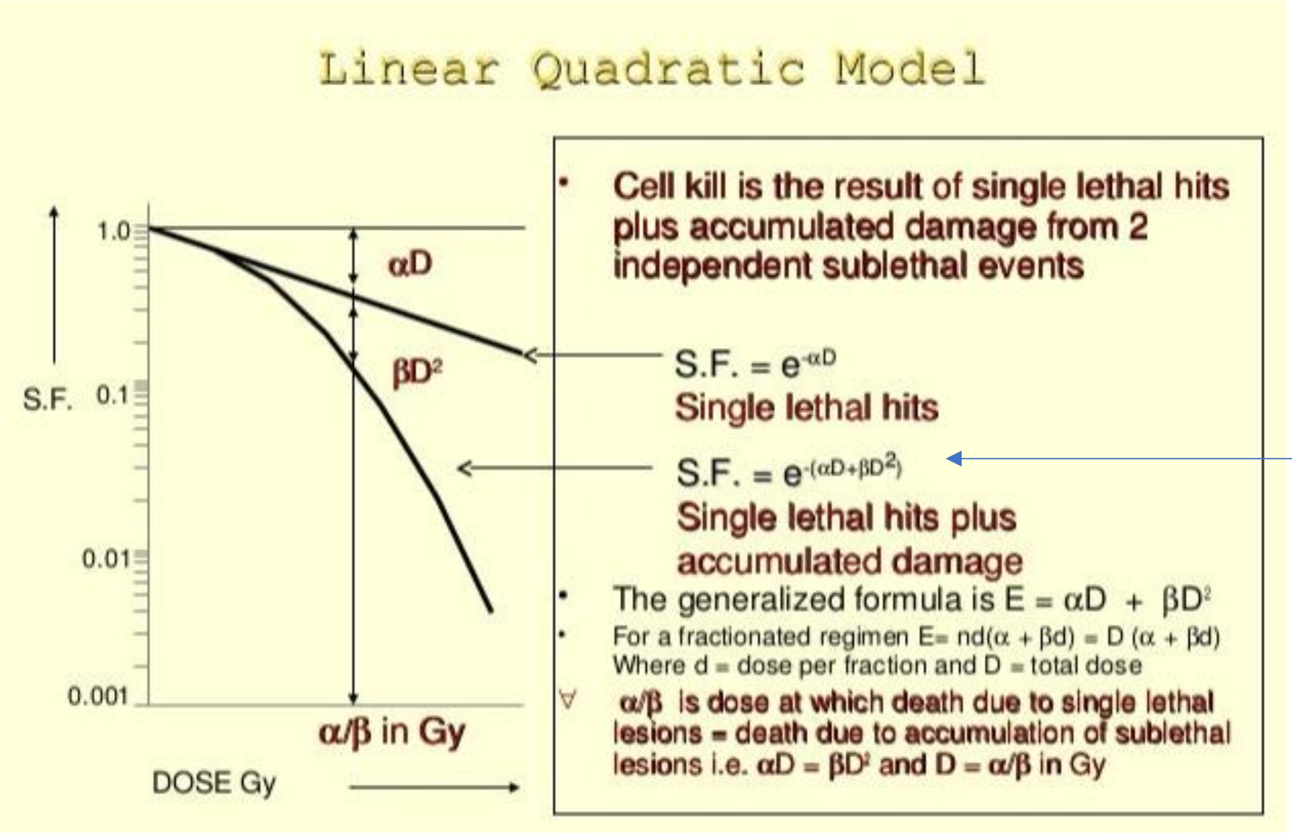
Origin of resistance to photons



In the presence of molecular oxygen at the time of or within microseconds after exposure, **low LET radiation ionizes water molecules**, producing high energy electrons and highly **Reactive Oxygen Species (ROS)**

DNA damage results from either **a direct** or **an indirect** (via ROS) effect of irradiation.



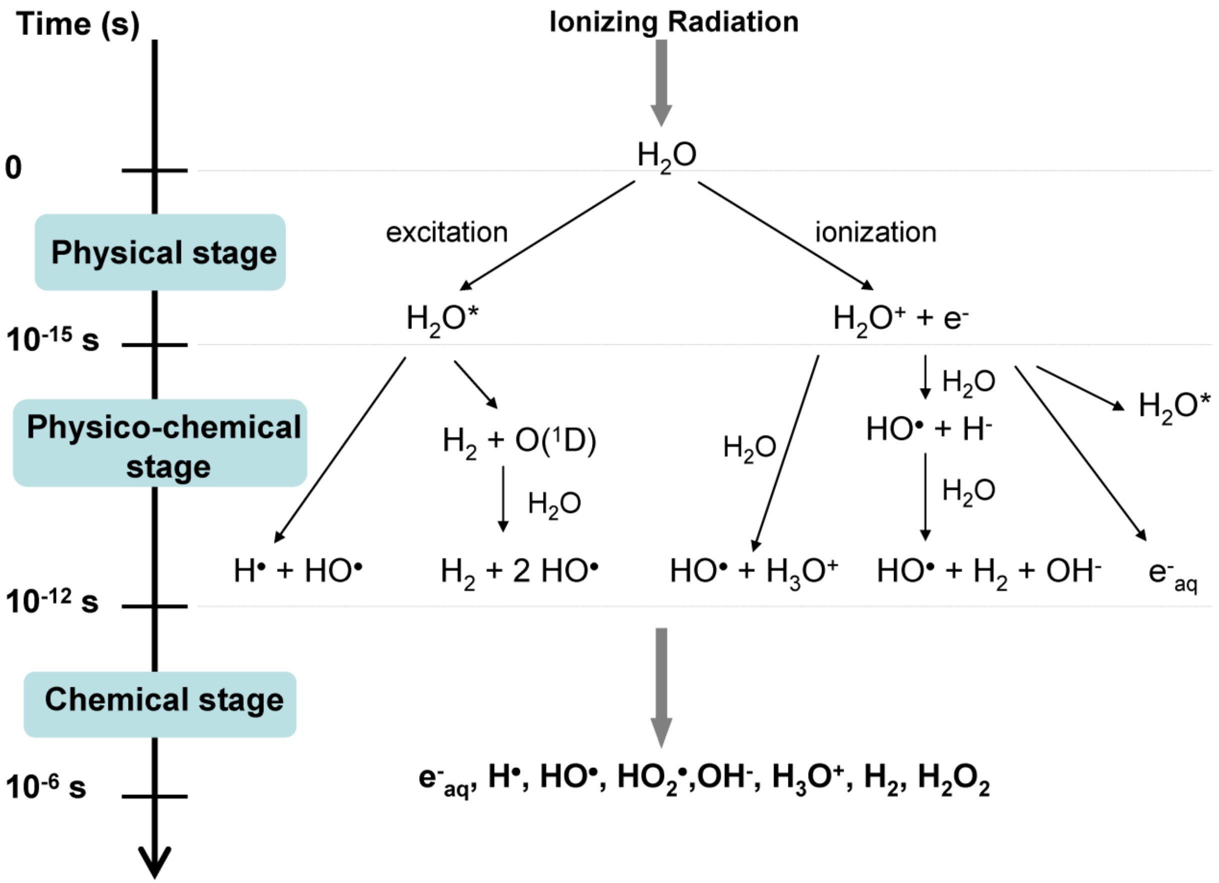


Presence of oxygen

ROS Water radiolysis (low LET particles)

H. LASER , The 'Oxygen-Effect' in Ionizing Irradiation, Nature, 174, page753; **1954**

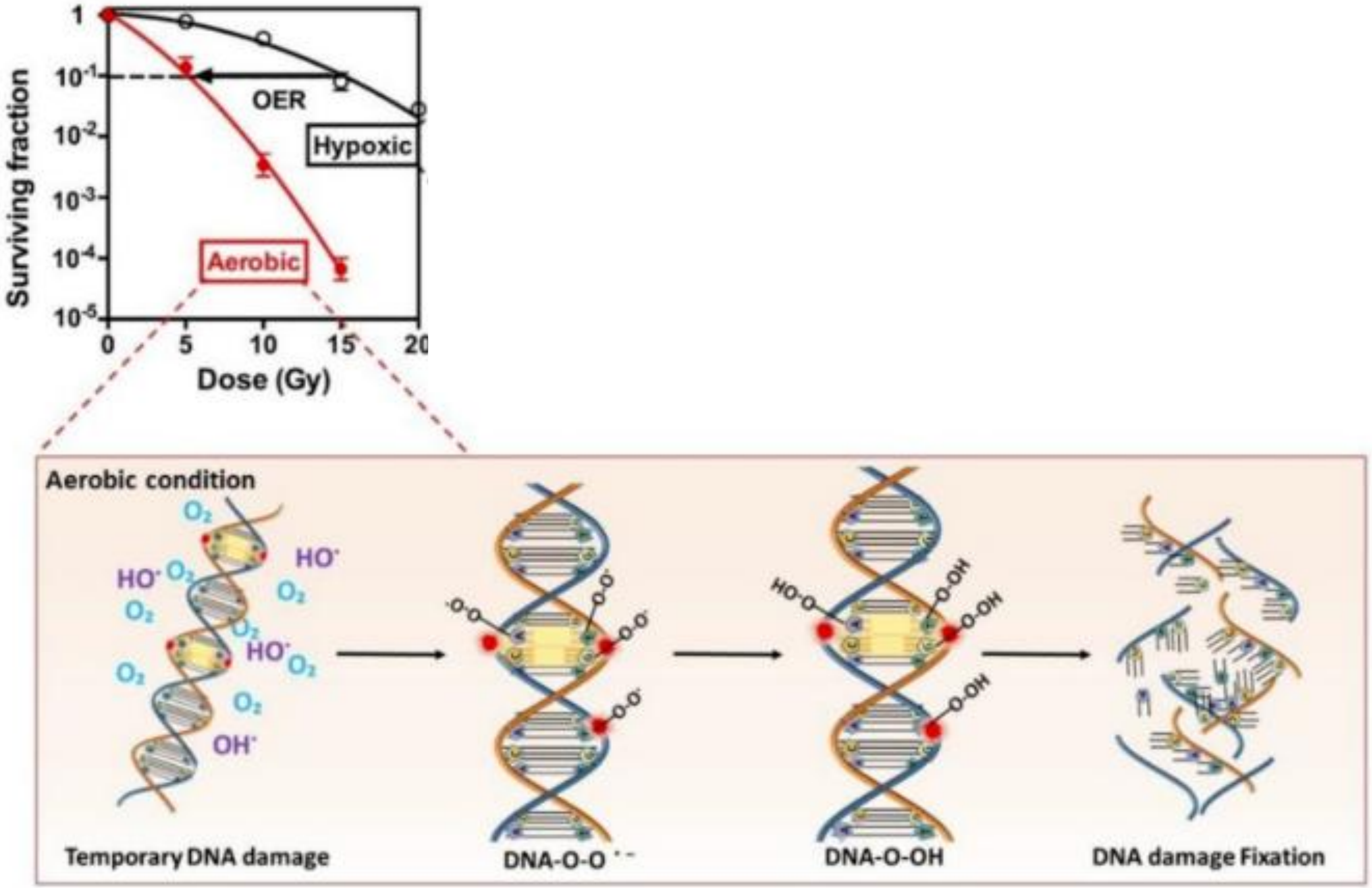
It is generally believed to be due to the deleterious effect on cells by the strongly oxidizing radical **HO_2** and, to some extent, by **hydrogen peroxide**, which are formed **on X-ray irradiation in aqueous media containing oxygen**,



$OH°$: Hydroxyl radical
$O°^-_2$: superoxyde anion
$^10_2$: singulet oxygen

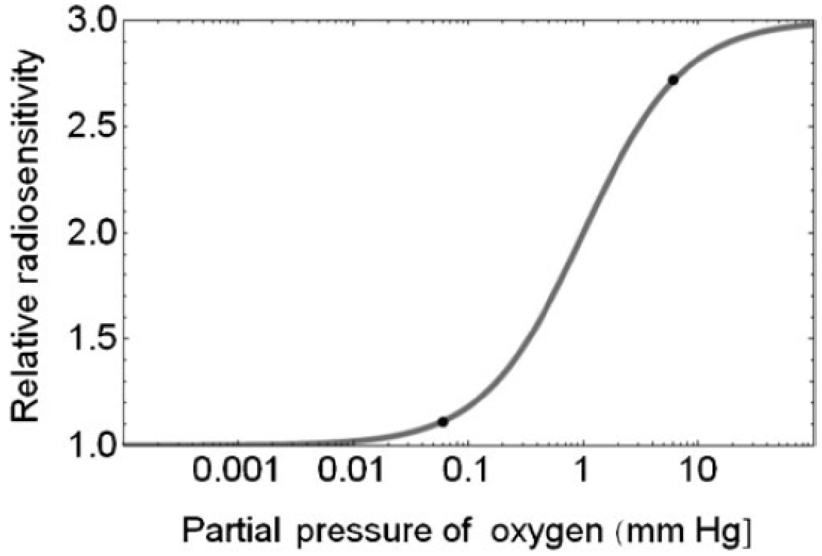
Water radiolysis and ROS

Under aerobic condition, radiation induced radicals result in permanent DNA damage and strand breaks.
Under hypoxic condition, the lack of oxygen enables the DNA radicals to be reduced that hampers the generation of strand breaks.



Cancers (Basel). 2019 Jan; 11(1): 112.

In the absence of oxygen, cell death is reduced for a given RT dose



Wilson 2012 BJR

Origin of resistance to photons

➔ **Introduction of the OER = oxygen enhancement ratio**

It refers to the enhancement effect of ionizing radiation due to the presence of oxygen.

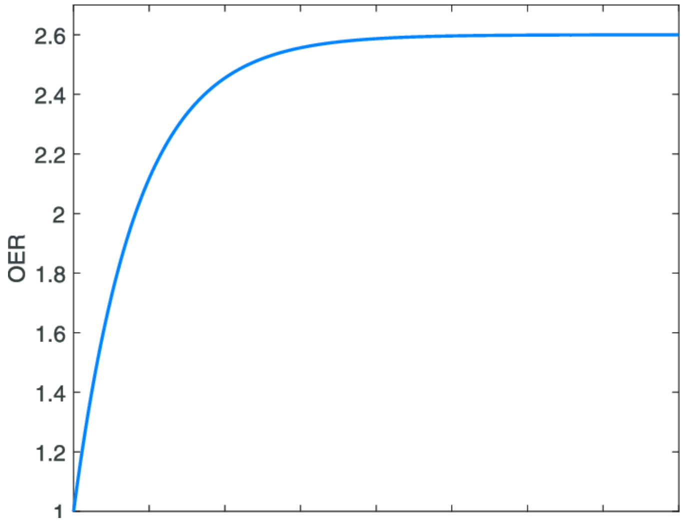
$$OER = \frac{Radiation\ dose\ in\ hypoxia}{Radiation\ dose\ in\ air}$$

OER typically has a maximum value of 2.7
=> suggesting that one would have to deliver 2.7 times the dose to an anoxic region to elicit the same level of cell killing.

In real life, OER is not linear with oxygen concentration.

Alper and Howard-Flanders' formula

$$\mathrm{OER}(pO_2) = \frac{m \cdot k + pO_2}{pO_2 + k}$$

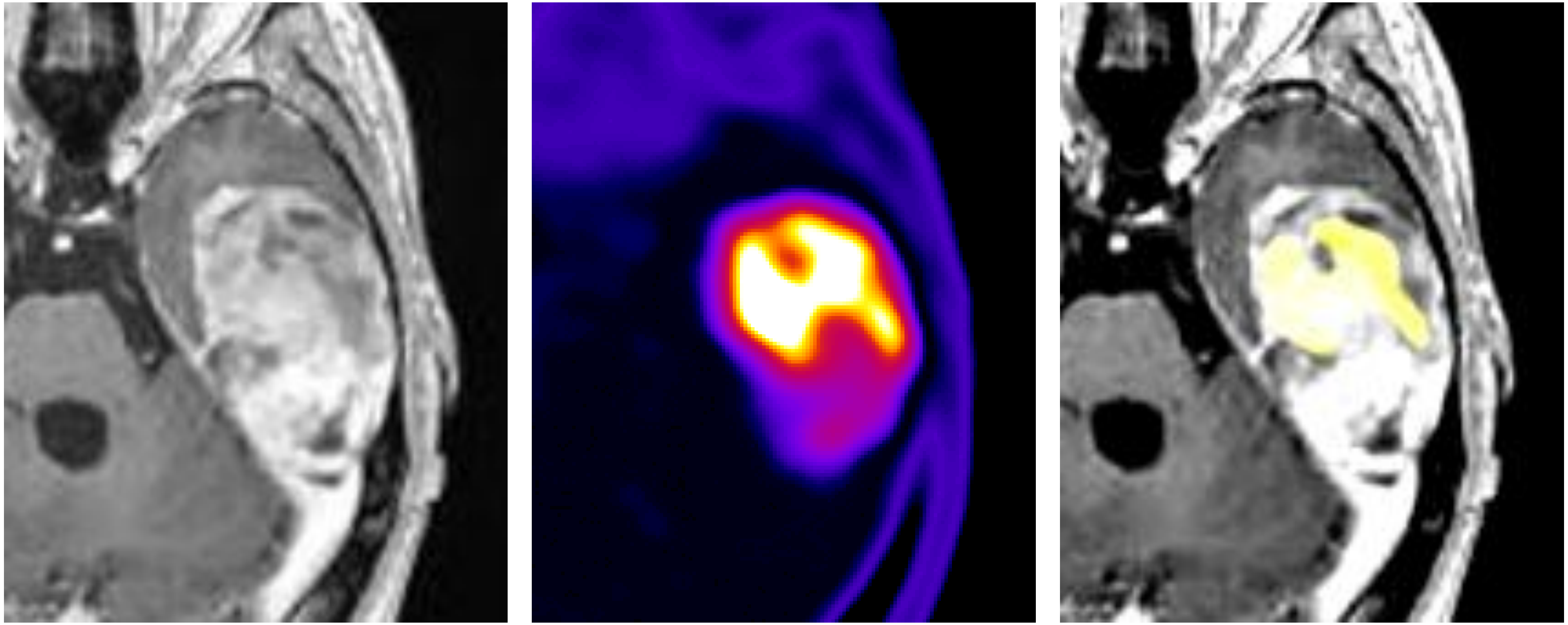


Oxygen pressure mmHg

Where :

- m is a maximum effect
- k is a concentration corresponding to a half-maximum sensitization, i.e. the pO2 value corresponding to the flex point of the sigmoid-shaped curve

Tinganelli W et al., 2015

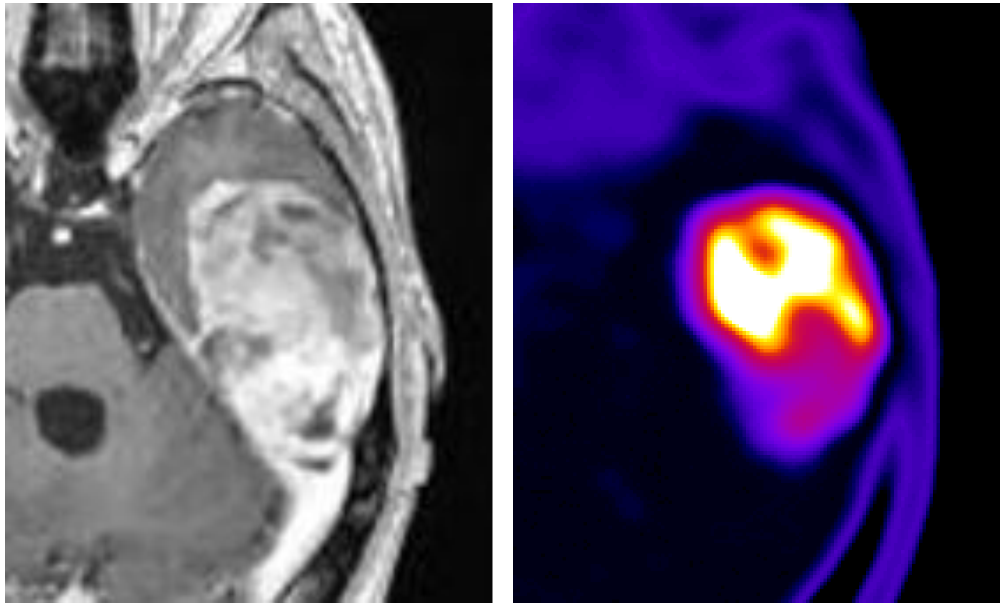


Adaptation of radiation therapy

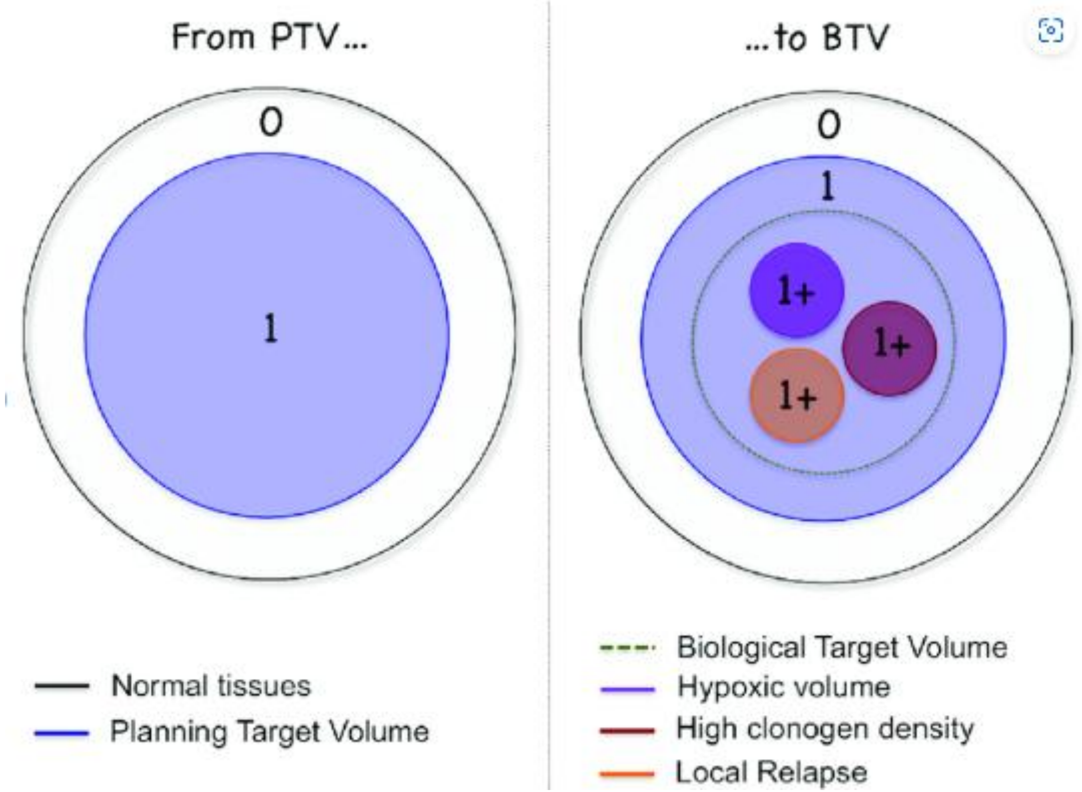
Increasing dose prescription **Changing RT regimen ?**

Increase the dose deposition in hypoxic regions

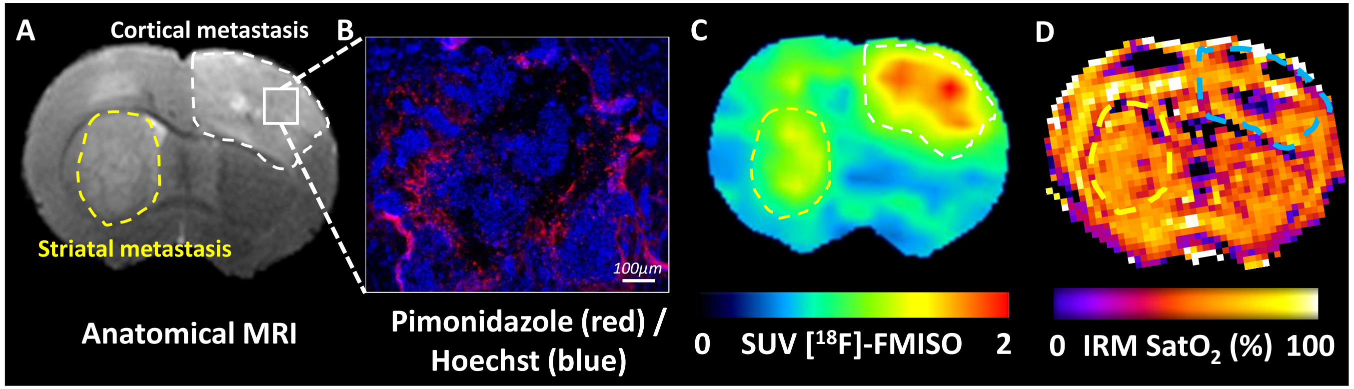
Use of particles *in vivo* in line with hypoxia

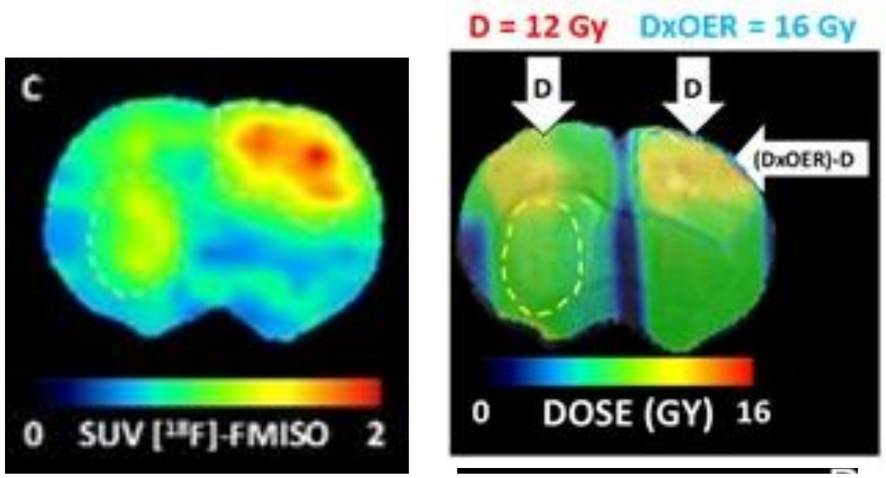


From hypoxia imaging to Biological target volumes

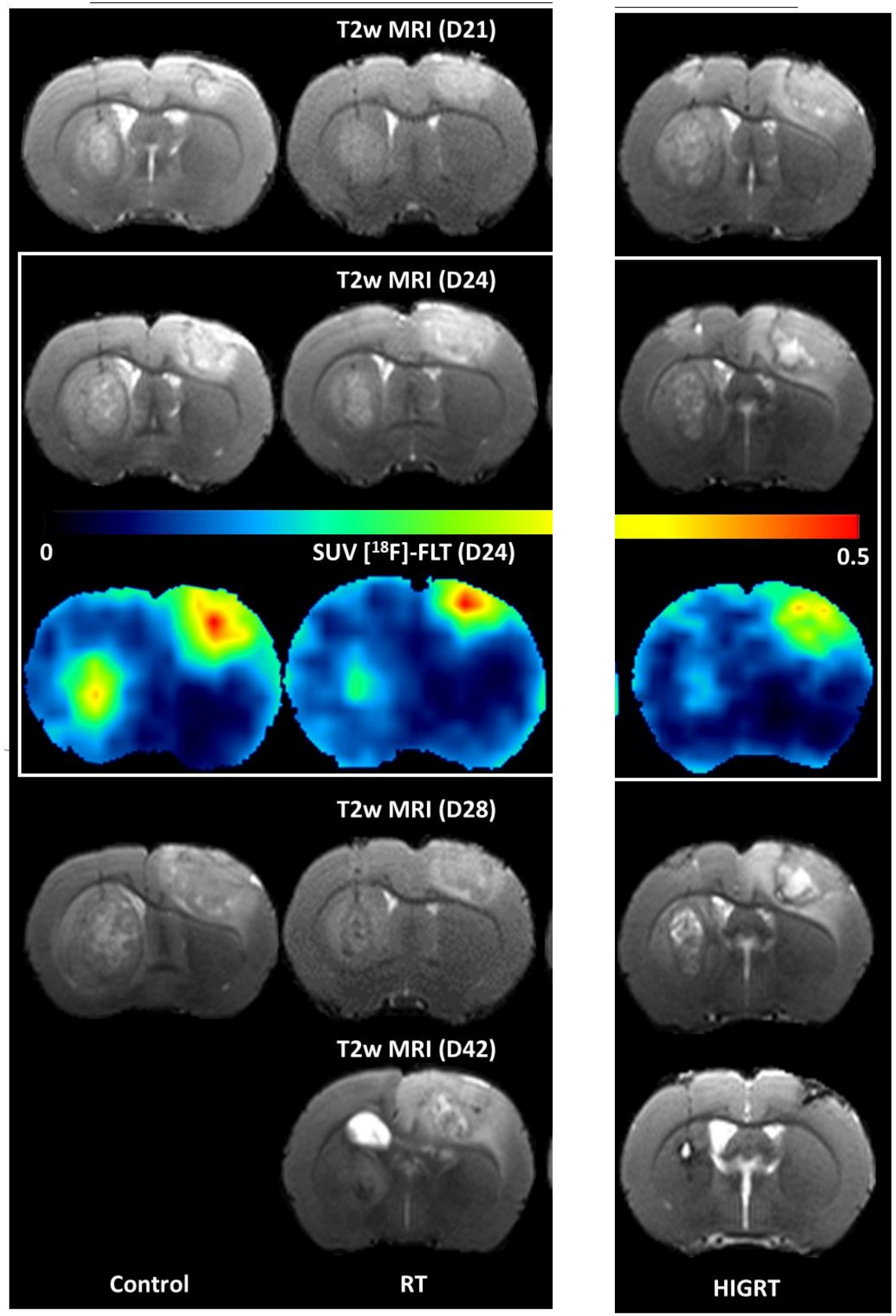


Tomasino et al., Transl Cancer Res 2017;6(Suppl 5):S807-S





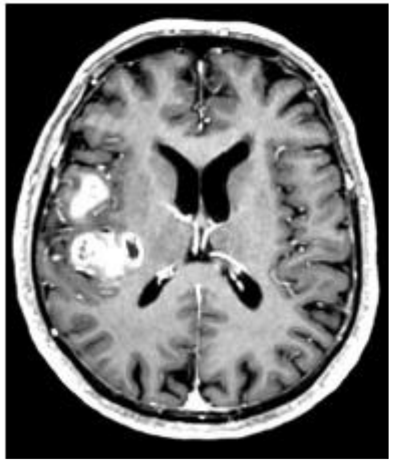
Corroyer-Dulmont et al., 2021, Sci Report.

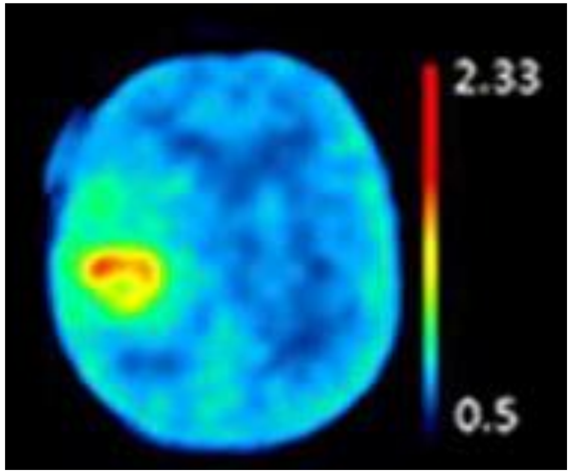


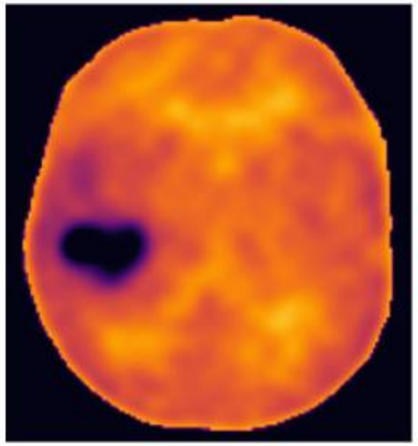
Dose adaptation based on hypoxia mapping

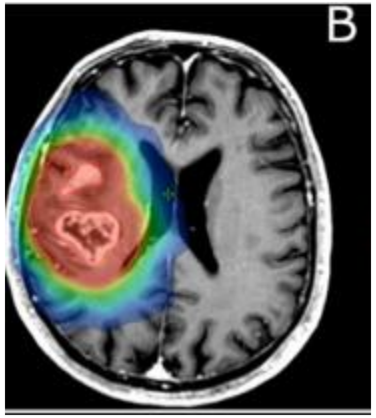
Ararat Chakhoyan *et al.*, 2017

Gérard M et al., 2019





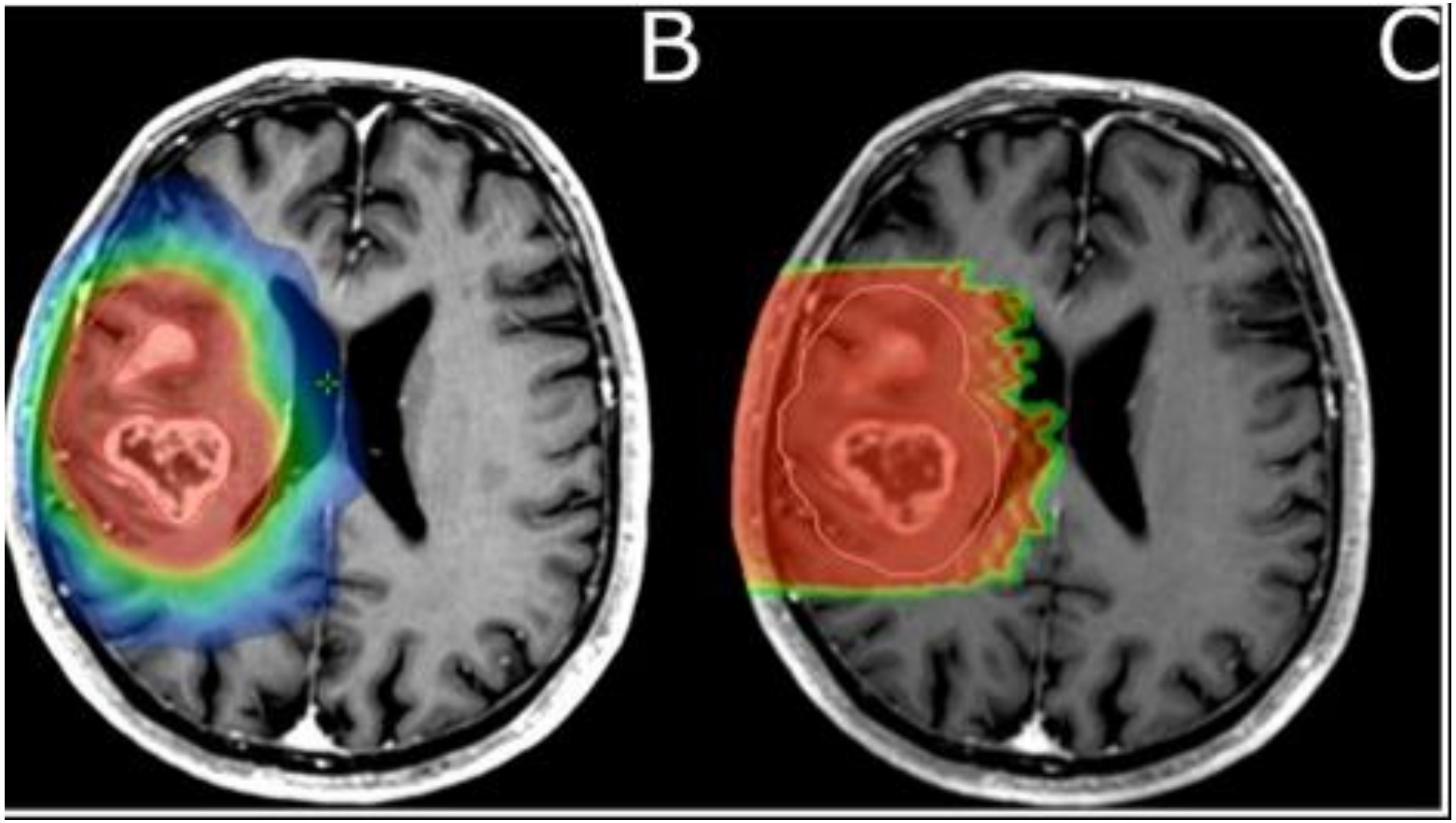




$$p_tO_2(\text{mmHg}) = \frac{c\,(a - u)}{b - a + u}$$

$$f = \frac{OER_{max}\,(k + pO_2)}{k + OER_{max} \times pO_2}$$

IMRT Proton beams



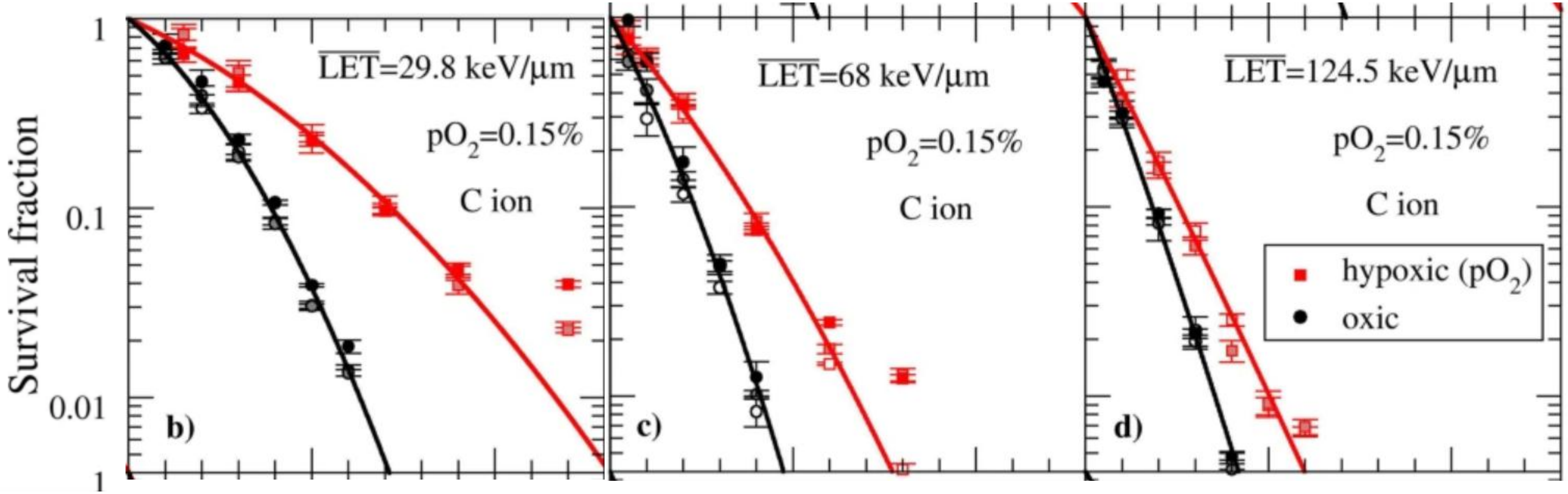
Gérard M et al., 2019, Front. Med.

Increase the dose deposition in hypoxic regions

Use of particles *in vivo* in line with hypoxia

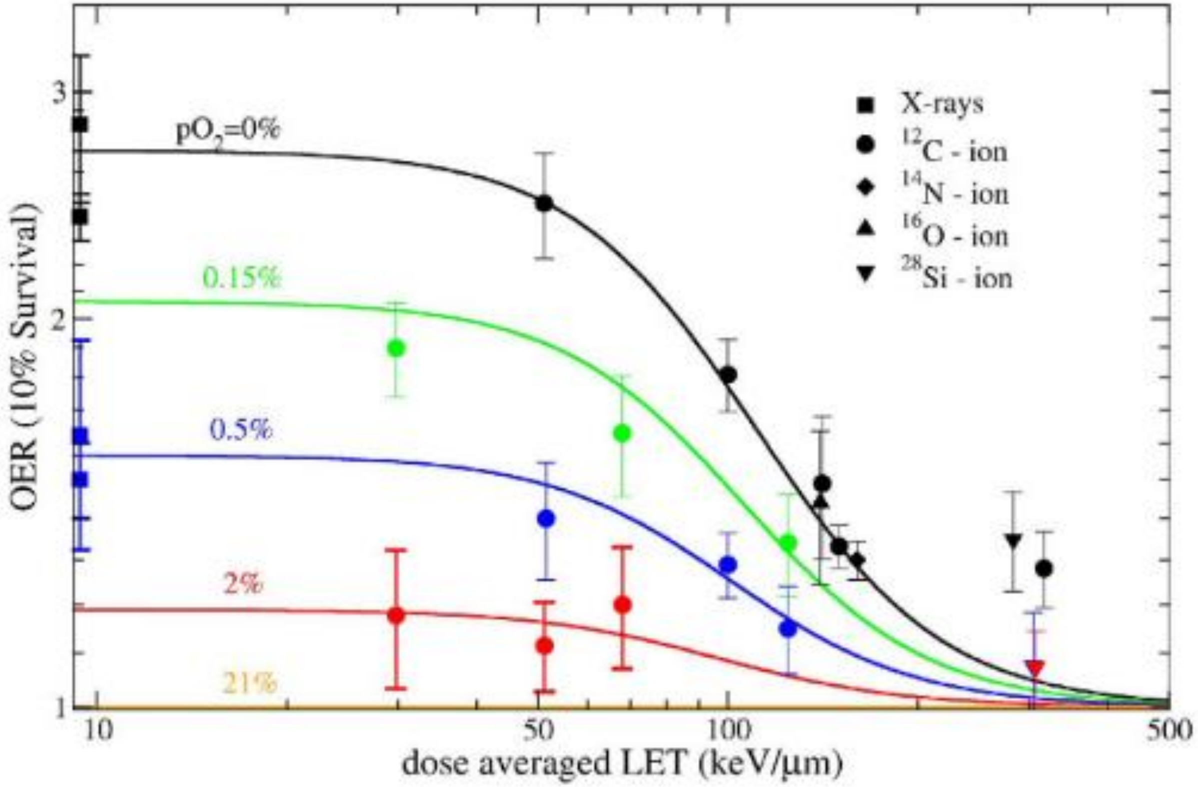
Introduction of the LET Dependancy

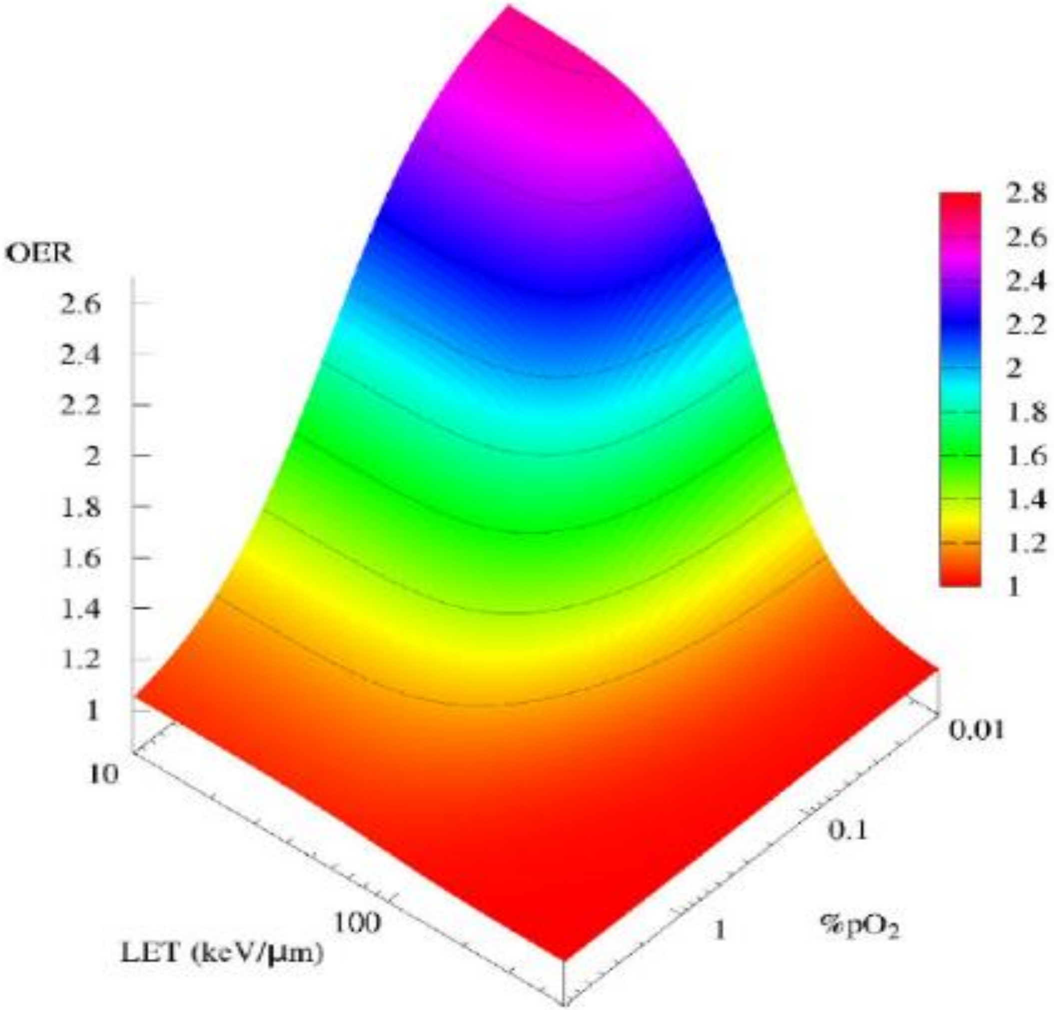
29.8 68 124.5



CHO cells and clonogenic assays

Tinganelli W, et al., 2015, Sci Report





Tinganelli W and Collaborators

BIOLOGY CONTRIBUTION

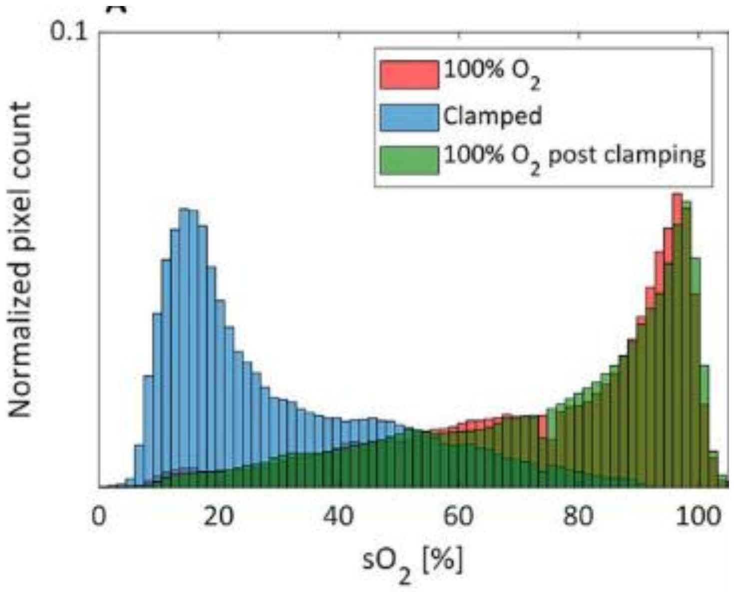
Irradiation with Carbon Ions Effectively Counteracts Hypoxia-related Radioresistance in a Rat Prostate Carcinoma

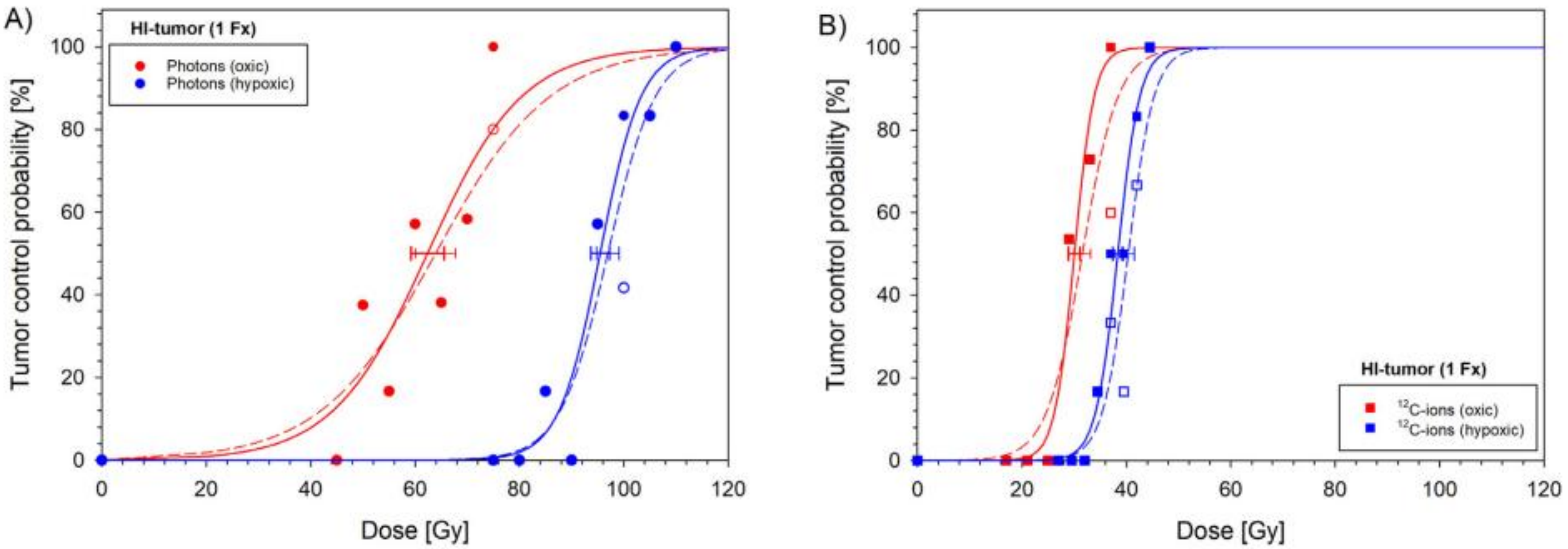
International Journal of Radiation Oncology*Biology*Physics
Available online 13 May 2024

Christin Glowa PhD [*,†,‡], Alina L. Bendinger PhD [†,‡,§], Rosemarie Euler-Lange BSc [†,‡,‖], Peter Peschke PhD [†,‡], Stephan Brons PhD [‡,¶], Jürgen Debus MD, PhD [*,‡,#], Christian P. Karger PhD [†,‡]

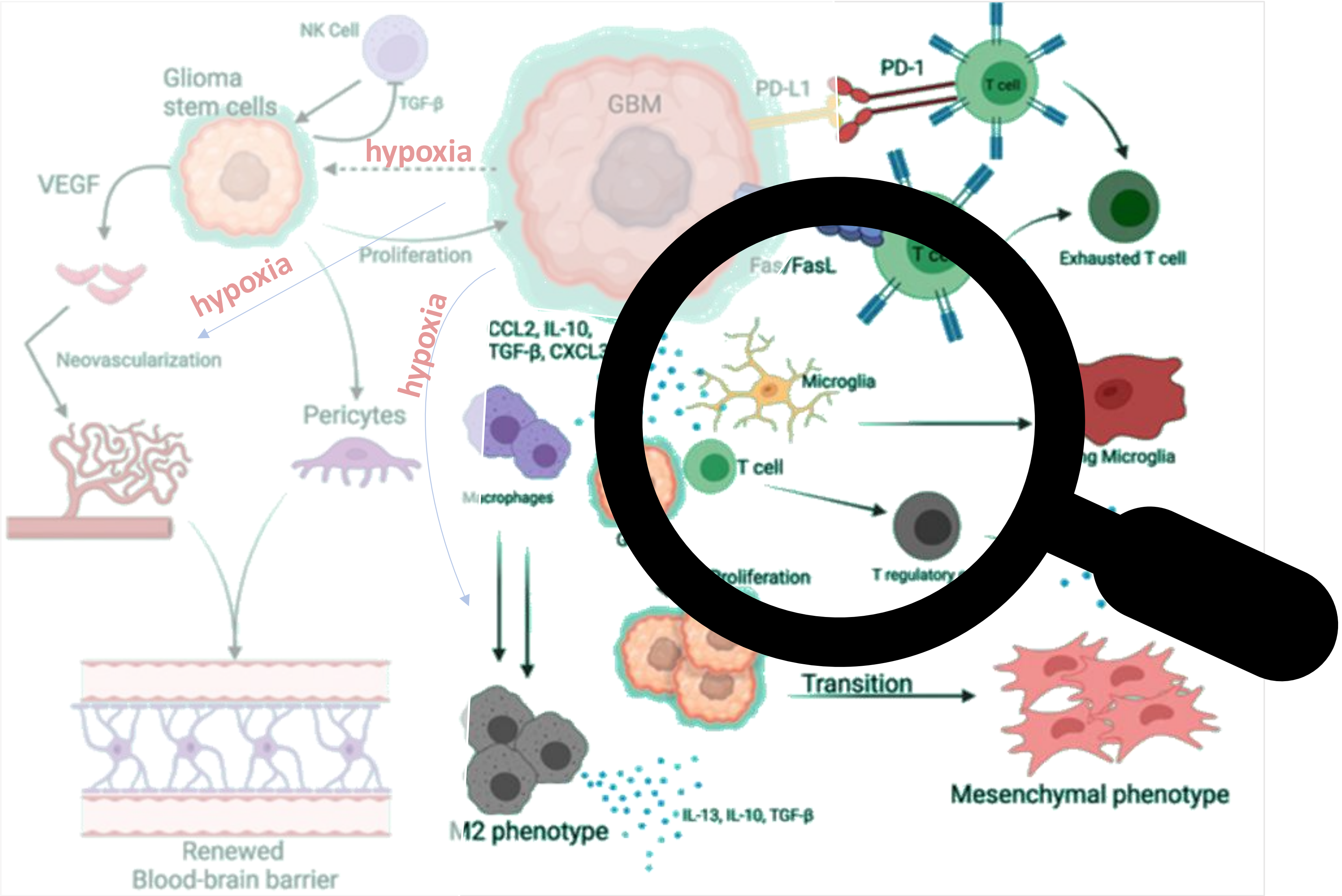
Subcutaneously prostate tumors irradiated with photons or carbon ions under acute hypoxic conditions

➔ Hypoxia was induced by clamping the tumor-supplying artery 10 min before and during irradiation.




A)
HI-tumor (1 Fx)
Photons (oxic)
Photons (hypoxic)
Tumor control probability [%]
Dose [Gy]
B)
HI-tumor (1 Fx)
^{12}C-ions (oxic)
^{12}C-ions (hypoxic)
Tumor control probability [%]
Dose [Gy]

Immune effects of Radiation therapy



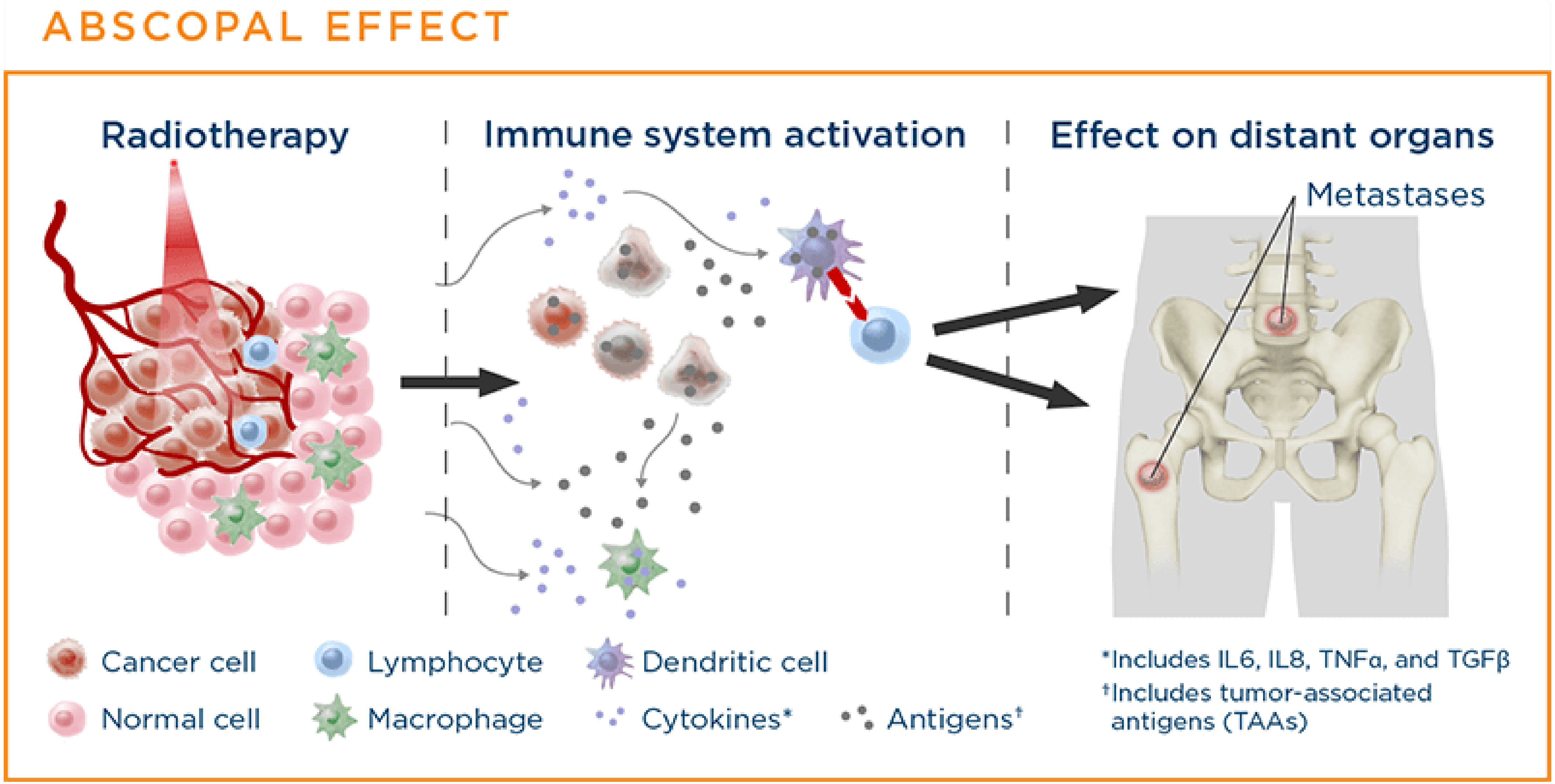
Abscopal Effect

Regression of **non-irradiated tumors** following localized radiation therapy.
Origin: introduced by Robin Mole in 1953 :
'ab' - away from, 'scopus' – target

Potential: Enables targeting of distant metastases without direct irradiation.

Clinical Importance
Paradigm Shift: Radiation therapy is no longer just a **local** treatment.
➔ No link between the Dose and the effect !

Radiotherapy and Abscopal effect



No clear dose dependency: Abscopal effects observed across a **wide range of doses and fractionation schemes**.

Factor	Role
Dose/Fractionation	**Hypofractionation (e.g., 8–10 Gy/fraction) may enhance immune activation.**
Radiation Type	**High LET (e.g., carbon ions) may potentiate immune response.**

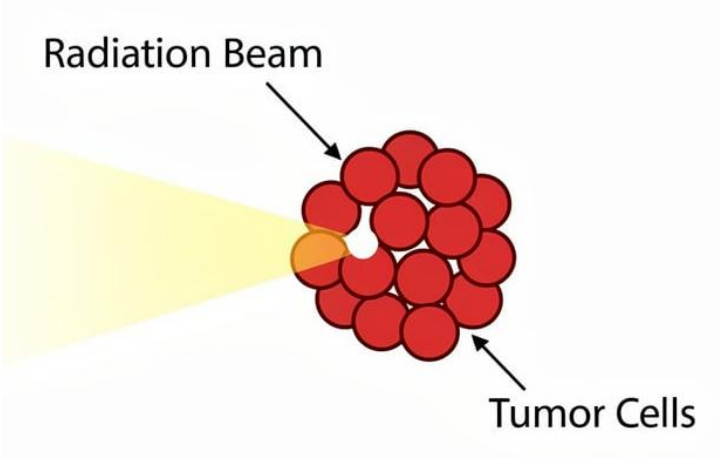
Key Takeaways

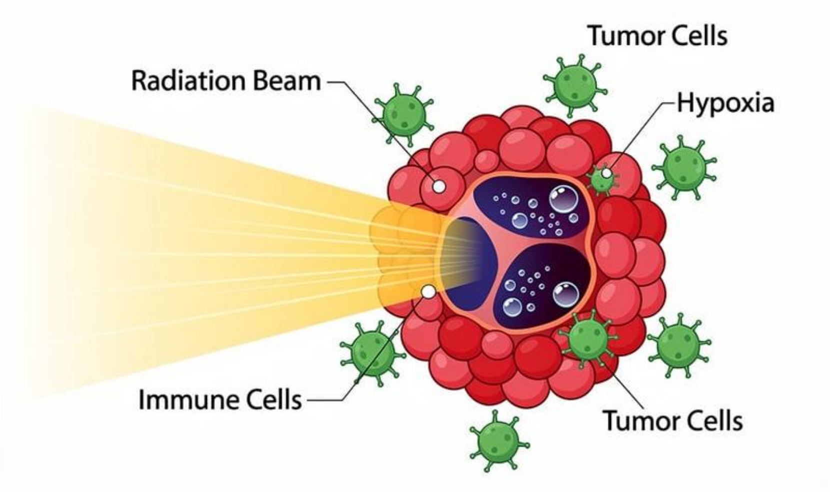
- **The abscopal effect is a systemic immune response triggered by local radiation**

Radiation therapy

inflammation

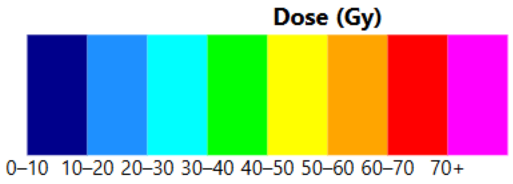
Hypoxia



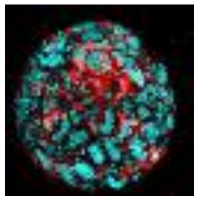


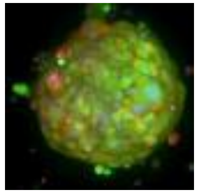
Monitoring tools

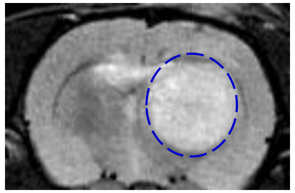
Dose



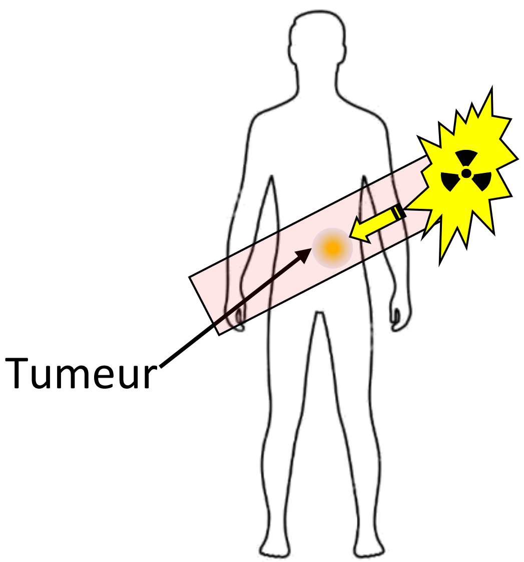
Effects



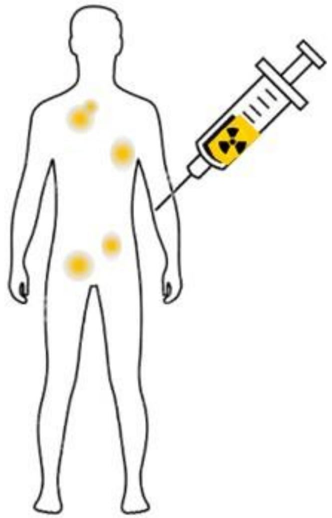




External beam radiotherapy



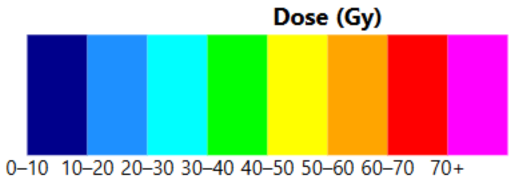
Targeted Internal Radiotherapy



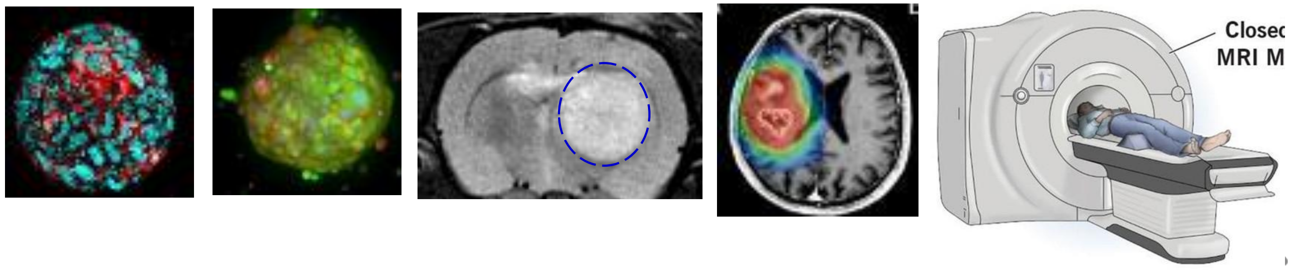
PI Dr Anne Marie FRELIN

Monitoring tools

Dose



Effects



And all our collaborators

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INVESTISSEMENTS D'AVENIR

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