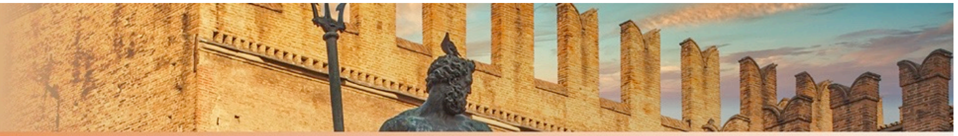
Frazionamento Spaziale Temporale

Monica Mangoni
Università degli Studi di Firenze

Associazione Italiana Radioterapia e Oncologia clinica
Società Italiana di Radiobiologia



DICHIARAZIONE

Relatore: MONICA MANGONI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

RT: biology-driven discipline

importance of the ‘**non-targeted**’ effects to improve the therapeutic index in RT

- cell signalling effects
- vascular changes
- stromal changes
- immunological changes

Mothersill C, et al. (2019). Cancers (Basel) 11, 1236–1261
Rodel F et al. (2015). Cancer Letters 356, 105–113.
Park HJ et al. (2012). Radiation Research 177, 311–327
Weichselbaum RR et al. (2017) Nature Reviews Clinical Oncology 14, 365–379

activation/modulation of the ‘non-targeted’ effects by tuning the physical parameters (dose delivery method) of irradiation

1 - Temporal schemes using **very high-dose** RT in one fraction could transform the immunosuppressive TME, resulting in an intense CD8 T-cell tumour infiltrate

Filatenkov A et al. (2015) Clinical Cancer Research 21, 3727–3739.

2 - Very high-dose rates (>40 Gy/s), as those employed in **FLASH**, appear to prevent both activations of the TGF-β/SMAD cascade and acute apoptosis in blood vessels resulting in a significant gain in normal tissue tolerances

Friedl AA et al. (2022) Mar;49(3):1993-2013.

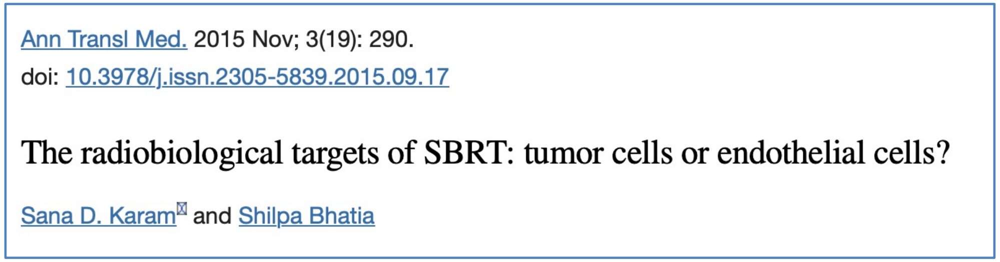
3 - The use of **protons** is advantageous mainly because of a more localized release of dose. Protons might also have distinct biological properties such as an enhanced ability to inhibit tumour angiogenesis or an increased sensitivity to T-lymphocyte killing of tumour cells

Girdhani S, et al (2013). Radiation Research 179, 257–272. Gameiro SR et al. (2016). IJROBP, 95, 120–130.

4 - The utilization of distinct spatial distributions, such as in **spatially fractionated radiotherapy (SFRT)** that uses a combination of spatial fractionation of the dose and narrow beams

Mohiuddin M et al. (1999) IJROBP 45, 721–727.

Temporal schemes using very high-dose



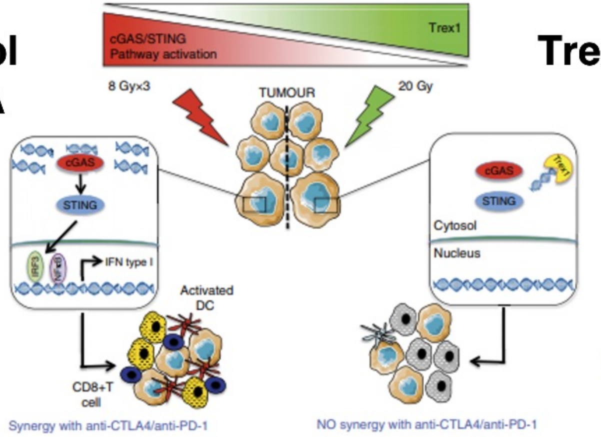
Ann Transl Med. 2015 Nov; 3(19): 290.
doi: 10.3978/j.issn.2305-5839.2015.09.17

The radiobiological targets of SBRT: tumor cells or endothelial cells?

Sana D. Karam and Shilpa Bhatia

Cytosol dsDNA

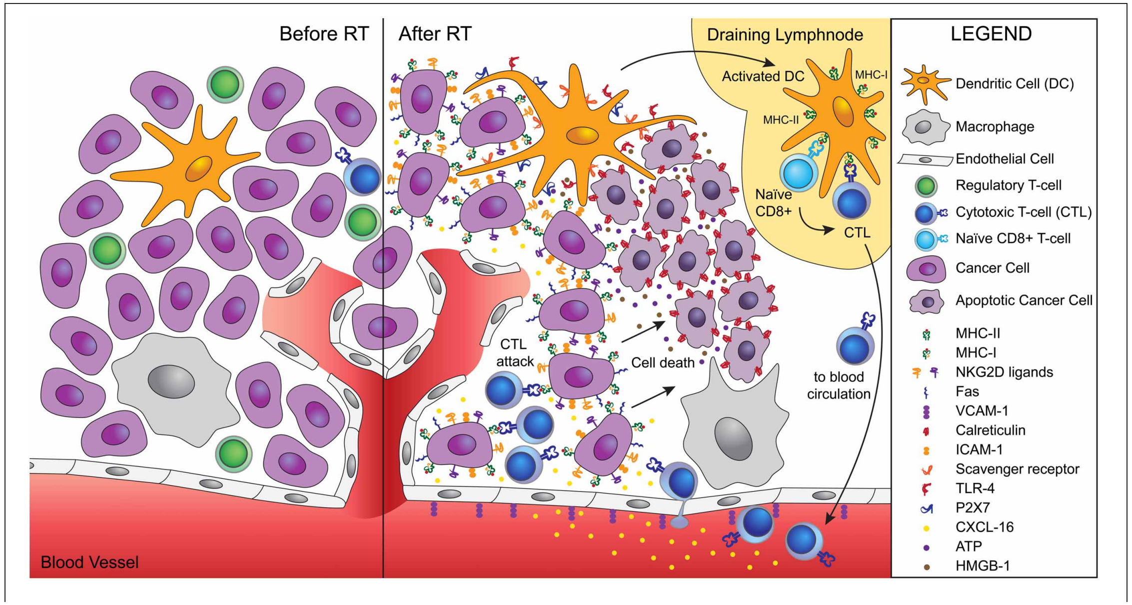
Trex1



+ −

8 Gyx3 **20 Gy**

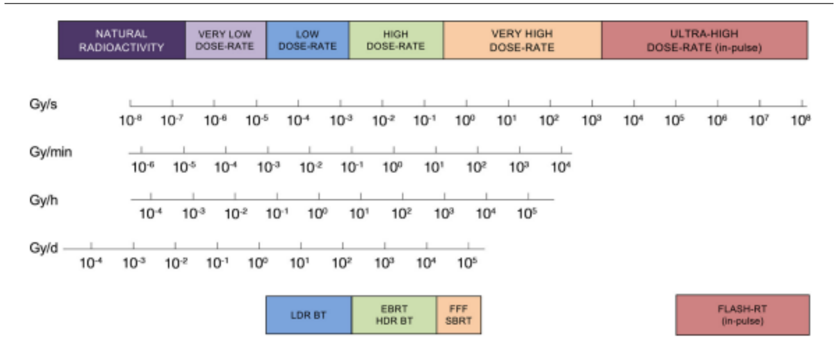
In situ vaccine

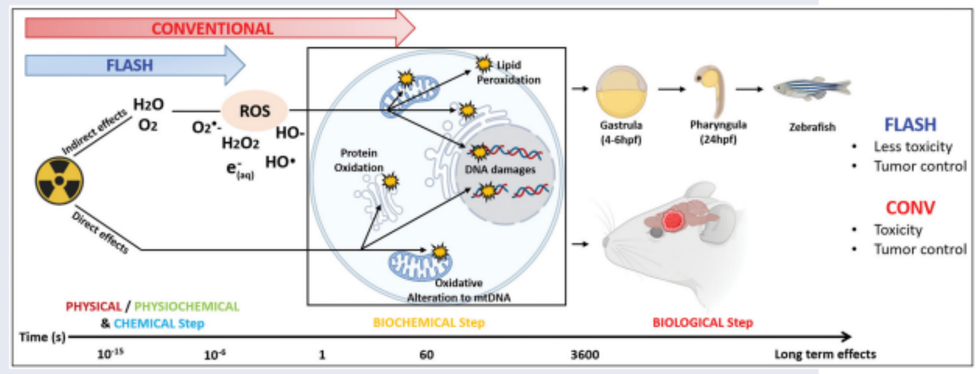


Demaria S, Frontiers in Oncology 2012
Formenti S, Demaria S, IJROBP 2012
Vanpouille-Box C, Clin Canc Res 2018

Temporal schemes using ultrahigh dose rates - FLASH

Very high-dose rates (>40 Gy/s)





FLASH effect was found to be reproducibile with
a) 1-10 pulses of 1,8-2 microsecond
b) an overall time <200 ms
c) a dose rate within the pulse $> 10^5$Gy/s

→Increase the differential effect tumors/normal tissues

→ Extremely short time of exposure: early modulation of radiochemical events that depend upon oxygen concentration in irradiated volume. FLASH could cause a rapid consumption of local oxygen and elicit a transient radiation-induced hypoxia.

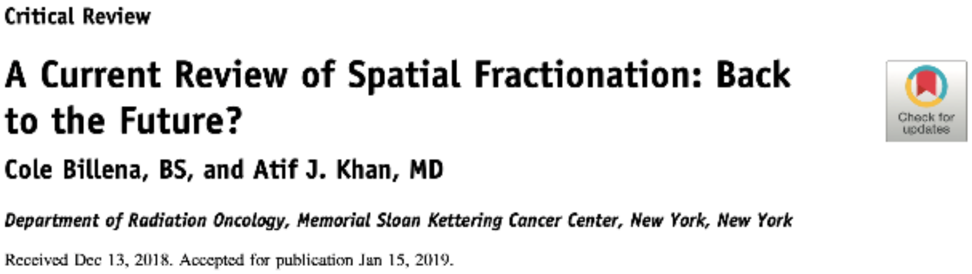
→ Prevent both activations of the TGF-β/SMAD cascade and acute apoptosis in blood vessels resulting in a significant gain in normal tissue tolerances

Beddok A, et al. IJROBP, Vol. 113, No. 5, pp. 985–995, 2022
Bourhis J, Radioth Onc 2019, 139. 11-17
Friedl AA et al. (2022) Mar;49(3):1993-2013.

spatially fractionated radiotherapy
SFRT

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org



Critical Review

A Current Review of Spatial Fractionation: Back to the Future?

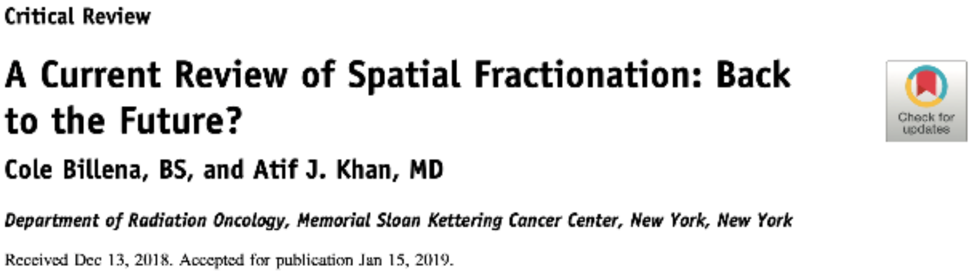
Cole Billena, BS, and Atif J. Khan, MD

Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

Received Dec 13, 2018. Accepted for publication Jan 15, 2019.

Laissue J, et al. Z Med Phys 2012;22:90-99.
Mohiuddin M, et al. Cancer 1990;66:114-118.

spatially fractionated radiotherapy SFRT


International Journal of Radiation Oncology biology • physics
www.redjournal.org

Critical Review

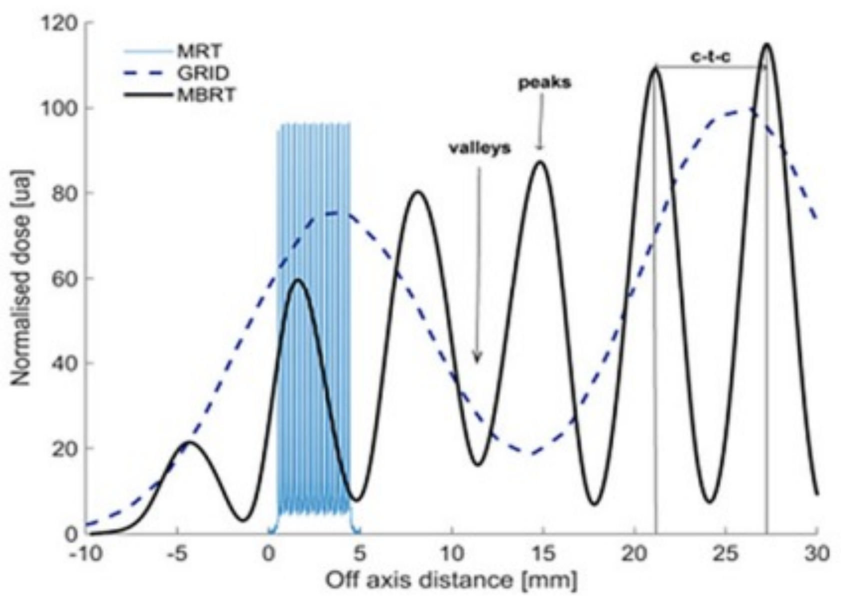
A Current Review of Spatial Fractionation: Back to the Future?

Cole Billena, BS, and Atif J. Khan, MD

Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

Received Dec 13, 2018. Accepted for publication Jan 15, 2019.

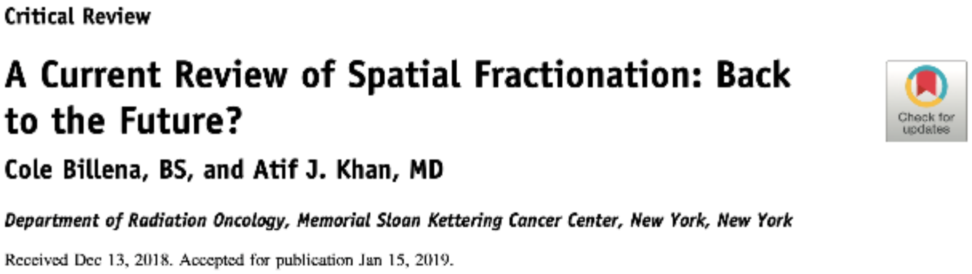
Expert Reviews in Molecular Medicine



Prezado Y (2022). Expert Reviews in Molecular Medicine 24, e3, 1–12.

spatially fractionated radiotherapy
SFRT

International Journal of
Radiation Oncology
biology • physics
www.redjournal.org



Critical Review

A Current Review of Spatial Fractionation: Back to the Future?

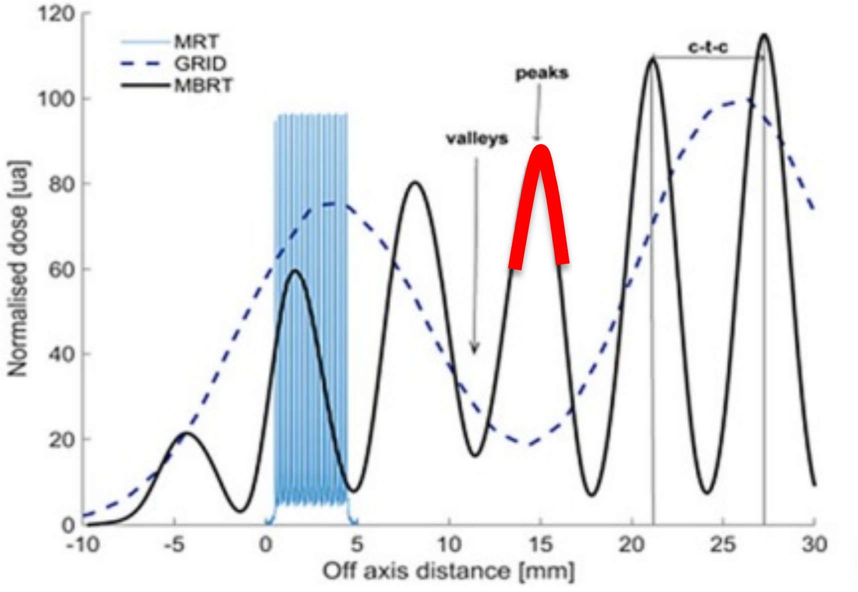
Check for updates

Cole Billena, BS, and Atif J. Khan, MD

Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

Received Dec 13, 2018. Accepted for publication Jan 15, 2019.

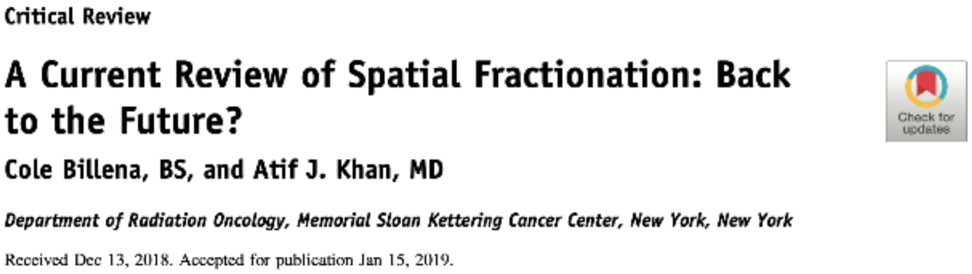
Expert Reviews in Molecular Medicine



Prezado Y (2022). Expert Reviews in Molecular Medicine 24, e3, 1–12.

spatially fractionated radiotherapy
SFRT

International Journal of
Radiation Oncology
biology • physics
www.redjournal.org



Critical Review

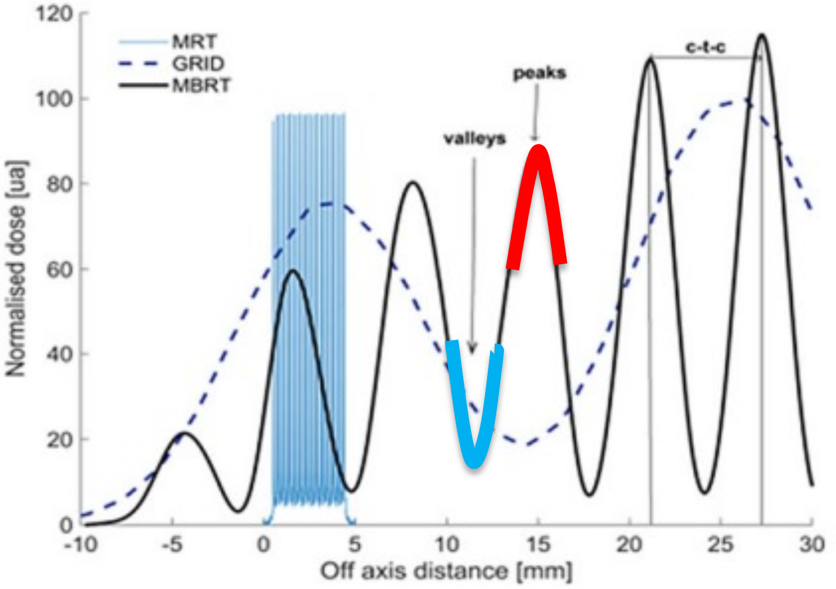
A Current Review of Spatial Fractionation: Back to the Future?

Cole Billena, BS, and Atif J. Khan, MD

Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

Received Dec 13, 2018. Accepted for publication Jan 15, 2019.

Expert Reviews in Molecular Medicine



Prezado Y (2022). Expert Reviews in Molecular Medicine 24, e3, 1–12.

spatially fractionated radiotherapy SFRT

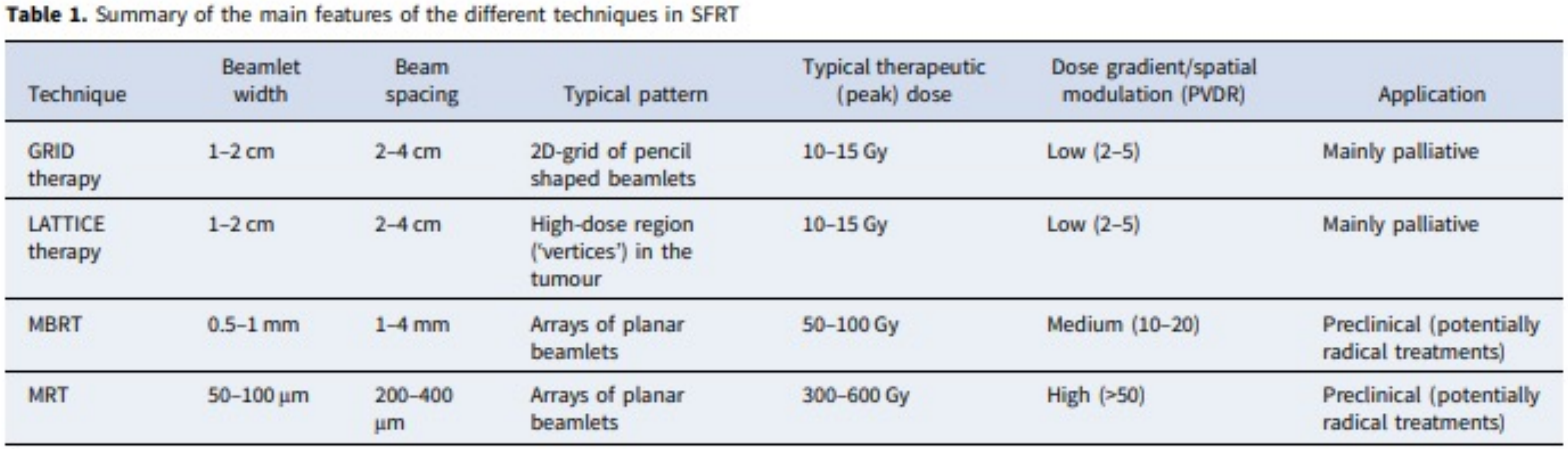
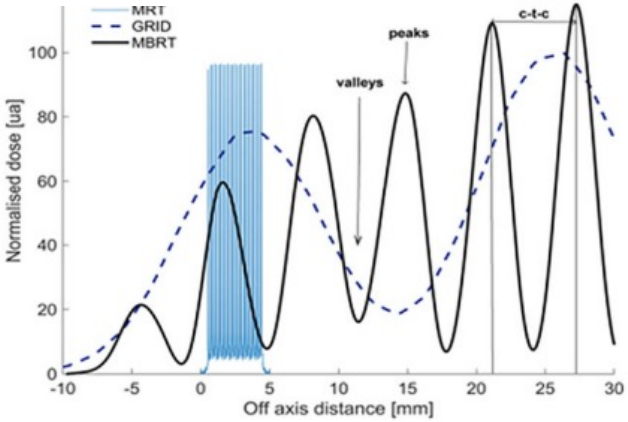


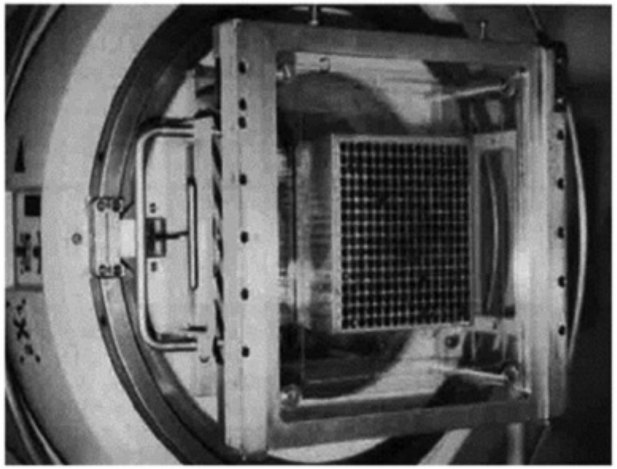
Table 1. Summary of the main features of the different techniques in SFRT

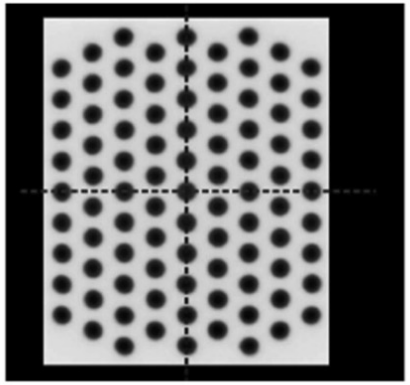
Technique	Beamlet width	Beam spacing	Typical pattern	Typical therapeutic (peak) dose	Dose gradient/spatial modulation (PVDR)	Application
GRID therapy	1–2 cm	2–4 cm	2D-grid of pencil shaped beamlets	10–15 Gy	Low (2–5)	Mainly palliative
LATTICE therapy	1–2 cm	2–4 cm	High-dose region ('vertices') in the tumour	10–15 Gy	Low (2–5)	Mainly palliative
MBRT	0.5–1 mm	1–4 mm	Arrays of planar beamlets	50–100 Gy	Medium (10–20)	Preclinical (potentially radical treatments)
MRT	50–100 μm	200–400 μm	Arrays of planar beamlets	300–600 Gy	High (>50)	Preclinical (potentially radical treatments)



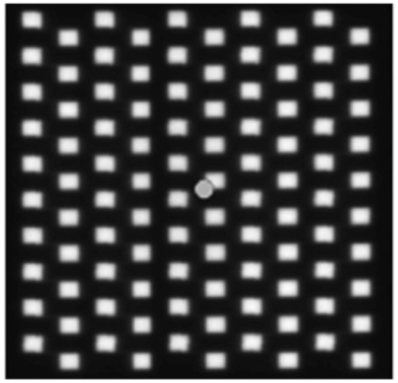
Prezado Y (2022). Expert Reviews in Molecular Medicine 24, e3, 1–12.

GRID

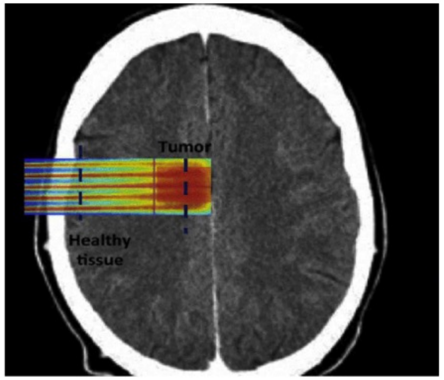




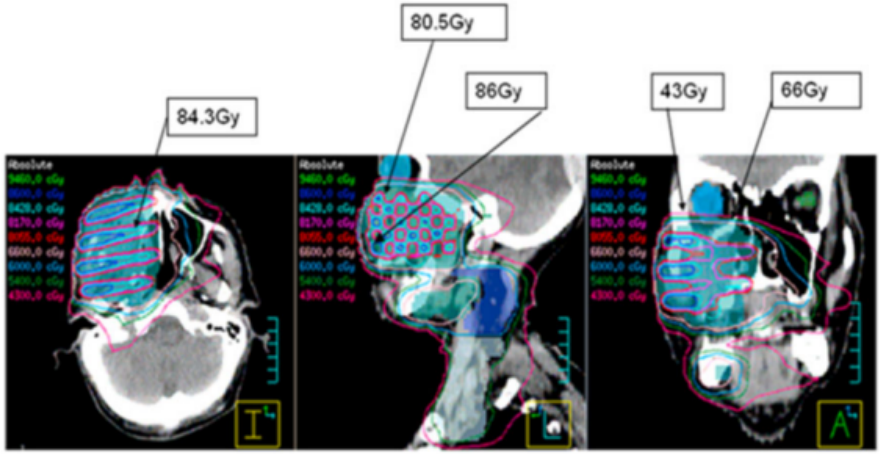
Collimator block

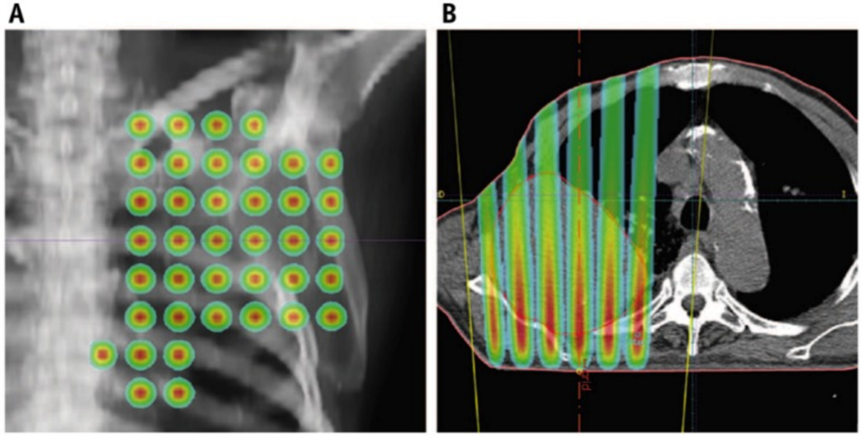


Multileaf collimator



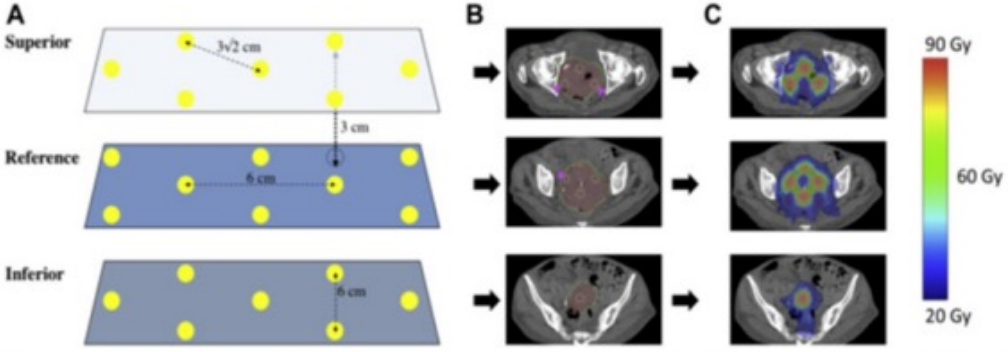
Proton GRID

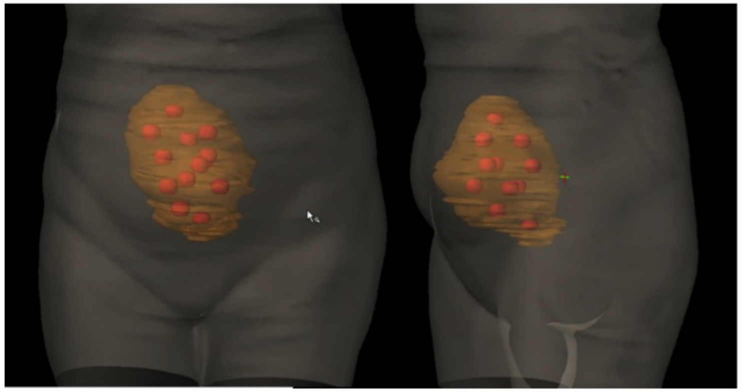




Billena C et al. (2019) IJROBP, Vol 104, No1, pp 177e187

LATTICE (3-dimensional GRID)

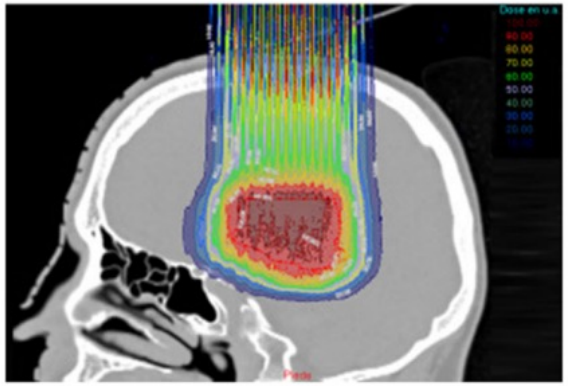




Microbeam radiation therapy MRT

25–100 µm-wide beams spaced by 200–400 µm in animal models: 300–600 Gy peak dose in one fraction

Minibeam radiation therapy MBRT/pMBRT



Clinical Trials

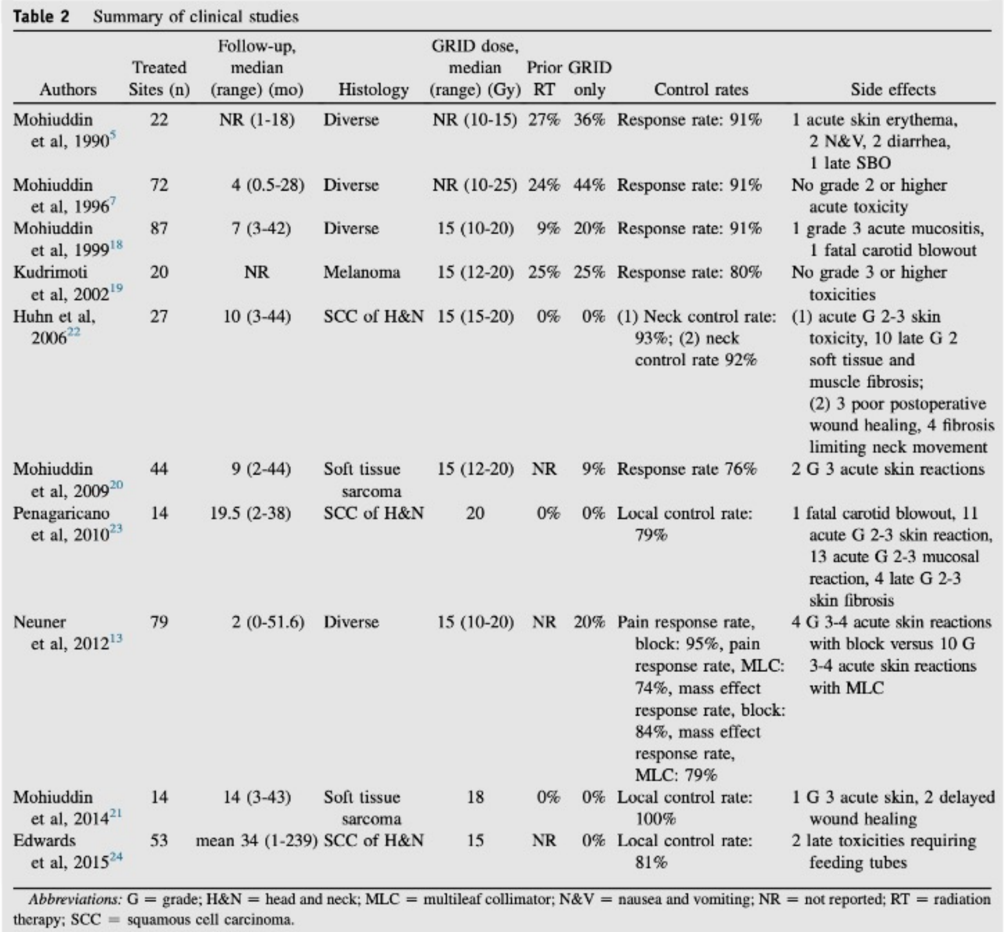
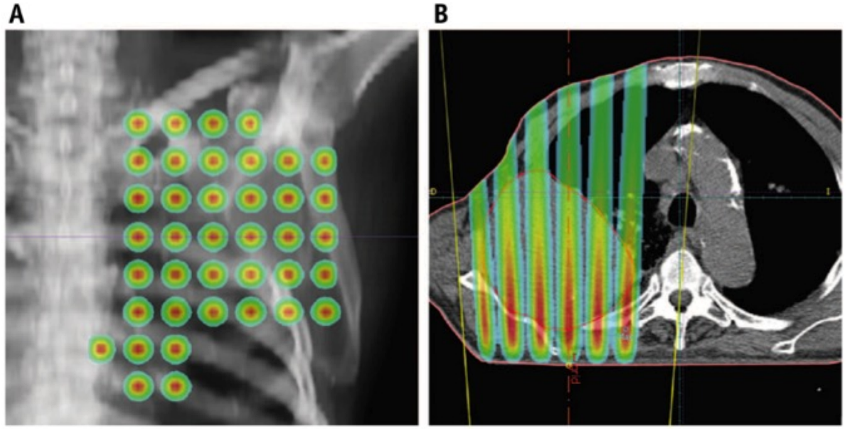


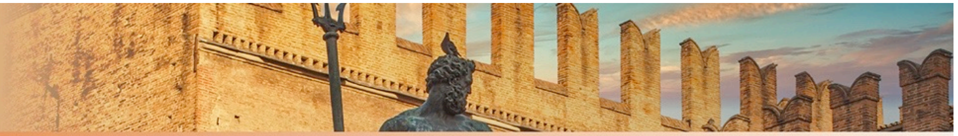
Table 2 Summary of clinical studies

Authors	Treated Sites (n)	Follow-up, median (range) (mo)	Histology	GRID dose, median (range) (Gy)	Prior RT	GRID only	Control rates	Side effects
Mohiuddin et al, 1990[5]	22	NR (1-18)	Diverse	NR (10-15)	27%	36%	Response rate: 91%	1 acute skin erythema, 2 N&V, 2 diarrhea, 1 late SBO
Mohiuddin et al, 1996[7]	72	4 (0.5-28)	Diverse	NR (10-25)	24%	44%	Response rate: 91%	No grade 2 or higher acute toxicity
Mohiuddin et al, 1999[18]	87	7 (3-42)	Diverse	15 (10-20)	9%	20%	Response rate: 91%	1 grade 3 acute mucositis, 1 fatal carotid blowout
Kudrimoti et al, 2002[19]	20	NR	Melanoma	15 (12-20)	25%	25%	Response rate: 80%	No grade 3 or higher toxicities
Huhn et al, 2006[22]	27	10 (3-44)	SCC of H&N	15 (15-20)	0%	0%	(1) Neck control rate: 93%; (2) neck control rate 92%	(1) acute G 2-3 skin toxicity, 10 late G 2 soft tissue and muscle fibrosis; (2) 3 poor postoperative wound healing, 4 fibrosis limiting neck movement
Mohiuddin et al, 2009[20]	44	9 (2-44)	Soft tissue sarcoma	15 (12-20)	NR	9%	Response rate 76%	2 G 3 acute skin reactions
Penagaricano et al, 2010[23]	14	19.5 (2-38)	SCC of H&N	20	0%	0%	Local control rate: 79%	1 fatal carotid blowout, 11 acute G 2-3 skin reaction, 13 acute G 2-3 mucosal reaction, 4 late G 2-3 skin fibrosis
Neuner et al, 2012[13]	79	2 (0-51.6)	Diverse	15 (10-20)	NR	20%	Pain response rate, block: 95%, pain response rate, MLC: 74%, mass effect response rate, block: 84%, mass effect response rate, MLC: 79%	4 G 3-4 acute skin reactions with block versus 10 G 3-4 acute skin reactions with MLC
Mohiuddin et al, 2014[21]	14	14 (3-43)	Soft tissue sarcoma	18	0%	0%	Local control rate: 100%	1 G 3 acute skin, 2 delayed wound healing
Edwards et al, 2015[24]	53	mean 34 (1-239)	SCC of H&N	15	NR	0%	Local control rate: 81%	2 late toxicities requiring feeding tubes

Abbreviations: G = grade; H&N = head and neck; MLC = multileaf collimator; N&V = nausea and vomiting; NR = not reported; RT = radiation therapy; SCC = squamous cell carcinoma.



Billena C et al. (2019) IJROBP, Vol 104, No1, pp 177e187



Biological mechanisms in SFRT

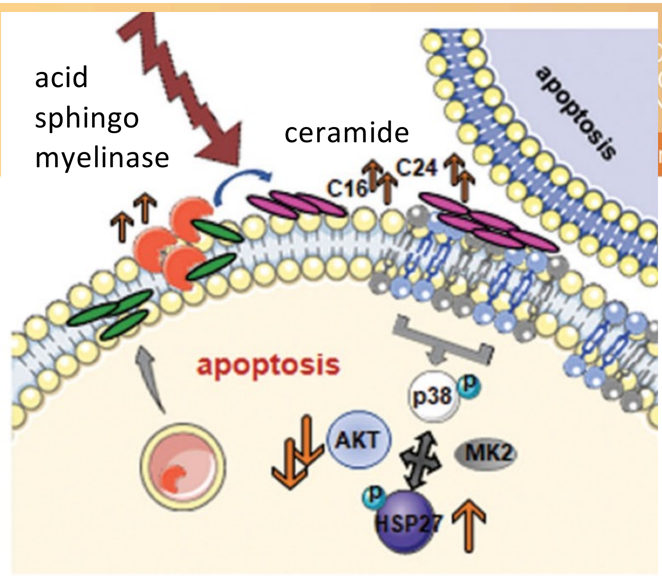
1 - Differential vascular effects

2 - Cell signalizing effects (bystander-like effects)/abscopal effects

3 - Inflammation and immunomodulatory effects

4 - Cell migration

5 - Free radical production and diffusion covering the valley regions in the tumours



Differential vascular effects

in **MRT** experiments:
preferential damaging effect on the immature vessels, while mature microvasculature is preserved

Sabatasso S et al. (2011) IJROBP 80, 1522–1532.

The effect might vary depending on the tumour type, the beam width, spacing and doses

Bouchet A et al. (2015) Physica Medica: PM 31, 634–641

MBRT: vascular effects at dose much higher than therapeutic doses

Bronnimann D et al. (2016) Scientific Reports 6, 33601

GRID: indirect observations on impact on vasculature → Enhanced sphingomyelinase activity and ceramide levels were only observed in patients with complete or partial response Sathishkumar S et al. (2005). Cancer Biology & Therapy 4, 979–986

LRT: mice bearing Lewis lung carcinoma: → serum exhibited increased acid sphingomyelinase levels

Kanagavelu S et al. (2014) Radiation Research 182, 149–162

Cell signalizing effects

bystander-like effects/ abscopal effects

GRID-adjacent cells → increased expression of genes involved in DNA repair, cell cycle arrest, heat shock protein and apoptosis after exposure

Asur RS et al. (2012). Radiation Research 177, 751–765.

Pts treated with GRID and mice with LRT→ significant increase of TNFα in the serum

Sathishkumar S et al. (2002) Technology in Cancer Research & Treatment 1, 141–147

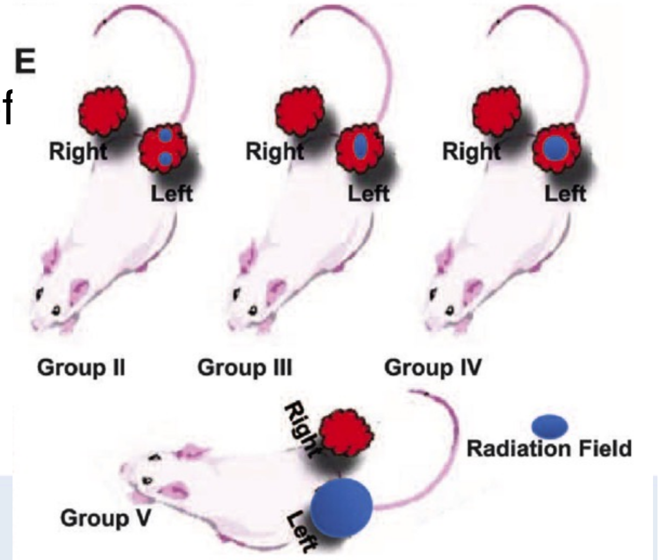
Kanagavelu S et al. (2014) Radiation Research 182, 149–162

Xenograft A549 lung adenocarcinoma implanted in the two flanks of mice, one of the two tumours irradiated with LRT

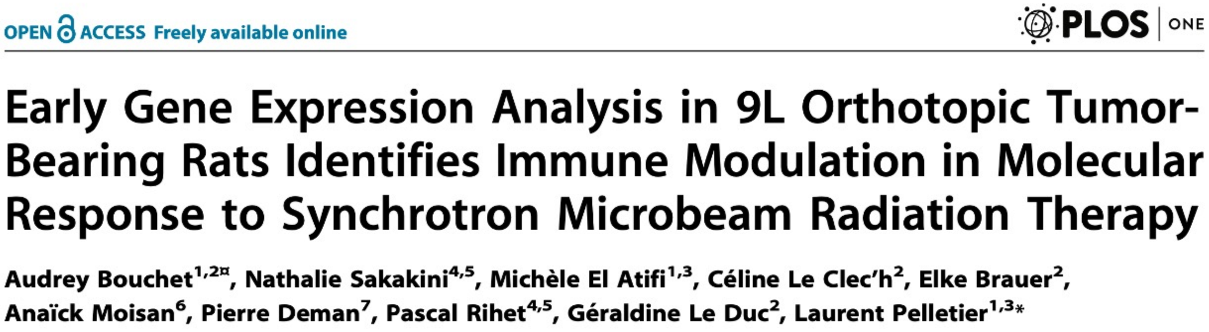
→ the growth of both tumours was reduced

→ increase in the number of infiltrating CD3+ T cells in both the irradiated site and the distant site

Kanagavelu S et al. (2014) Radiation Research 182, 149–162



Immunomodulation

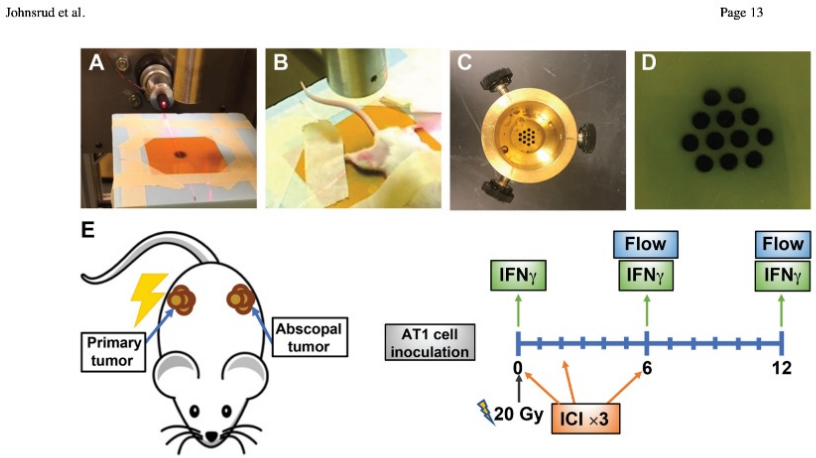


OPEN ACCESS Freely available online PLOS ONE

Early Gene Expression Analysis in 9L Orthotopic Tumor-Bearing Rats Identifies Immune Modulation in Molecular Response to Synchrotron Microbeam Radiation Therapy

Audrey Bouchet[1,2¤], Nathalie Sakakini[4,5], Michèle El Atifi[1,3], Céline Le Clec'h[2], Elke Brauer[2], Anaïck Moisan[6], Pierre Deman[7], Pascal Rihet[4,5], Géraldine Le Duc[2], Laurent Pelletier[1,3*]

Bouchet A et al. (2013). PLoS ONE 8, e81874.



Johnsrud et al. Page 13

Johnsrud AJ et al. (2020)
Radiation Research 194, 688–697.

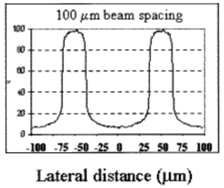
Front Oncol. 2020; 10: 548132. PMCID: PMC7907519
Published online 2021 Feb 12. doi: 10.3389/fonc.2020.548132 PMID: 33643893

Combined High-Dose LATTICE Radiation Therapy and Immune Checkpoint Blockade for Advanced Bulky Tumors: The Concept and a Case Report

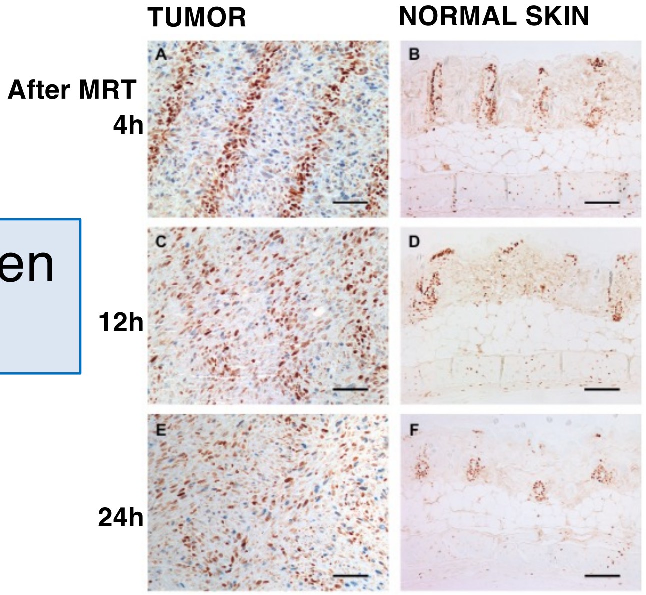
Liuqing Jiang,[1,†] Xiaobo Li,[1,2,3,†] Jianping Zhang,[1] Wenyao Li,[1] Fangfen Dong,[1] Cheng Chen,[1,2] Qingliang Lin,[1,2,3] Chonglin Zhang,[1] Fen Zheng,[1] Weisi Yan,[4] Yi Zheng,[5] Xiaodong Wu,[1,5,*] and Benhua Xu[1,2,3,*]

Cell migration

Hypothesis: the sparing of normal tissue could be explained by the migration and proliferation of stem cells in the valley regions to repair the tissue regions under the peak

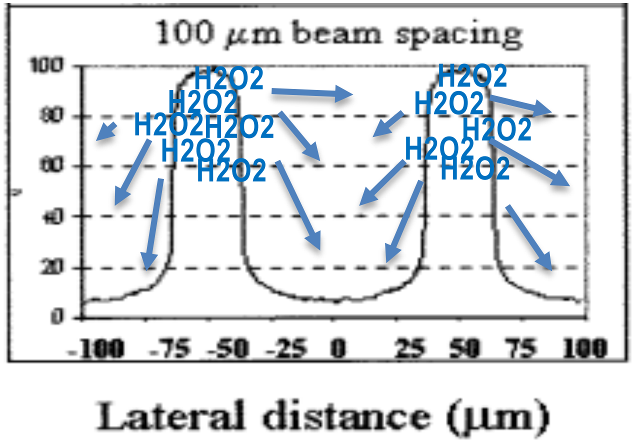


different migration patterns between tumour and healthy tissues



Crosbie JC et al. (2010) IJROBP77, 886–894

Free radicals production



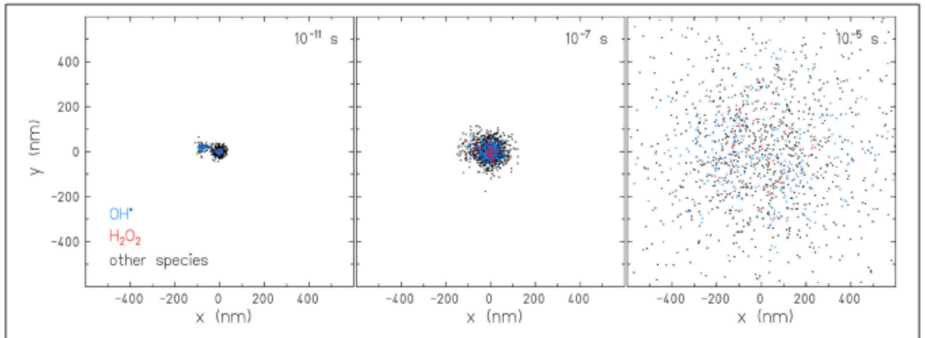
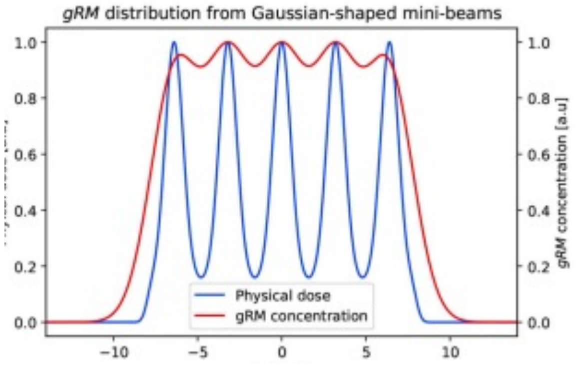


FIGURE 2 | Two dimensional representation of the temporal diffusion of molecules and radicals simulated with the software TRAX-CHEM. The events displayed are produced by a proton beam with kinetic energy $E_k = 92$ MeV in water.



The H2O2 produced in the dose-peaks diffuses to the dose-valleys during beam-on leading to a homogeneous ROS distribution over the target.
Model tested on three previous independent photon micro-beam and proton mini-beam animal experiments.

Wealth of evidence that ROS contribute to the bystander effect extracellularly and also intracellularly through a continuous cascade of events.

The ROS generation in proton beams is more important than that of photon radiation

Dal Bello R, et al(2020) Front. Phys. 8:564836 Mitteer RA et al. (2015). Scientific Reports 5, 13961 Azzam EI et al. (2002). Cancer Research 62, 5436–5442

Spatiotemporal fractionation

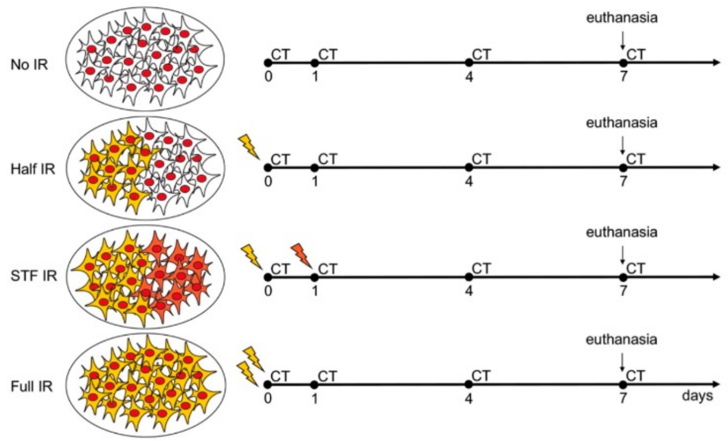
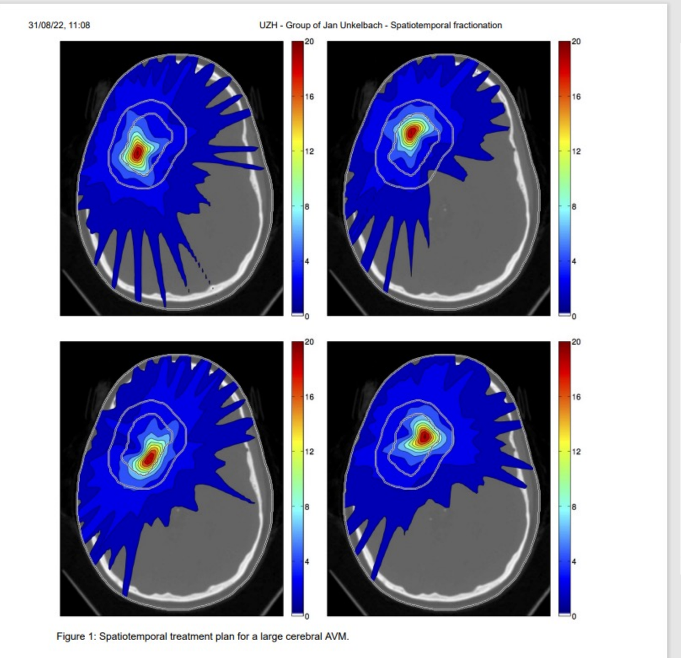
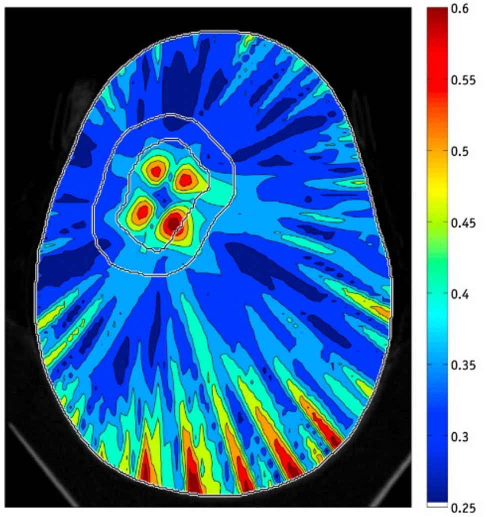


Figure 1. Schematic illustration of the study design and treatment schedule as described in Materials & Methods, subsection Study design.

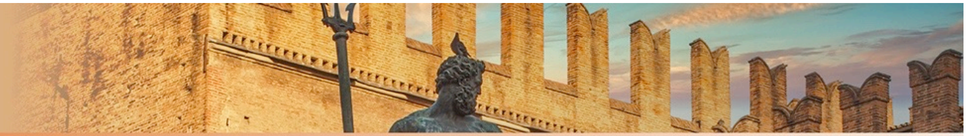


31/08/22, 11:08 UZH - Group of Jan Unkelbach - Spatiotemporal fractionation

Figure 1: Spatiotemporal treatment plan for a large cerebral AVM.



Telarovic J, ett al. Phys. Med. Biol. 65(22):22NT02, 2020
Unkelback J et al. IJROBP, Vol. 95, No. 3, pp. 1067e1074, 2016



Conclusions

The advancement of both technology and radiobiology knowledge is generating a considerable interest in spatial and temporal fractionation

Non-targeted effects improve the the therapeutic index in RT

Radiobiological experiments support the participation of radiation-induced bystander effects, vascular alterations, and immunologic interactions.

The use of charged particles may modify the underlying mechanisms and their relative weights with respect to photons (i.e. charged particles are more effective activating the immune system)

Combination with immunotherapy to explore

New modalities using radically different ways of depositing the dose can offer enormous opportunities for optimal patient treatments