Physics Colloquium
Zeuthen
24. Feb. 2021 – 14:00

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Charité – University Medicine Berlin

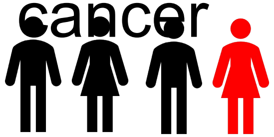
FLASH Irradiation

can cancer be treated within a second?

1. Introduction

1. Introduction *Cancer*

18.1 million cases in 2018
1 in 4 people will develop cancer



The most common cancers are:

Tumor side	cases
Lung	2.090 k
Breast	2.090 k
Colorectal	1.800 k
Prostate	1.280 k
Skin (non-melanoma)	1.040 k
Stomach	1.030 k

9.6 million deaths in 2018
1 in 6 deaths is due to cancer

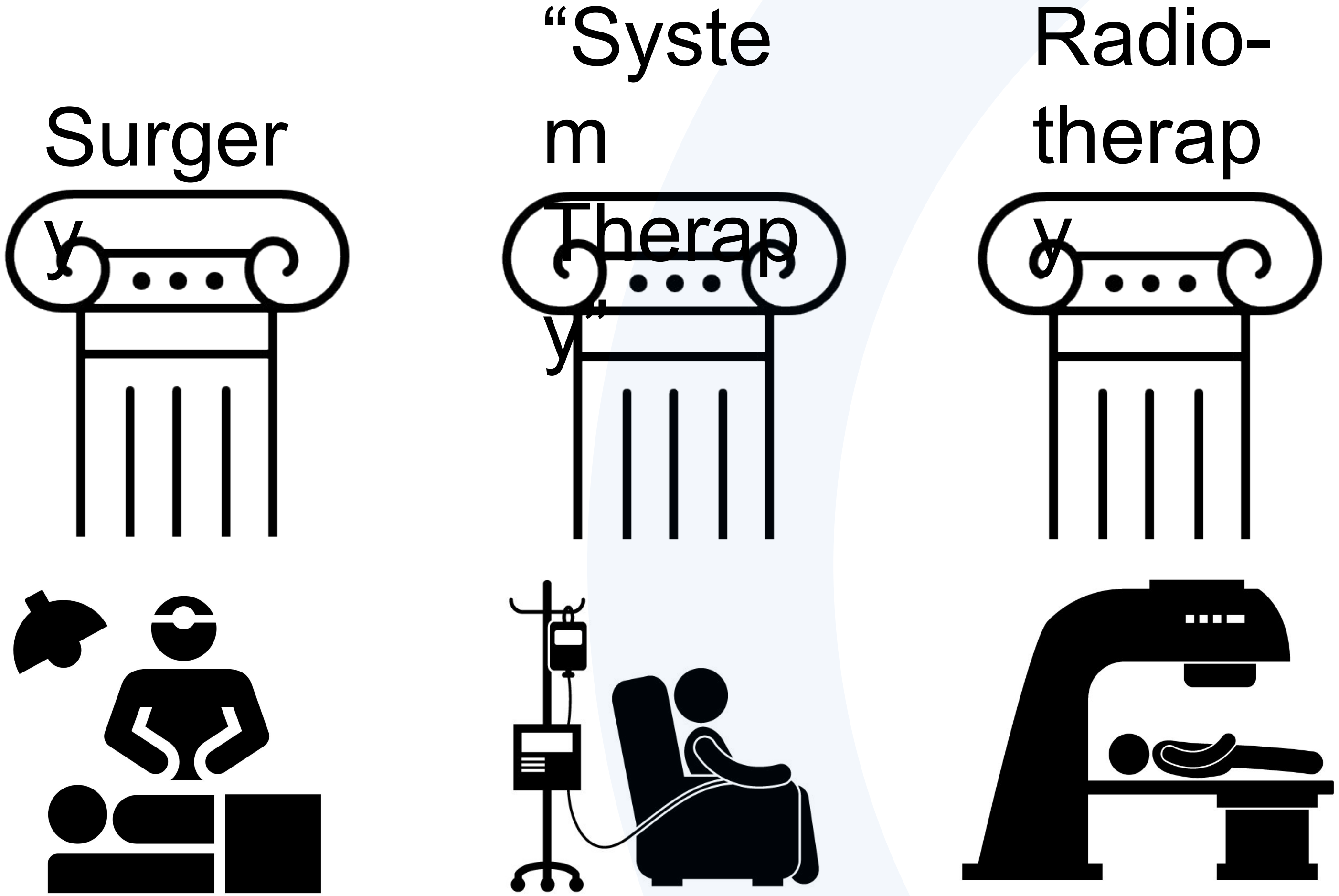
The most common causes of cancer death are:

Tumor side	Deaths
Lung	1.760 k
Colorectal	862 k
Stomach	783 k
Liver	782 k
Breast	627 k

… is the 2nd leading cause of death globally

1. Introduction *Cancer treatment*

The 3 columns of cancer treatment



https://thenounproject.com/term/surgery/599/

https://www.vecteezy.com/vector-art/349016-hospital-medical-therapy-treatment-stick-figure-pictogram-icon-cliparts

1. Introduction

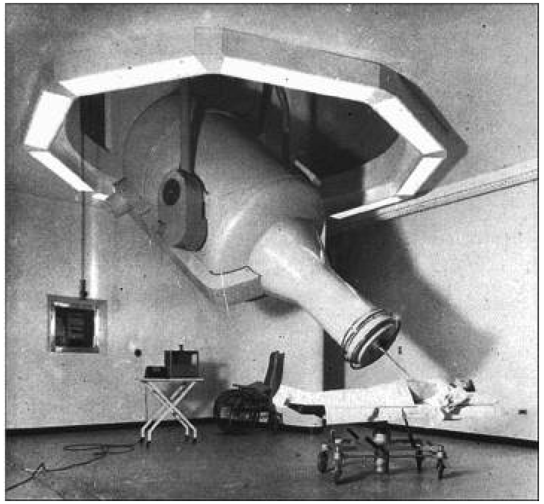
Radiation Oncology

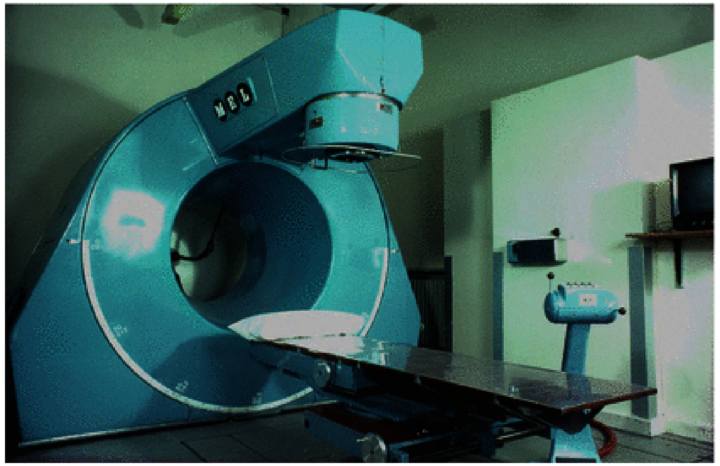
Use of ionizing radiation to kill tumorcells

Electromagnetic radiation (X-Ray, γ-Ray)

Particle radiation (Electrons, Protons, Heavy ions…)

1. Introduction *Radiation Oncology*





https://iopscience.iop.org/article/10.1088/0031-9155/51/13/R20

https://de.wikipedia.org/wiki/Cyberknife

https://www.medicaltourismitaly.com/true-beam/

1. Introduction *Radiation*

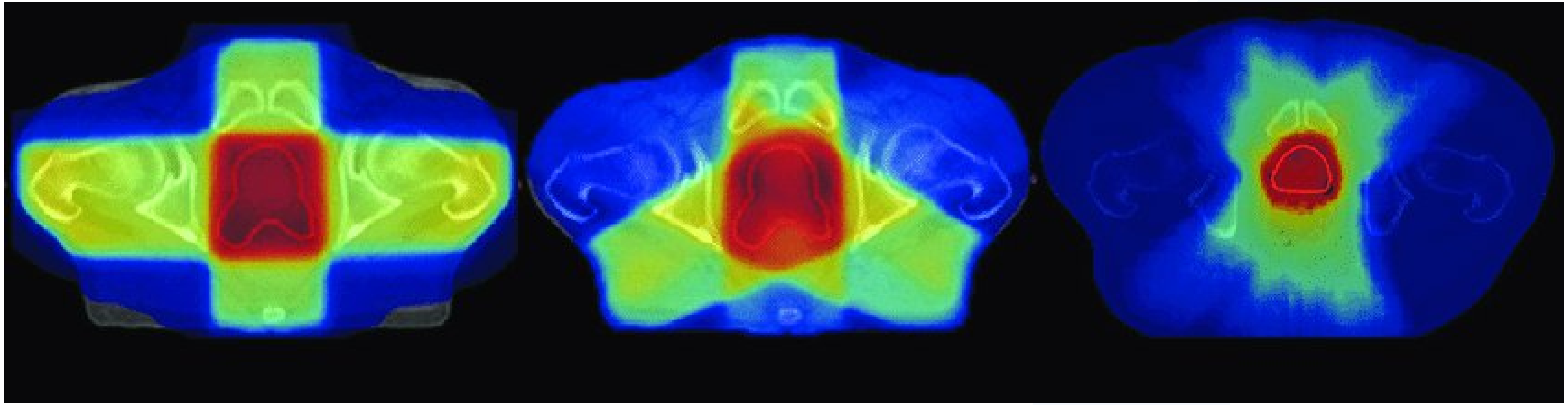
Oncology

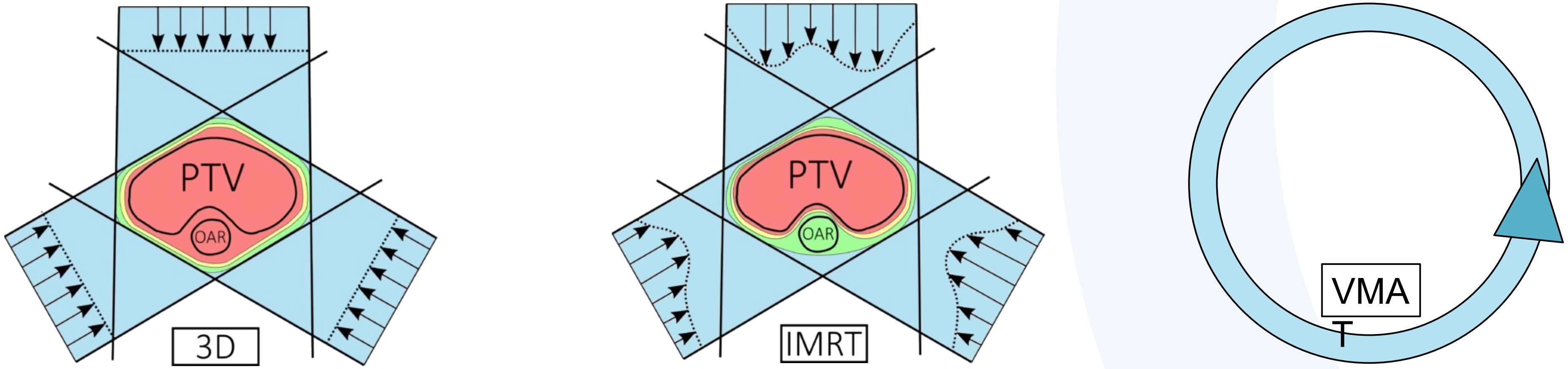
Ionizing radiation → DNA strand breaks → Cell death

→ Cancer cells

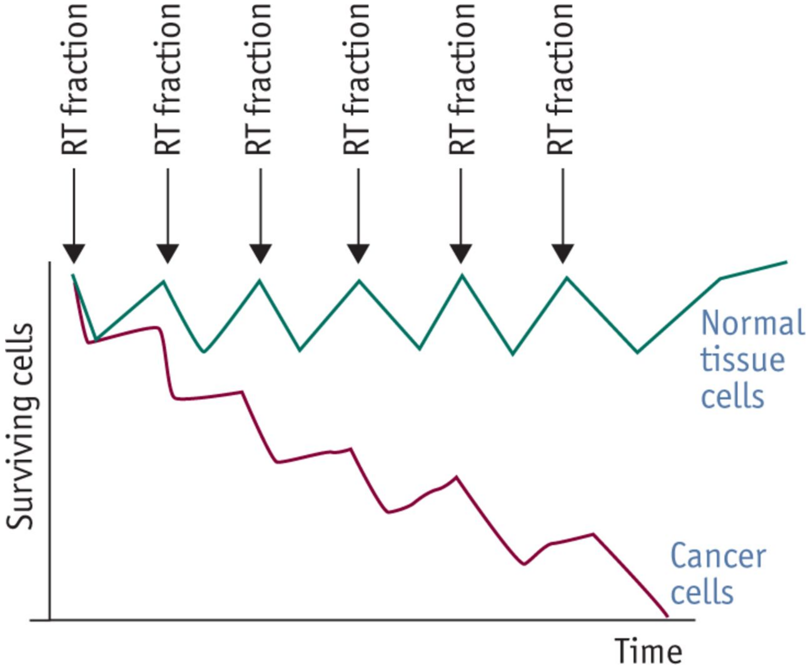
→ Normal cells

FOCUSING



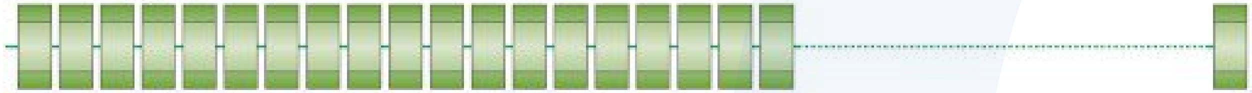


FRACTIONATION

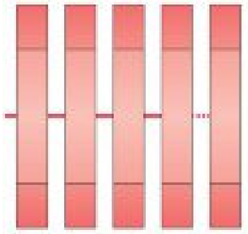


Conventional fractionation

Moderate hypofractionation



Extreme hypofractionation



	Fractionation schedule		
	Conventional	Moderate	Extreme
Total dose (Gy)	76–80	57–70.2	38–50
Total treatment duration (weeks)	8–9	4–6	1–2
Number of fractions (n)	38–40	19–30	4–5
Dose per fraction (Gy)	1.8–2	2.4–4	6–10
Interval between fractions (days)	1	1	1–2

https://breathe.ersjournals.com/content/8/2/134
https://www.nature.com/articles/nrurol.2016.106?WT.feed_name=subjects_prostatic-diseases

Better images
(CT/MRT/PET)

Better medicine
(Chemo-
/Immunotherapy)

Better planning
systems
(new: artificial intelligence)

Better irradiation
devices
(linear/partical accelerator)

Better
irradiation

But…

SINCE DECADES ONE THING DIDN‘T CHANGE AT ALL

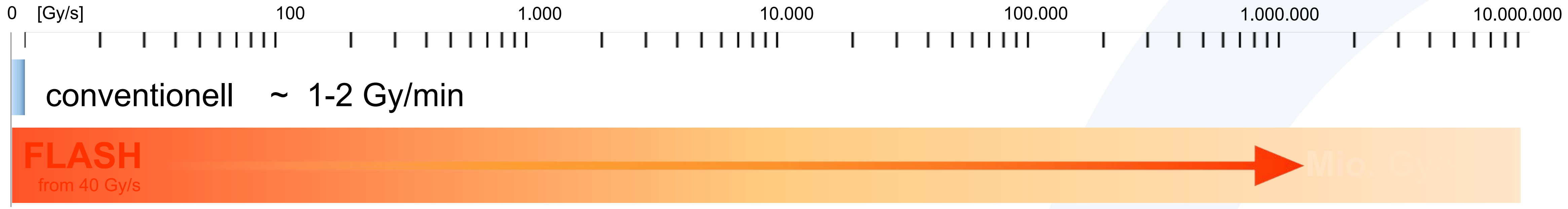
DOSE

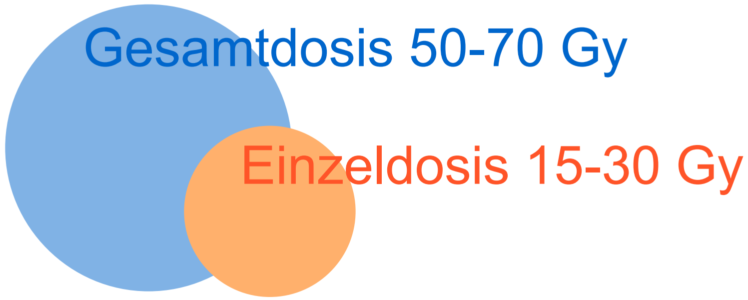
https://www.vecteezy.com/vector-art/349016-hospital-medical-therapy-treatment-stick-figure-pictogram-icon-cliparts

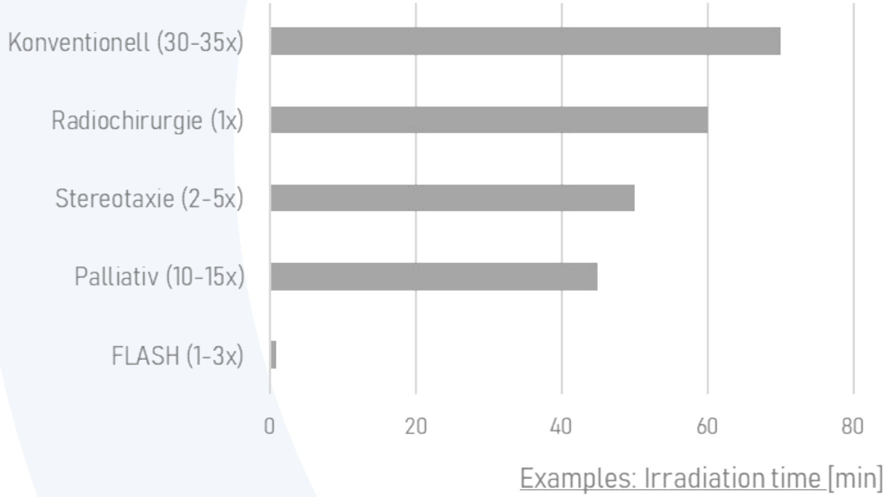
2. FLASH Irradiation

What is FLASH Irradiation?

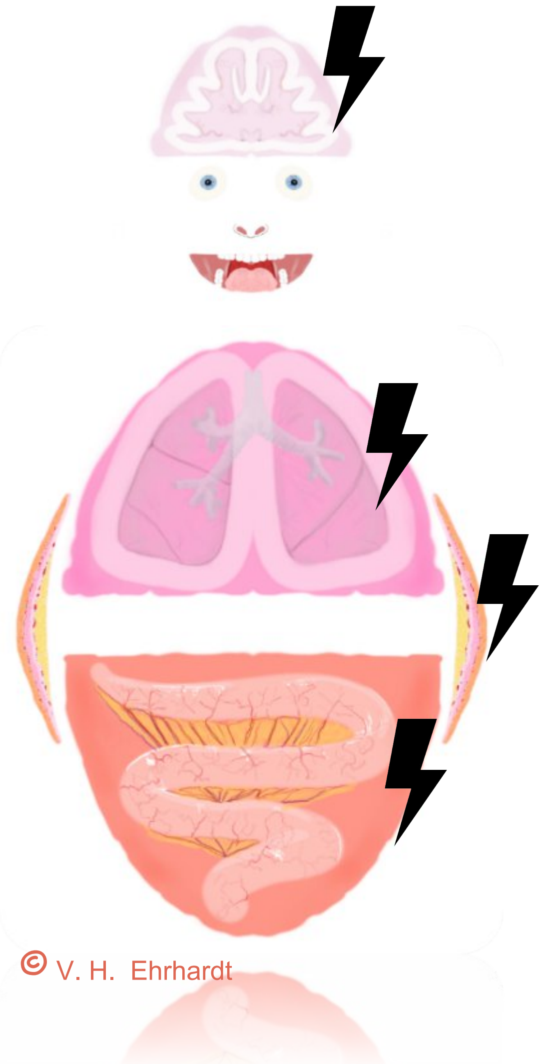
2. FLASH Irradiation







2. FLASH Irradiation



Brain

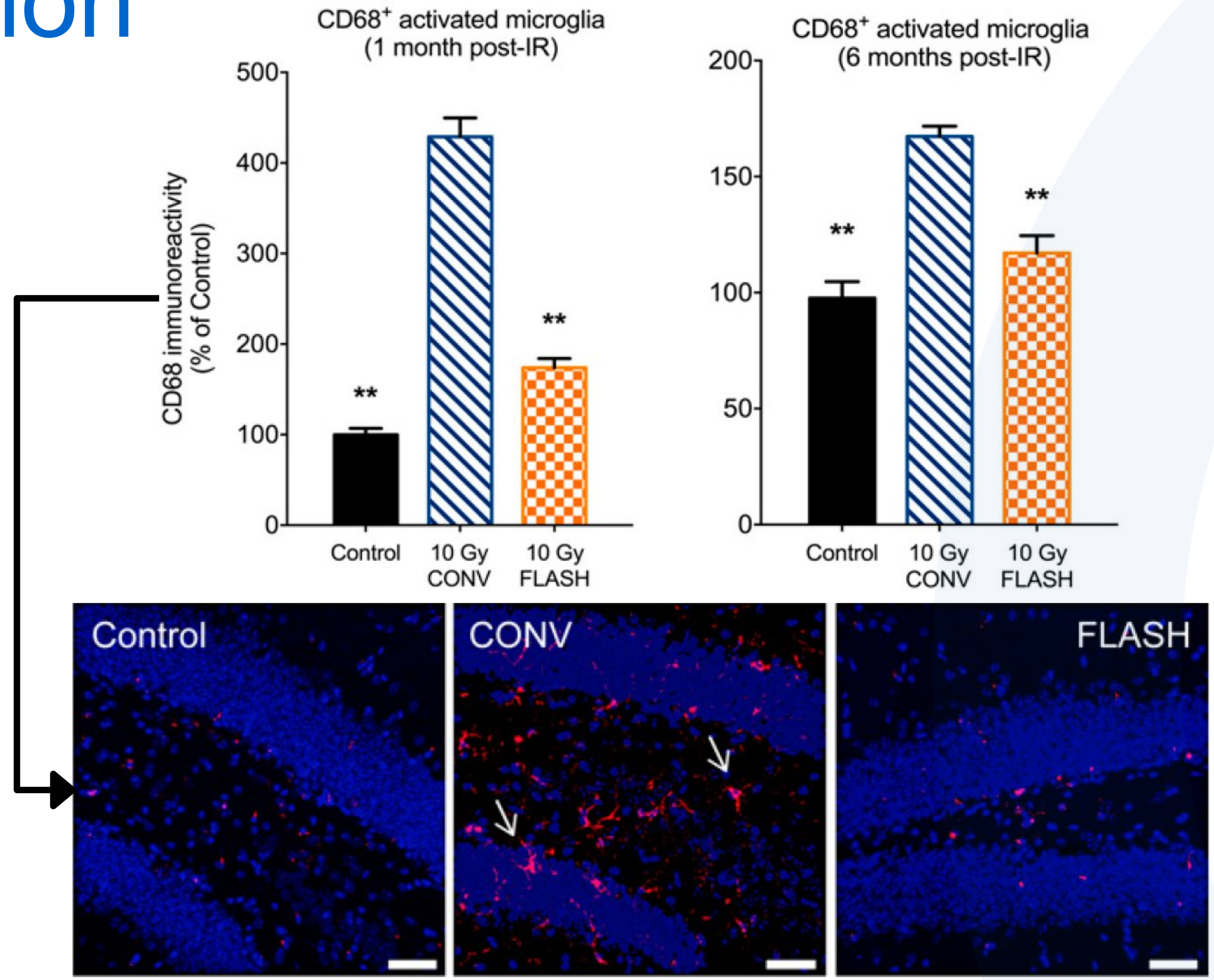
Lung

Skin

Gut

Inflammation

Activated microglia

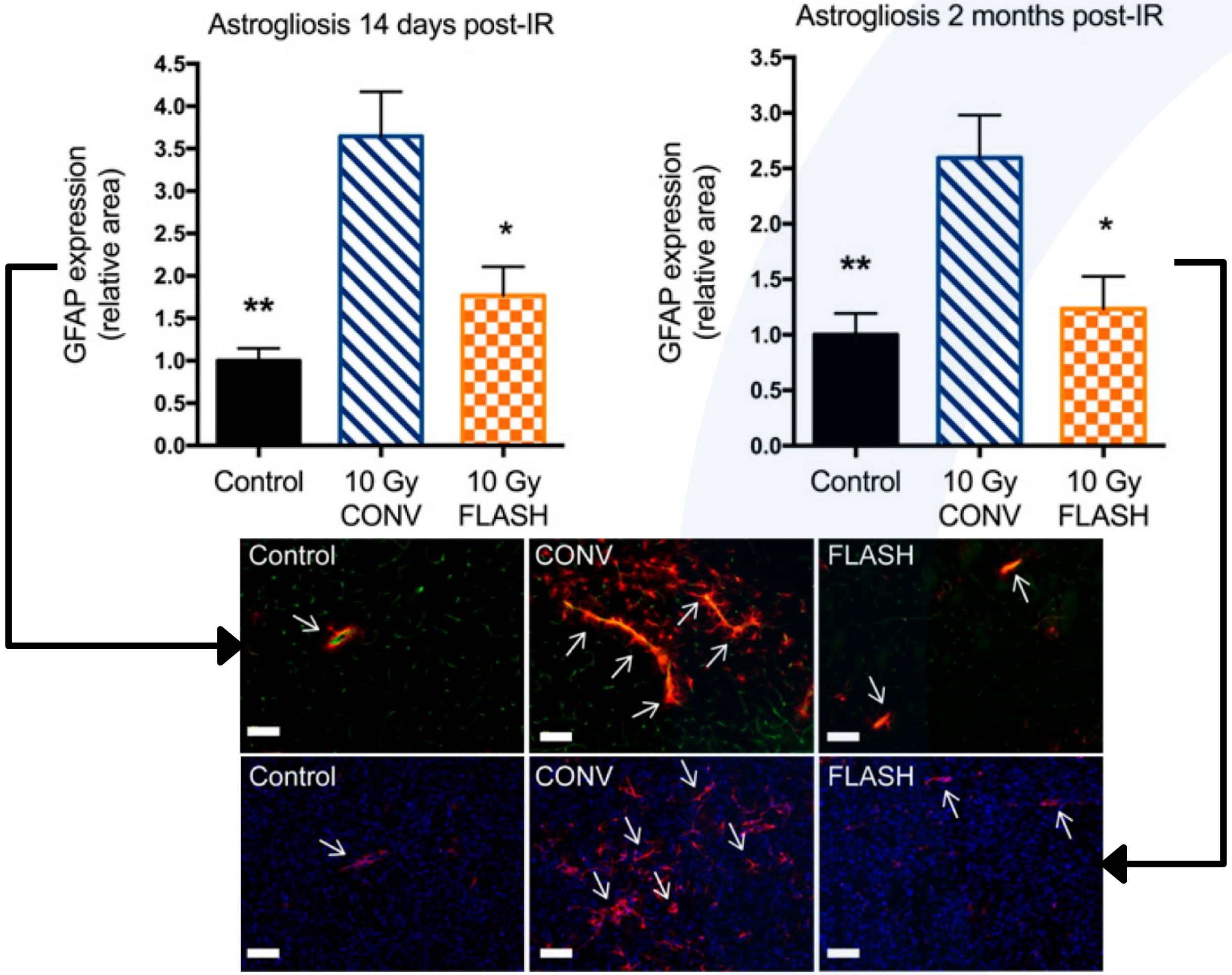


Montay-Gruel P et al., 2017

2. FLASH Irradiation *Brain*

Structural changes

Astrogliosis

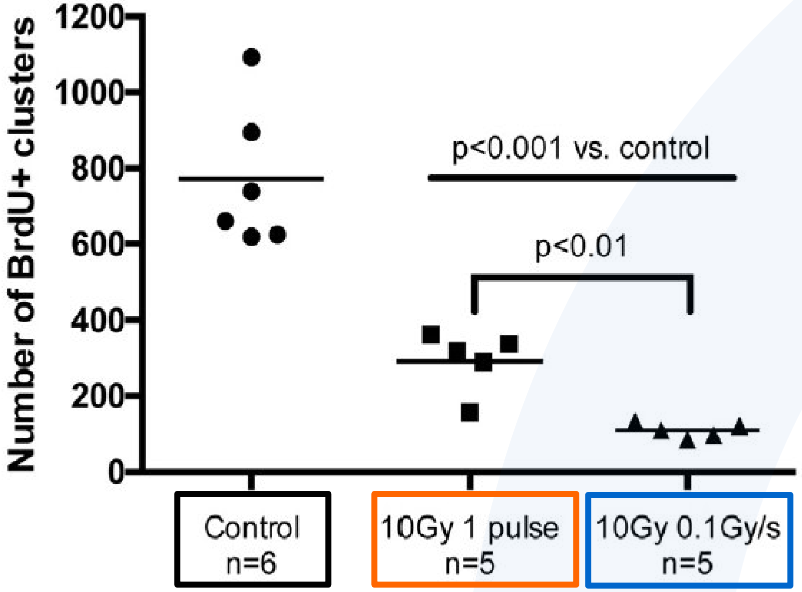


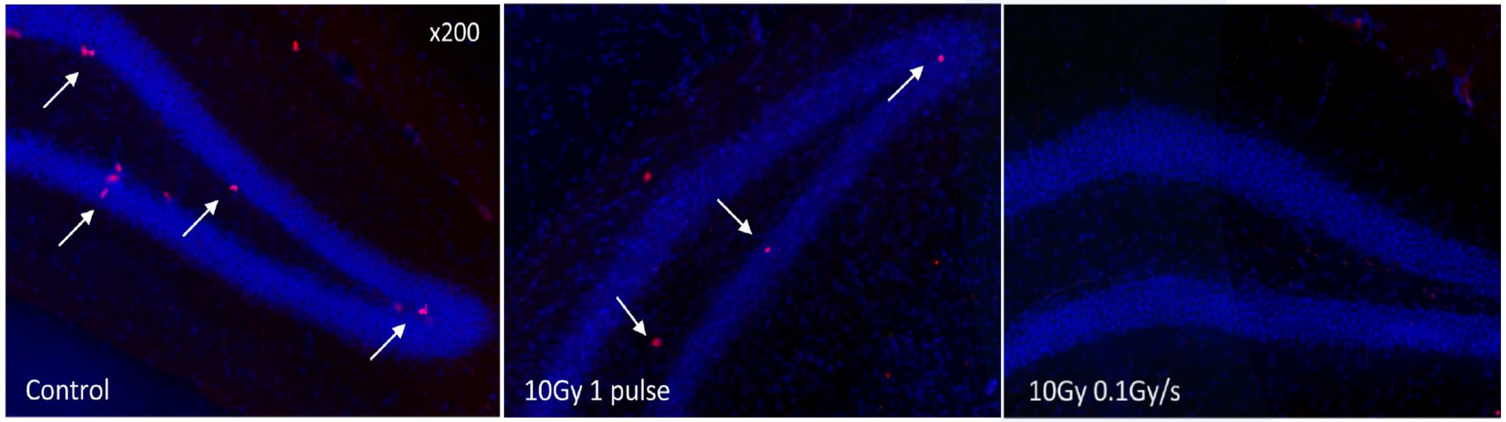
Montay-Gruel P et al., 2017

2. FLASH Irradiation *Brain*

Regeneration

Neurogenesis



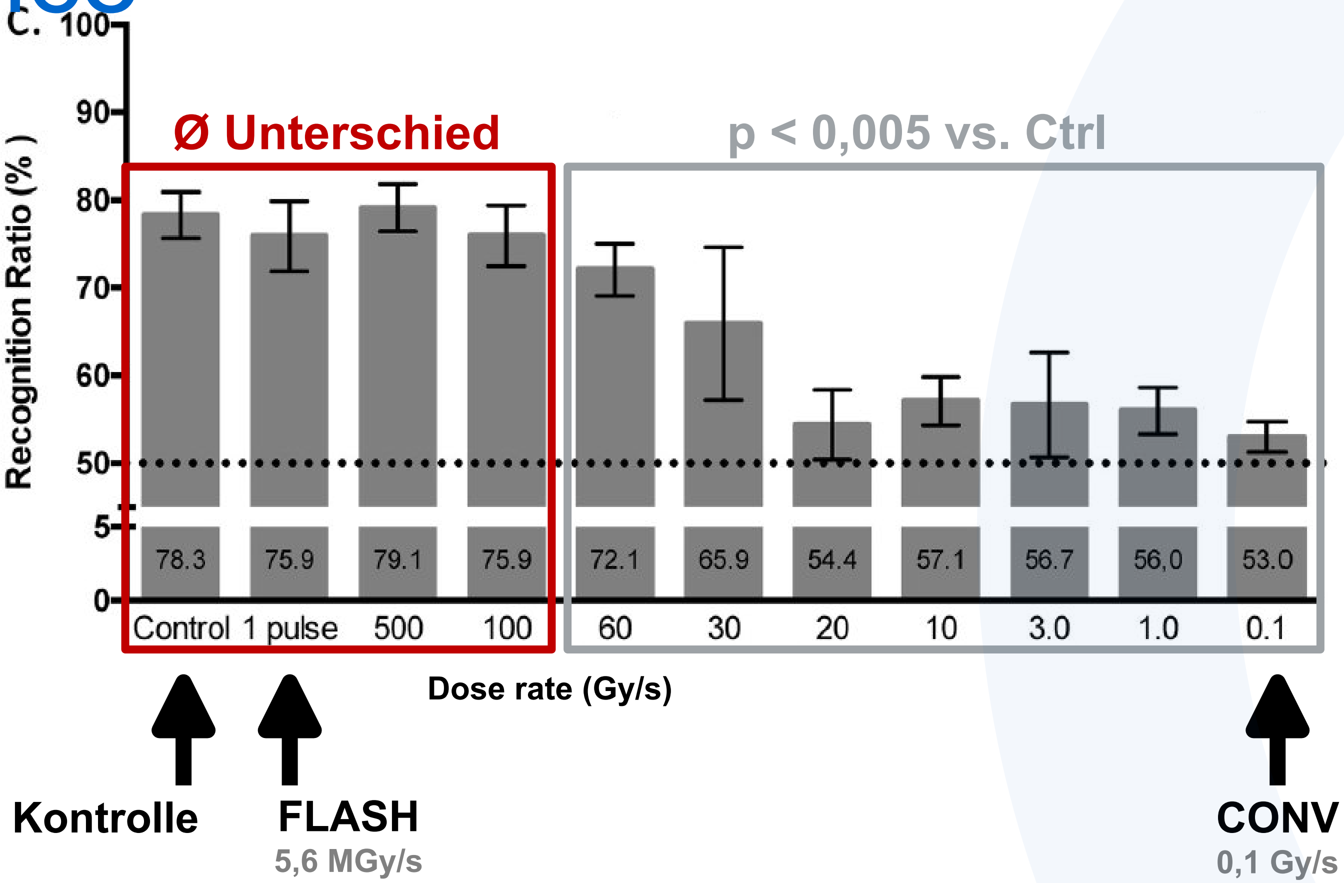


Control FLASH Conventiona

Montay-Gruel P et al., 2017

2. FLASH Irradiation *Brain*

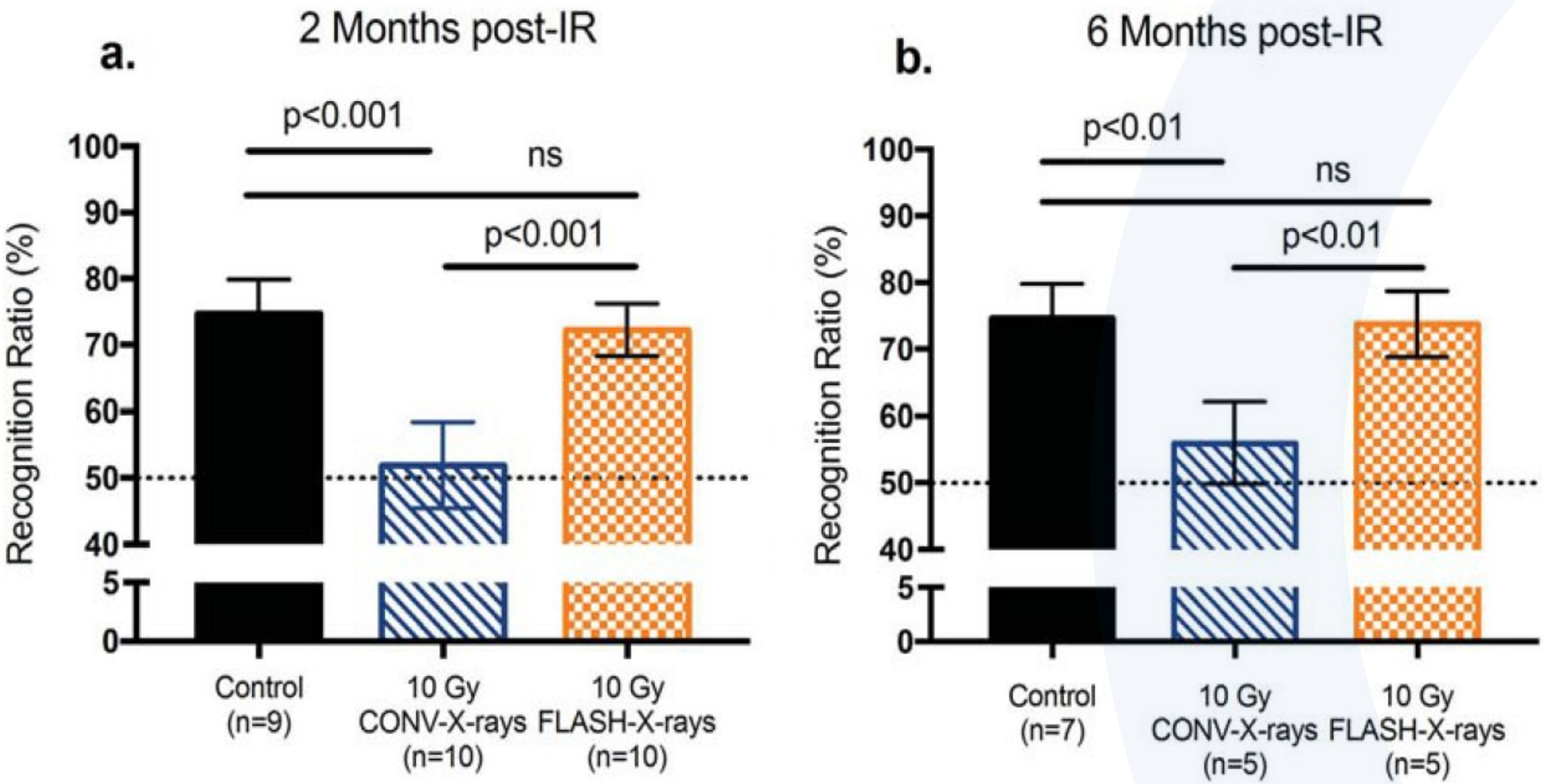
Cognitive performance



Montay-Gruel P et al., 2017

2. FLASH Irradiation *Brain*

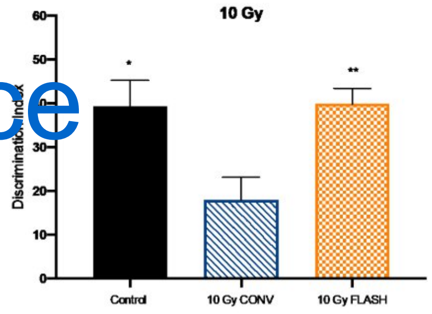
Cognitive performance



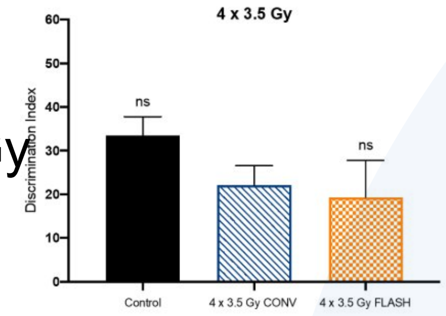
Montay-Gruel P et al., 2017

2. FLASH Irradiation *Brain*

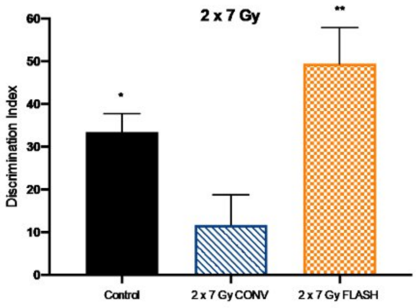
Cognitive performance



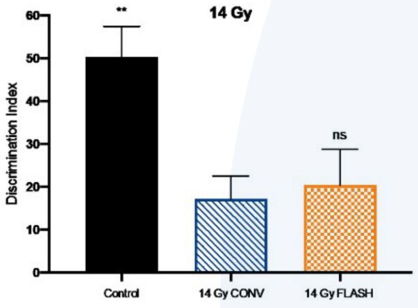
1 x 10 Gy
P<0,05



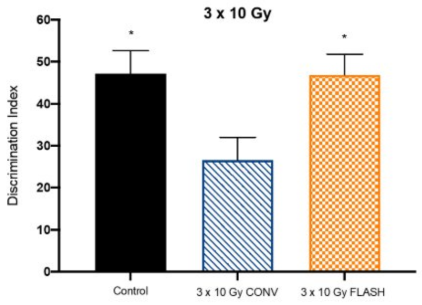
4 x 3,5 Gy
ns



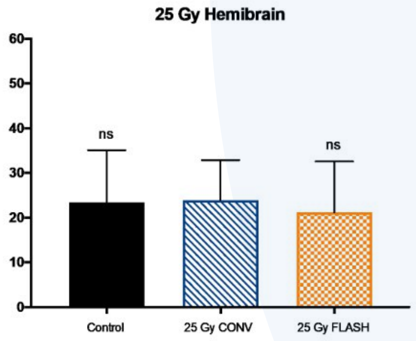
2 x 7 Gy
P<0,05



1 x14 Gy
ns



3 x 10 Gy
P<0,05

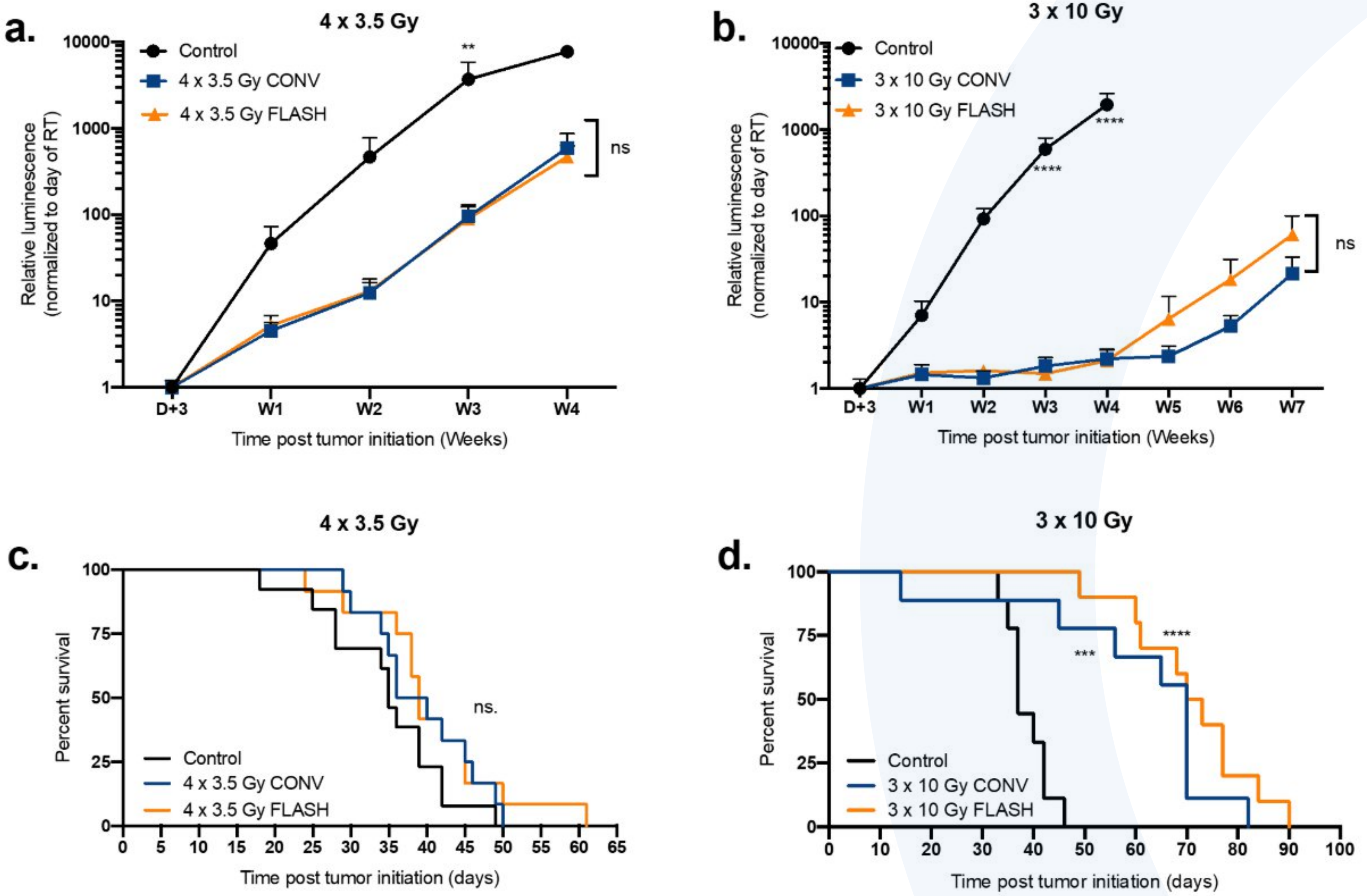


1 x 25 Gy
ns

Montay-Gruel P et al., 2020

2. FLASH Irradiation *Brain*

Tumor control



Montay-Gruel P et al., 2020

2. FLASH Irradiation *Brain*

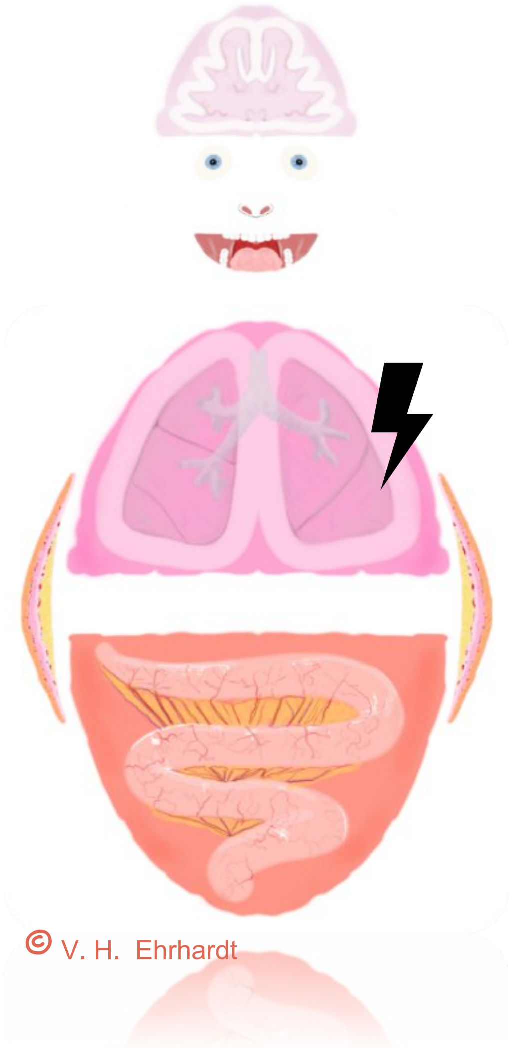
Summery

•Less inflammatory
•Less tissue changes
•Preserved regerative capaciy
•Preserved functionality
•Isoeffective tumor control

•CAVE: FLASH effect depends on many factors such as total dose, fractionation, dose rate and beam characteristics

Montay-Gruel P et al., 2020

2. FLASH Irradiation



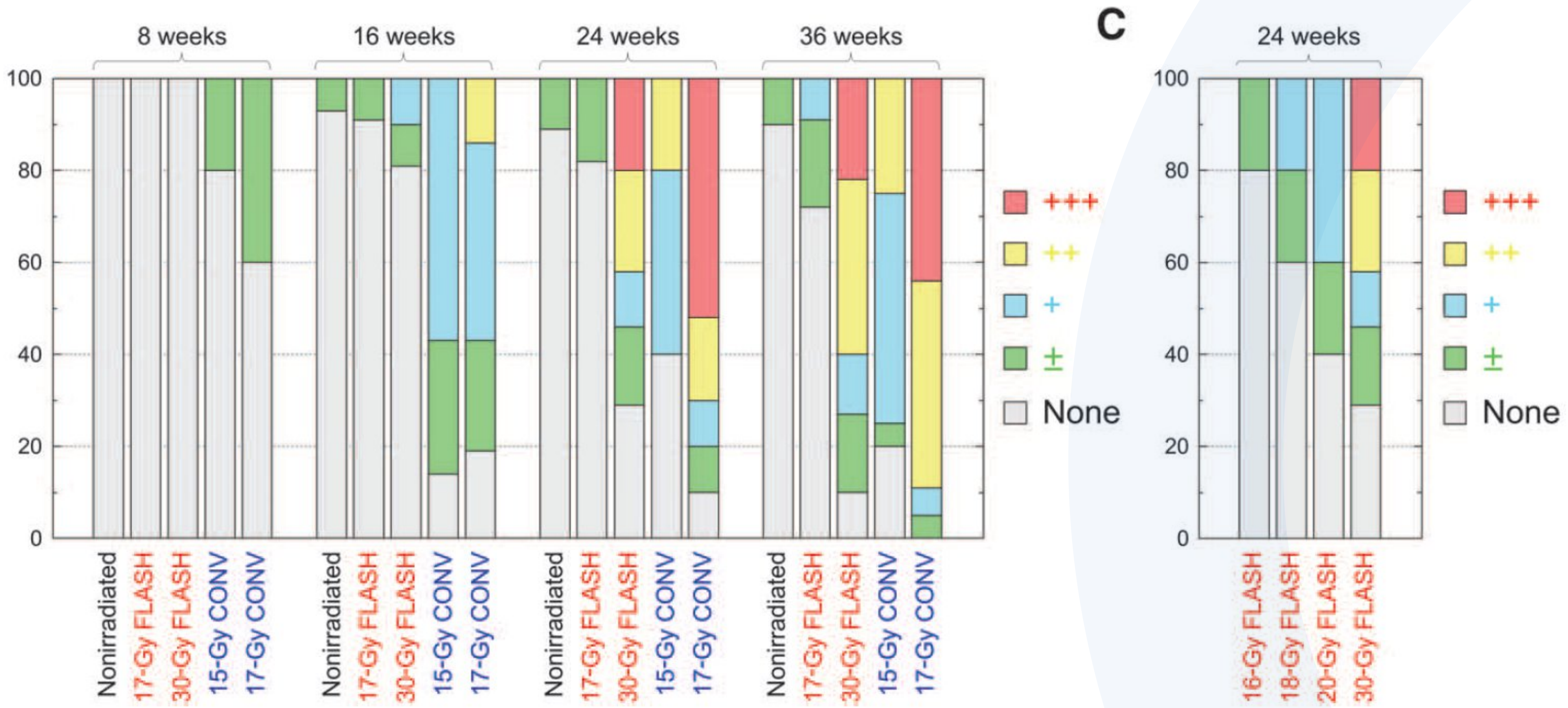
Lung

Montay-Gruel P et al., 2017/2019

2. FLASH Irradiation *Lung*

Inflammation

Acute side effects

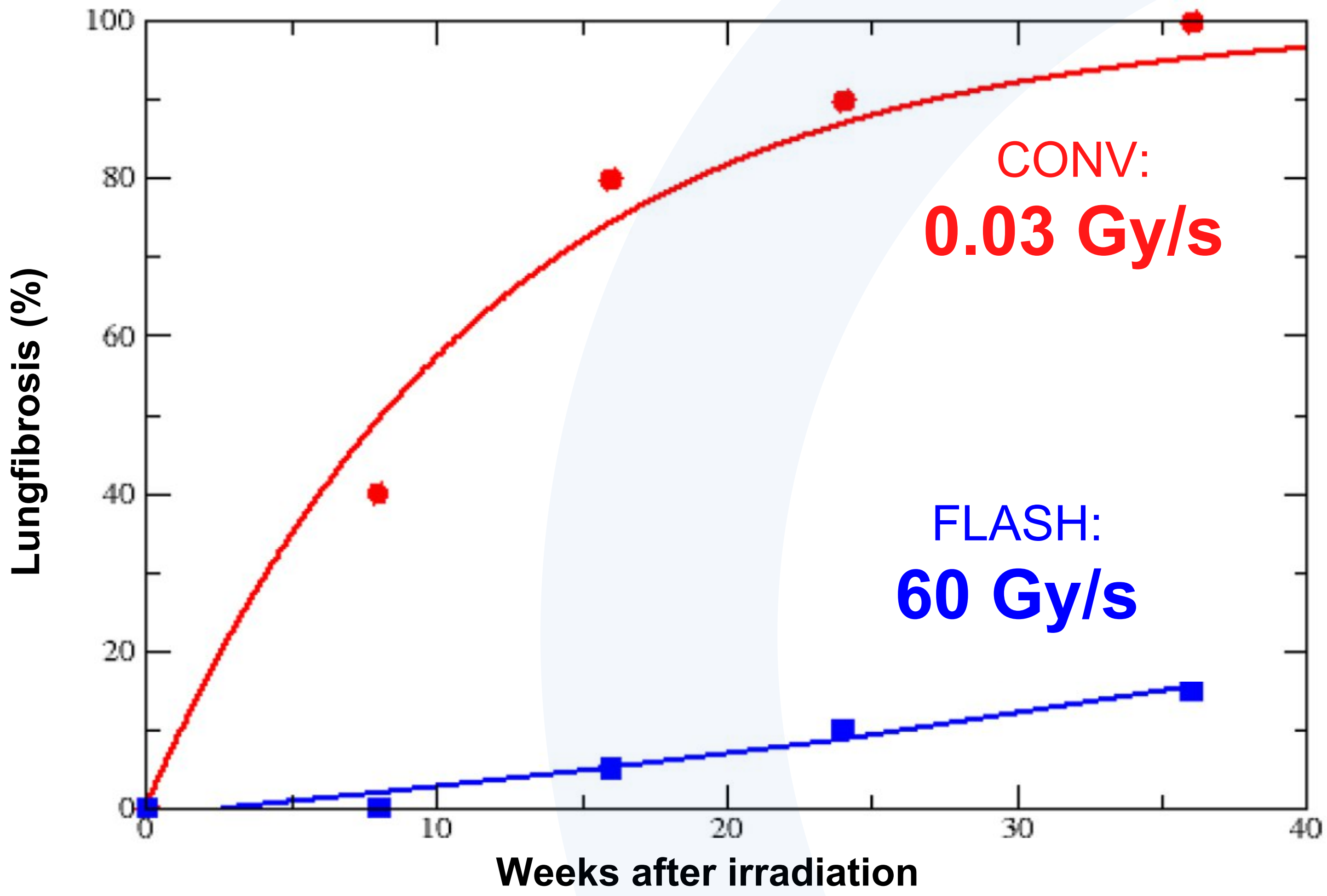


Favaudon et al., 2014

2. FLASH Irradiation *Lung*

Structural changes

Fibrosis

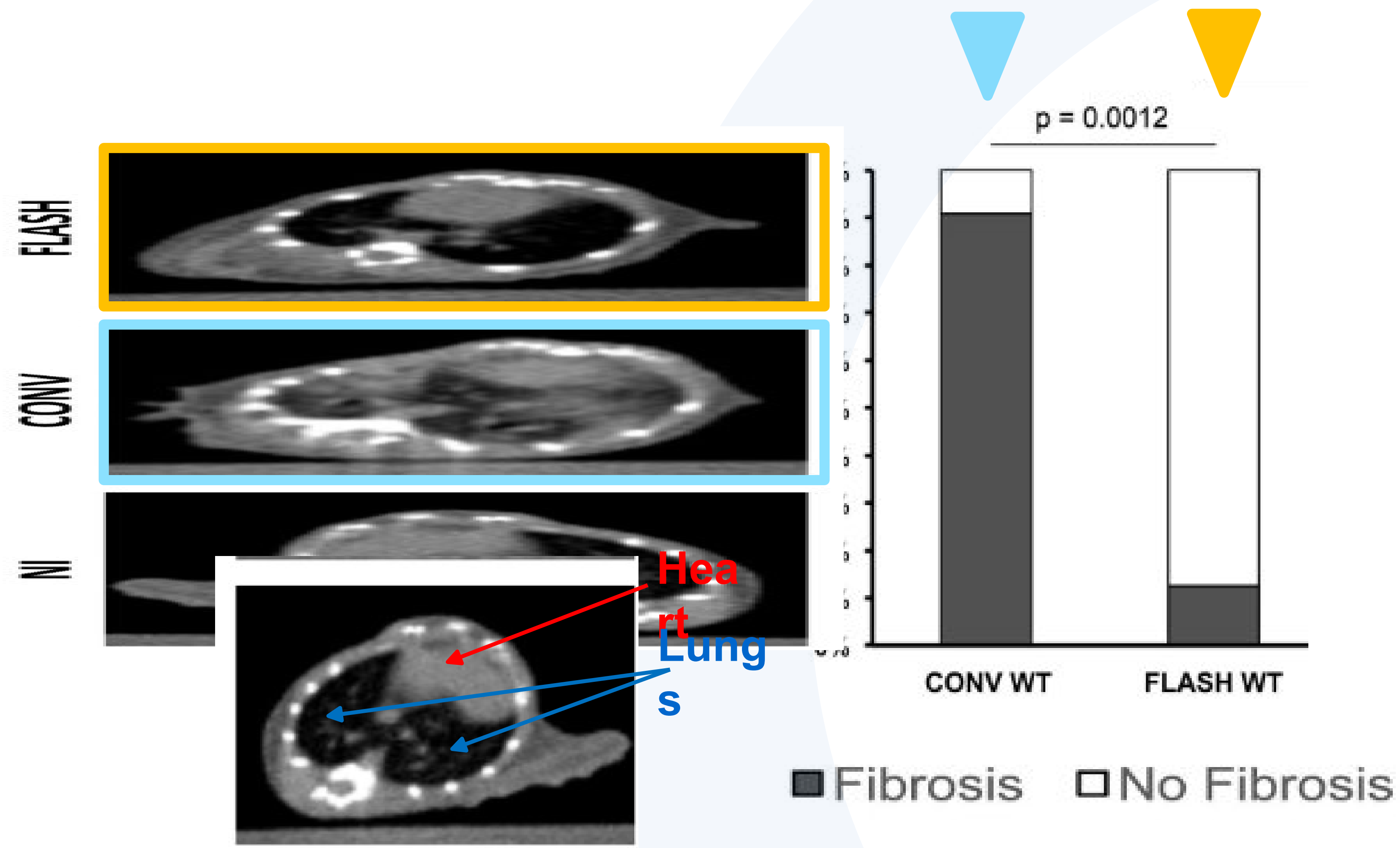


Favaudon et al., 2014

2. FLASH Irradiation *Lung*

Structural changes

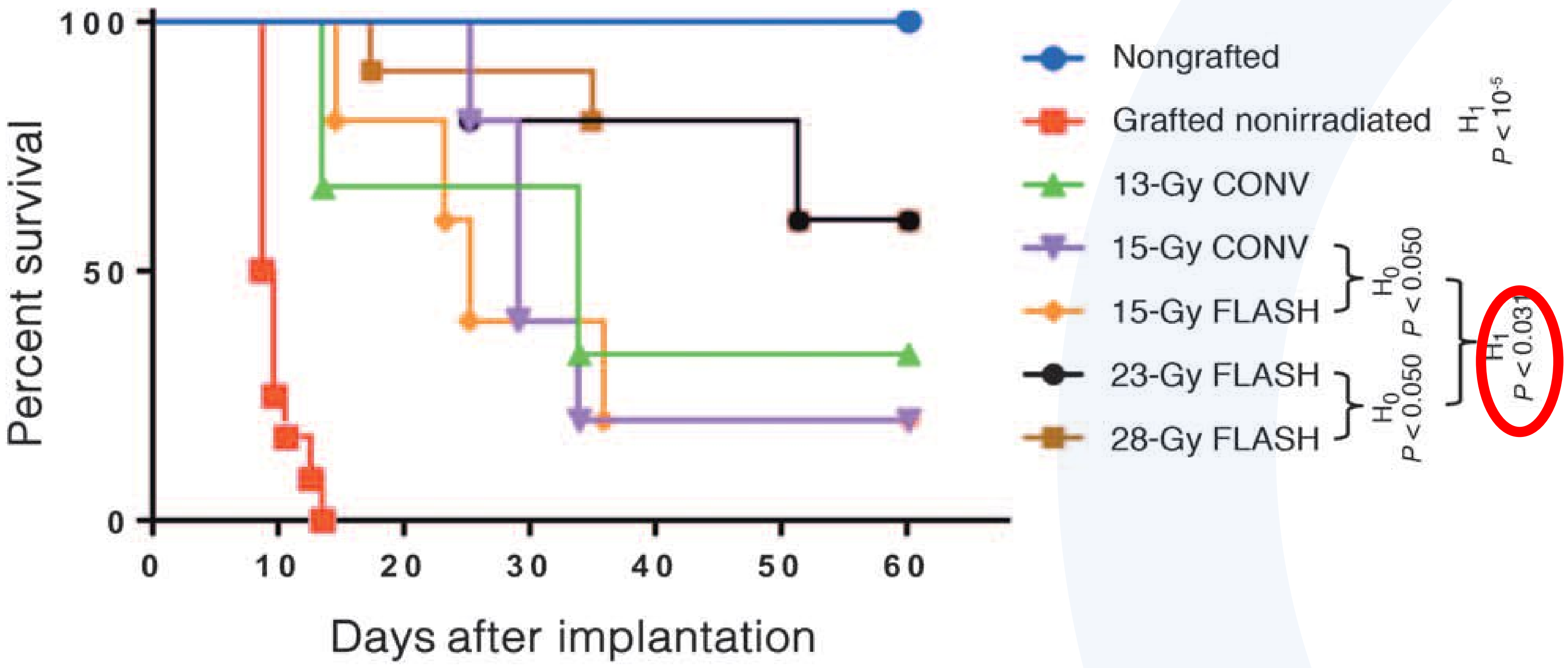
Fibrosis



Fouillade et al., 2019

2. FLASH Irradiation *Lung*

Tumor control



p < 0,0031

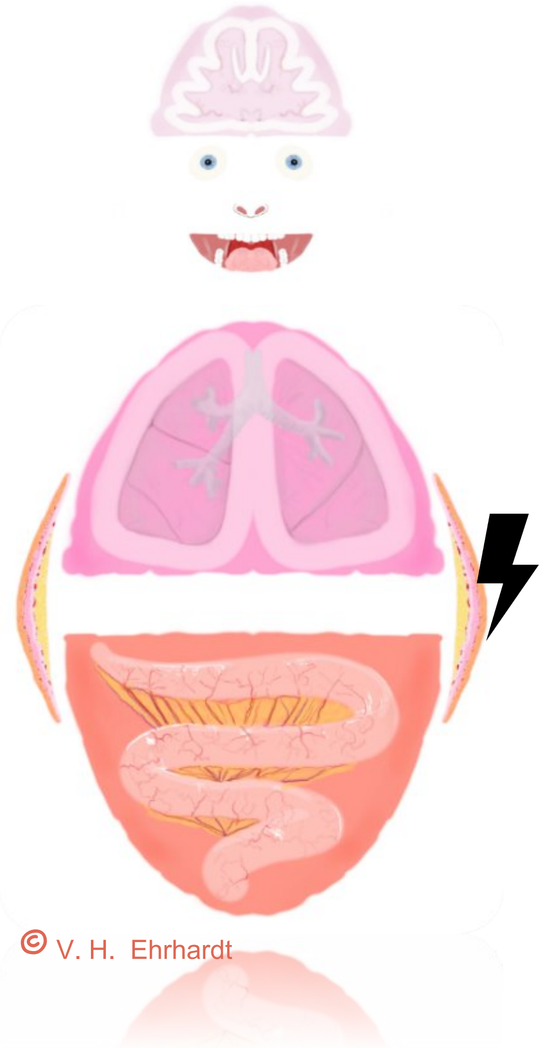
Favaudon et al., 2014

2. FLASH Irradiation *Lung*

Summery

- Less inflammatory
- Less tissue changes / cell death
- Isoeffective tumor control or better

2. FLASH Irradiation



Skin

2. FLASH Irradiation *Skin*

Radiodermatitis

(A) Grade 3 dermatitis with contact bleeding occurred at one week after bioradiotherapy. (B) Resolution of dermatitis at 4 weeks after bioradiotherapy.

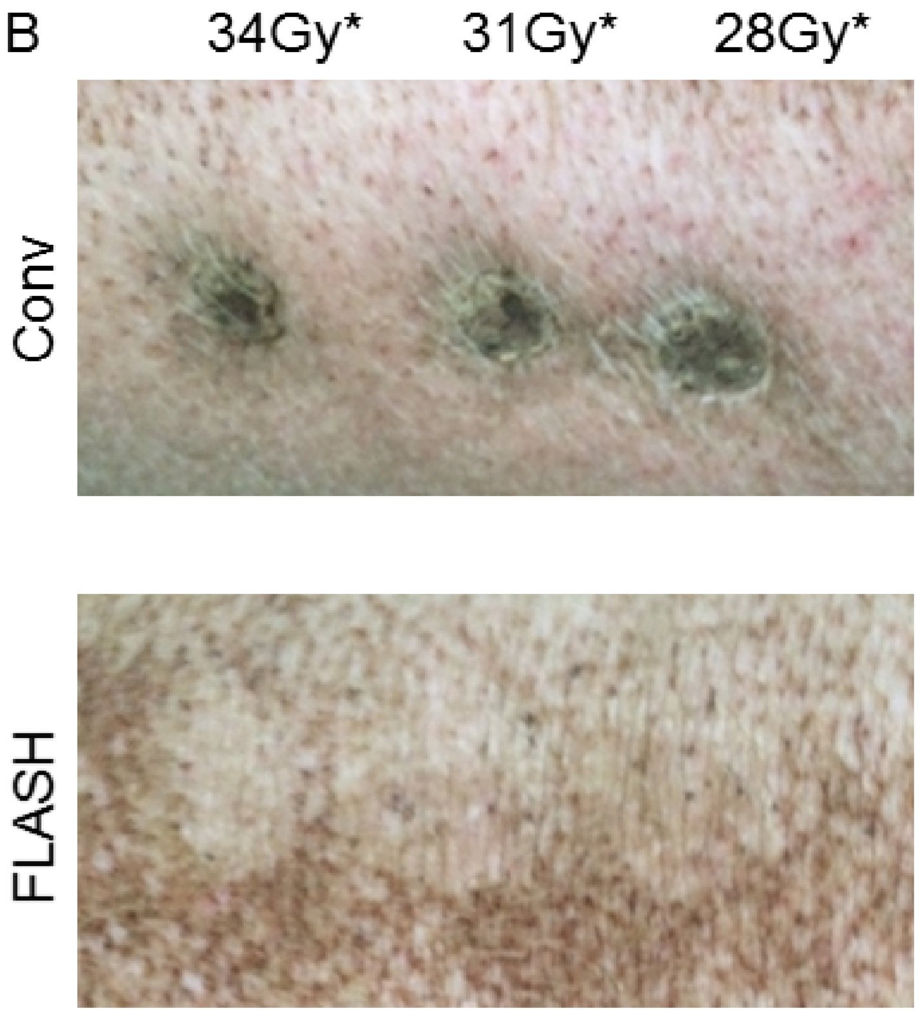
http://radiationtherapyheimabu.blogspot.com/2015/12/recovery-after-radiation-therapy.html

https://www.researchgate.net/publication/280030965_Initial_experience_of_radiotherapy_plus_cetuximab_for_Japanese_head_and_neck_cancer_patients

2. FLASH Irradiation *Skin*

Skin reaction

Long-term side effects



Vozenin et al., 2018

2. FLASH Irradiation *Skin*

Skin reaction

Long-term side effects

CONV

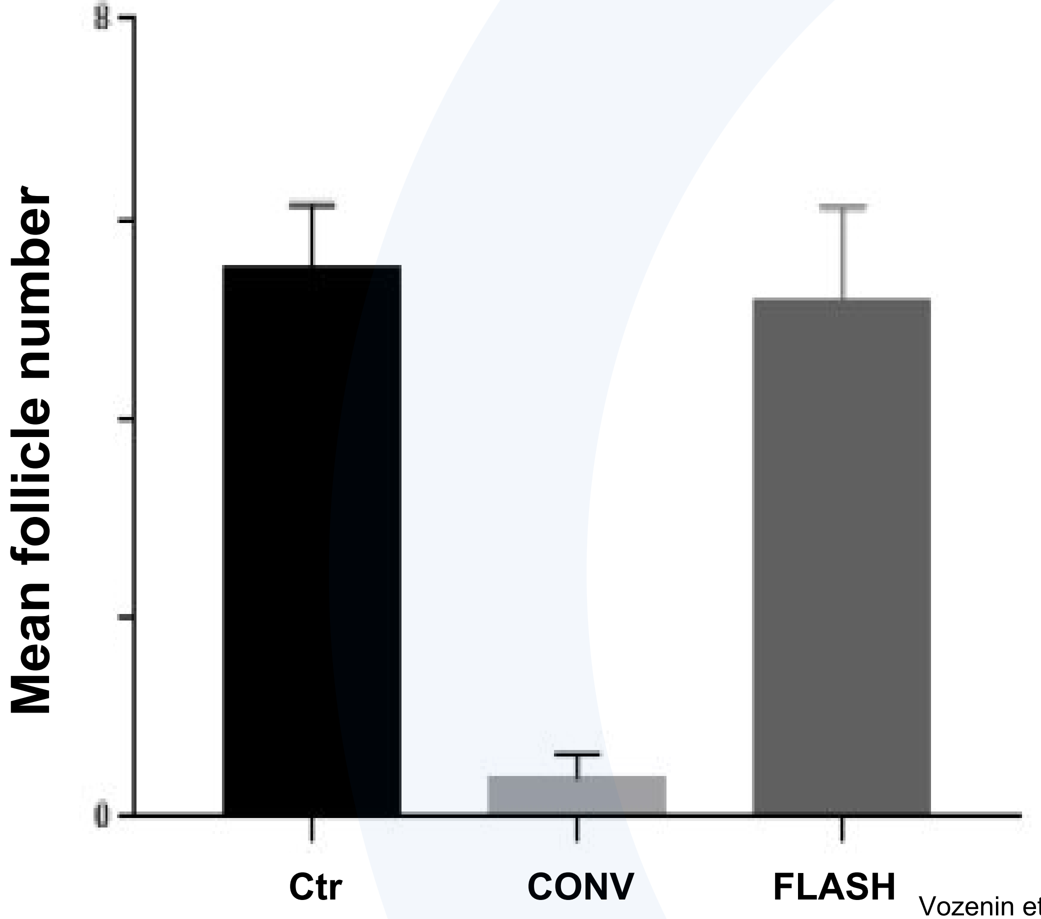
- 80 % hair loss after 32 weeks

FLASH

- 20 % hair loss after 32 weeks

BIOPSY

- Follicle protection after FLASH
- No difference between FLASH and control



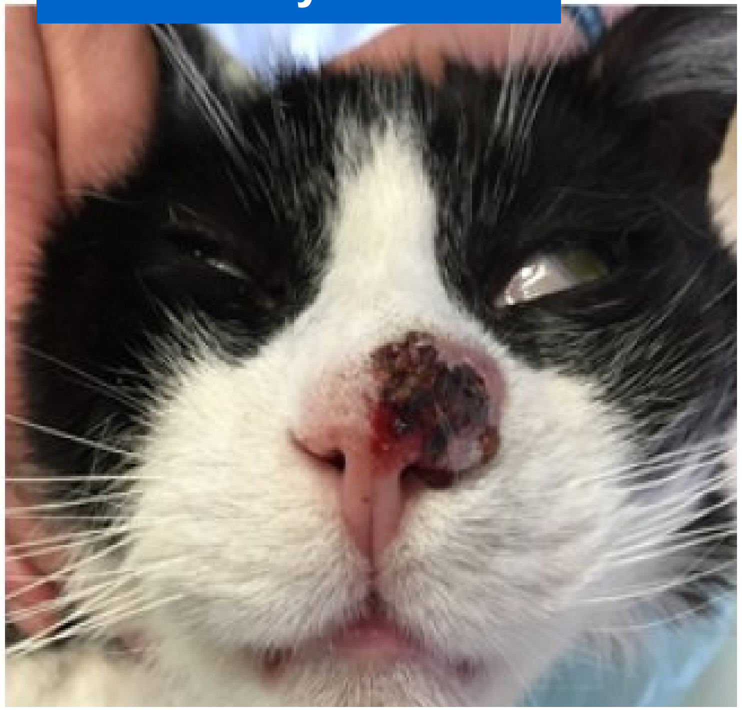
Vozenin et al., 2018

2. FLASH Irradiation *Skin*

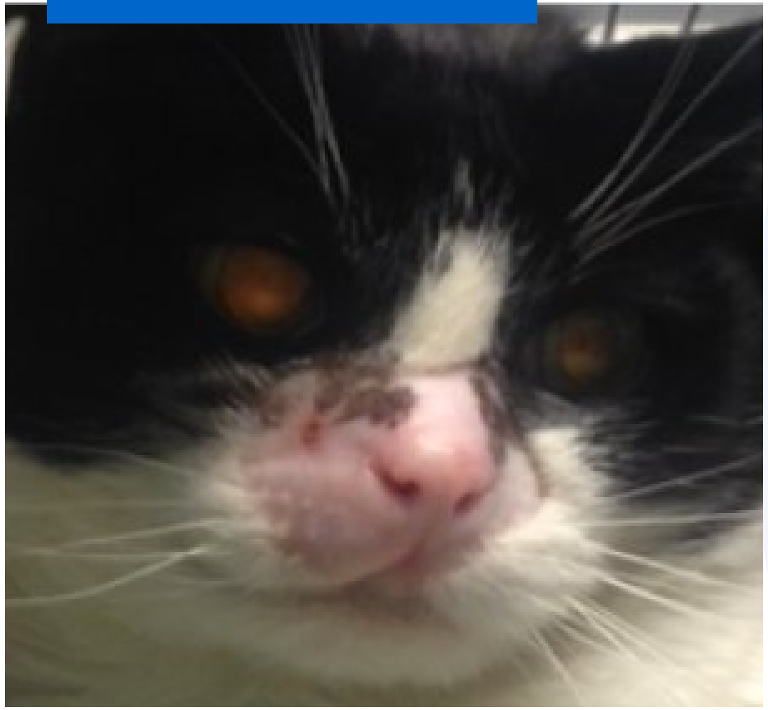
Tumor controll

- **100 % after 16 month**
- **83% after 18 month**
- **50 % after 20 month**

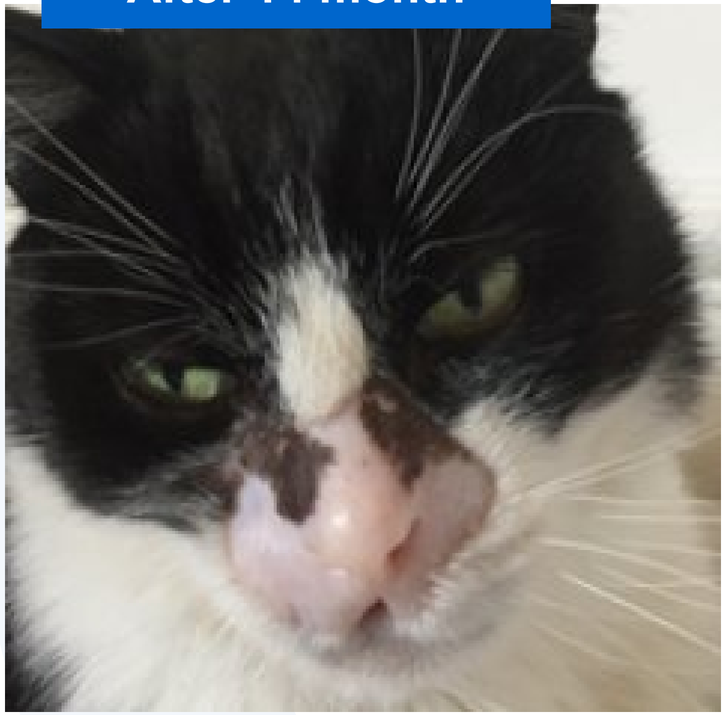
Day 0



After 7 month



After 14 month



Vozenin et al., 2018

2. FLASH Irradiation *Skin*

Tumor

First human patient!!

Day 0

After 3 weeks

After 5 month

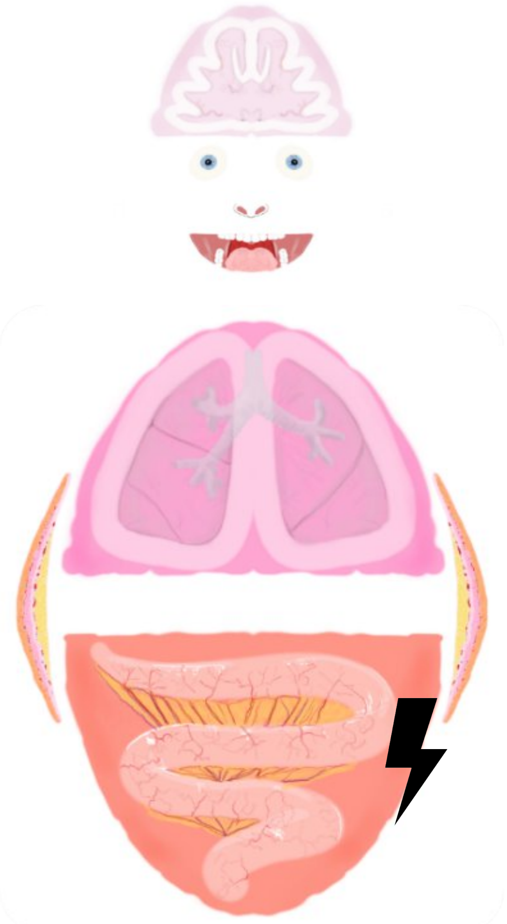
Bourhis et al., 2019

2. FLASH Irradiation *Skin*

Summery

- No long term side effects
- Effective tumor control

2. FLASH Irradiation



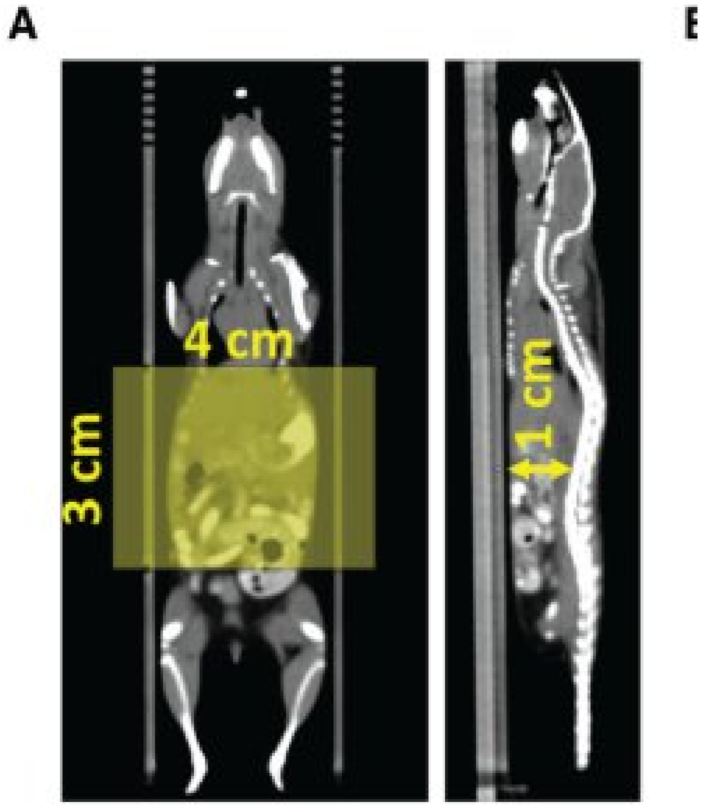
Gut

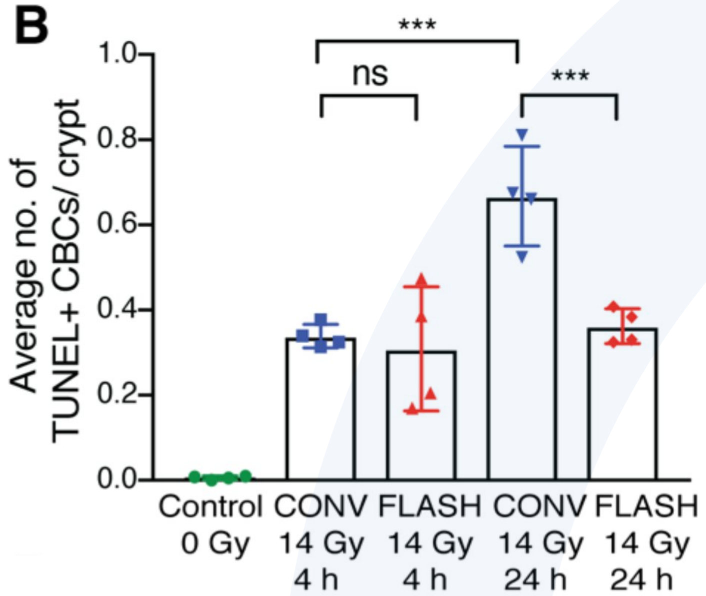
Montay-Gruel P et al., 2017/2019

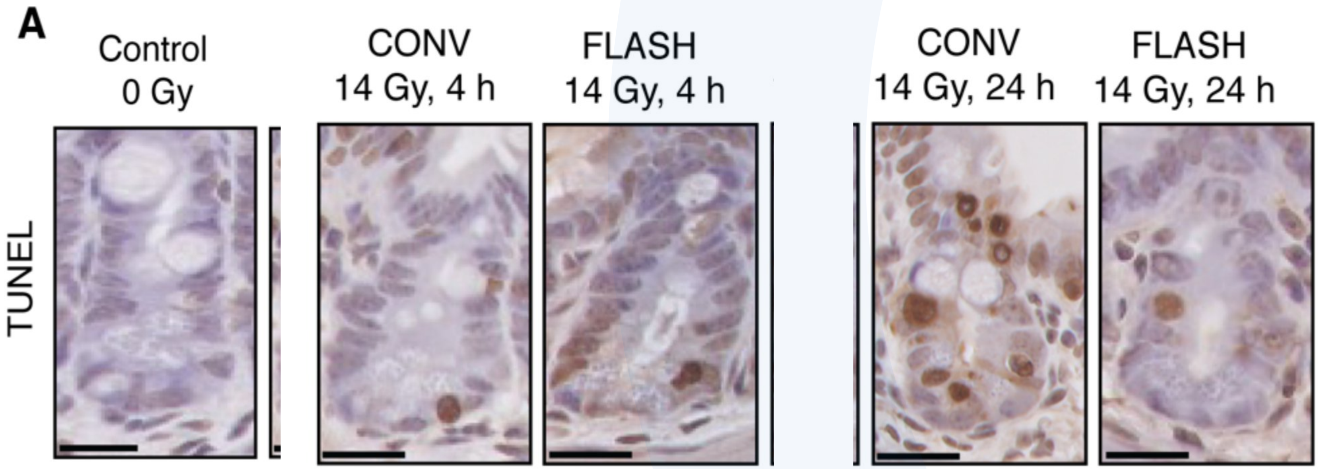
2. FLASH Irradiation *Gut*

Apoptosis

„Cell death“





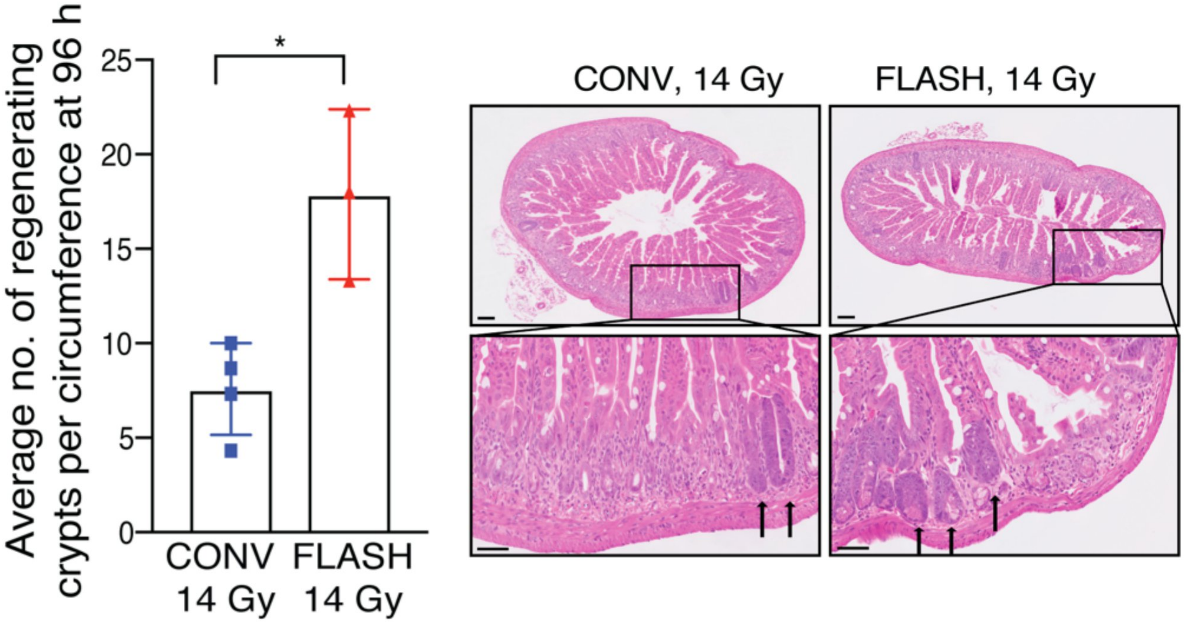


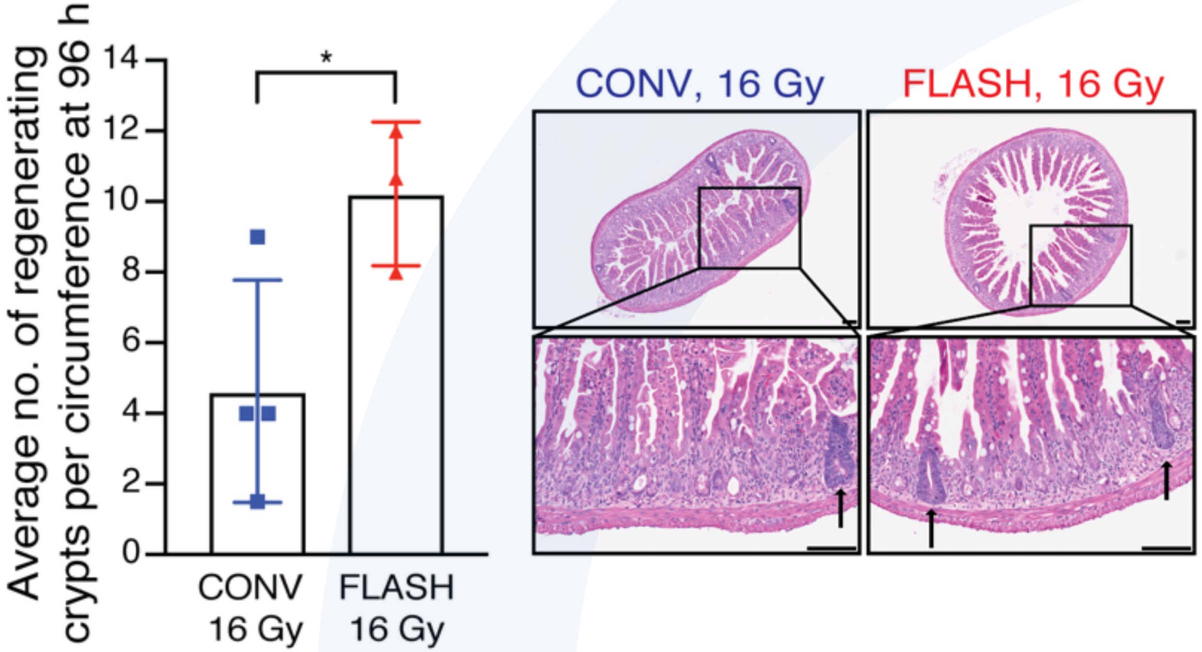
Levy, Natarajan, Wang et al., 2019

2. FLASH Irradiation *Gut*

Regeneration

…after 4 days



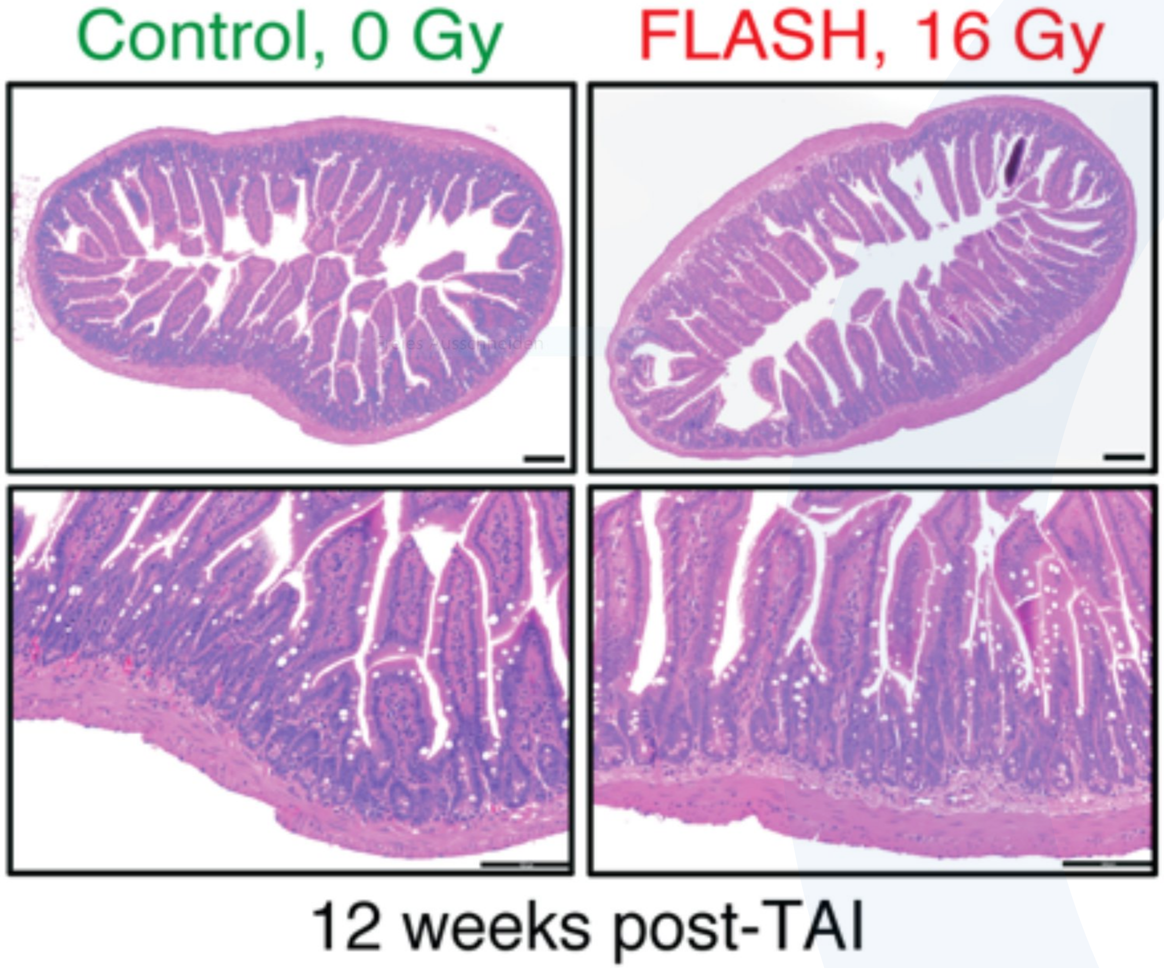


Levy, Natarajan, Wang et al., 2019

2. FLASH Irradiation *Gut*

Regeneration

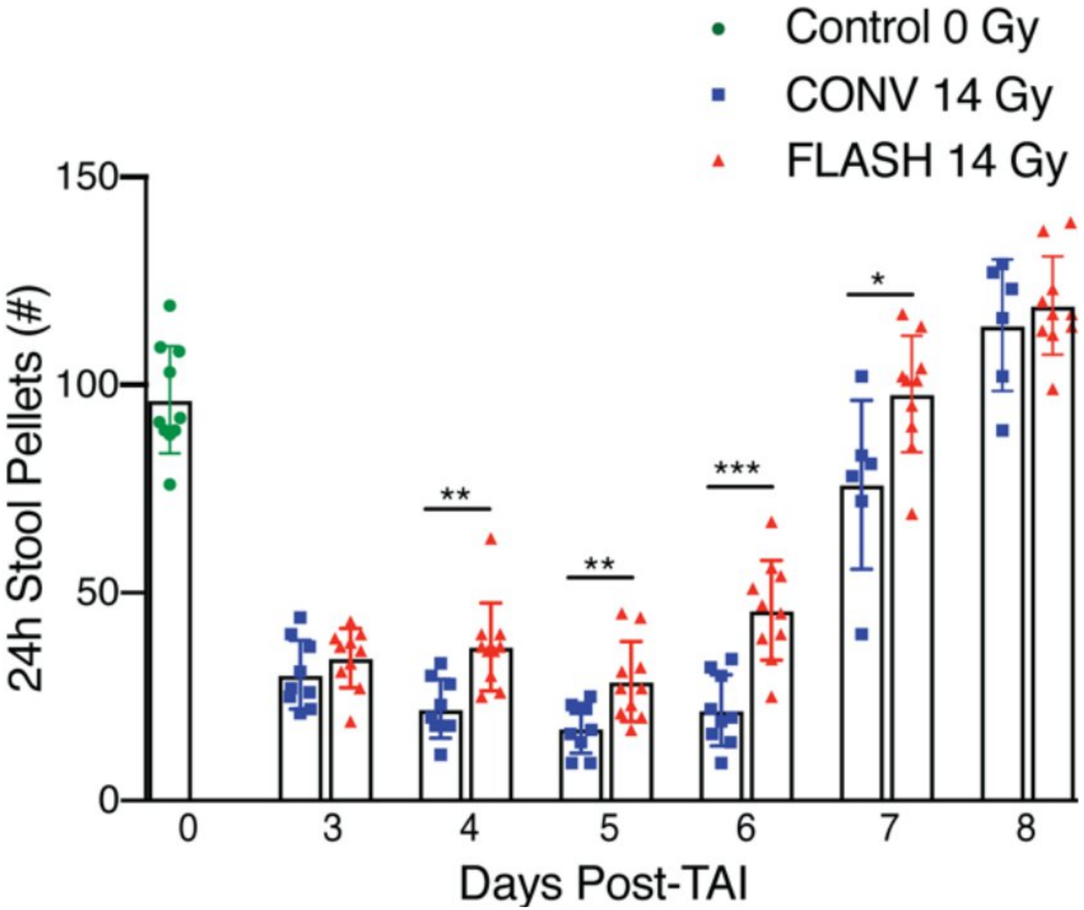
No long term difference



Levy, Natarajan, Wang et al., 2019

2. FLASH Irradiation *Gut*

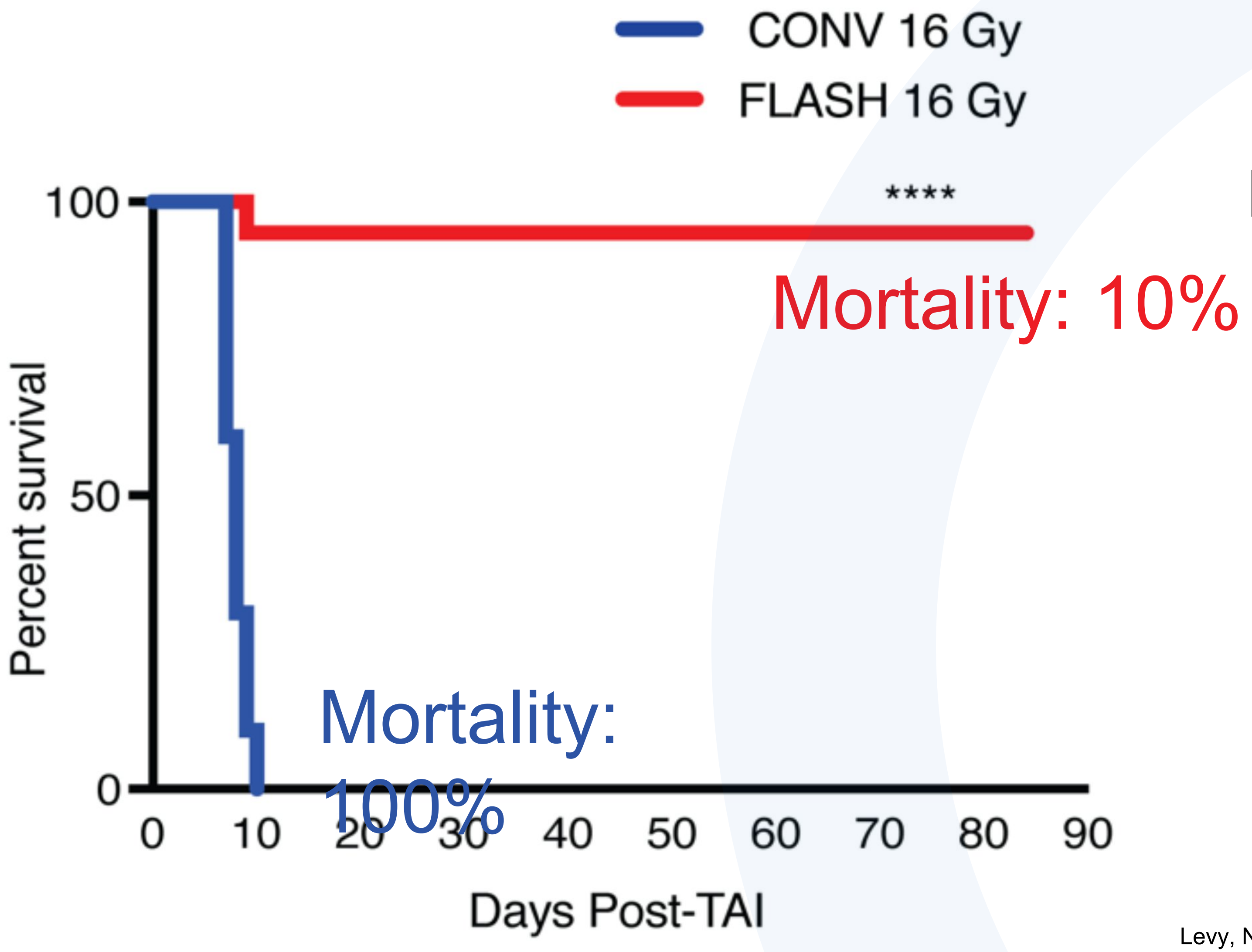
Intestinal function



Levy, Natarajan, Wang et al., 2019

2. FLASH Irradiation *Gut*

Survival

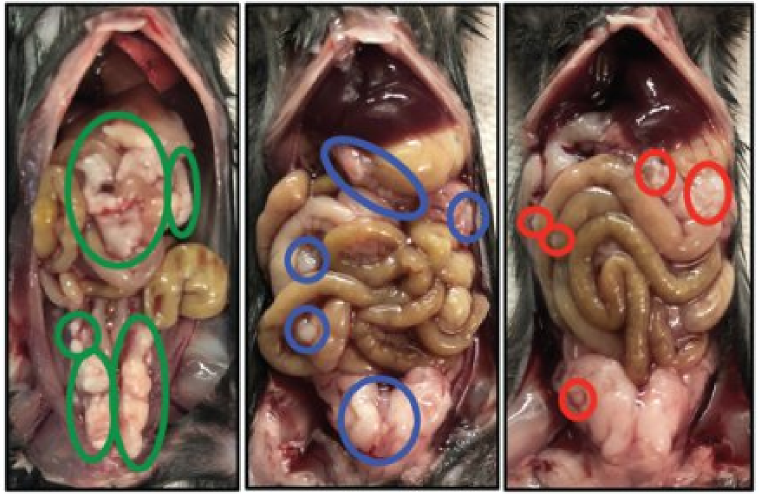


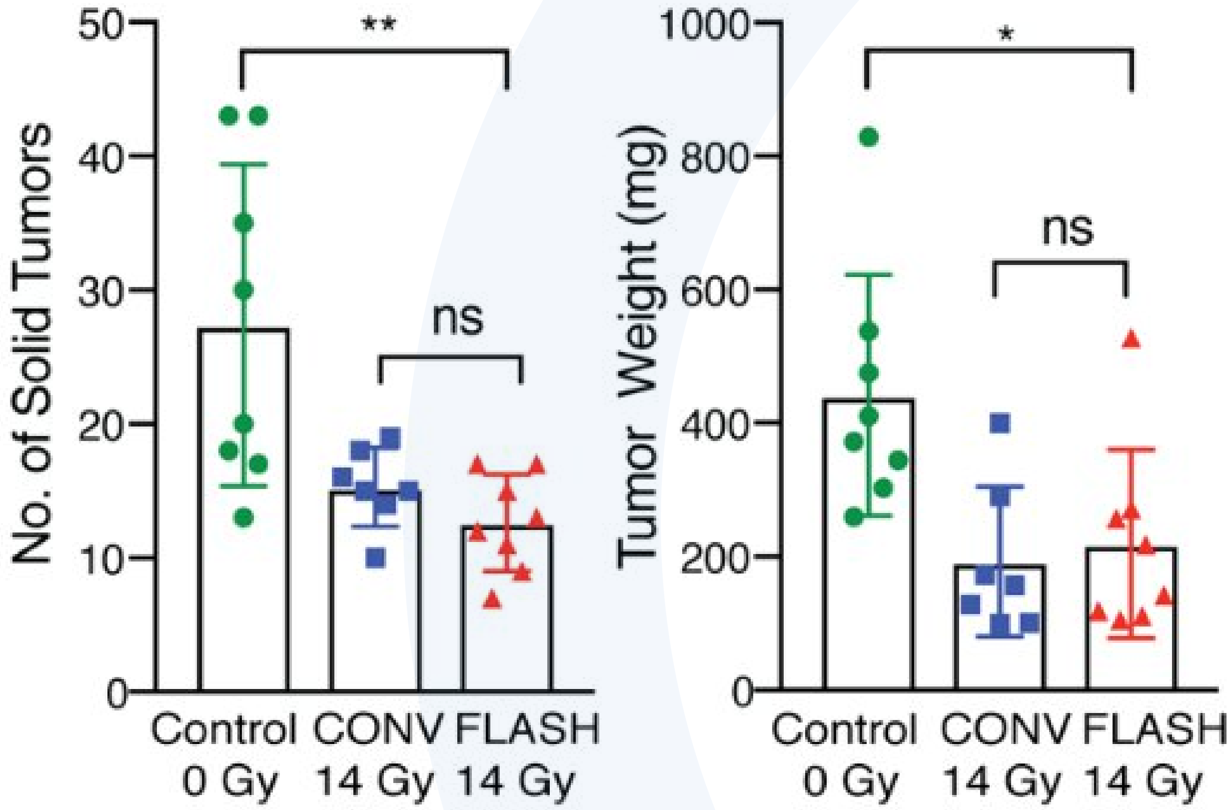
p<0.0001

Levy, Natarajan, Wang et al., 2019

2. FLASH Irradiation *Gut*

Tumor controll





Levy, Natarajan, Wang et al., 2019

2. FLASH Irradiation *Gut*

Summery

- Less apoptotic cells
- Preserved regerative capaciy
- Better intestinal function
- Less mortality
- Isoeffective tumor control

2. FLASH Irradiation *Conclusion*

Normal tissue

Organ	N (in vivo)	Tier	Outcome better in…
Brain	5x	5x Mouse	FLASH
Lungs	4x	5x Mouse	FLASH
Abdominal	4x	5x Mouse	FLASH
Skin	3x	1x Pig 1x Mouse	FLASH
Total body	3x	1x Mouse 2x Zebrafish	FLASH

J. Hughes, J Parsons et al. 2020

2. FLASH Irradiation *Conclusion*

Tumor

Tumor	Outcome	Literature
Head&Neck cancer	FLASH = CONV	Favaudon et al. 2014
Breast cancer	FLASH = CONV	Favaudon et al. 2014
Ovarial cancer	FLASH = CONV	Levy et al. 2020
Carcinoma nose	-	Vozenin et al. 2019
Glioblastoma	FLASH = CONV	Montay-Gruel et al. 2020
Pancreatic cancer	FLASH = CONV	Diffenderfer et al. 2019
Lung cancer	FLASH = CONV	Favaudon et al. 2014,

J. Hughes, J Parsons et al. 2020

2. FLASH Irradiation *Conclusion*

Table 1. Evidence of normal tissue sparing from FLASH irradiation.

Model (Site of Irradiation)	Assay/Endpoint	Dose (Gy)	Dose Rate (Gy/s)	Radiation Source	Reference
Mice (WBI) [1]	Memory tests, neurogenesis	10	>100	Electron	[13]
Mice (WBI) [1]	Neurocognitive tests, mature/immature neurons, growth hormone levels	8	4.4 × 10^6	Electron	[22]
Mice (WBI) [1]	Neurocognitive tests, dendritic spine density, microglial activation, inflammation	30	200/300	Electron	[20]
Mice (WBI) [1]	Neurocognitive tests, neuroinflammation,	10	>100	Electron	[23]
(abdomen)					
Mice (abdomen)	Survival, stool production, crypt cell regeneration, apoptosis, DNA damage	12–16	216	Electron	[18]
Mice (abdomen)	Intestinal crypt cell proliferation	15 Gy	78	Proton	[27]
Mice (local intestinal)	Fibrosis	18 Gy	78	Proton	[27]
Mini-pig (skin)	Skin toxicity/injury	22–34	300	Electron	[14]
Zebrafish Embryo	Morphology	8	>100	Electron	[23]

[1] WBI refers to whole brain irradiation.

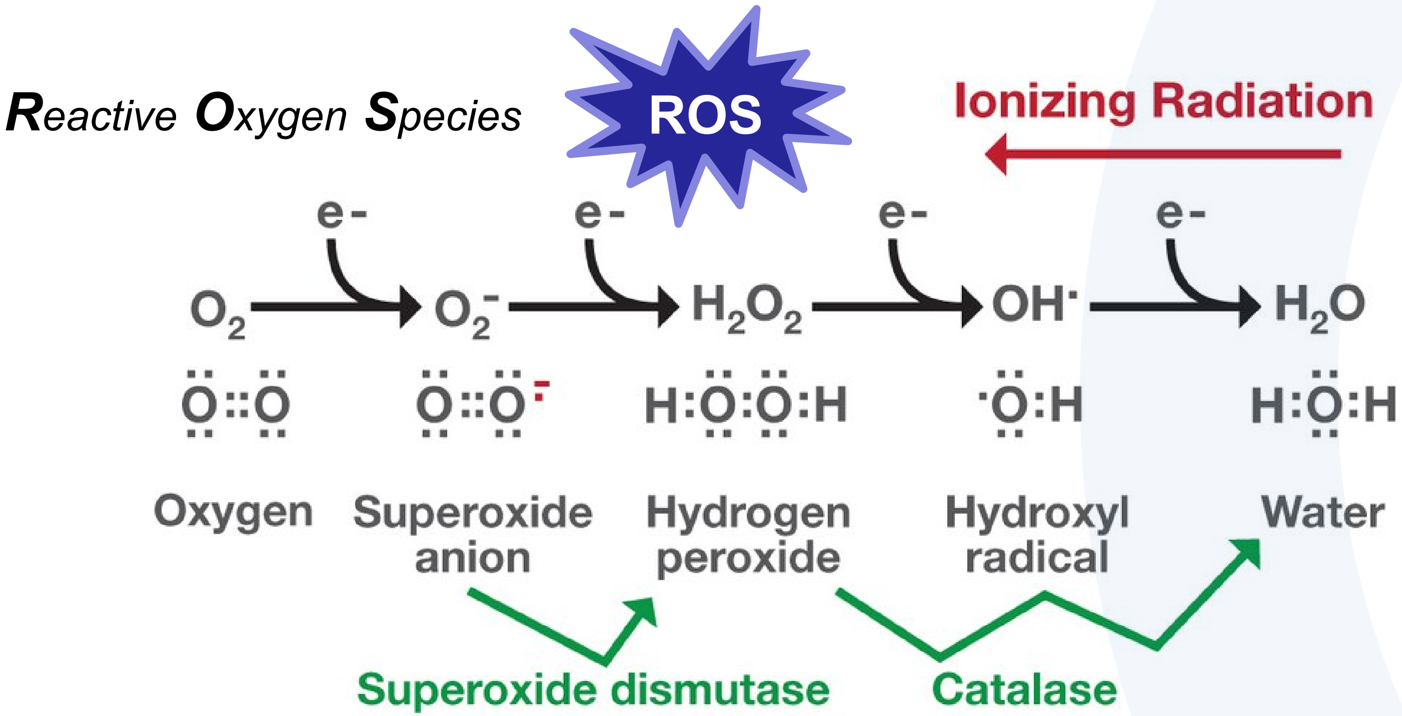
Table 2. Evidence of tumor control from FLASH irradiation.

Model	Assay/Endpoint	Dose (Gy)	Dose Rate (Gy/s)	Radiation Source	Reference
(local)	Tumor growth			Electron	[14]
Human, CD30+ T-cell cutaneous lymphoma	Tumor response	15	167	Electron	[15]

J. Hughes, J Parsons et al. 2020

Biggest Questions

What is the reason for the FLASH effect?



https://www.caymanchem.com/Article/2165

2. FLASH Irradiation *Conclusion*

Biggest Questions

Optimal (instantaneous) dose rate

Exposed tissue volume

Optimal irradiation time

Optimal irradiation modality

Optimal application

Optimal total dose

Optimal number of pulses

Optimal fractionation

Optimal puls width

Optimal repetition rate (frequency)

Montay-Gruel P et al., 2020

2. FLASH Irradiation *Conclusion*

The most common cancers are:

Tumor side	cases
Lung	2.090 k
Breast	2.090 k
Colorectal	1.800 k
Prostate	1.280 k
Skin (non-melanoma)	1.040 k
Stomach	1.030 k

The most common causes of cancer death are:

Tumor side	Deaths
Lung	1.760 k
Colorectal	862 k
Stomach	783 k
Liver	782 k
Breast	627 k

and many more!

3. FLASH Network

Benefits of collaboration

3. FLASH Network

Projects at Charité

The effect of FLASH irradiation with protons on normal eye tissue of mice

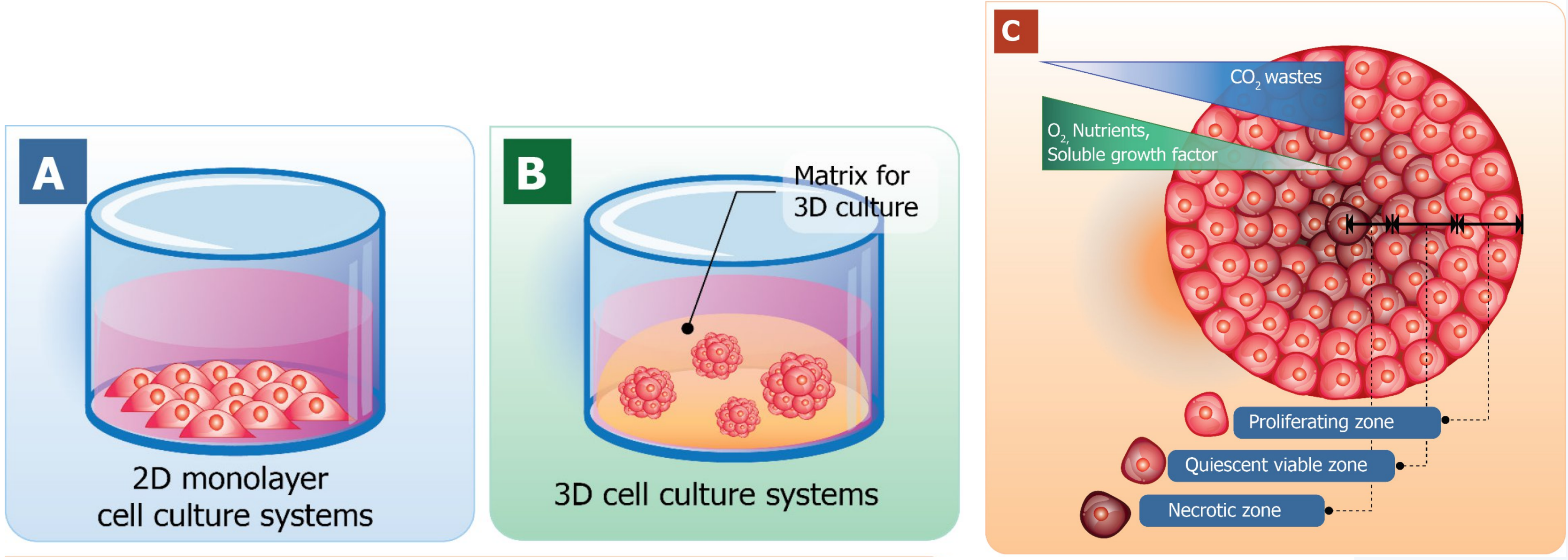
Our hypothesis: FLASH reduces the blindness after irradiation

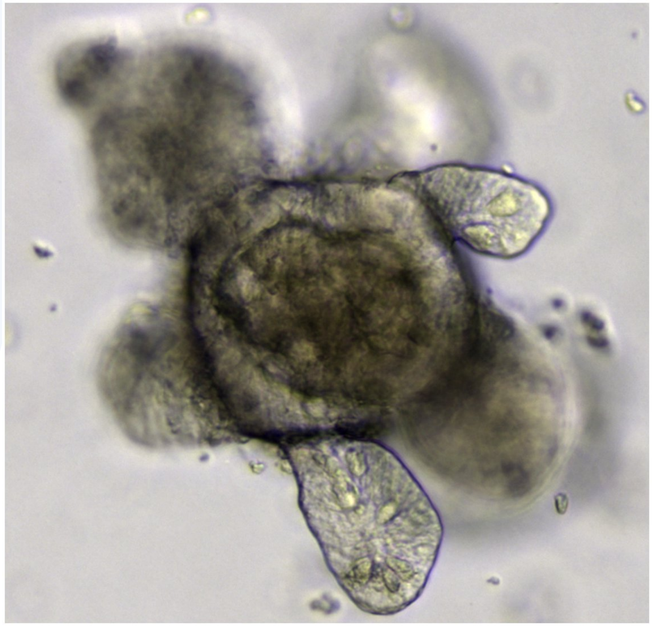
Our methods:
- Unilateral eye-irradiation of 80 mice
- Control of lens opcity and retinal damages after six month

Current state:
- All mice were irradiated
- All mice tolerated the irradiation well
- The investigastions are still ongoing
- The first results are expected in a few month

3. FLASH Network *Projects*

The effect of FLASH irradiation (with protons) on normal tissue organoids and cancer spheroids





https://www.wjgnet.com/1948-0210/full/v11/i12/1065.htm https://en.wikipedia.org/wiki/Organoid

3. FLASH Network *Projects*

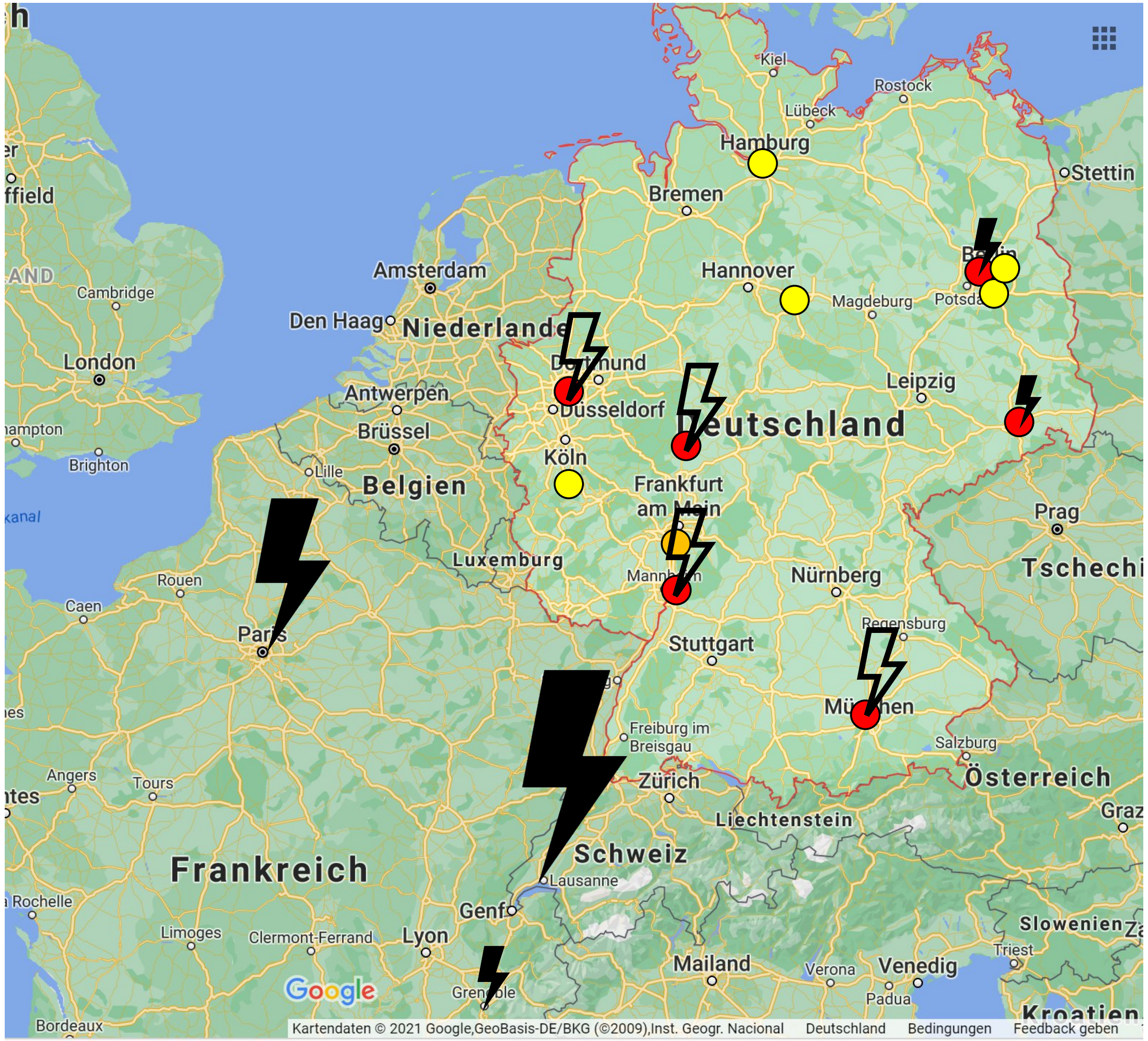
The effect of FLASH irradiation (with protons) on normal tissue organoids and cancer spheroids

The idea:	The reduction of animal studies and the development of alternative methods.
Our methods:	▪Irradiation of different organoids with protons and photons at different dose rates. ▪Analysis of cell changes after irradiation using histological and molecular markers.
Current state:	▪First organoids were successfully irradiated ▪Results are expected in a few weeks ▪Many more interesting organoid models (>15) to test

3. FLASH Network

But why should we collaborate?

3. FLASH Network *Collaboration*



- Particle therapy facilities in clinical operation
- Nuclear research facilities and other particle accelerators
- FLASH facilities (published data)
- Ongoing FLASH experiments expected

3. FLASH Network *Collaboration*

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

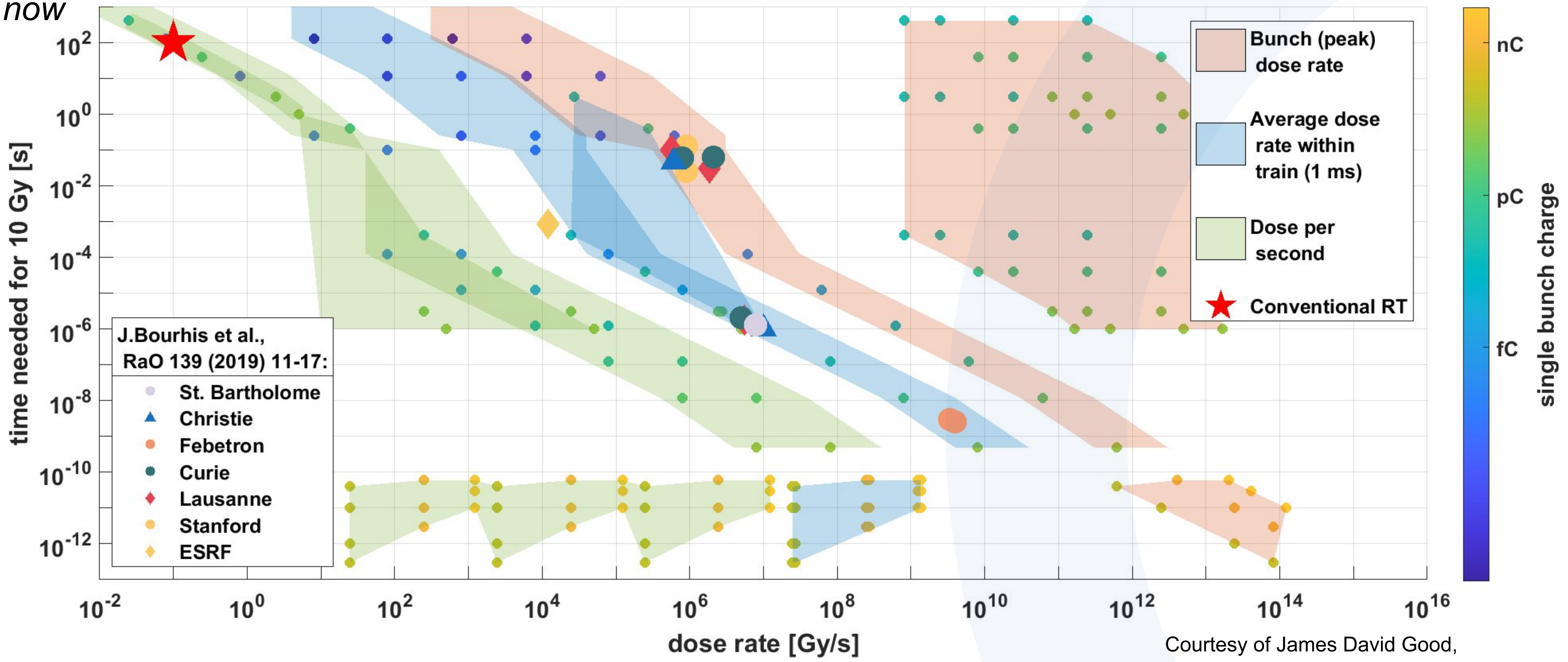
HELMHOLTZ
SPITZENFORSCHUNG FÜR
GROSSE HERAUSFORDERUNGEN

DESY

HZB Helmholtz
Zentrum Berlin

3. FLASH Network *Collaboration*

Parameter space available at PITZ *In comparison with the state-of art up to now*



Courtesy of James David Good, Marie-Catherine Vozenin, Jean-Francois Germond

Thank you!