FLASH Radiotherapy

in the era of Omics and AI ?

Pr Jean Bourhis

Lausanne University Hospital, Switzerland

32th MRO, October 2022, Roma

Disclosure

R & D projects with PMB

Research projects with IntraOp

Member of Varian FLASH forward consortium

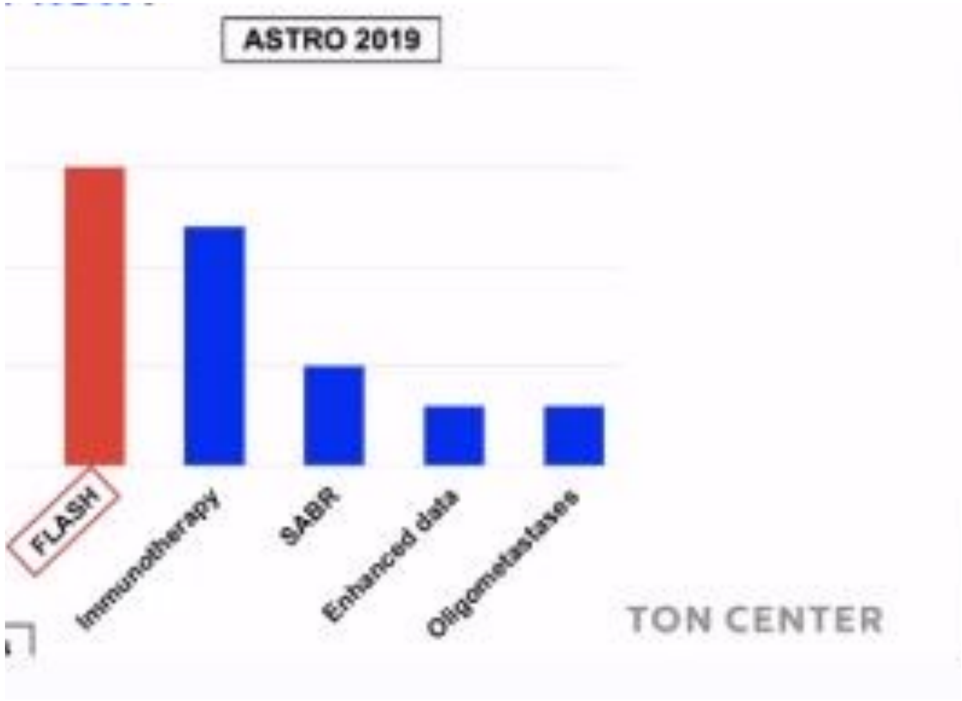
Advisory role for

MSD, ASTRA Zeneca, Mevion

BMS, Debiopharm, Roche,

Merck, Nanobiotix

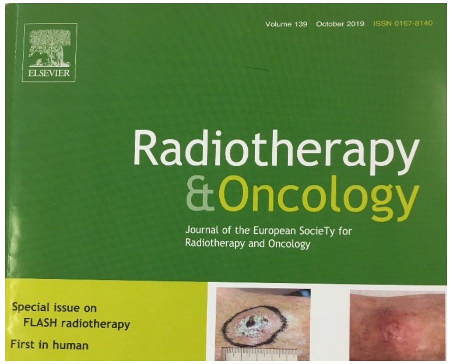
FLASH seems like a « hot » topic



AMERICAN SOCIETY FOR RADIATION ONCOLOGY

Radiother Oncol :

FLASH = highly citated topic in 2020-2022



What is FLASH ?

Delivery time

When comparing

ultra-high → milliseconds

versus

conventional dose rates → minutes

less radiation toxicity to normal healthy tissues,

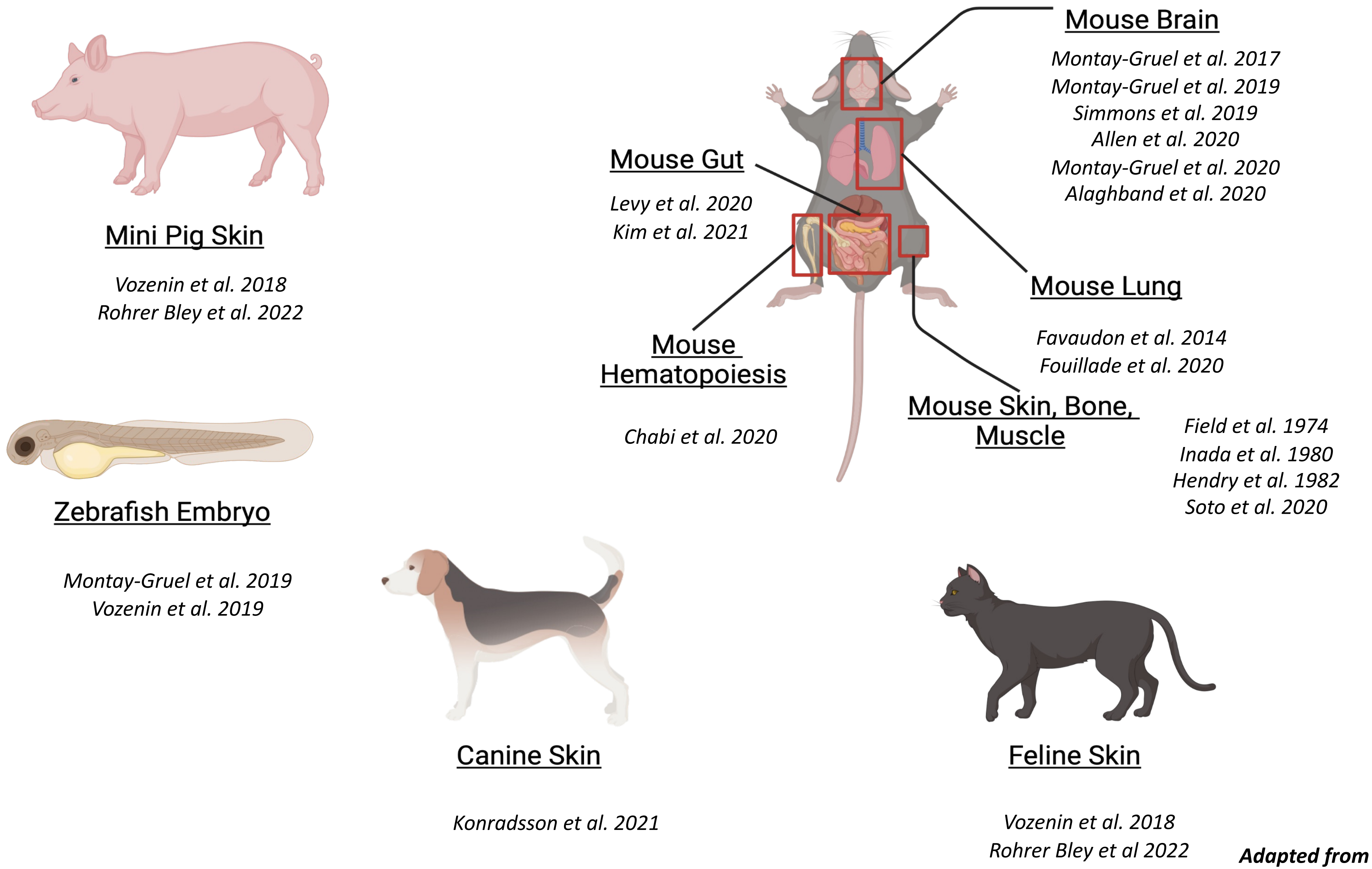
while maintaining a similar effect on tumors

= "FLASH effect"

FLASH *versus* CONV dose rate :

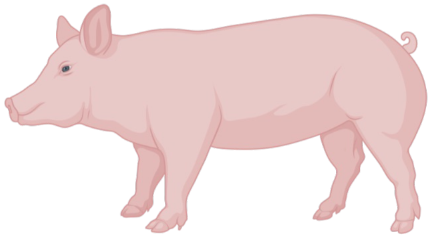
Normal tissues

Normal tissue sparing : FLASH versus CONV



Adapted from Montay-Gruel, 2022

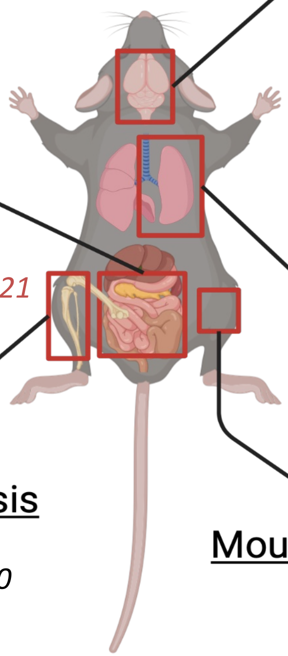
Normal tissue sparing : FLASH versus CONV



Mini Pig Skin

Vozenin et al. 2018
Rohrer Bley et al. 2022

Protons



Mouse Gut

Levy et al. 2020
Velalopoulou et al. 2021
Kim et al. 2021

Mouse Brain

Montay-Gruel et al. 2017
Montay-Gruel et al. 2018
Montay-Gruel et al. 2019
Simmons et al. 2019
Allen et al. 2020
Montay-Gruel et al. 2020
Alaghband et al. 2020

X-rays

Mouse Lung

Favaudon et al. 2014
Fouillade et al. 2020

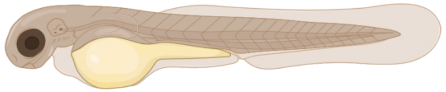
Mouse Hematopoiesis

Chabi et al. 2020

Mouse Skin, Bone, Muscle

Field et al. 1974
Inada et al. 1980
Hendry et al. 1982
Soto et al. 2020
Cunningham et al. 2021
Velalopoulou et al. 2021
Sorensen et al. 2022
Tinganelli et al. 2022

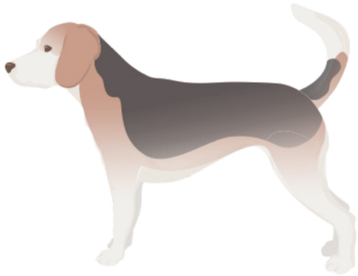
Protons



Zebrafish Embryo

Montay-Gruel et al. 2019
Vozenin et al. 2019
Beyreuther et al. 2019

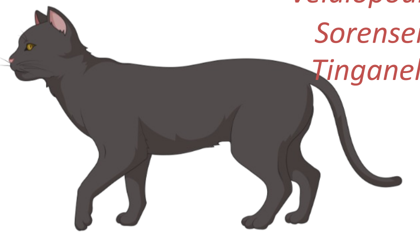
Protons



Canine Skin

Konradsson et al. 2021
Velalopoulou et al. 2021

Protons



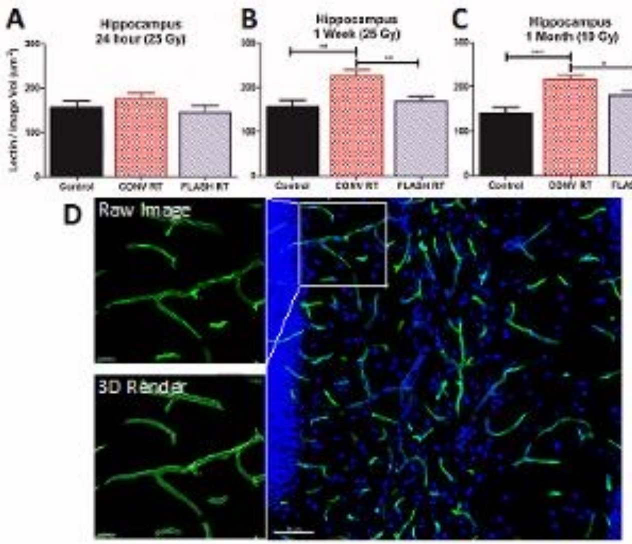
Feline Skin

Vozenin et al. 2018
Rohrer Bley et al 2022

Reproducible in 30 studies in different species

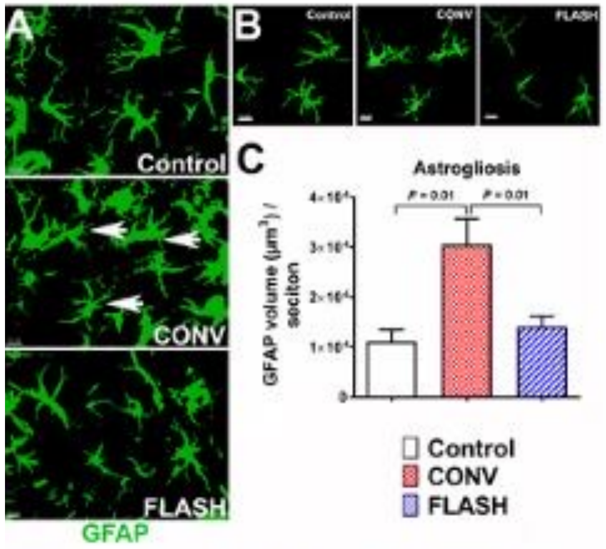
Adapted from Montay-Gruel, 2022

Ex : Mouse Brain / FLASH *versus* CONV dose rate



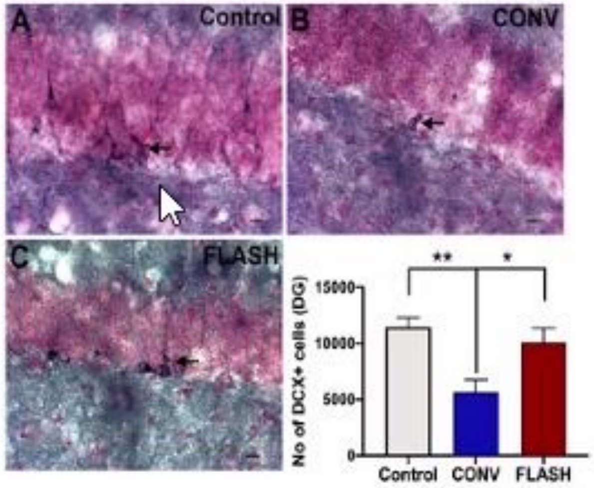
Allen et al, Rad Res, 2020

Less inflammation



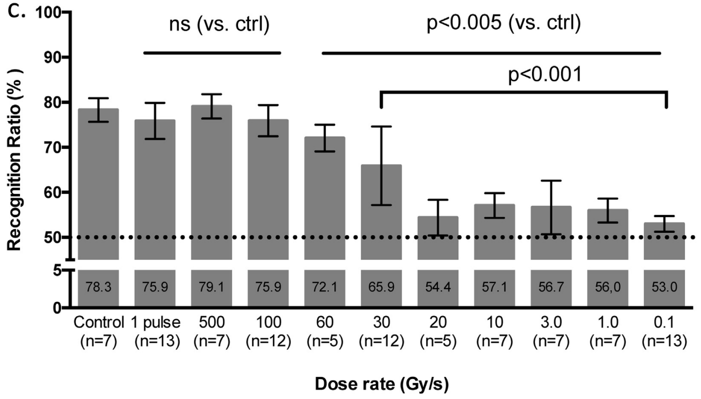
Montay-Gruel et al, Rad Res, 2020

Blood vessel protection



Alaghband et al, Cancers, 2020

Protection of juvenile brain



Montay Gruel Radiother Oncol 2017

Preserving neuro-cognition

FLASH *versus* CONV dose rate

Tumors ?

Ultra high *versus* CONV dose rate : ***in vivo* tumor models** *(rodents proton / electrons)*

Favaudon 2014	Xenograft (leg) Ortho Syngenic	Breast HBCc-12A HNSCC HEP2 Lung TC1	Growth Delay mm Growth Delay mm Growth Delay biolum.	Isoeffect
Bourhis 2019	Xenograft (flank) Orthotopic	Glioma U87 Glioma H454	Growth delay mm Growth delay biolum.	Isoeffect
Montay Gruel 2020	Xenograft (flank) Orthotopic	Glioma U87 Glioma H454	Growth delay CT Growth delay biolum.	Isoeffect
Chabi 2020	Xenograft (leukemia)	3 Patient-derived T-ALL	Cell number	Cell-specific Effect
Diffenderer 2020	Allograft (flank)	Pancreas MH641905	Growth delay mm	Isoeffect
Levy 2020	Orthotopic Syngenic	Ovarian (ID8)	Number & weight of tumors	Isoeffect
Cunningham	Allograft Syngenic	SCC (MOC 1 & 2)	Growth Delay mm	Isoeffect
Konradsson 2021	Rat	Glioma	Growth delay / cure	isoeffect

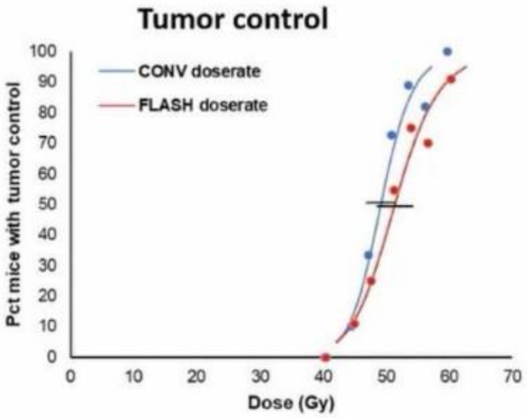
FLASH for tumors : data compatible with iso-effectiveness but …

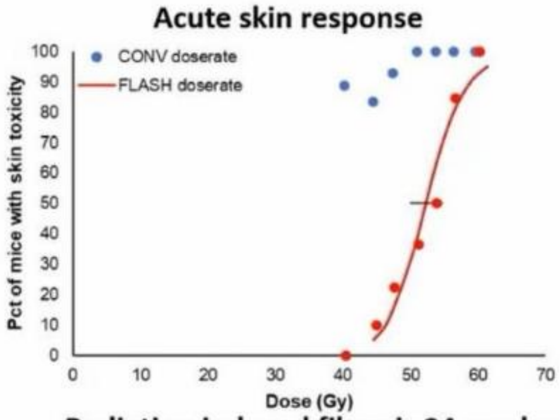
- Regrowth delay assays = measure the most radiosentitive tumor cell sub-population

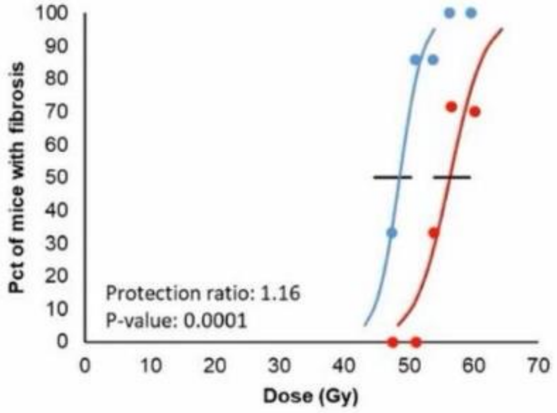
- **Tumor assays are not sufficiently sensitive to detect small variations**

→ More tumor cure experiments needed

→ More studies with comparable quantities / uncertainties : TCP /NTCP







CONV (minutes)

versus

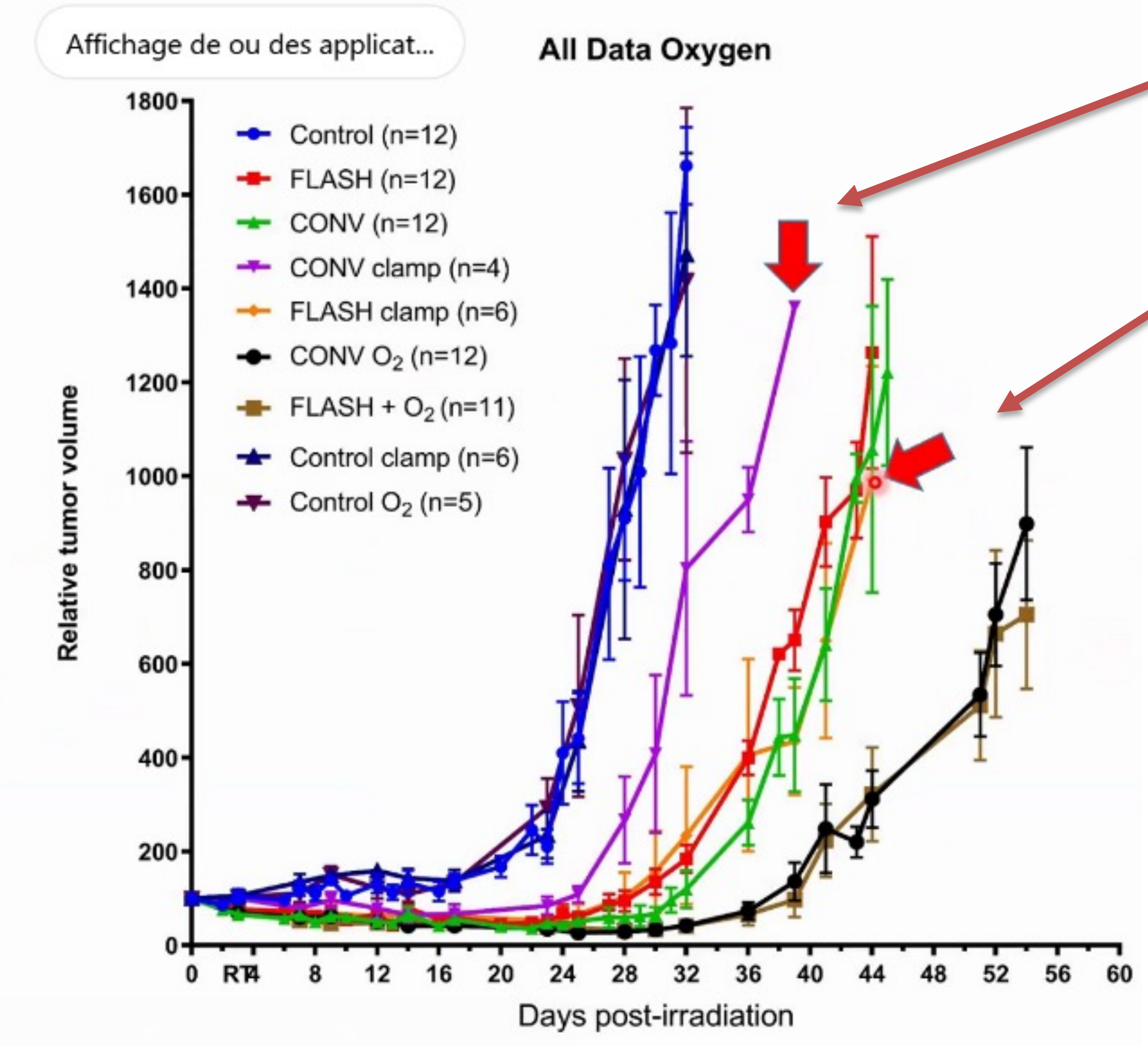
FLASH (milliseconds)

ESTRO 2022

Brita Singers SØRENSEN
(DENMARK)

Ask a question

FLASH more active than CONV in hypoxic tumor ??

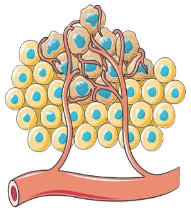


Clamped tumors with FLASH significantly better than CONV

Ron Leawitt
FRPT 2021

Potential Mechanisms … ?

Oxygen dependency



Montay Gruel PNAS 2019)

DNA Damage ?

Reactive
oxygen species

Lipid Peroxidation markedly reduced with FLASH

↓

Biological meaning ?

Vascular Damage

↑ TGFβ

↑ MPO

Vascular leakage ↓

Inflammatory response ↓

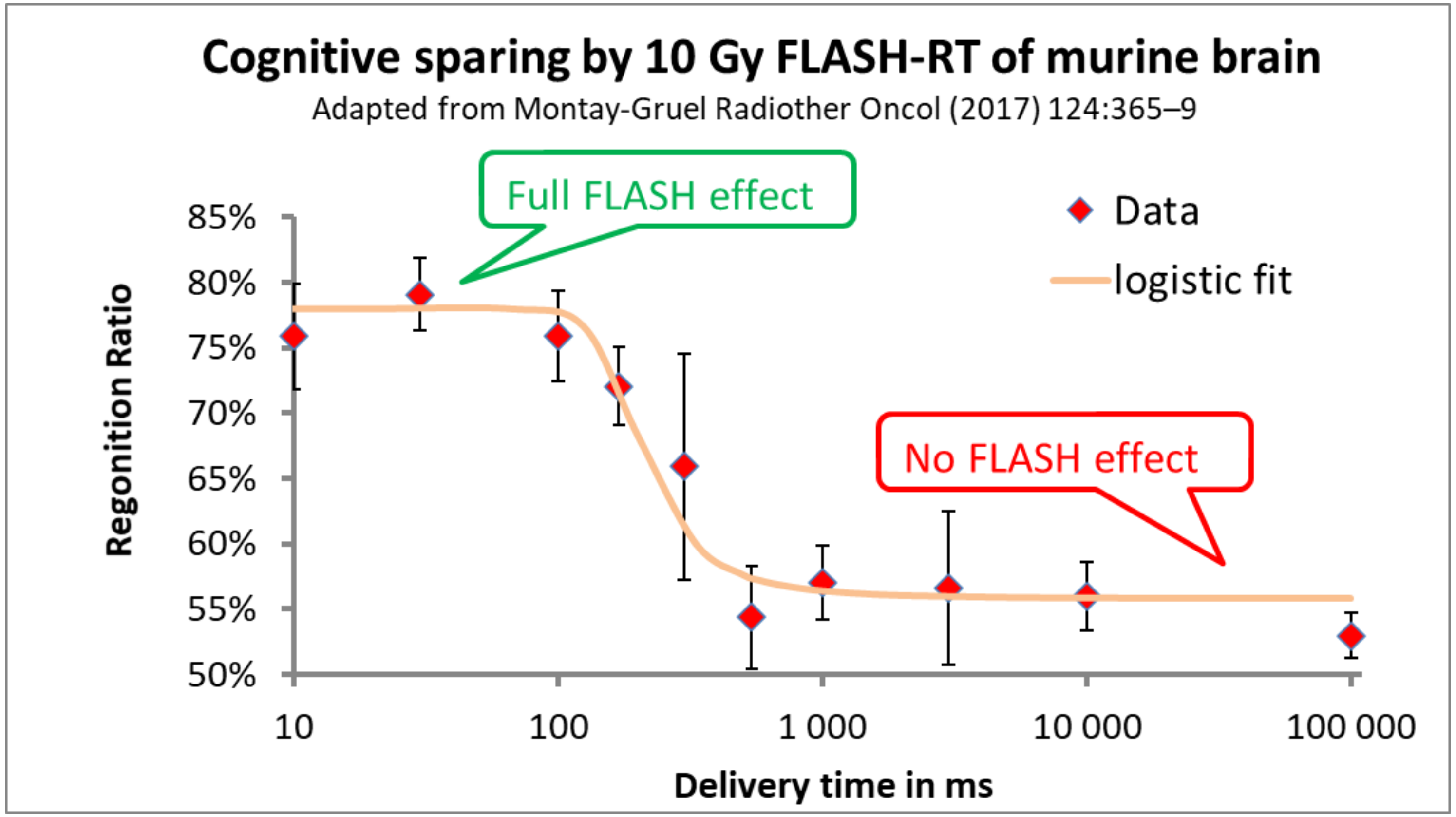
Myelocytic infiltration ↓

For clinical use, the FLASH effect has to be :

-1) Robust ?

-2) Reproducible ? → what are the optimal parameters ?

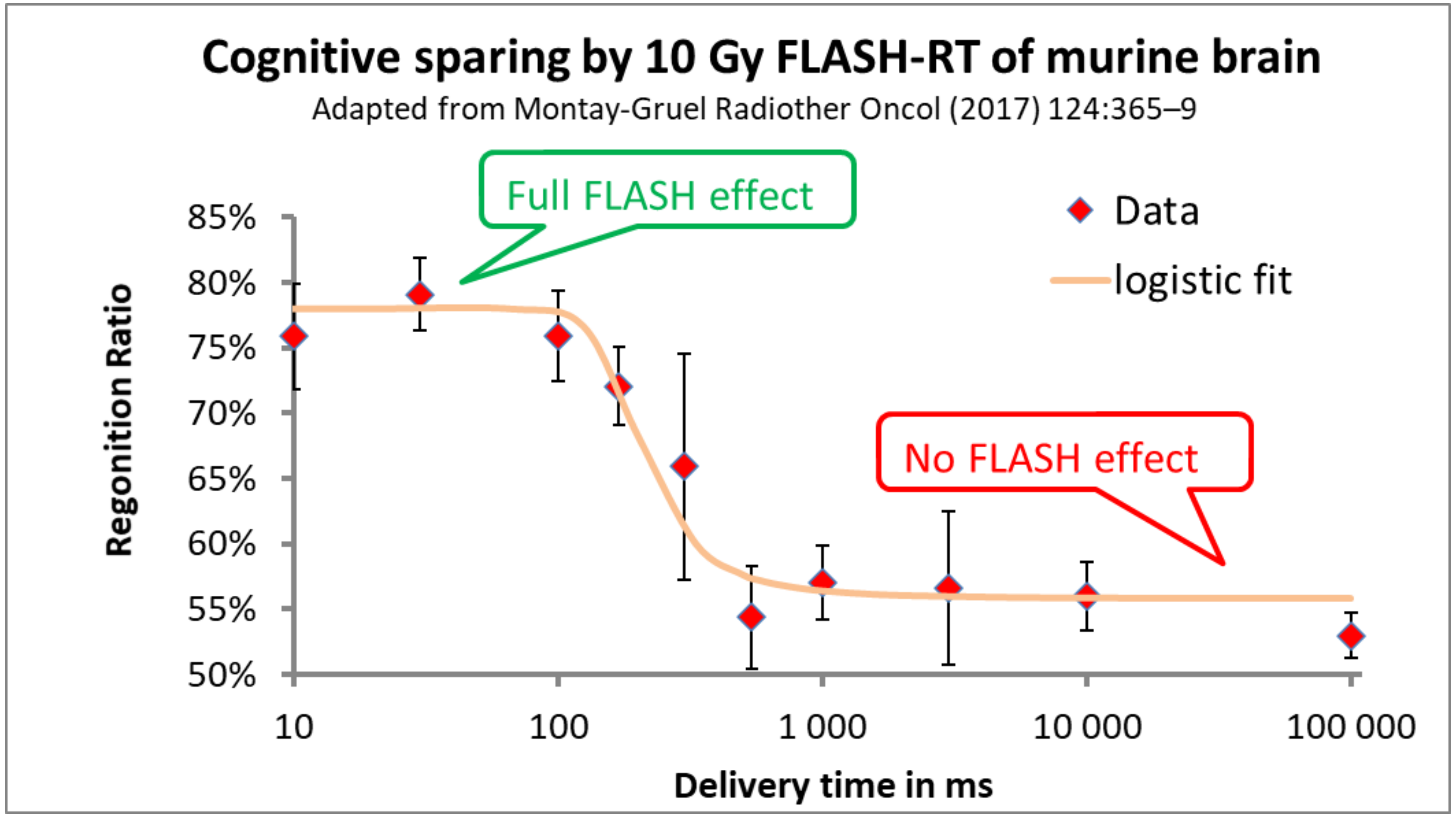
Overall delivery time is important …



<= 100 ms

JF Germond, CHUV Lausanne

Overall treatment delivery time is important …



<= 100 ms

Other parameters ?

Critical : Interval bewteen beams ++ ?

JF Germond, CHUV Lausanne

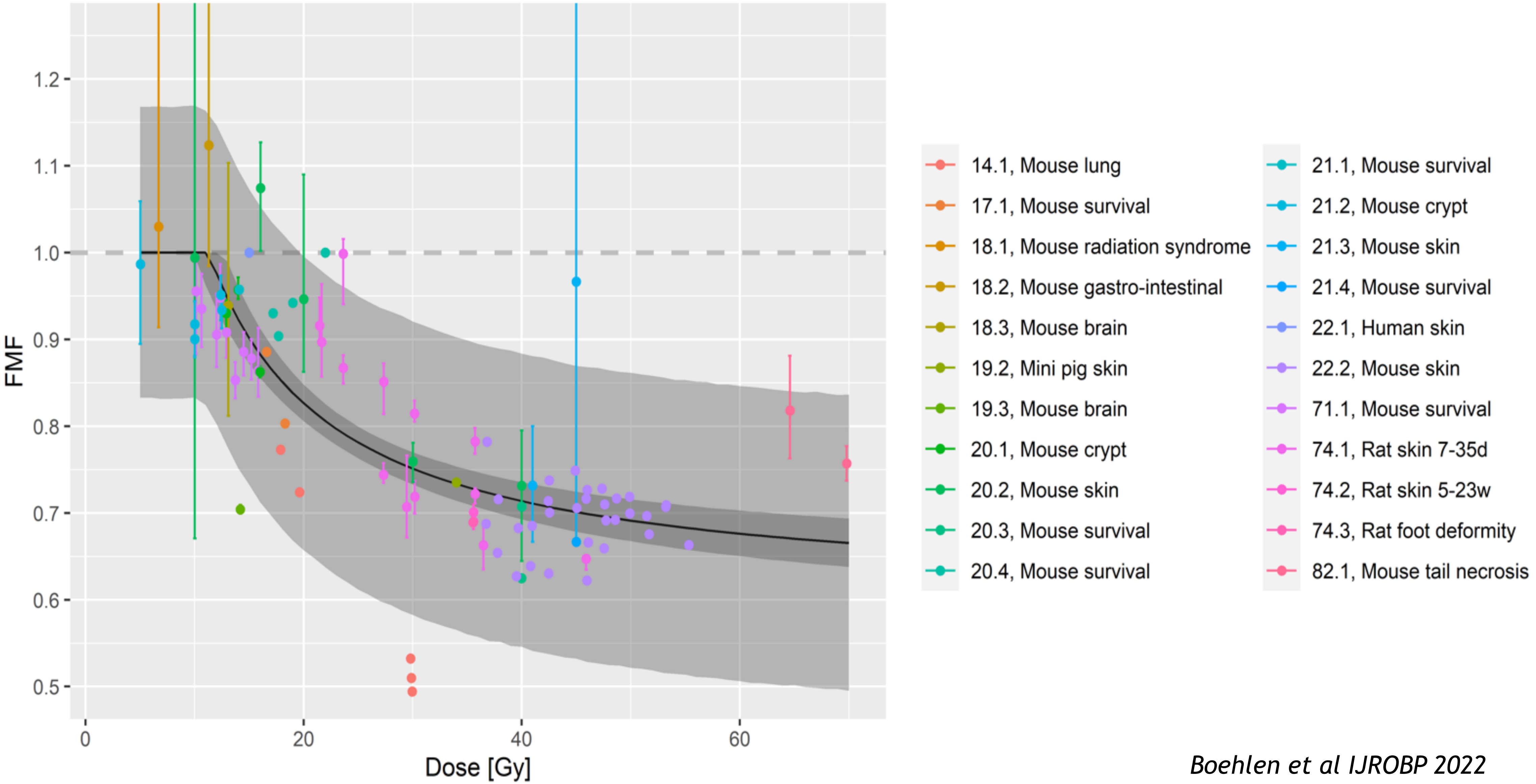
For clinical use, FLASH has to be :

-1) Robust ?

-2) Reproducible ?

-3) Clinically meaningful ?

What is the FLASH Modifying Factor (FMF) in mammalian tissues ?



Boehlen et al IJROBP 2022

CONV   Ultra High Dose

Rate

in
2.87 minutes

Day 0

15 Gy

in
90 ms

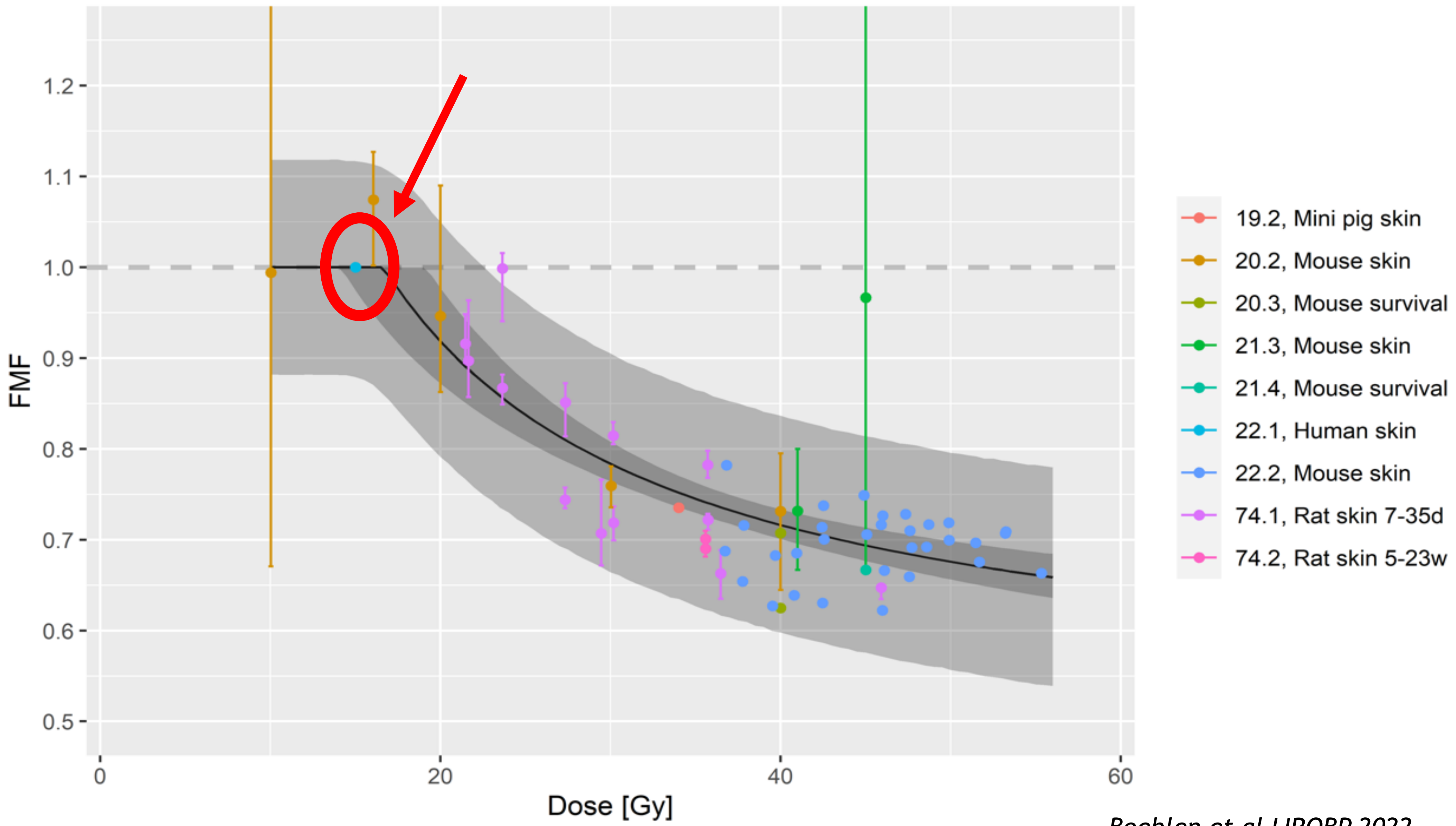
Day 17: grade 1
(CTCAE v5)

Same toxicity also
@ 2 years
(mild dermititis
on biopsies)

Patient
with a cutaneous lymphoma

Gaide et al,
Radiother Oncol
2022

Clinical findings compatible with FMF for mammalian skin



Boehlen et al IJROBP 2022

For clinical use, the FLASH effect has to be :

-4) Maintained in large volumes ?

-5) Compatible with fractionated RT ?

-6) Compatible with high precision RT delivery ?

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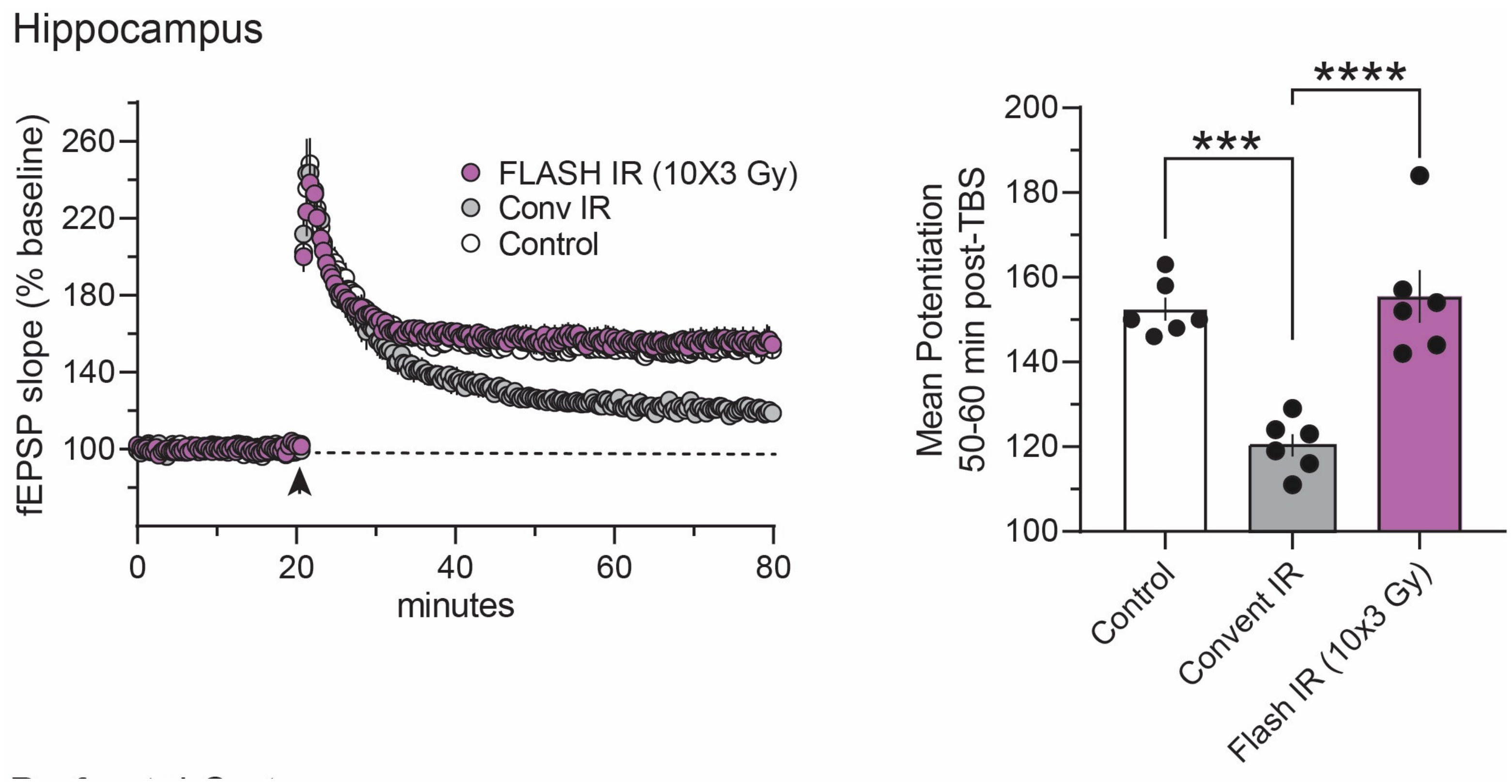
-4) Maintained in large volumes ?

-5) Compatible with fractionated RT ?

-6) Compatible with high precision RT delivery ?

FRACTIONATION
??



Recent results by CHUV and
UCI showing the FLASH effect in the brain with 10 x 3 Gy

Limoli, Vozenin, unpublished

FLASH versus CONV

in a veterinarian randomized

clinical trial

University of Zurich[UZH]
Division of Radiation Oncology

UNIL | Université de Lausanne

CHUV Centre hospitalier universitaire vaudois

vetsuisse-fakultät

A Randomized Clinical Phase-III-Trial Comparing Single High-Dose FLASH-Radiotherapy in Cat-Patients with Squamous Cell Carcinoma: Early Stopping Due to Late Toxicity

Carla Rohrer Bley[1], Friederike Wolf[1], Patrik Gonçalves Jorge[3], Ioannis Petridis[2], Benoit Petit[2], Jean Bourhis[2], Valeria Meier[1], Marie-Catherine Vozenin[2]

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Are such high single dose doable with FLASH ?

Cat patients
SCC
nasal planum
T1-2 N0

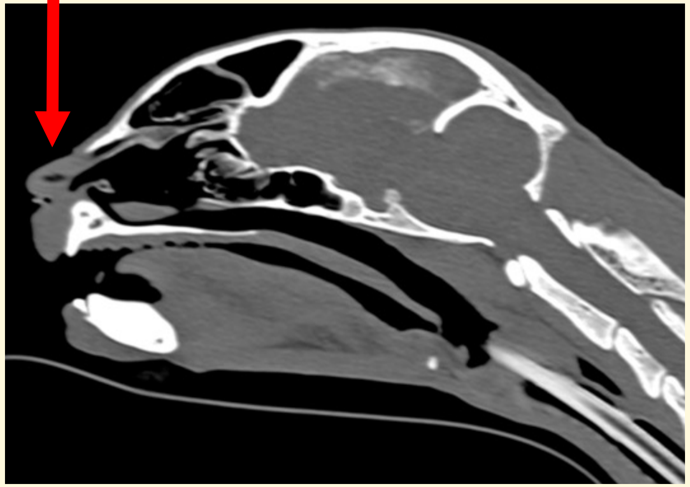
Randomized

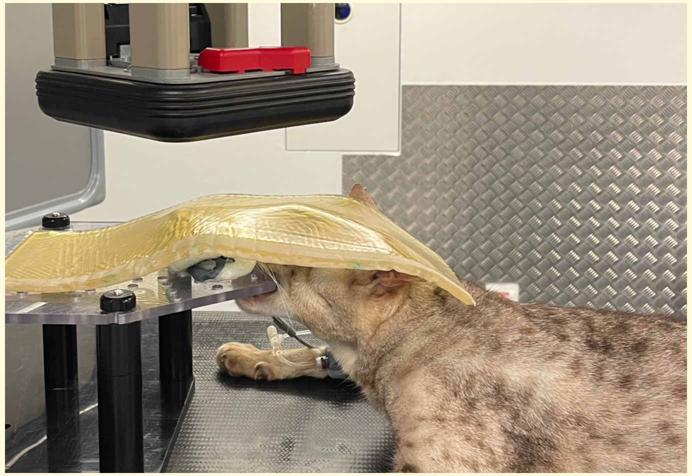
Ultra High Dose Rate
30 Gy in 20 ms

CONV Dose Rate
48 Gy in 10 fractions and 1 week

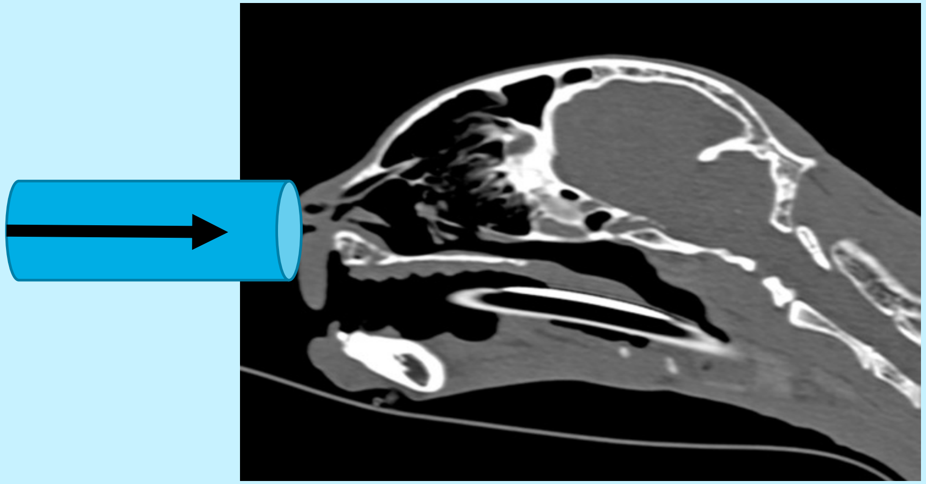
Rohrer et al Clin Cancer Res 2022

Arm 1: SoC
Fractionated 48 Gy





Arm 2: FLASH
Single dose 30 Gy+
(hot spots > 40 Gy)



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Tumor cure

Cat patients
SCC
nasal planum
T1-2 N0

Randomized

Ultra High Dose Rate
30 Gy in 3 pulses and 20 ms

1/7 tumor failure

CONV Dose Rate
48 Gy in 10 fractions and 1 week

1/9 tumor failure

Rohrer et al Clin Cancer Res 2022

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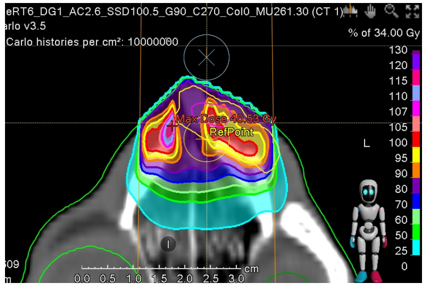


Cat patients
SCC
nasal planum
T1-2 N0

Randomized

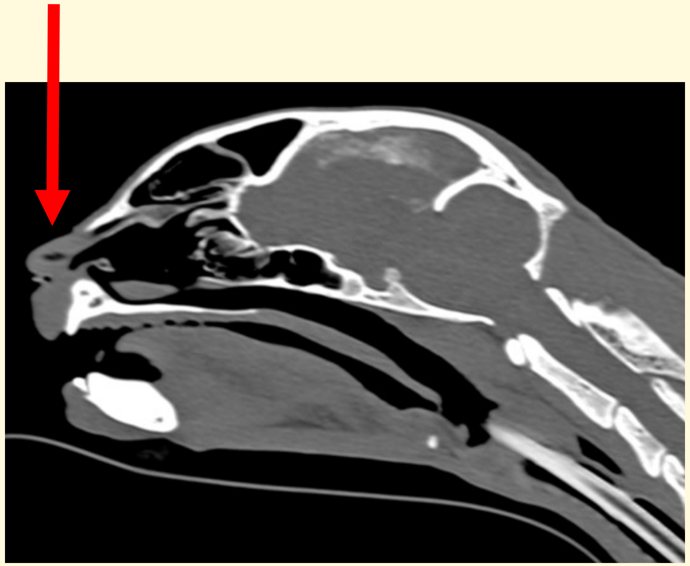
Ultra High Dose Rate
30 Gy in 20 ms
Hot spots > 40 Gy

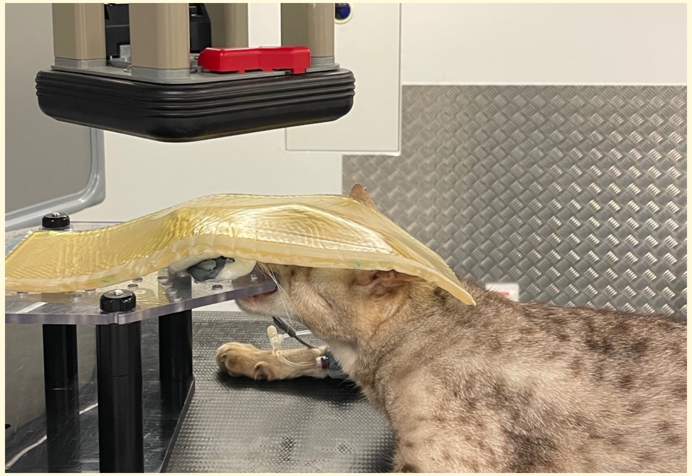
3/7 late necrosis

CONV Dose Rate
48 Gy in 10 fractions and 1 week

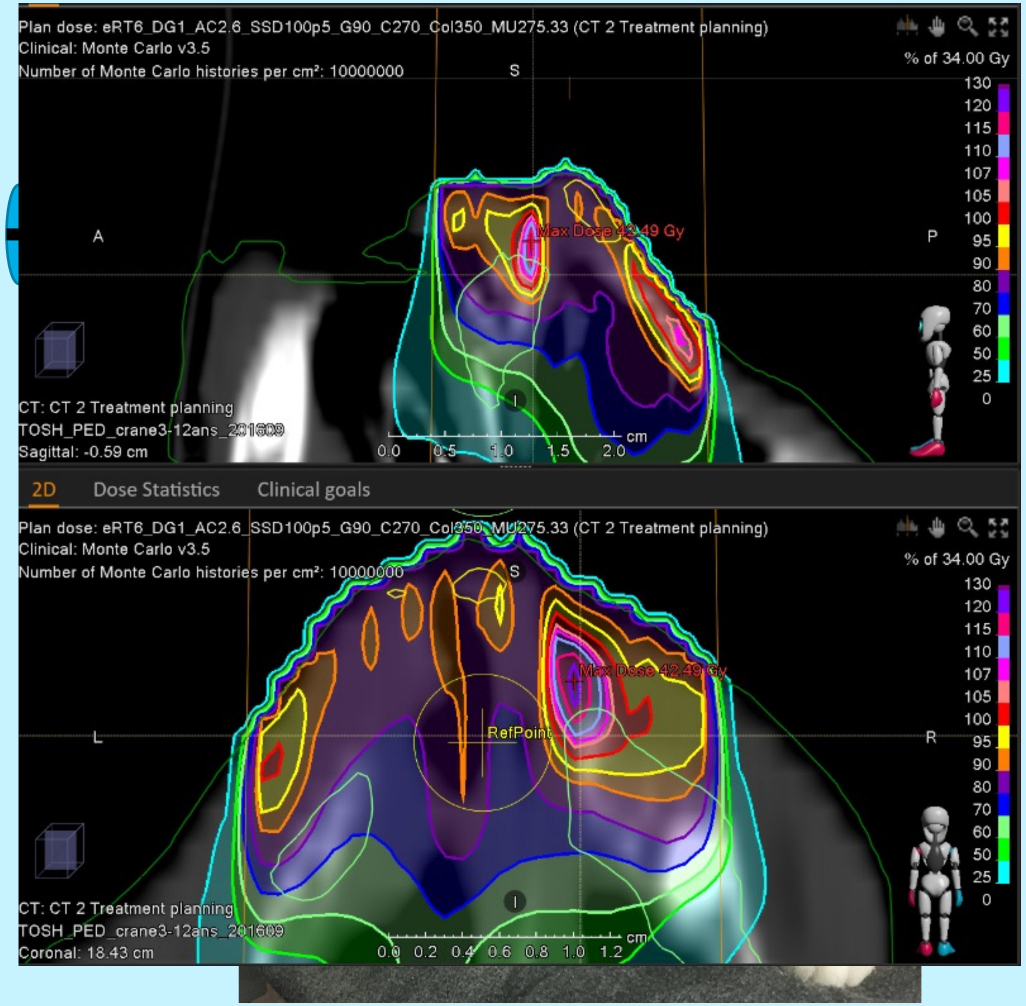
0/9 late necrosis

Arm 1: SoC





Arm 2: FLASH



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UHDR does not (fully) compensate for the lack of fractionation … and sub optimal conformality

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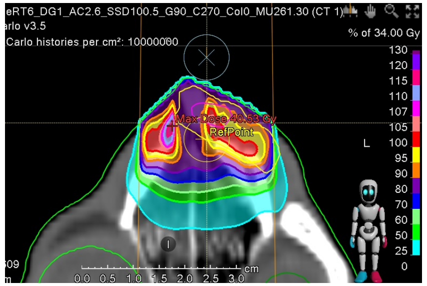

Cat patients
SCC
nasal planum
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Randomized

Ultra High Dose Rate
30 Gy in 20 ms
Hot spots > 40 Gy

3/7 late necrosis

CONV Dose Rate
48 Gy in 10 fractions and 1 week

0/9 late necrosis

In the era of Omics and AI …

Clinical translation was initiated in a very simplistic way … !

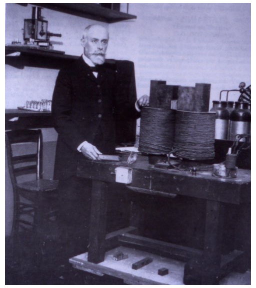
Electrons (< 10 MeV)

Protons (transmission beam)

More radiation effects on tumors than on normal tissues …?

Biology

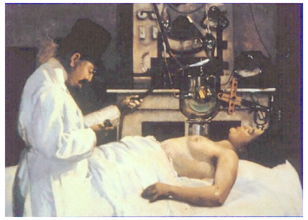
Technology



1895 2022

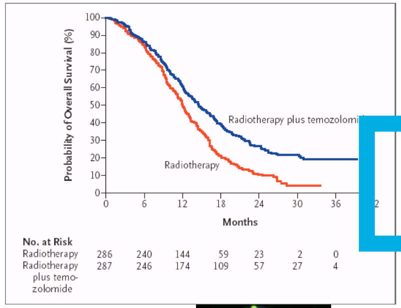
More radiation effect on tumors than on normal tissues …

Biology



2) Fractionation ….

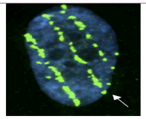
4) Combination with drugs



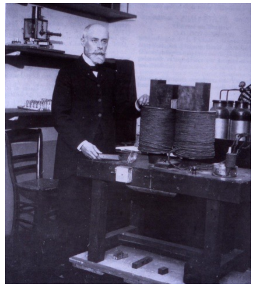
FLASH …

Hyperthermia

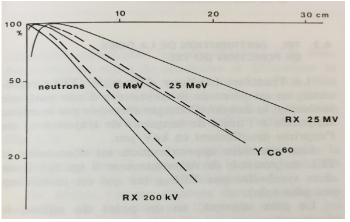
Carbon ions



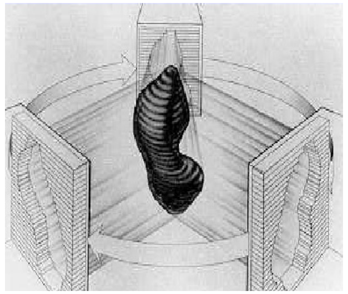
Technology

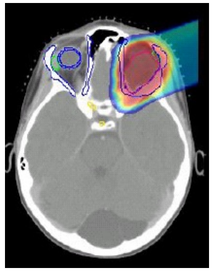


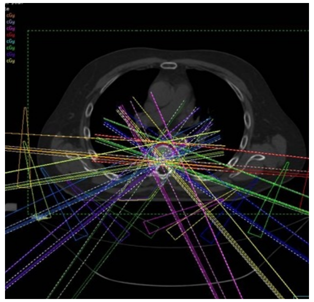
1) High energy…



3) higher and higher conformality ….





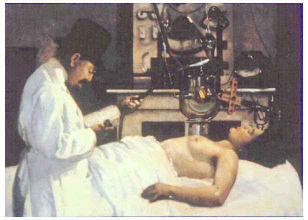


1895

2022

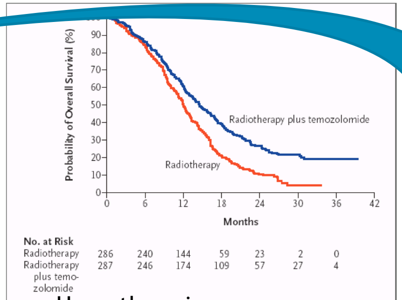
More radiation effect on tumors than on normal tissues …

Biology



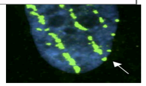
Fractionation ……………

Combination with drugs



Hyperthermia

Carbon ions

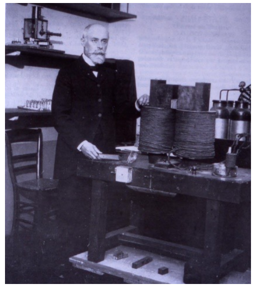


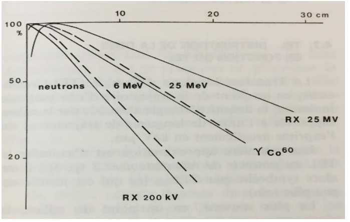
FLASH … ?

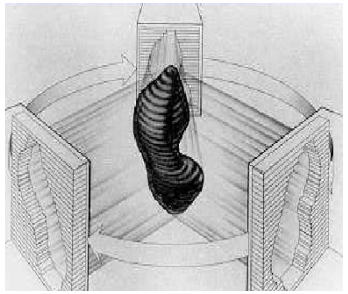
Technology

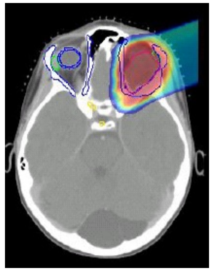
High energy…

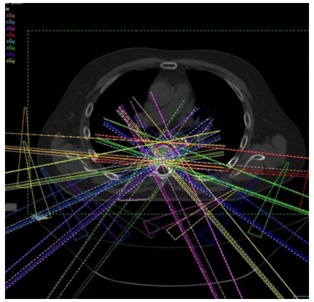
higher and higher conformality ….











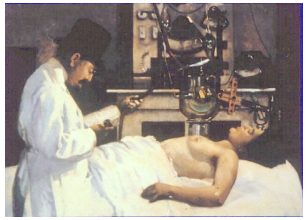
1895

2022

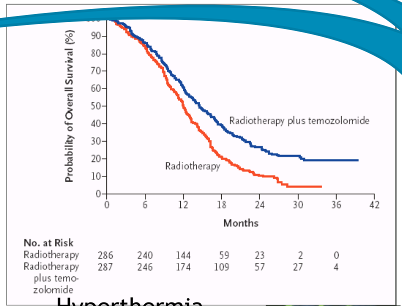
More radiation effect on tumors than on normal tissues …

Biology

Fractionation …………….

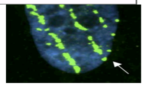


Combination with drugs



Hyperthermia

Carbon ions

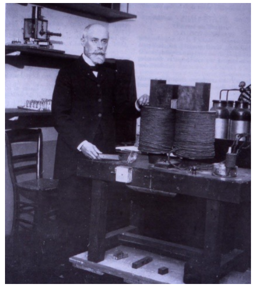


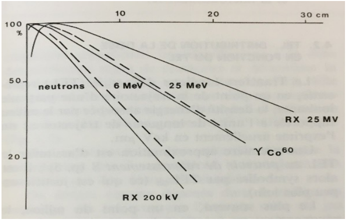
FLASH … ?

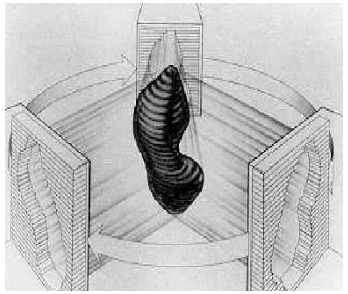
Technology

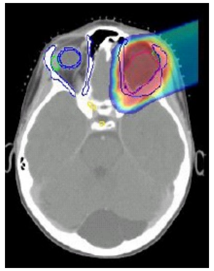
High energy…

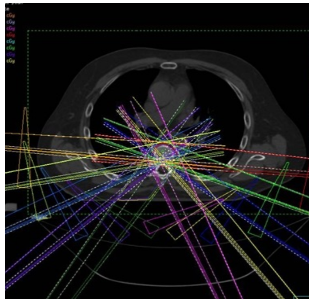
higher and higher conformality ….











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2022

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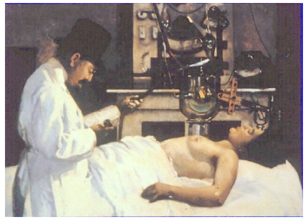

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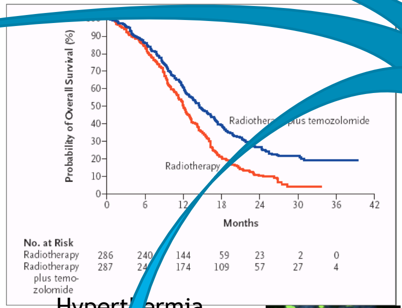
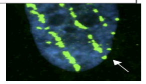
Combination with drugs



FLASH … ?

Hyperthermia

Carbon ions



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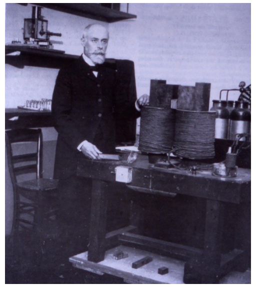
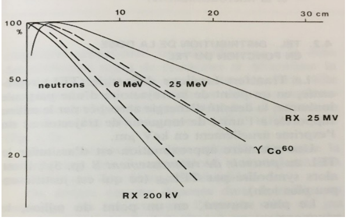
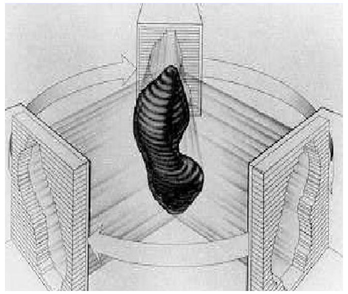
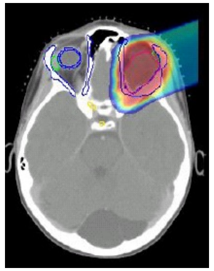
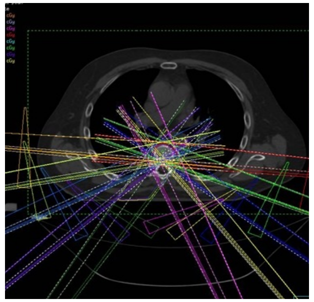








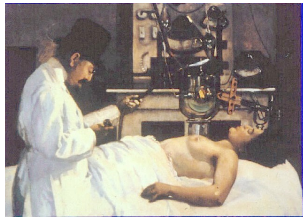


1895 **2022**

CHUV

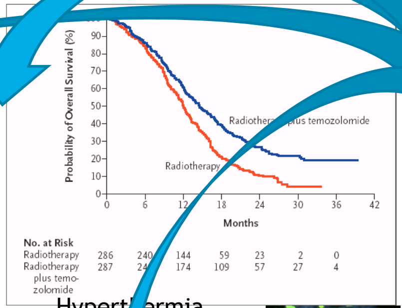
More radiation effect on tumors than on normal tissues …

Biology



Fractionation …………….

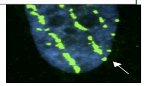
Combination with drugs



FLASH … ?

Hyperthermia

Carbon ions



Technology

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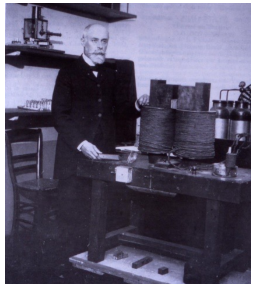
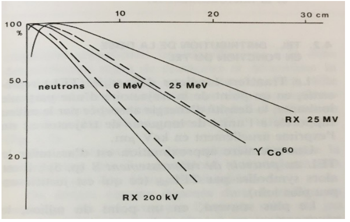
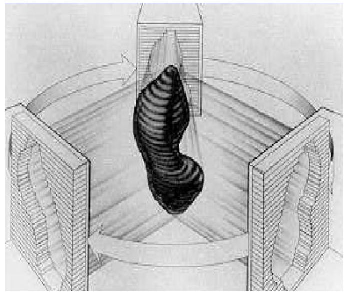
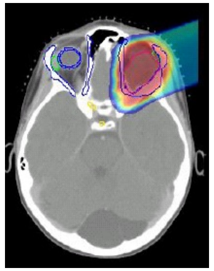
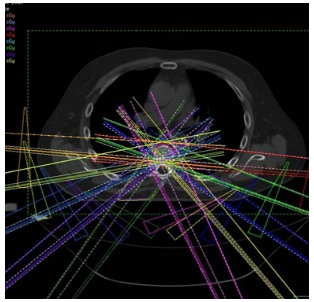










1895 **2022**

Clinical translation : where are we ?

Electrons

Protons (deep seated tumors)

Limitations

superficial targets
small volumes,

single beam direction
Transmission fields

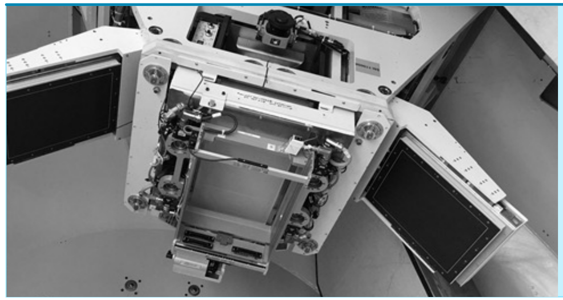
FAST-01 : first clinical trial with Proton-FLASH

Cincinnati Children's/UC Health Proton Therapy Center

Single palliative dose of 8 Gy

10 patients

56 Gy/s on average
Transmission beam



7.5 x 20 cm maximum field size

Co-primary : feasibility & AEs

FAST 02 : To assess toxicities and pain relief of 8 Gy FLASH radiotherapy for bone metastases in the thorax

Sharma et al Lausanne FLASH Worshop 15th Sept and to be reported @ ASTRO 2022

Clinical translation

started with what we know and what is available

Limitations

Electrons (low energy)

Superficial targets
Single beam direction
Small volumes

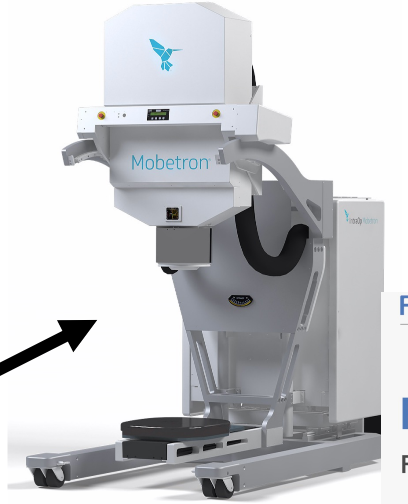
Protons (deep seated tumors)

Single beam direction

Clinical translation of FLASH electron-therapy @ CHUV

1) FLASH electron therapy for superficial skin cancers :

- IMPULSE phase I dose escalation trial (2021)
- Randomized trial FLASH versus conventional RT (2022)



2) Intra-operative FLASH electron therapy

for incompletely resected tumors (first patient 2022)

3) FLASH VHEE for deep seated tumors with CERN (being built)

Press Release

Lausanne and Geneva, September 15th 2020

Lausanne University Hospital and CERN collaborate together on a pioneering new cancer radiotherapy facility

IMPULSE dose escalation trial

(Vozenin 2019)

UHDR parameters

> 2 Gy / pulse
< 10 pulses
Delivery time < 100 ms

Phase I dose escalation trial for melanoma skin metastases

3 x 3 dose escalation : 22 Gy to 34 Gy

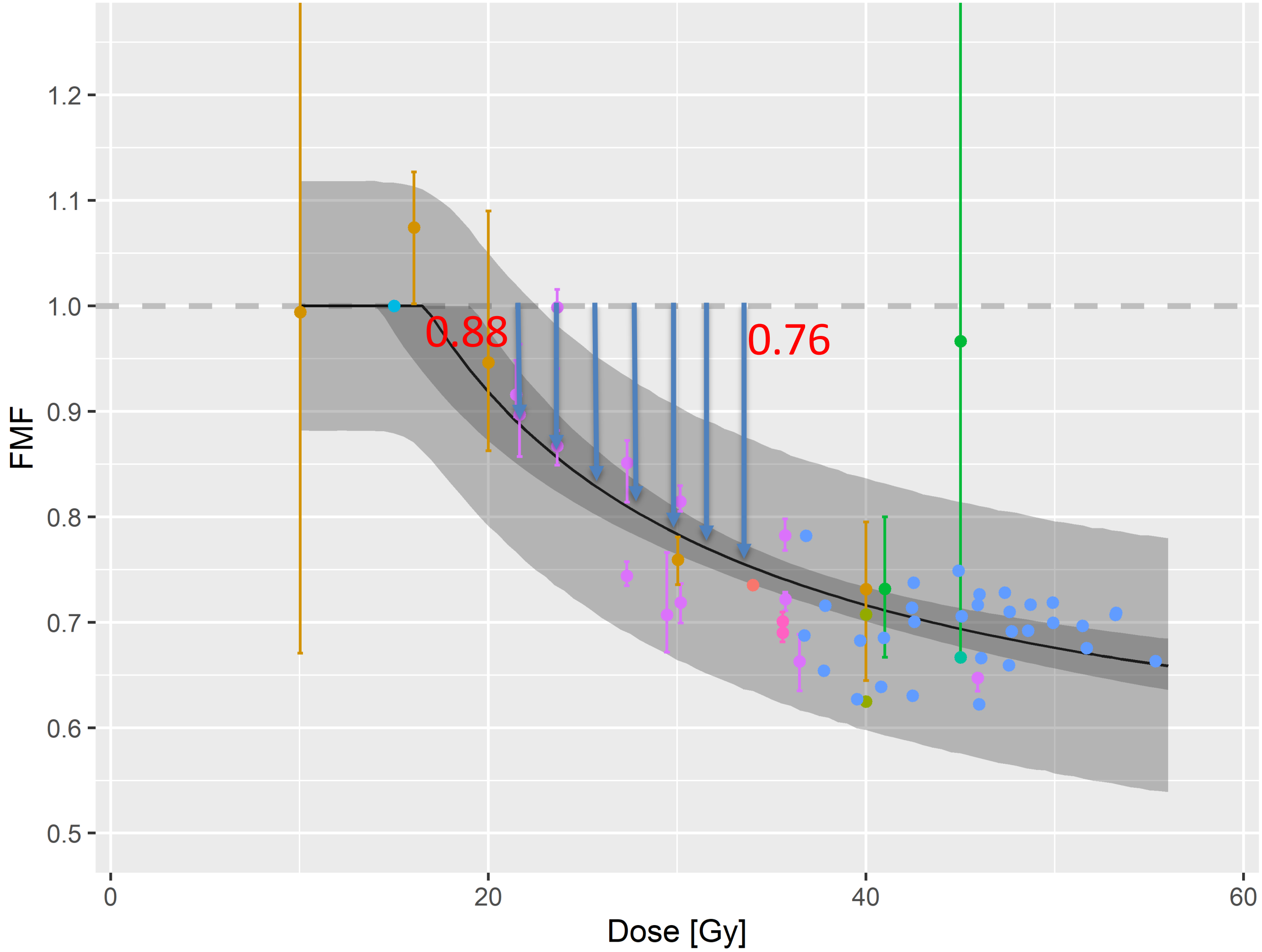
Primary endpoint : DLT / MTD

Small fields	**Large fields**
< 30 cc	30-100 cc

Status : recruiting (7 patients)

Dose escalation trial

7 dose levels (22- 34 Gy in steps of 2 Gy)



Hypothesis tested :

D_{UHDR}=34Gy ≙ D_{FMF}= 25.8 Gy (21.8-29.9)

D_{UHDR}=32Gy ≙ D_{FMF}= 24.6 Gy

D_{UHDR}=30Gy ≙ D_{FMF}= 23.4 Gy (20.1-27.3)

D_{UHDR}=26Gy ≙ D_{FMF}= 21.6 Gy (18.7-24.7)

Impulse : a phase I of high dose rate RT in patients with skin metastases from melanoma

Current dose level

Dose level	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	Level 7
FLASH dose	22 Gy	24 Gy	26 Gy	28 Gy	30 Gy	32 Gy	34 Gy

2,2 Gy / pulse

3.4 Gy / pulse

10 pulses
100 ms

Second Investigational Trial of UHDR vs normal dose rate for skin cancers

(with O Gaide, R Kinj, W Jeanneret, F Duclos, R Moeckli, P Jorge, and J Bourhis)

This is a randomized selection phase II study, with 1 to 1 randomization to:

For T1 (small) lesions:

- Arm A : 22 Gy single dose FLASH radiotherapy
- Arm B : 22 Gy single dose conventional radiotherapy

For T2 (large) lesions:

- Arm C : 5 x 7 Gy fractionated dose FLASH therapy (5 fractions in 2 weeks)
- Arm D : 5 x 7 Gy fractionated dose conventional radiotherapy (5 fractions in 2 weeks)

Intra Operative RadioTherapy with FLASH electrons : (IORT)

1) Could FLASH revigorate IORT ?

- High single dose electrons are already used in conventional IORT

- *FLASH could allow + 4-5 Gy*

2) Need for a stepwise and careful approach +++

- *Toxicity from surgery can be high and perhaps not wise to use it as primary endpoint*

3) Ongoing Initiatives :

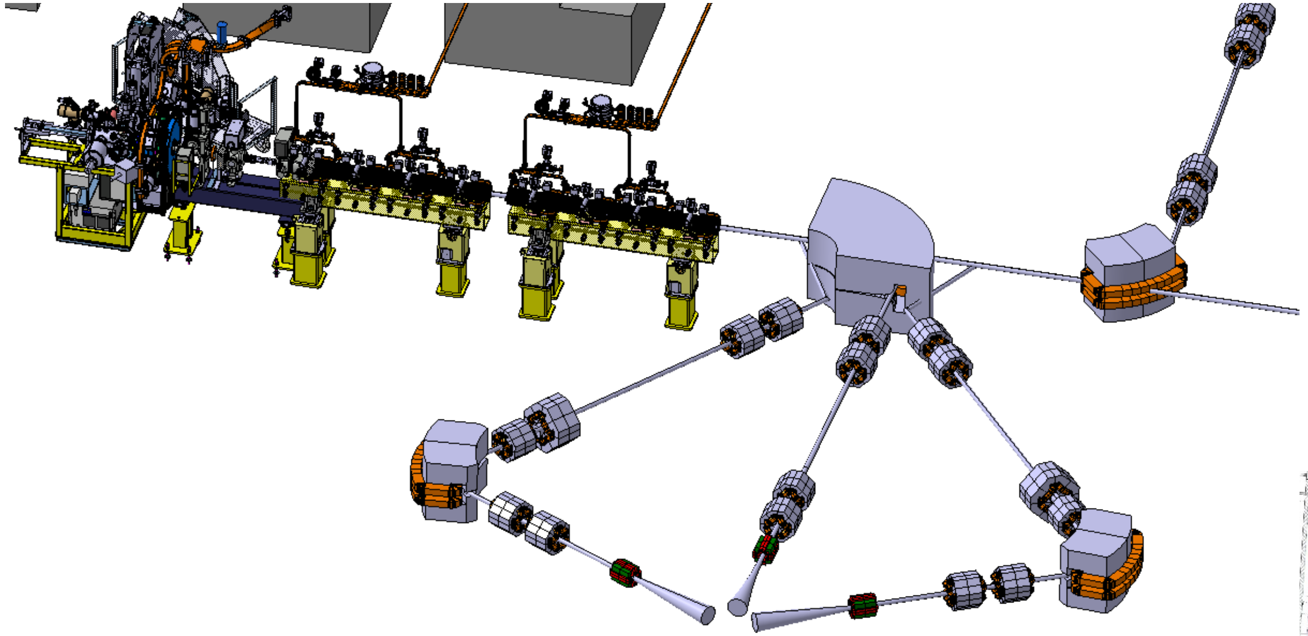
- IntraOp with Mobetron. Brussels, Heidelberg, MDACC (2023) : pancreatic cancers

- PMB with FLASHKNiFE (start in 2023) : head and neck, abdominal expected to be R1

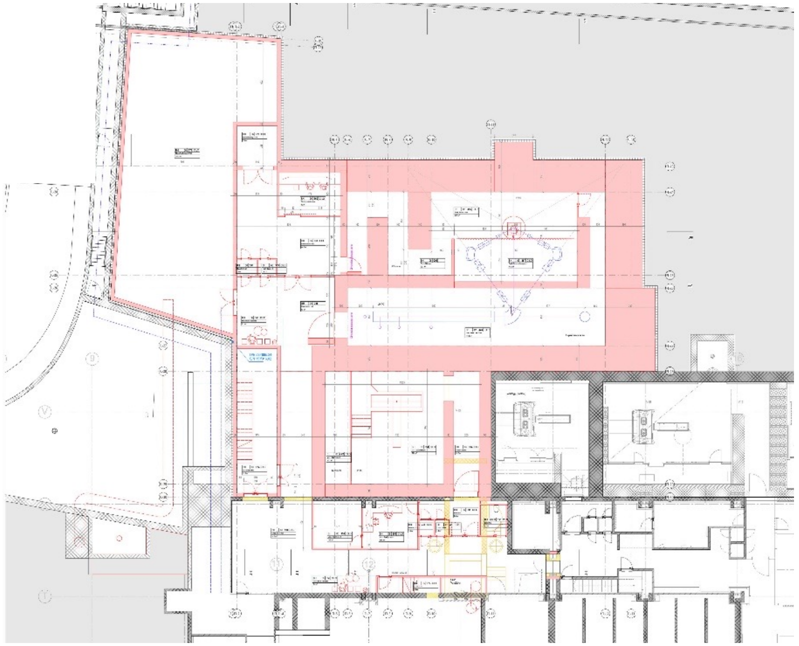
- SIT (Antwerpen) : Breast cancers 2023

-

FLASH for large deep seated tumors ? CERN-CHUV VHEE project



Integration
@ CHUV
in a compact
horizontal layout



Status : ongoing

FLASH in the era of OMICs and AI :
temporary conclusions

1) **Potential additional tool for increasing the differential effect tumor / normal tissues ?**

- Promising and consistent

- *Q ? mechanisms ? effects on tumor cure ? combination with drugs ?*

2) **Optimal parameters for a FLASH effect ?**

- Overall delivery time < 100-200 ms

- *Q ? large fields ? Fractionation ?, interval between beams able to maintain sparing effect at the margin of the PTV ?*

3) **Beam control, diagnostics, monitoring**

- Available for first clinical testing

4) **Clinical translation : stepwise approach**

- First trials ongoing for skin tumors with electrons + deep seated tumors with transmission beam protons (palliative)

- *Q : how to maintain high conformality in 100 ms ?*

Acknowledgments

To the CHUV FLASH therapy team

Pr Vozenin

Pr Bochud (IRA)

UNIL & CHUV : Pr P Eckert, Mr O Peters, Pr JD Tissot, Pr PF Leyvraz,
DO : Pr Coukos, Pr Kandalaft & l'équipe du CTE
Sponsors : **ISREC & Biltema Foundation**, Foundation CePO, Fond'Action, FNS, ANR, PO1, Foundation CHUV
Partners : PMB, CERN, IntraOp, RaySearch