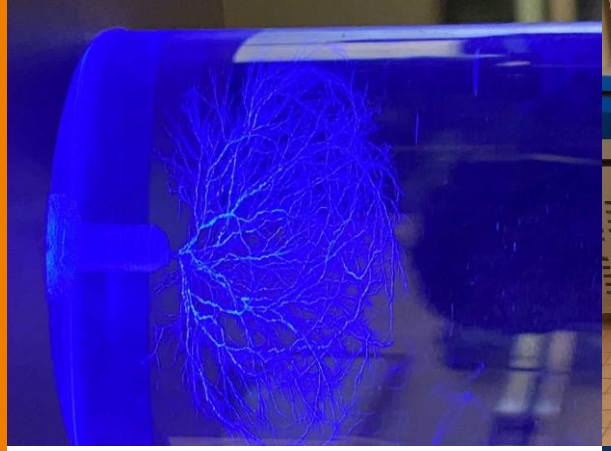
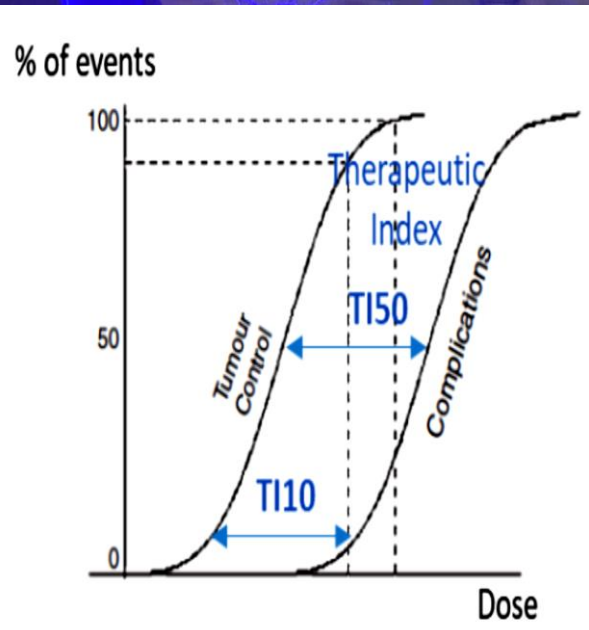
Strathclyde Virtual Workshop:

Ultra-high Dose Rate RadioTherapy

16/09/2021

Clinical translation of FLASH radiation therapy: What has been done and the challenges still ahead.





ENSEMBLE, PRENONS
LE CANCER DE VITESSE

Sophie Heinrich
Team "DNA Repair, radiations and innovative cancer therapies"
UMR 3347/U1021 – Signaling, Radiobiology and Cancer

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Outline

1. Veterinary experience

2. Ongoing / Upcoming clinical trials

3. Some remaining challenges for clinical use of FLASH (VHEE) therapy

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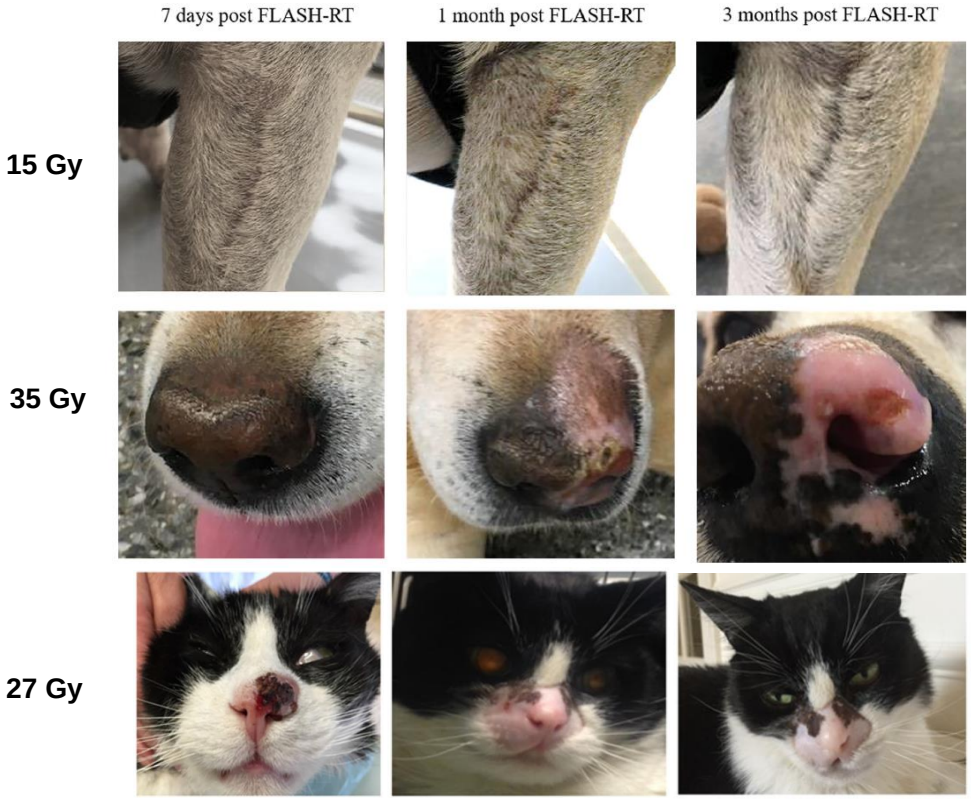
1. Veterinary experience: Cats & Dogs – Electrons



Feasibility / Safety studies, Dose-escalation
Superficial tumors:

- Feline Nasal Planum Squamous Cell Carcinoma
- Canine Sarcoma, Mastocytoma, Plasmacytoma, Melanoma, Squamous Carcinoma

Vozenin et al. Clin Can Res 2019

Konradsson et al. Front Oncol 2021

- Experimental / Modified medical LINAC, Electron 4.5 - 6 , 10 MeV
- Single-fraction
- Single-beam
- A few pulses (µs, > 1 Gy) per fraction
- Dose rate : 130 – 500 Gy/s

	Dose escalation	Treatment time (ms)	Field size (mm^2)
Cats	25 – 41 Gy	80 - 300	20 x 30
Dogs	15 – 35 Gy	30 - 75	80 x 40

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1. Veterinary experience: Cats & Dogs – Electrons

Feasibility / Safety studies, Dose-escalation
Superficial tumors:

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Vozenin et al. Clin Can Res 2019

Konradsson et al. Front Oncol 2021

- **Complete response:** 5/6 cats, 5/10 dogs
- **Partial response / Stable disease:** 3/10 dogs
- **Recurrence / Progressive disease:** 1/10 cats, 2/10 dogs
- **Side effects:** mild (depilation, grade 1), except 1 dog (35 Gy), medium (moist desquamation, grade 3); no severe early or late reactions.

Fidel et al. Vet Radiol Ultrasound, 2001

- **Protons**
- **40 – 45 Gy** (equiv. Co-60)
- **Hypofractionated: 8 fractions**
- **Equivalent tumor responses**
- **Minimal side effects, no severe early or late reactions.**

1. Veterinary experience: Dogs – Protons

Patient ID	Breed	Age (years)	Sex	Weight (kg)	Dose rate (Gy/s)	Dose (Gy)	FLASH or standard
1	Black Lab	11.0	F	33.1	76.2	8.1	F
2[a]	St Bernard	4.5	M	61.4	61.0	4.0	F
3	Mastiff	6.0	F	57.0	103.0	8.1	F
4	Mastiff	6.5	M	59.6	0.5	8.0	S
5	Rottweiler	8.0	M	55.2	111.5	8.0	F
6	Mixed Breed	8.0	M	25.2	0.5	8.1	S
7	Doberman/Great Dane Mix	5.5	F	45.9	0.5	8.1	S
8	Mixed Breed	7.0	M	29.8	111.5[b]	7.6	F
9	Golden Retriever	9.0	M	40.2	114.8[b]	8.0	F
10	Shepherd Mix	9.0	M	35.7	0.5[b]	8.0	S
11	Great Pyrenees	9.0	M	42.9	101.9	12.1	F
12	American Bulldog	10.0	M	45.4	0.5	12.0	S
13[a]	Mixed Breed	8.0	F	36.0			
14[a]	Doberman	8.0	M	36.5			
15	Labradoodle Mix	10.0	M	42.5			
16	Great Dane	5.0	F	71.0			
17	Rottweiler	6.0	F	34.4			
18	Rottweiler/Husky	10.0	M	46.3			
19	Greyhound	1.5	M	28.0			

Canine Osteosarcoma

Velalopoulou et al. Cancer Res 2021

Keith Cengel, ESTRO 2021

	Dose	Treatment time (ms)	Field size
Dogs	8 – 12 Gy	~ 100	~ cm²

- Medical Cyclotron, Proton 230 MeV
- Single-fraction
- Single beam (Double scattering), before BP
- Quasi-continuous beam
- Dose rate : 60 – 130 Gy/s (FLASH) + 0.5 Gy/s (CONV)

- Side effects, within 5 days (preoperatively) : 1 tumor lysis.
- Absence of increase of inflammation marker (TGF-β1), comparable with preclinical mouse models.

Outline

1. Veterinary experience

2. Ongoing / Upcoming clinical trials

3. Some remaining challenges for clinical use of FLASH (VHEE) therapy

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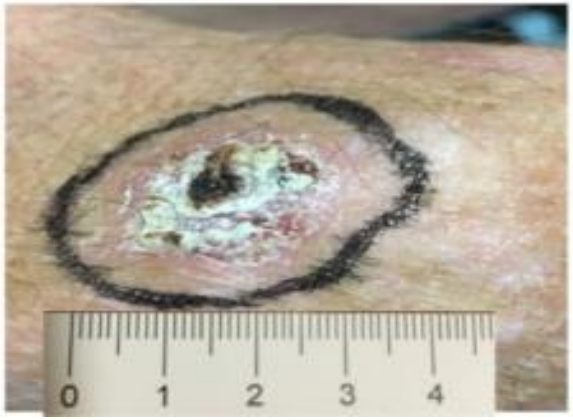
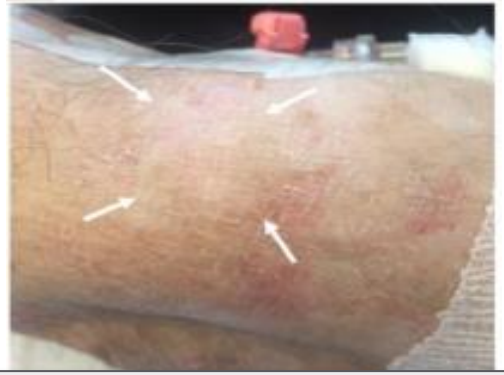
2. Ongoing / Upcoming clinical trials: Cutaneous Lymphoma

Before



3 weeks
after 15 Gy FLASH

5 months
after 15 Gy FLASH



First human patient treated with FLASH RT
Bourhis et al. Radiother&Oncol 2019

- Experimental LINAC, Electron 6 MeV
- Single-fraction
- Dose: 15 Gy
- Single beam
- 10 pulses (1µs) per fraction
- Field size: 3.5-cm diameter
- Treatment time: 0.09s
- Dose rate: 167 Gy/s

Jean Bourhis, ESTRO 2021

- Complete response
- Side effects: redness, oedema, no severe early or late reactions.

Ongoing:
- Dose escalation trial (skin melanoma metastasis) 22 – 34 Gy
- Randomized trial FLASH vs CONV

FAST-01 (FeAsibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases)

Cincinnati Children's/UCHealth Proton Therapy Center, 2020

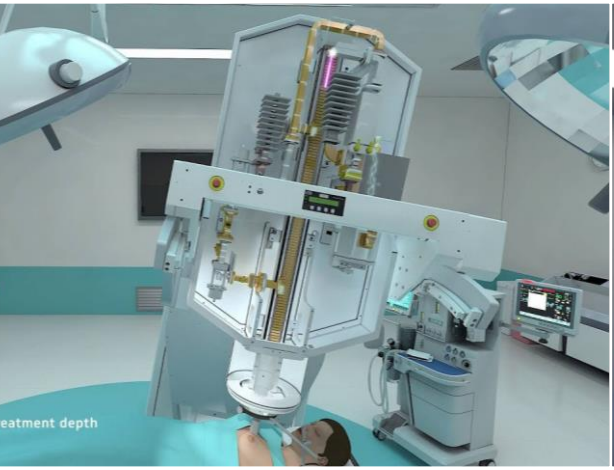
PI: John Breneman, MD

Palliative treatment of Bone metastasis

- Medical Cyclotron, Proton
- Single-fraction
- Dose: 8 Gy
- Single beam, before BP
- Quasi-continuous beam
- treatment field sizes: 7.5 cm x 7.5 cm; 7.5 cm x 10 cm; 7.5 cm x 12 cm; 7.5 cm x 14 cm; 7.5 cm x 16 cm; 7.5 cm x 18 cm; 7.5 cm x 20 cm

- Endpoints :
  - Equivalent Pain response
  - Any possible adverse side effects
  - Workflow feasibility

2. Ongoing / Upcoming clinical trials: Intraoperative electron RT



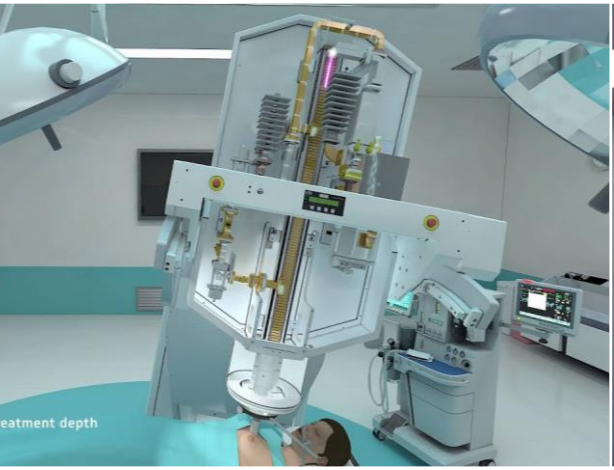
Mobetron – IntraOp

FLASH LIAC – SIT

FlashKnife – PMB

- Electron 6 – 10 – 12 MeV
- Single-fraction
- Dose: 10 – 35 Gy
- Single beam
- A few pulses per fraction
- Field size: 3 – 12 cm diameter
- Dose rate: Hundreds of Gy/s

2. Ongoing / Upcoming clinical trials: Intraoperative electron RT



Mobetron – IntraOp

FLASH LIAC – SIT

FlashKnife – PMB

eIORT Indication	Goal
Partial breast irradiation	Volume/Dose increase
Breast Boost	Lowered Side effects
Extremities Soft Tissue Sarcoma	Lowered Side effects
Skin cancer - Non-melanoma	Lowered Side effects, Hypofractionation
Recurrent Rectal Cancer	Both
Unresected pancreatic Cancer	Both
Retroperitoneal Soft Tissue Sarcoma	Both
High-grade Brain Tumor	Both
Skin cancer - Melanoma	Both (EBRT)

Philip Poortmans, ESTRO 2021

ESTRO 2021

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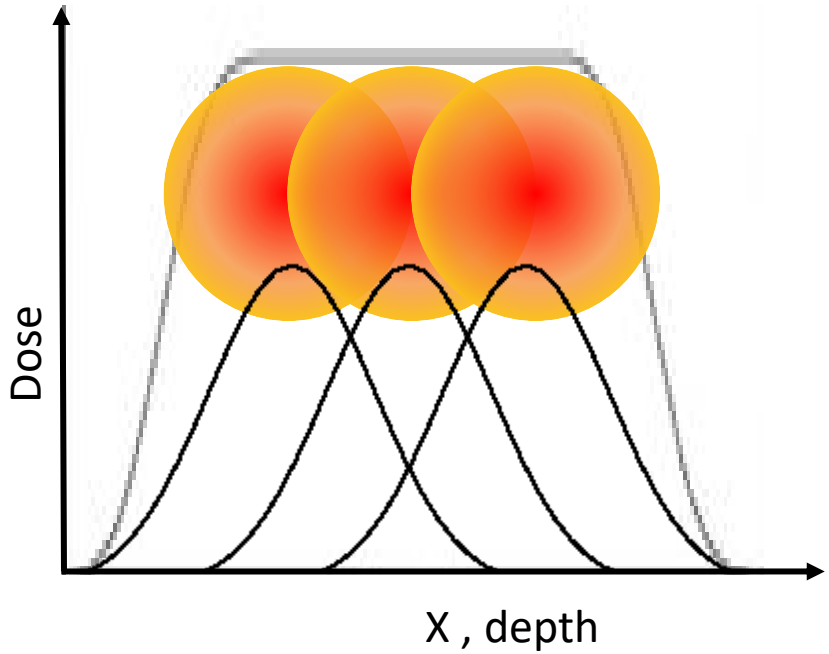
FEASIBILITY

1. **Large volumes**
   - Higher fluence (particle/cm²)
   - Scanning technique
     - ➢ Re-irradiation of parts of the volume
     - ➢ Within < ~ 300 ms ???
2.
3.
4.
5.
6.
7.



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3. Some remaining challenges for clinical use of FLASH (VHEE) therapy

FEASIBILITY

1. **Large volumes**
2. **Reference dose**
3.
   - Direct reading
4.
   - Accuracy / spatial resolution
5.
   - Traceability
6.
   - VHEE?
7.

UHDpulse

EMPIR

The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

EURAMET

Coord. **Andreas Schüller**

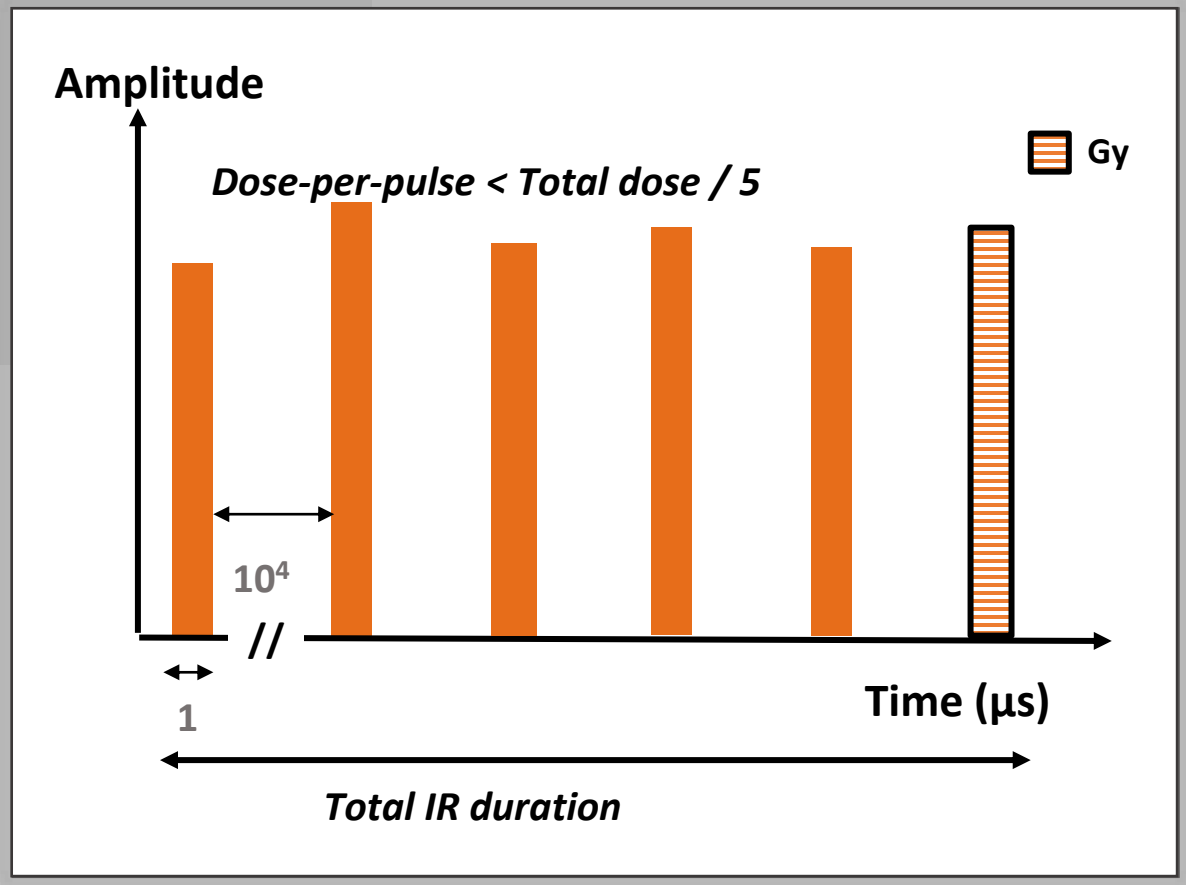
Task Group No. 359 – Chair Dimitris Mihailidis
FLASH (ultra-high dose rate) radiation dosimetry

AAPM AMERICAN ASSOCIATION of PHYSICISTS IN MEDICINE

ESTRO

FEASIBILITY

1. Large volumes
2. Reference dose
3. Beam monitoring
4.
5.
6.
7.



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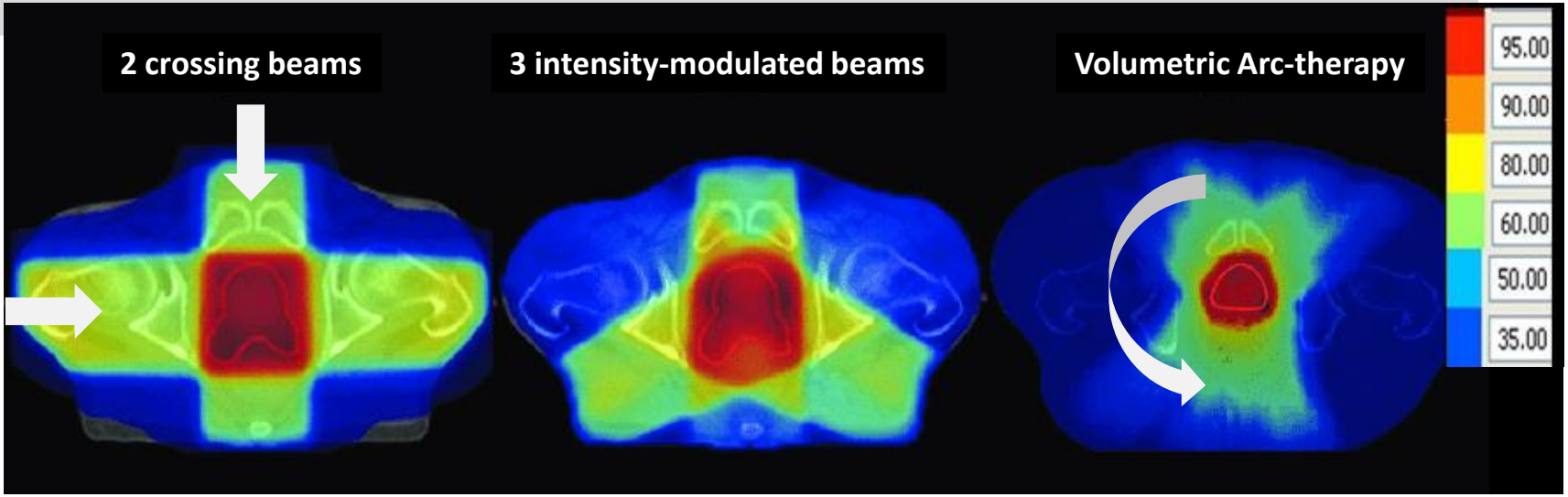
3. Some remaining challenges for clinical use of FLASH (VHEE) therapy

EFFICACY FLASH have to compete with modern RT techniques

1. **Large volumes**
2. **Reference dose**
3. **Beam monitoring**
4. **Multiple beams to achieve conformational dose distribution**
5.
6.
7.

- Re-irradiation of parts of the volume
- Within < ~ 300 ms ???



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EFFICACY FLASH have to compete with modern RT techniques

1. Large volumes
2. Reference dose
3. Beam monitoring
4. Multiple beams to achieve conformational dose distribution
5. Daily fractionation
6.
7.

$$BED = D\left[1 + \frac{d}{\alpha/\beta}\right] - \mathrm{K}\,(\mathrm{T} - T_K)$$

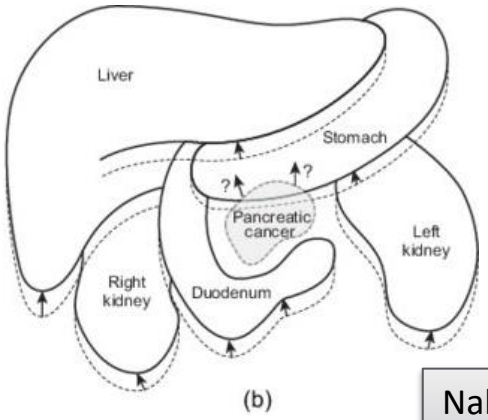
Where D is the total dose
d is the fractional dose
T is the overall time of the treatment

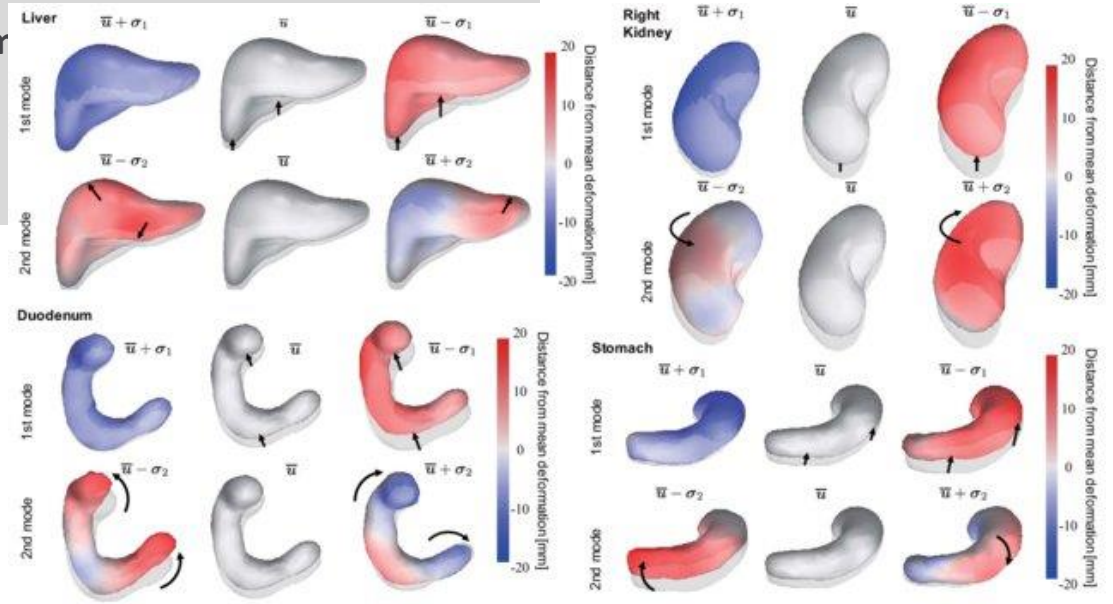
- α/β ratio of 10 is typically used for tumors.
- α/β ratio of 3 is typically used for normal tissues.

3. Some remaining challenges for clinical use of FLASH (VHEE) therapy

ACCURACY FLASH have to compete with modern RT techniques

1. Large volumes
2. Reference dose
3. Beam monitoring
4. Multiple beams to achieve conform
5. Daily fractionation
6. Patient / Tumor positioning
7.





Nakao & al. (2019). Statistical Deformation Reconstruction Using Multi-organ Shape Features for Pancreatic Cancer Localization.

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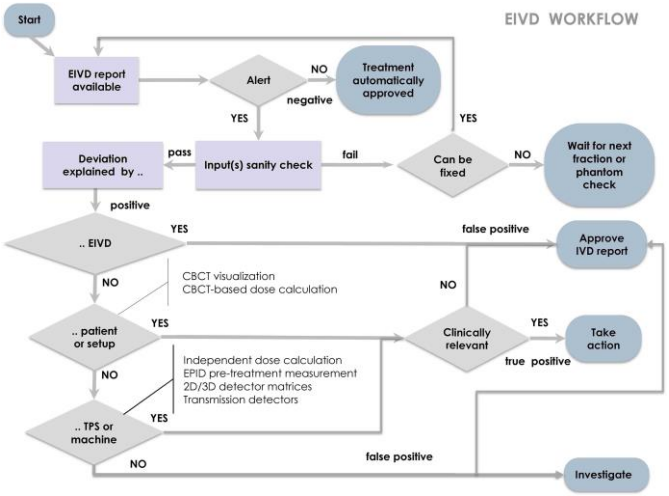
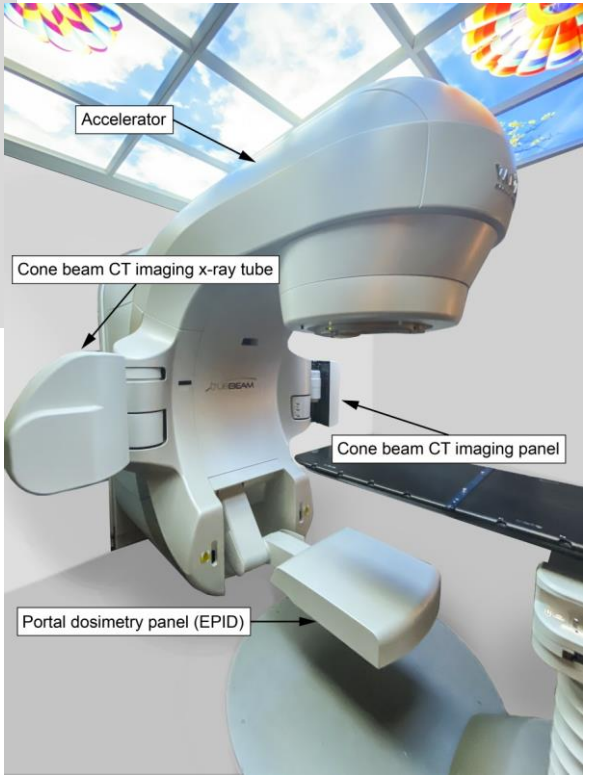
ACCURACY FLASH have to compete with modern RT techniques

1. Large volumes
2. Reference dose
3. Beam monitoring
4. Multiple beams to achieve conformational dose distribution
5. Daily fractionation
6. Patient / Tumor positioning
7. In-vivo dosimetry
8. …





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GREAT HOPES…
BUT A LOT TO THINK ABOUT!

Thank you for your attention

This project (18HLT04) has received funding from the EMPIR programme co-financed by the Participating States and from the European Union's Horizon 2020 research and innovation programme.