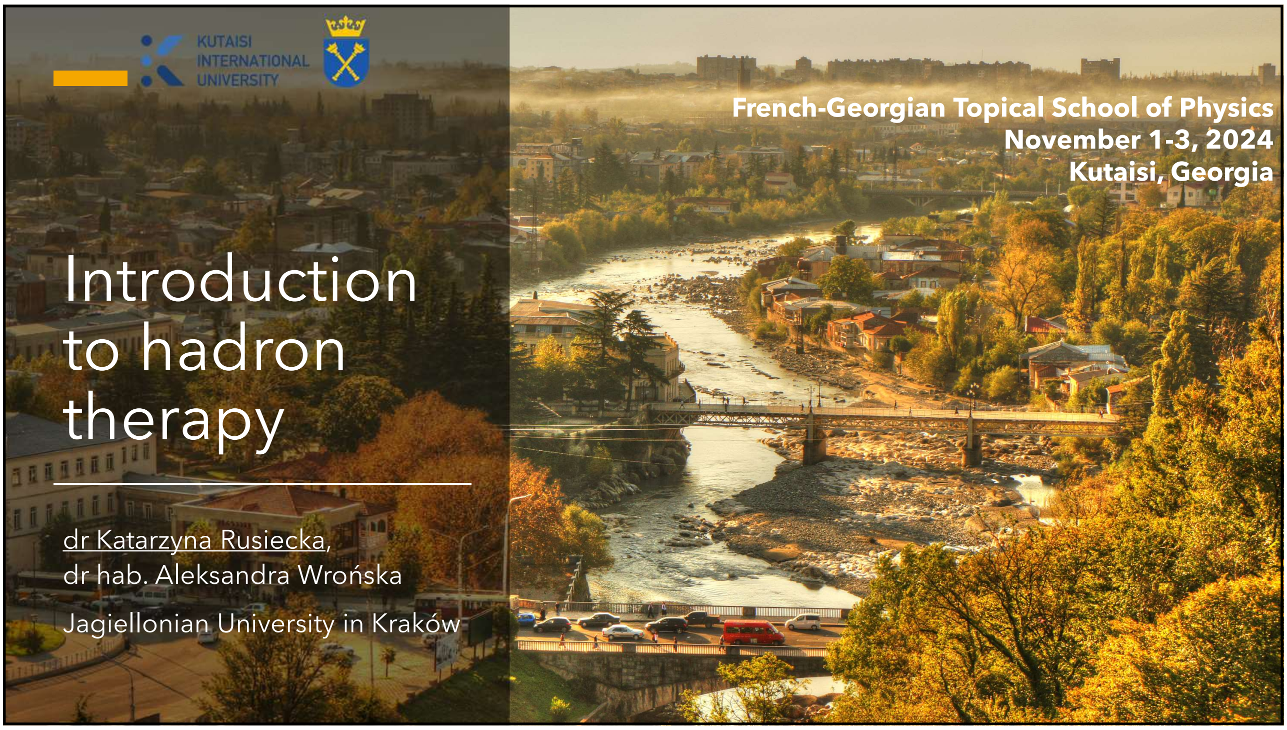
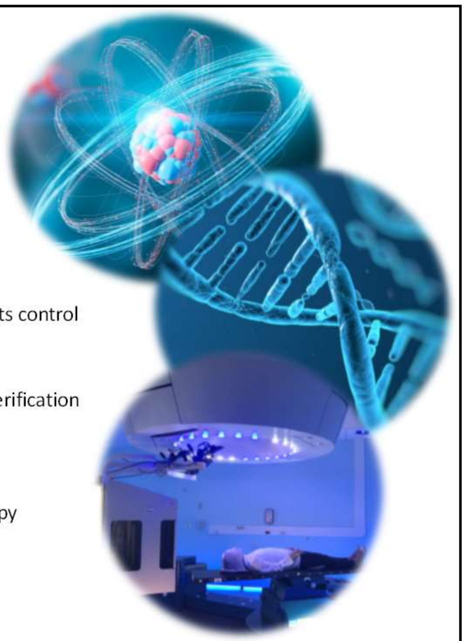


1

Outline

Yesterday…

- **Context**
  - Cancer as societal problem
  - Cancer treatment methods and their limitations
- **Physical rationale**
  - Interaction of ionizing radiation with matter
  - Pioneers of proton therapy
- **Biological aspects**
  - Biological effects of irradiation
  - Basic definitions
- **Technologies**
  - Accelerators for hadron therapy
  - Irradiation modes
  - Different ion species
  - Simulations of the interaction of particles with matter
- **Clinical procedures**
  - Clinical workflow
  - Treatment planning
  - Quality control
  - Patient positioning and its control
- **Emerging techologies**
  - Real-time beam range verification
  - FLASH
  - Adaptive therapy
  - Proton radiography
  - Big data in hadron therapy
  - Mini beams



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3

Clinical workflow

- Diagnostics and qualification for treatment
- Preparation of immobilization systems, virtual simulations, CT scanning
- Determination of target volumes and organs at risk
- Determination of the therapeutic dose and fractionation
- Preparation of treatment plan: geometry, optimization
- Dosimetric verification
- Resimulation
- Irradiation

FGTSP 2024, Introduction to hadron therapy, K. Rusiecka 4

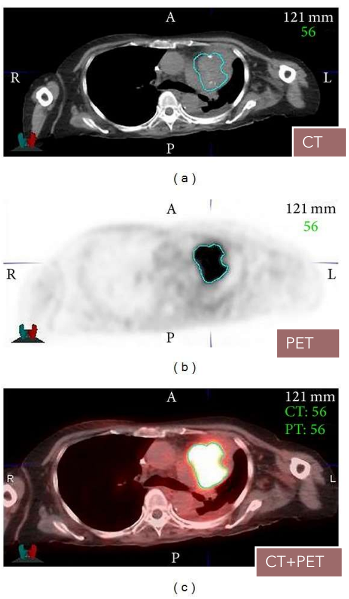
Patient immobilization

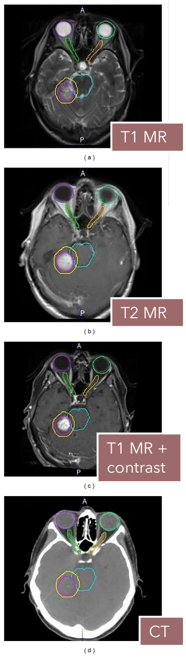
https://rtmedical.com.br/immobilization-devices-for-radiotherapy/?lang=en
https://www.nl-tec.com.au/product/bionix-securevac-cushion-vacfix-vacbags-vacuum-bag-vac-vacqfix-vac-cushion/
https://www.orfit.com/radiation-oncology/products/stereotactic-radiotherapy-solutions

Before irradiation – imaging

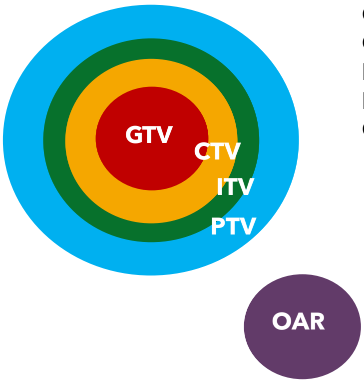
- Basic imaging modality for treatment planning: computed tomography (CT)
  - response of tissues to X-rays
  - 3D, voxelized map of a patient
  - needs to be translated to response to ions → ucertainties
  - improvement: dual energy CT
- Auxiliary imaging modalities:
  - positron emission tomography (PET) – metabolism
  - magnetic resonance imaging (MRI) – better contrast than CT
- Goal: segmentation and contouring
  - organs at risk
  - tumour volume
  - target volume

https://doi.org/10.1155/2014/231090





Treatment planning

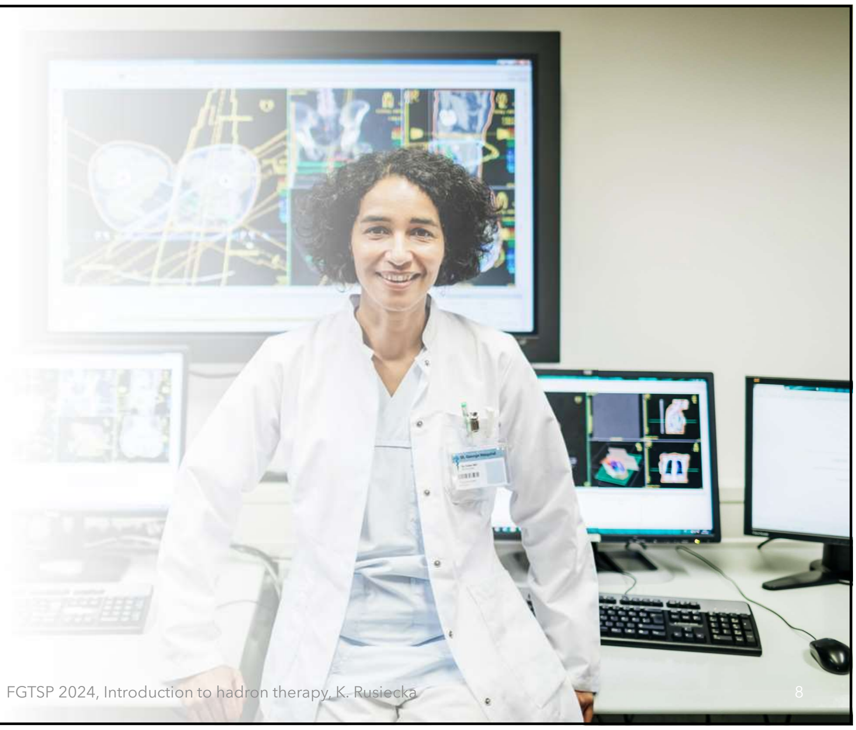


GTV – gross target volume – tumor volume visible in medical imaging
CTV – critical target volume – GTV + sublinical/invisible invasion
ITV – internal target volume – CTV + internal margin for organ motion
PTV – planning target volume – ITV + setup margin
OAR – organ at risk

<u>Requirements:</u>
- PTV – 95% of the prescribed dose should cover at least 98% of the volume
- CTV – 100% of the prescribed dose should cover 98% of the volume
- Not more than 2% of PTV covered with dose larger than 107% of prescribed
- OARs should be considered first!

Quality control

- Daily checks of the beam delivery systems: dose delivery repeatability, radiation field parameters, beam spot characteristics
- Weekly checks: Bragg peak profile
- Before irradiation: treatment plan verification
- Before irradiation: patient positioning



Irradiation

- Irradiation divided into fractions
- Typically, approx. 2 Gy per fraction
- For proton therapy approx. 10^8 protons per beam spot in 10 ms
- Irradiation itself lasts only a few minutes

DOI:10.1186/s13014-017-0835-7
DOI: 10.1016/j.ejmp.2018.10.002

Issue of patient motion

Tumours in certain locations cannot be immobilized (e.g. lungs)

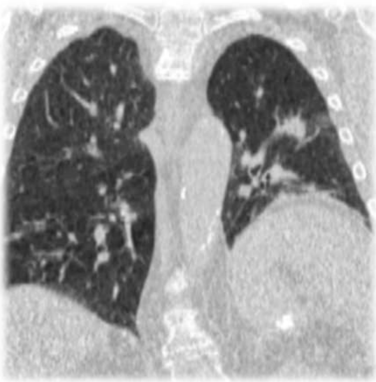
Interplay effect between the moving scanning beam the the moving tumour

Various strategies:

- *breath-hold*; discomfort for a patient
- *gating* (irradiation only in certain phases of breathing); takes longer
- *repainting* – multiple irradiation of each voxel with reduced beam intensity within a single fraction
- *tracking* – adjusting the lateral beam position to the current position of the target voxel;

Prerequisites:

- A good model of organ/tumour motion
- 4D CT (limited time resolution, only beam-off)
- 4D CBCT
- 4D MRI
- Optical systems
- Fiducial markers



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Hadron therapy – precision therapy

NuPECC report „Nuclear Physics for Medicine", 2014

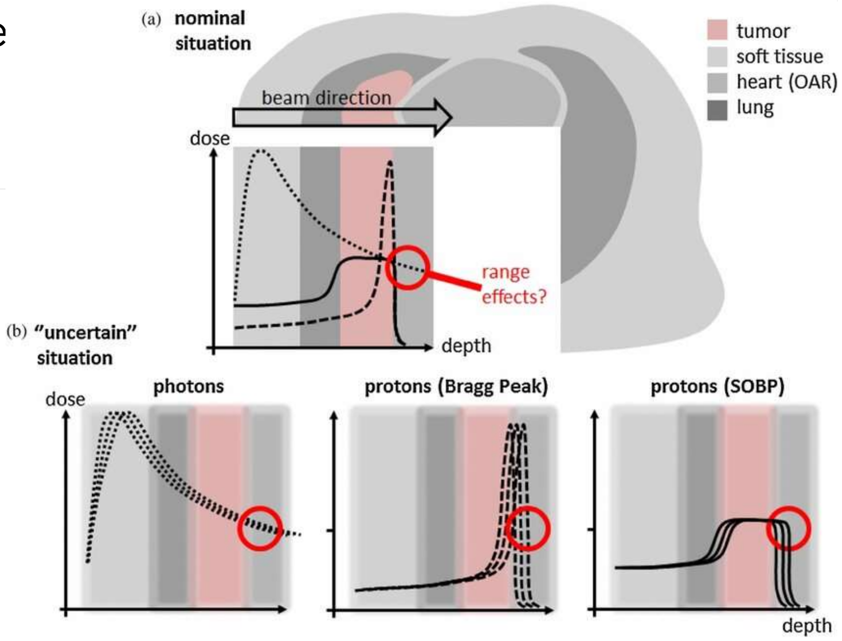
- Presence of Bragg peak and steep slope of dose distribution – benefit/issue
- Tumours located close to critical organs (spinal cord, brain step) need precision in dose delivery
- IBT has many sources of uncertainties
- Clinical practice: range uncertainty → need to comprimise dose conformality and treatment safety (safety margins)
- „In vivo range verification methods would represent an optimal solution for full exploitation of the advantages afforded by the ion beam"
  - Reduction of safety margins, better treatment plan
  - Potential to treat new patient categories

Source of range uncertainty in the patient	Range uncertainty
Independent of dose calculation:	
Measurement uncertainty in water for commissioning	± 0.3 mm
Compensator design	± 0.2 mm
Beam reproducibility	± 0.2 mm
Patient set up	± 0.7 mm
Dose calculation:	
Biology (always positive)	+ 0.8%
CT imaging and calibration	± 0.5%
CT conversion to tissue (excluding I-values)	± 0.5%
CT grid size	± 0.3%
Mean excitation energies (I-values) in tissue	± 1.5%
Range degradation; complex inhomogeneities	- 0.7%
Range degradation; local lateral inhomogeneities*	± 2.5%
Total (excluding *)	**2.7% + 1.2 mm**
Total	**4.6% + 1.2 mm**

DOI: 10.1088/0031-9155/57/11/R99

12

Consequence of of range uncertainties



DOI:10.1088/0031-9155/58/15/R131

1-cm cavity appears:

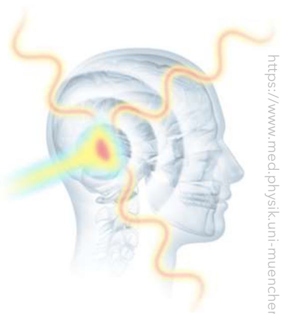
- Photons: dose larger by 5%
- Protons: Bragg peak moves by 1 cm

Runny nose??

Methods of hadron therapy monitoring

Idea: exploit by-products of patient irradiation with ion beam:

- **Protons**
  - forward-peaked
  - modified by tissue on the way out
  - feasible only for C-ion beams
- **Neutrons**
  - forward-peaked,
  - difficult to detect,
  - modified by tissue on the way out
- **β+ emitters** (consequently 511-keV gamma pairs)
  - PET - well established technology
  - tissue transparent for gamma quanta
  - large detectors
- **γ radiation**
  - Prompt Gamma Imaging – emerging technology
  - tissue transparent for gamma quanta, even more than for those from annihilation (higher energies)
  - various imaging modalities



https://www.med.physik.uni-muenchen.de/

What does hadron therapy monitoring mean?

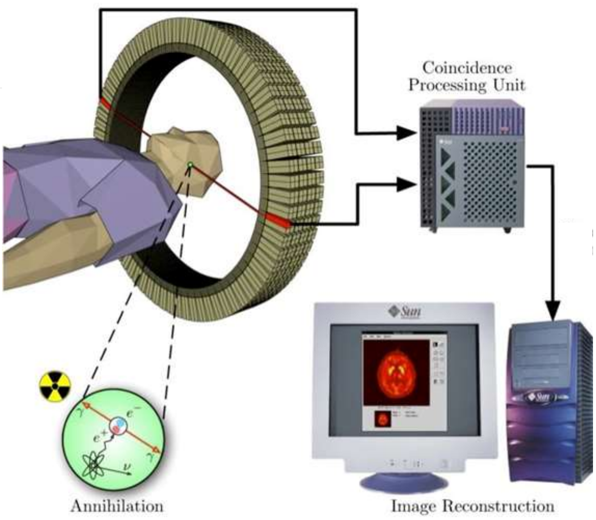
Different possible goals:

- check if the deposited dose distribution agrees with the predicted one (1D, 2D, 3D?)
- check if the Brag peak position is located in the clinical target volume
- check if the Bragg peak position is located where predicted by treatment plan
- …

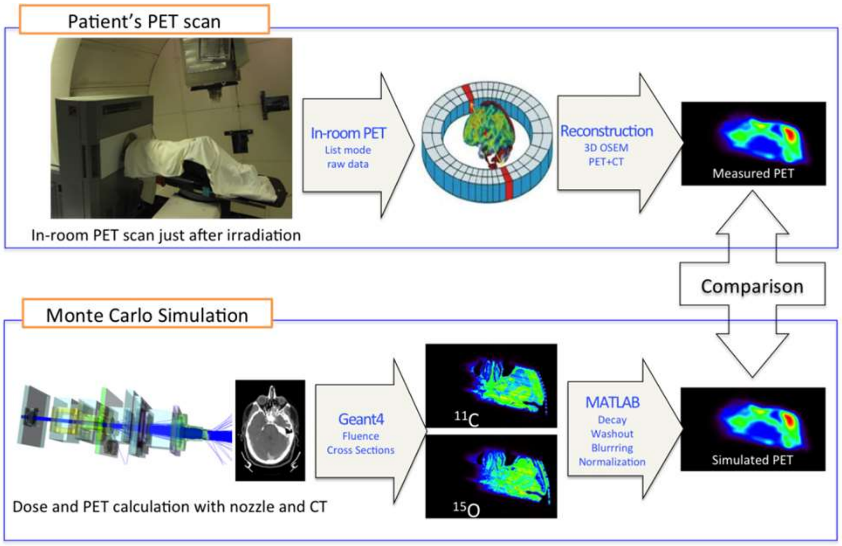
PET for online monitoring of hadron therapy

- Beam protons interact with tissue nuclei
- Some of them transmute into instable nuclei – β+ emitters, and decay emitting positrons
- Those positrons anihilate with tissue electrons, emitting two back-to-back 511-keV gamma quanta
- Those gamma quanta can be detected
- After detection of many of such pairs, 3D image can be reconstructed
- PET technology, but radioactivity produced in patient by the beam, not delivered from outside

https://jens-maus.de/ftp/langner_mscthesis.pdf



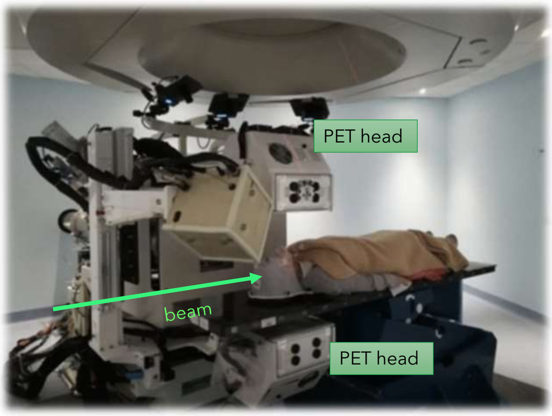
PET for online monitoring of hadron therapy



https://gordon.mgh.harvard.edu/research/pet-monitoring-of-therapy/

PET for online monitoring of hadron therapy

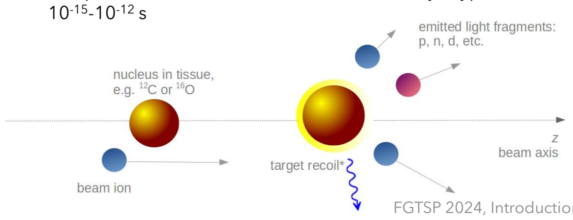
- Main problems of the method:
- β+ emitters are relatively long lived (up to a few minutes!)
- effect of biological washout
- production cross section is not very large
- commercial PET scanners have too small acceptance to collect sufficient statistics in reasonable time
- large acceptance, dedicated scanners needed
- incompatible with gantries
- Break-through project of CNAO
  Ferrero et al. DOI: 10.1038/s41598-018-22325-6

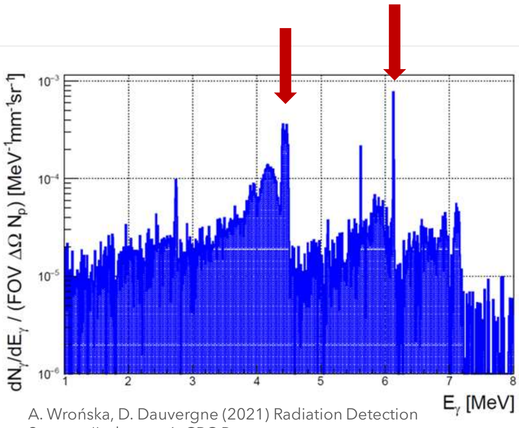


Fischetti et al., DOI: 10.1038/s41598-020-77843-z

Methods based on prompt gamma imaging

- Beam protons interact with tissue nuclei
- Some of the nuclei get excited
- When they de-excite, they emit their characteristic gamma radiation
- Its yield depends on proton energy, thus is spatially correlated with depth
- Detection of this radiation (including position and energy) gives insight into beam range
- The process is much faster than with β+ decays, typical times 10^{-15}-10^{-12} s





A. Wrońska, D. Dauvergne (2021) Radiation Detection Systems II, chapter 6, CRC Press

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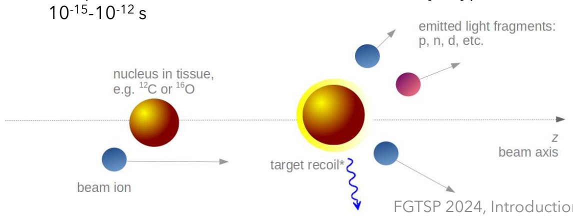
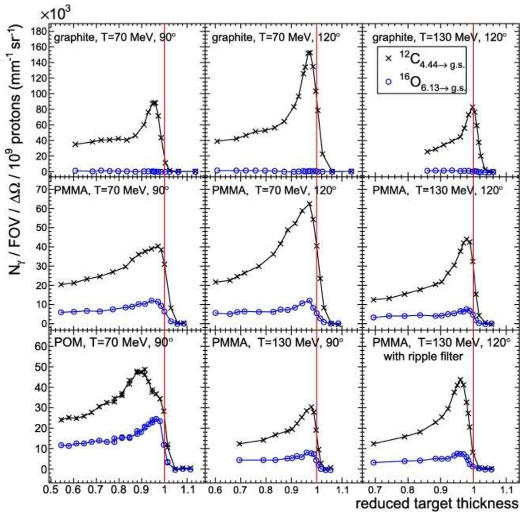
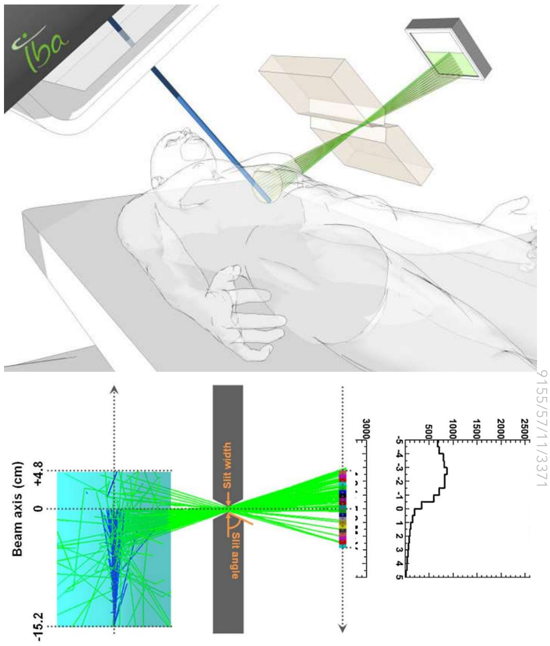




https://doi.org/10.1016/j.ejmp.2017.01.003

Prompt-gamma imaging 1D

- A slit camera developed at Dresden/Rossendorf
- First PGI approach tested clinically on a patient
- 1D projection of gamma yield → 1D projection of dose profile
- Beam range determination ±2 mm

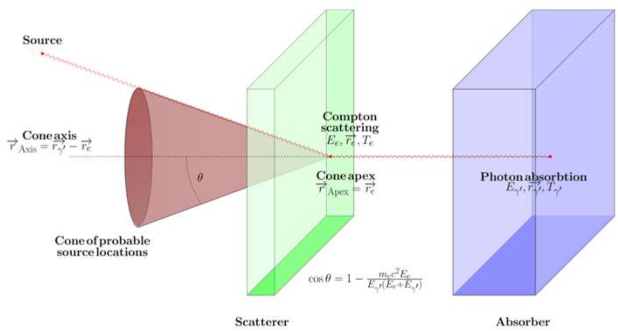


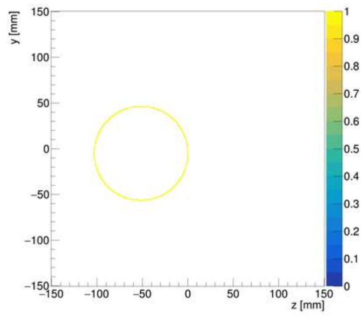
Richter et al, DOI: 10.1016/j.radonc.2016.01.004 Smeets et al, DOI: 10.1088/0031-9155/57/11/3371

Prompt-gamma imaging 3D

- Two-module detector: Compton camera
- Aim: register a Compton-scattering event, positions and energies in both layers, reconstruct Compton cone
- Superimpose intersections of many of such cones → 3D image
- No prototype feasible to work at close-to-clinical beam intensities and exposures
- At JU the SiFi-CC project: https://bragg.if.uj.edu.pl/sificc

https://publications.rwth-aachen.de/record/856966





https://youtu.be/lN3pB7IZbLA?si=e2eYjDQFf70-ZwJj

FLASH effect

- reported case: mini-pig
- irradiation with electron beams
- Vozenin, DOI: 10.1158/1078-0432.CCR-17-3375

- **FLASH radiotherapy** is the delivery of **ultra-high dose rate** radiation several orders of magnitude higher than what is currently used in conventional clinical radiotherapy.
- **FLASH effect**: the ultra-high dose rate radiation reduces the normal tissue toxicities while still maintaining local tumor control.
- This effect can be seen typically for dose rates larger than **40 Gy/s**.
- Effect independent on the radiation type, present also in IBT.
- Term FLASH coined in 2014 by V. Favaudon et al.

FLASH vs conventional radiotherapy

Parameter	FLASH delivery	Conventional delivery
Mean dose rate	≥ 40 Gy/s	≤ 1 Gy/min
Delivery time	< 200 ms	> 1 min
Dose delivery	High dose in a single fraction	Low dose in a single fraction
Tumour control	Effect similar as in conv. delivery	Effective tumour killing
Normal tissue sparing	Damage to healthy tissues reduced	Acute and late damage to healthy tissues
Defects	Early stages of development / new facilities 2019 – first human patient 2023 – first clinical trial	Radiation injury, limited treatment window

FLASH effect - mechanism

The biological/biochemical background not quite clear.

- **Oxygen depletion** hypothesis assumes that FLASH RT, due to water radiolysis, creates hypoxic environment in healthy tissue, making it less radiosensitive. Hypothesis widely believed at first, however, recent (2023-24) research show that this is not likely to be the dominating mechanism.
- **Blood volume** – as blood flows through the irradiated volumes, less blood volume is irradiated in FLASH. Blood carries, aside of oxygen, also immune cells. Blood cells are largely spared in FLASH (5-10% damage) comopared to conventional (90-100% damage). Also, proinflammatory signalling is reduced in FLASH.
- Adult **stem cells** reside in so-called niches. They are essential in recovery from certain cancer types. Studies showed that hypoxic stem cell niches are preserved more readily through FLASH RT. In CONV, the surrounding of stem cells is damaged, they can become oxygenated and thus more radiosensitive.

Hughes, DOI: 10.3390/ijms21186492
Rudigkeit, DOI: 10.1038/s41598-024-51951-6

FLASH with protons – scarce data

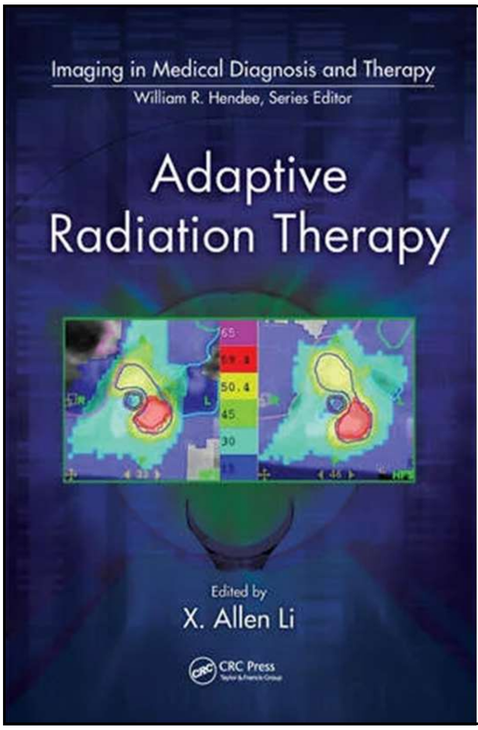
Summary of outcomes in in vivo studies comparing FLASH and conventional dose-rate PBT.

Model	Dose (Gy)	FLASH Dose-Rate (Gy/s)	Outcome
Zebrafish embryo	0–43	100	No survival difference
Mice (thorax)	15/17.5/20	40	Normal tissue protection with FLASH
Mice (thorax)	15/17.5/20	40	Normal tissue protection with FLASH
Mice (abdomen)	15	78	Normal tissue protection with FLASH
Mice (local intestinal)	18	78	Normal tissue protection with FLASH
Mice, orthotopic engrafted Lewis lung carcinoma (thorax)	18	40	Improved tumor control with FLASH, increased T-lymphocyte tumor infiltration
Mice, pancreatic MH641905 flank tumor	12/15	78	No difference in tumor control
Mice, FaDu head, and neck squamous cell carcinoma transplantation	17.4	$>10^9$	No difference in tumor control

FLASH = a very promising option, stay tuned next years!

World-class players: Varian, IBA and Mevion invest in the development of FLASH PBT machinery and research

Hughes, DOI: 10.3390/ijms21186492



Adaptive proton therapy

- Radiation therapy is usually planned based on a single image set
- Patient anatomy is assumed not to change much, and his/her position with respect to the system is controlled with X-ray imagers
- But patients do change their anatomy
- and so change the tumour shapes and volumes,
- for certain locations, also tumour positions may change
- Adaptive radiation therapy aims to take this into account

Adaptive proton therapy

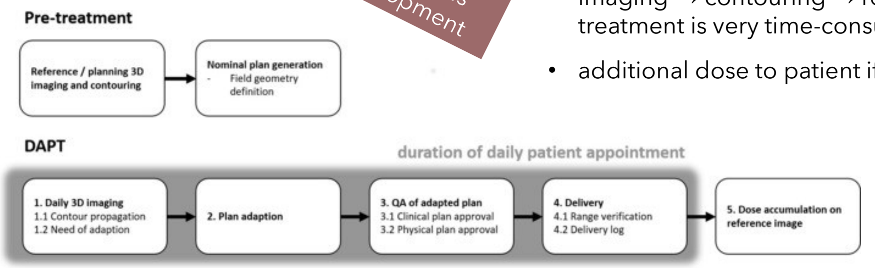
Benefits:

- TPS tailored on a daily basis to patient current geometry
- Reduction of CTV possible when tumour shirinks
- Smaller total delivered dose
- Safer treatment

Difficulties:

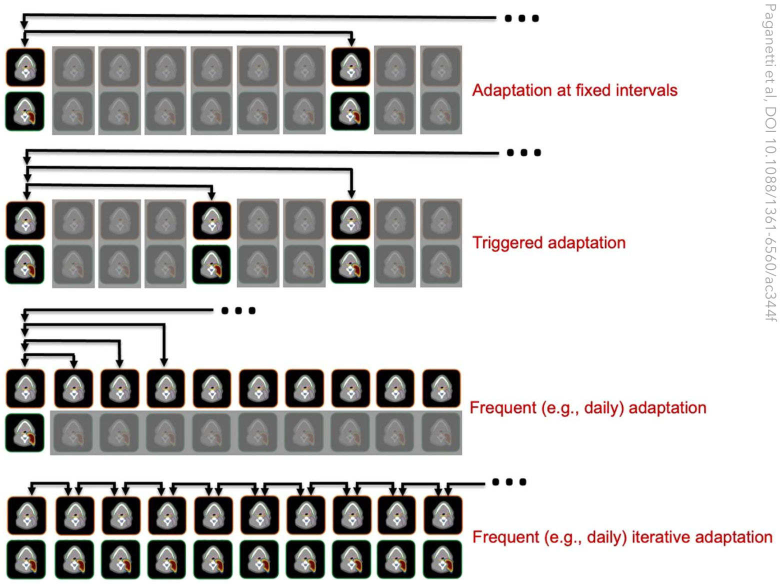
- daily workflow of imaging → contouring → re-planning → verification → treatment is very time-consuming!
- additional dose to patient if dedicated CT scans taken daily

Different strategies with different goals under development



DOI: 10.1259/bjr.20190594

Adaptive proton therapy



Paganetti et al. DOI 10.1088/1361-6560/ac344f

https://raptor-consortium.com/

Proton radiography – better imaging for hadron therapy

CT is the golden standard as input for TPS

But: CT is a response of tissue to X-rays.

Translation of HU $\rightarrow -\frac{dE}{dx}$ is a source of uncertainty.

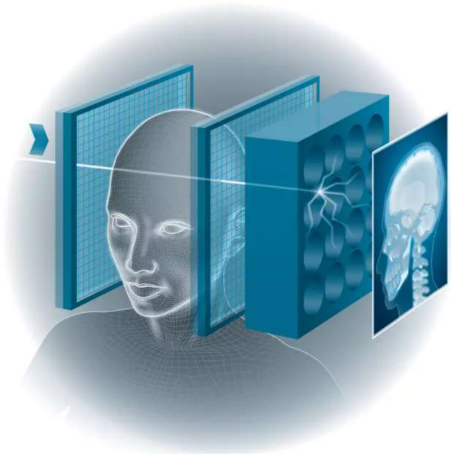
Could we eliminate it...?

Use protons for imaging!

Protons must have enough energy to penetrate through a patient (more than for therapy!)

A monoenergetic proton field impinges onto a patient and is registered on the other side, for each proton its energy is also measured.

A 2D image can be obtained from a single geometrical setting, but also – from a series of measurements from different angles – a 3D tomographic image can be reconstructed.



https://protonvda.com

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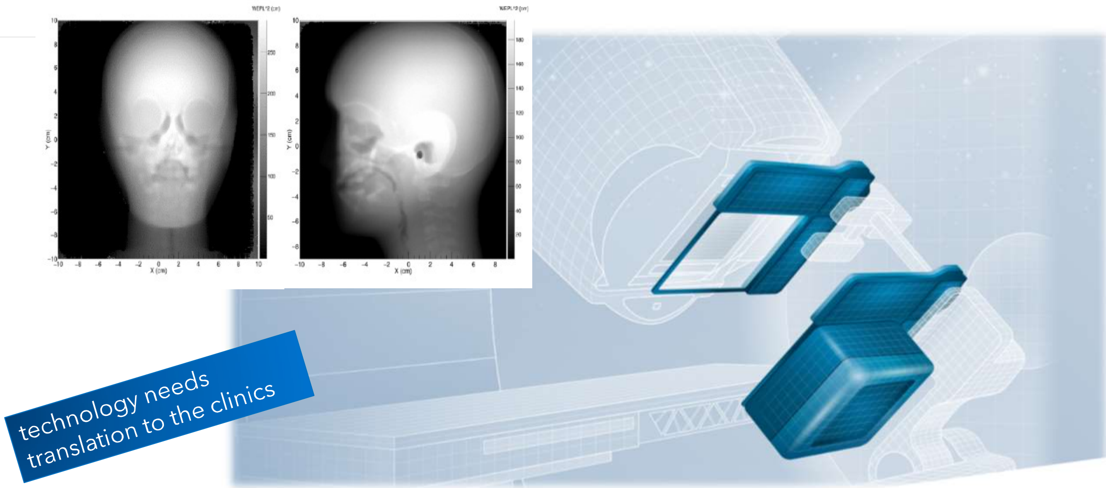


https://protonvda.com

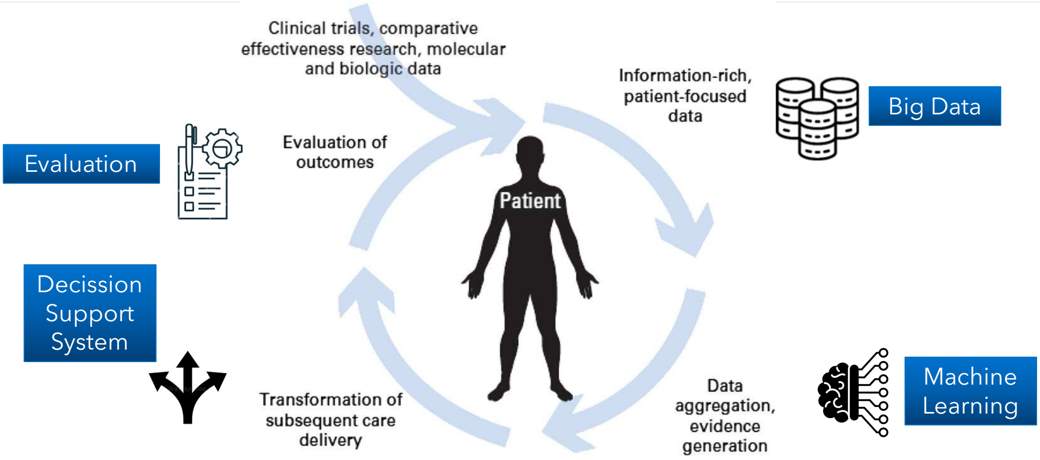
Big data in hadron therapy

- Goal: personalized medicine
- Status: Evidence-based medicine uses randomised trials, assuming homogenous population ☹
- How to take into account individual parameters?
  - patient biology
  - pathology
  - medical images
  - blood test results
  - given medication
  - dose in organs at risk
  - dose in target volume
  - fractionation
  - genomic data

many parameters
limits of human cognitive capacity

predictive modeling using Big Data

Big Data in hadron therapy



adapted from van Wijk et al., Advances in Particle Therapy CRC Press

Big Data in hadron therapy

adapted from van Wijk et al., Advances in Particle Therapy CRC Press

Evaluation

Evaluation using robust data to test if outcome as expected

Decission Support System

- ❑ Support for physicians, tumour board and patient in choosing treatment options;
- ❑ Information about tumour control, rate of metastases, complication probability, overall survival, cost-effectiveness

- ❑ volume
- ❑ velocity
- ❑ variety
- ❑ veracity

- ❑ format
- ❑ de-identification
- ❑ centralization

Initiatives like RLHC, CancerLinQ, EuroCAT

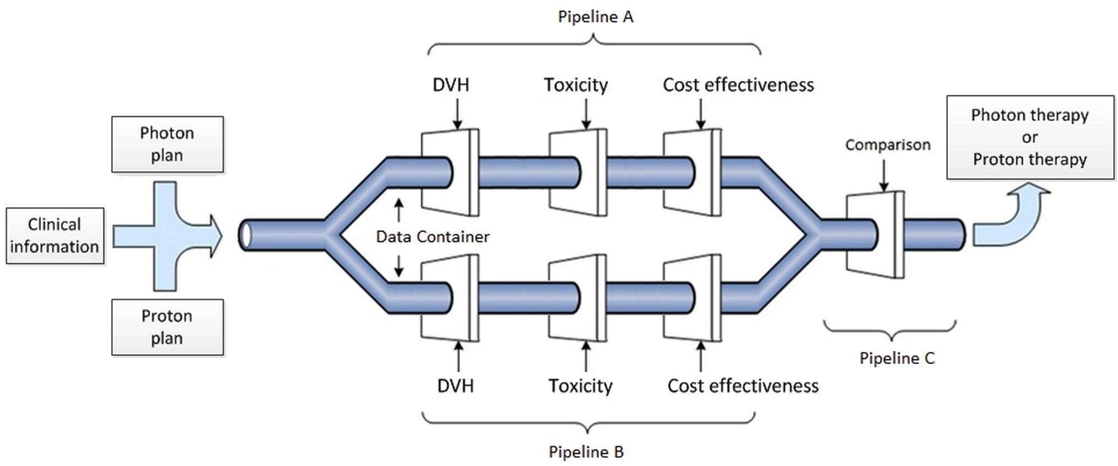
Big Data

Predictions on:
- ❑ tumour control
- ❑ complication risks

Machine Learning

Maastro, https://www.youtube.com/watch?v=nQpqMluHyOk

Big Data in hadron therapy

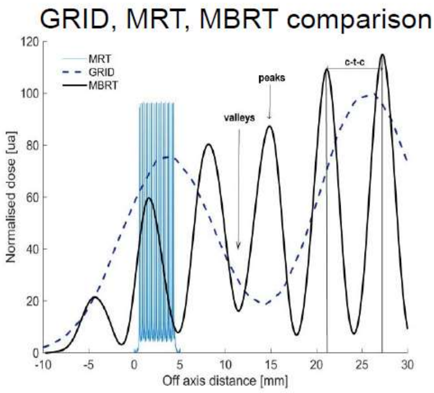


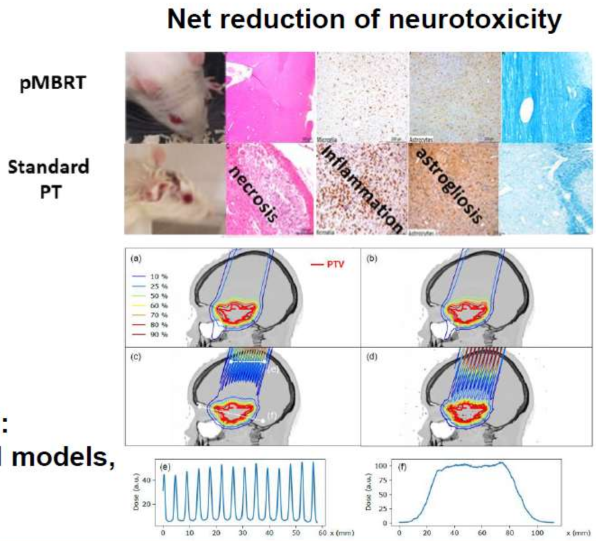
Cheng et al, doi: 10.1016/j.radonc.2015.12.029

Proton mini-beams

by Samuel Meyroneinc

Proton mini-beams at Institut Curie (Courtesy Ludovic De Marzi -Institut Curie)





Developments for a clinical trial:
Clinical softwares, dosimetry, biological models, optimisation algorithms…

Questions?

Thank you for your attention!

Katarzyna Rusiecka
katarzyna.rusiecka@uj.edu.pl
Jagiellonian University