

Application of accelerators on living matter: therapeutic strategies with innovative radiotherapies

Atelier "Accélérateurs, Recherche et Société"

GdR SCINEE, SCIPACS et MI2B

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➤ Introduction to radiation therapy for cancer treatment

- **Introduction to cancer treatment**
- **Use of ionizing radiation** : physical interactions and radiobiological aspects on living matter

➤ Therapeutic strategies in radiation therapy

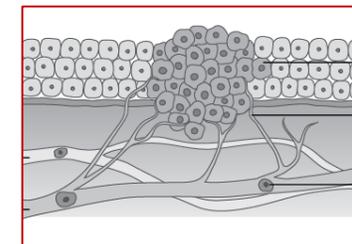
- **Conventional external beam radiation therapy (EBRT) and limitations**: technological evolution improving the dose conformation to the tumor with **X-ray beams**
- **Use of different particles: Hadrontherapy** (protons, carbon ions...), high energy electrons (**VHEE**), neutrons...
- **Play on dose delivery**: temporal fractionation of the dose, very-high dose-rate radiation (**FLASH** therapy), spatial fractionation of the dose (**Grid, MBRT, MRT**)
- **Combined radiotherapies (with molecular vector): radionuclide therapy** (alpha targeted therapy), **BNCT**, **nanoparticle-enhanced** radiotherapy...

➤ Summary

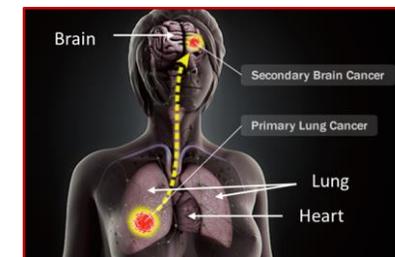
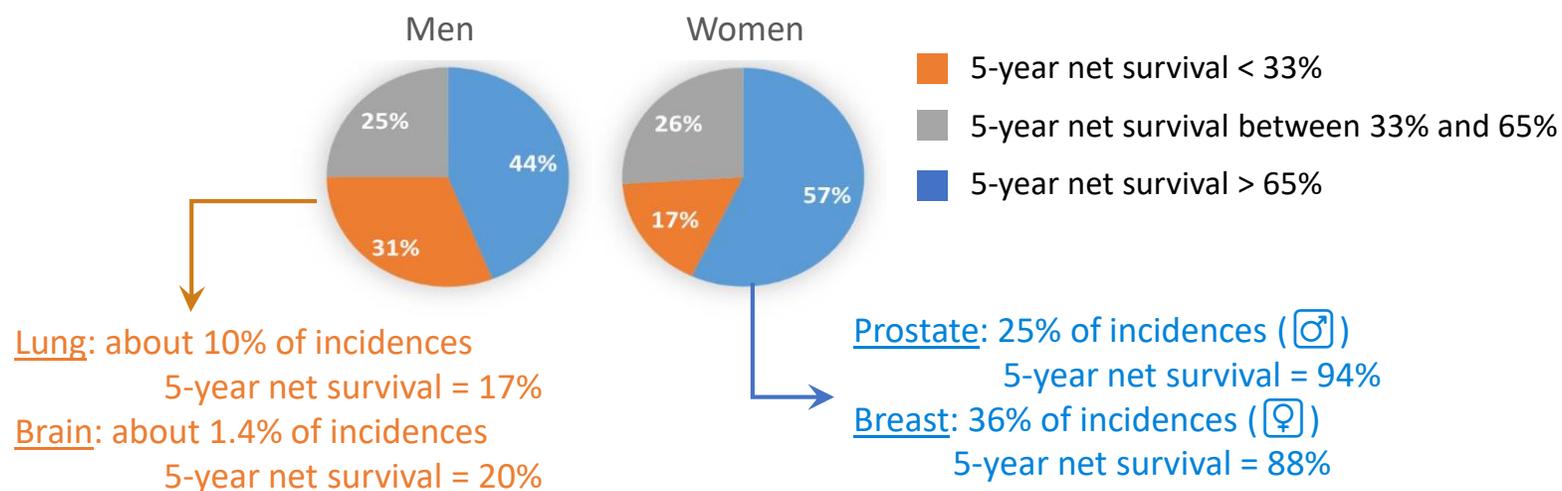
Introduction on the use of ionizing radiation on living matter

Introduction: Cancer figures for France

- Population aging → First cause of death in France
157 400 deaths in 2018 (over ~430 000 new cases per year, <https://www.e-cancer.fr/>)
- **Significant progress in prevention**, early diagnosis and treatment:
Mortality rate: **-18%** between 2005 and 2018
- **Heterogeneity between different cancers:** stage (local, growth, metastasis...), locations and cancer types



Cancer = abnormal cell division. Becomes a tumor with blood vessel recruitment



Tumor cell propagation (lymphatic, blood) → metastasis

➔ **Cannot exist only one universal cancer treatment.**

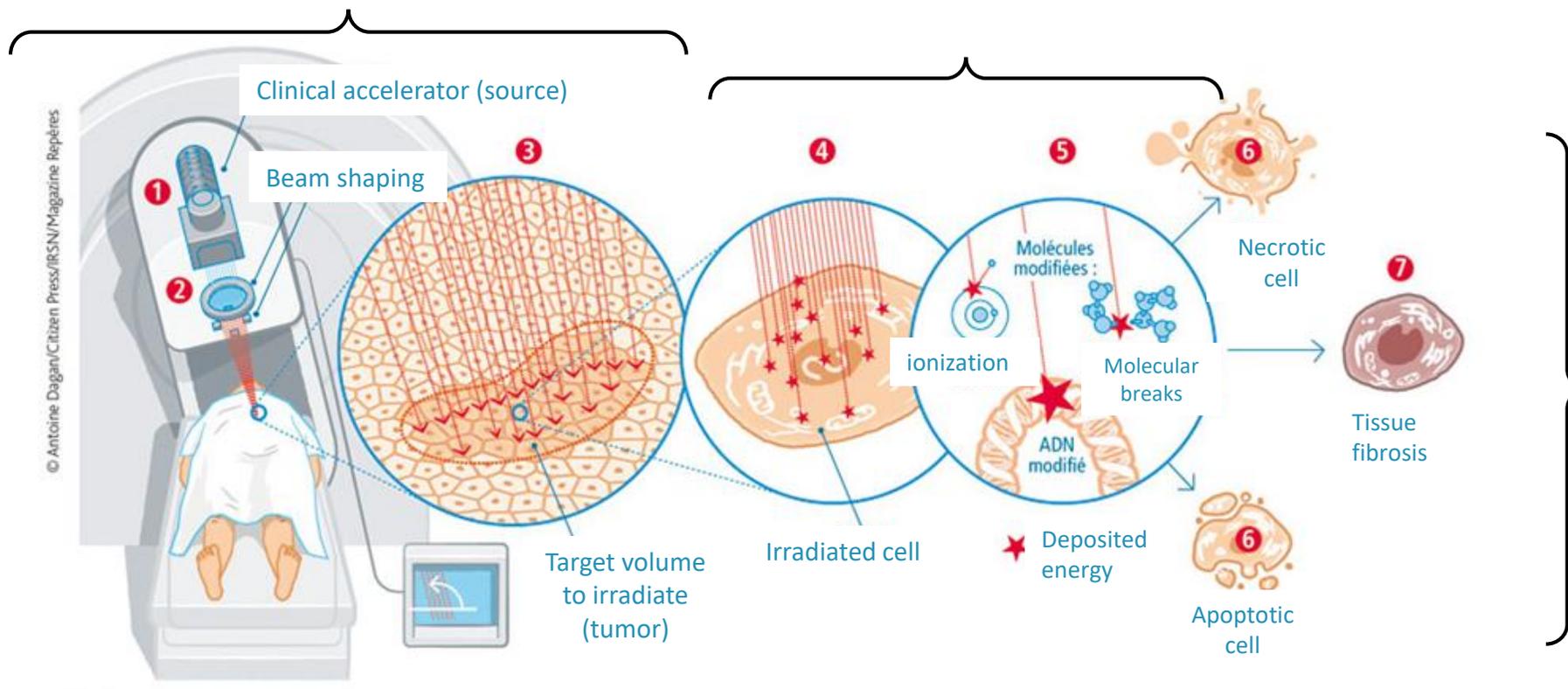


**Ionizing radiations
= Radiotherapy**
Use in ~60% of cancer treatment cases

Use of ionizing radiation: (external) radiotherapy (RT) principle

Tumor irradiation with a radiation beam
(X-ray, electrons, protons...)

Energy deposition by radiation in tissues
→ Alterations to molecules, DNA, cells and eventually tissues



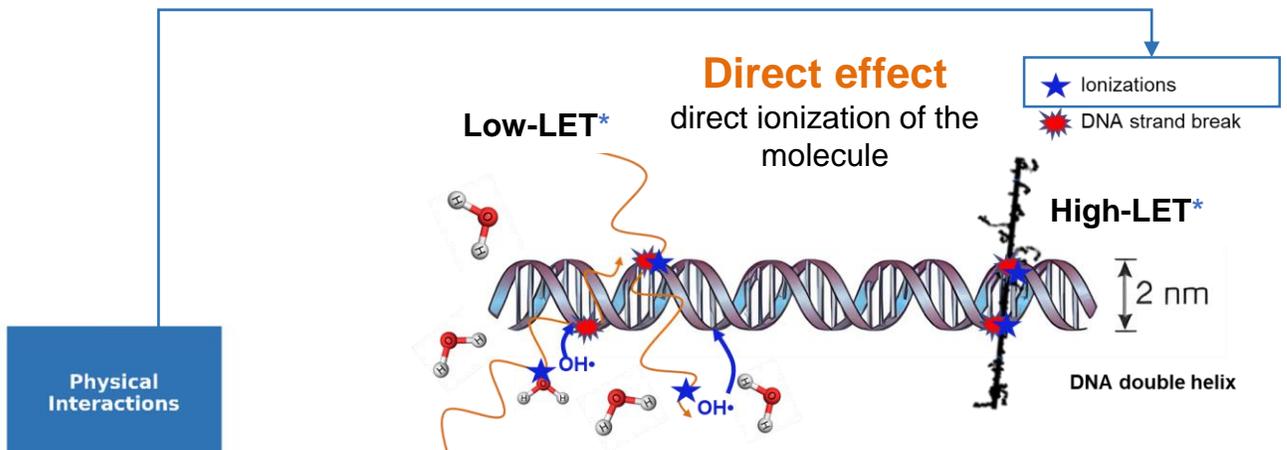
Radiotherapy challenge:

Guaranty treatment efficacy while limiting side effects.

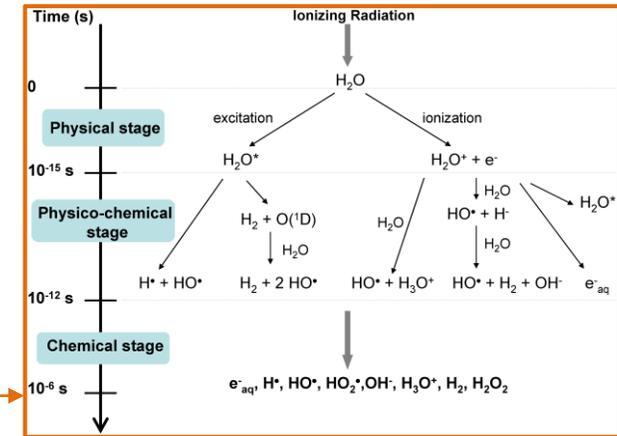
Different treatment strategies to be as selective as possible (kill "only" cancer cells)

Use of ionizing radiation: from physical to biological effects

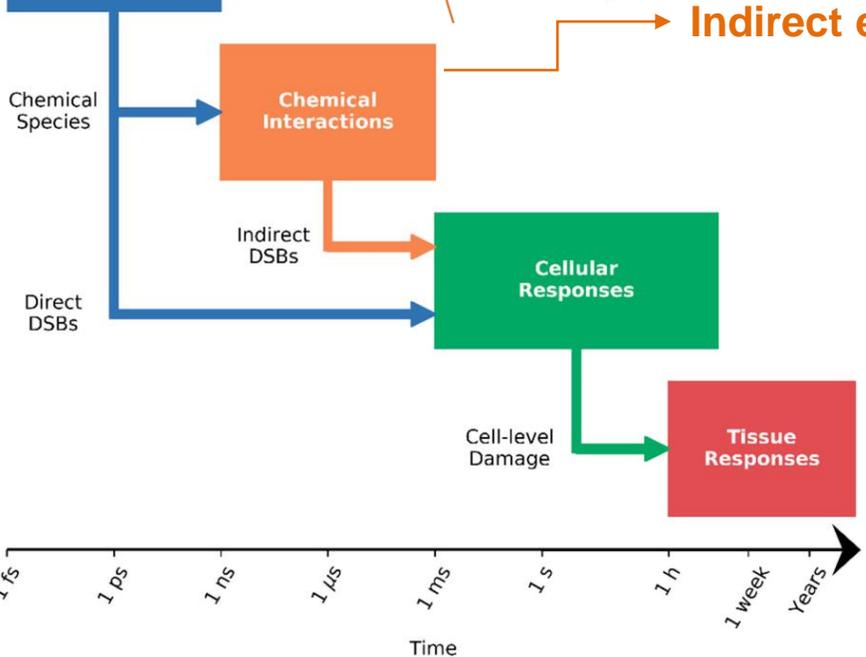
*LET = Linear Energy Transfer



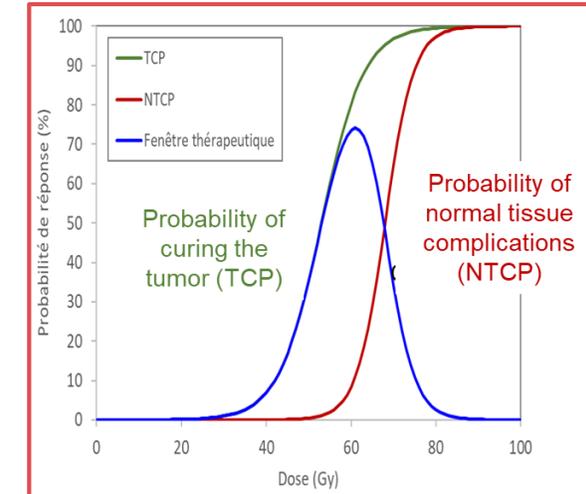
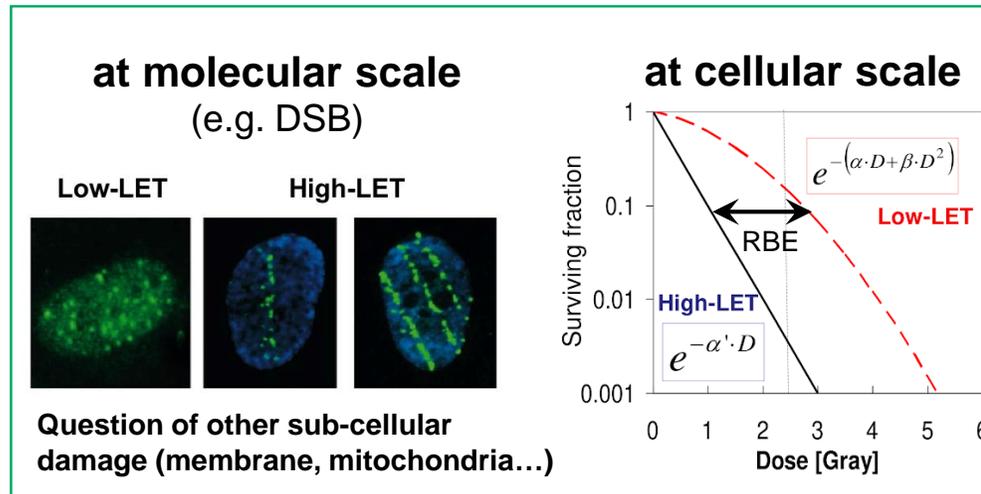
Water radiolysis:
creation of reactive chemical species (OH•, H₂O₂, e⁻_{aq}...) that will interact with organic molecules



+ tumor microenvironnement, immune response...



Biological damage



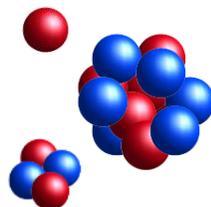
➤ Types of particles used in radiation therapy

○ Uncharged particles :

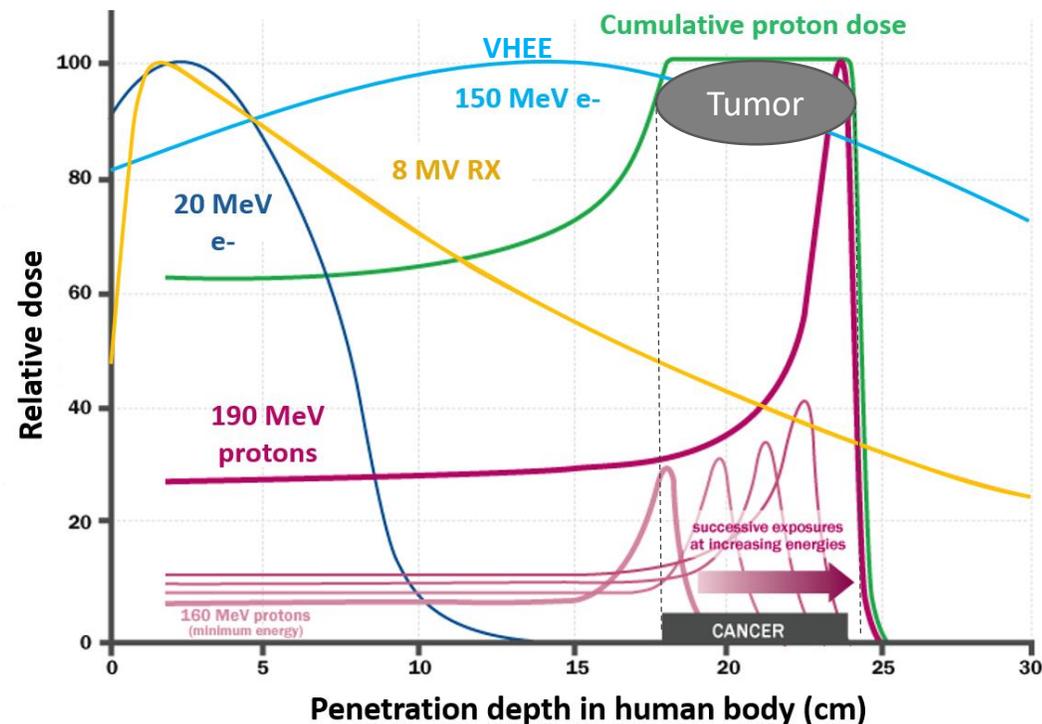
- **Photons (X-rays, γ)** ~ 1 MeV
vast majority of treatments (> 95%)
- **Neutrons** epithermal (< 10keV)

○ Charged particles

- **Clinical Electrons (or β)** < 20 MeV
- **Very-high energy electrons (VHEE),** ~ 70 -300 MeV
- **Protons** < 200 MeV
- **Carbon ions** < 4800 MeV (400 MeV/n)
- **α particles** $\sim 5 - 9$ MeV



Typical depth-dose profiles
for mono-incident beams delivering a dose to the tumor

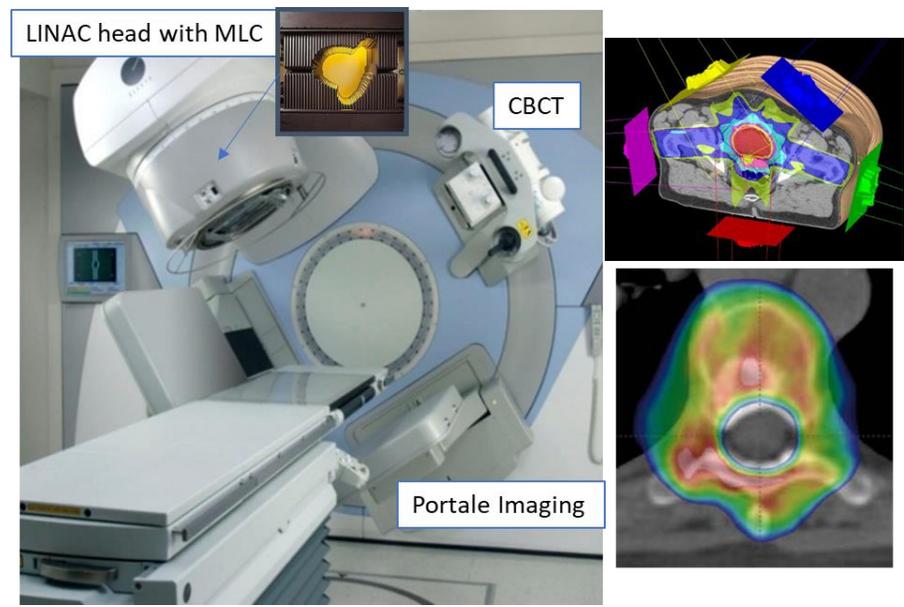


Therapeutic strategies in radiation therapy

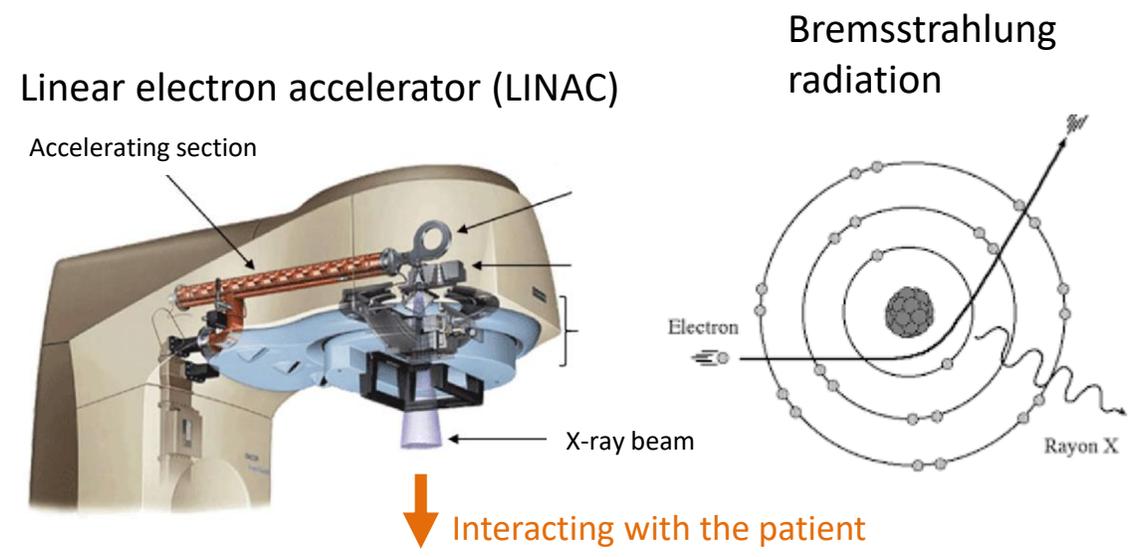
Conventional external beam radiation therapy (EBRT) and
limitations

« Conventional » external beam radiotherapy (EBRT)

➤ X-rays EBRT (~95% of all RT treatments)



Standard clinical accelerator (IMRT, VMAT) with embedded imaging systems



Typical treatment characteristics:

Particles: X-rays 6-25 MV (all tumors), electrons 3-25 MeV (surface)

Time fractionation: 2 Gy/session, 5 session/week

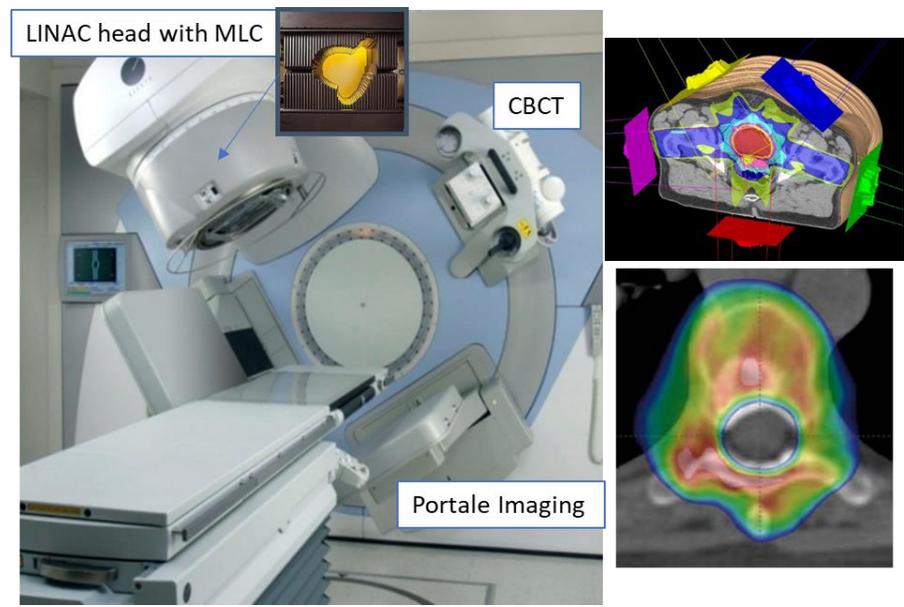
Dose: 40-70 Gy

Dose rate: 30-70 mGy/s (2 Gy/min)

Field sizes: 2 - 40 cm² (homogeneous dose coverage)

« Conventional » external beam radiotherapy (EBRT)

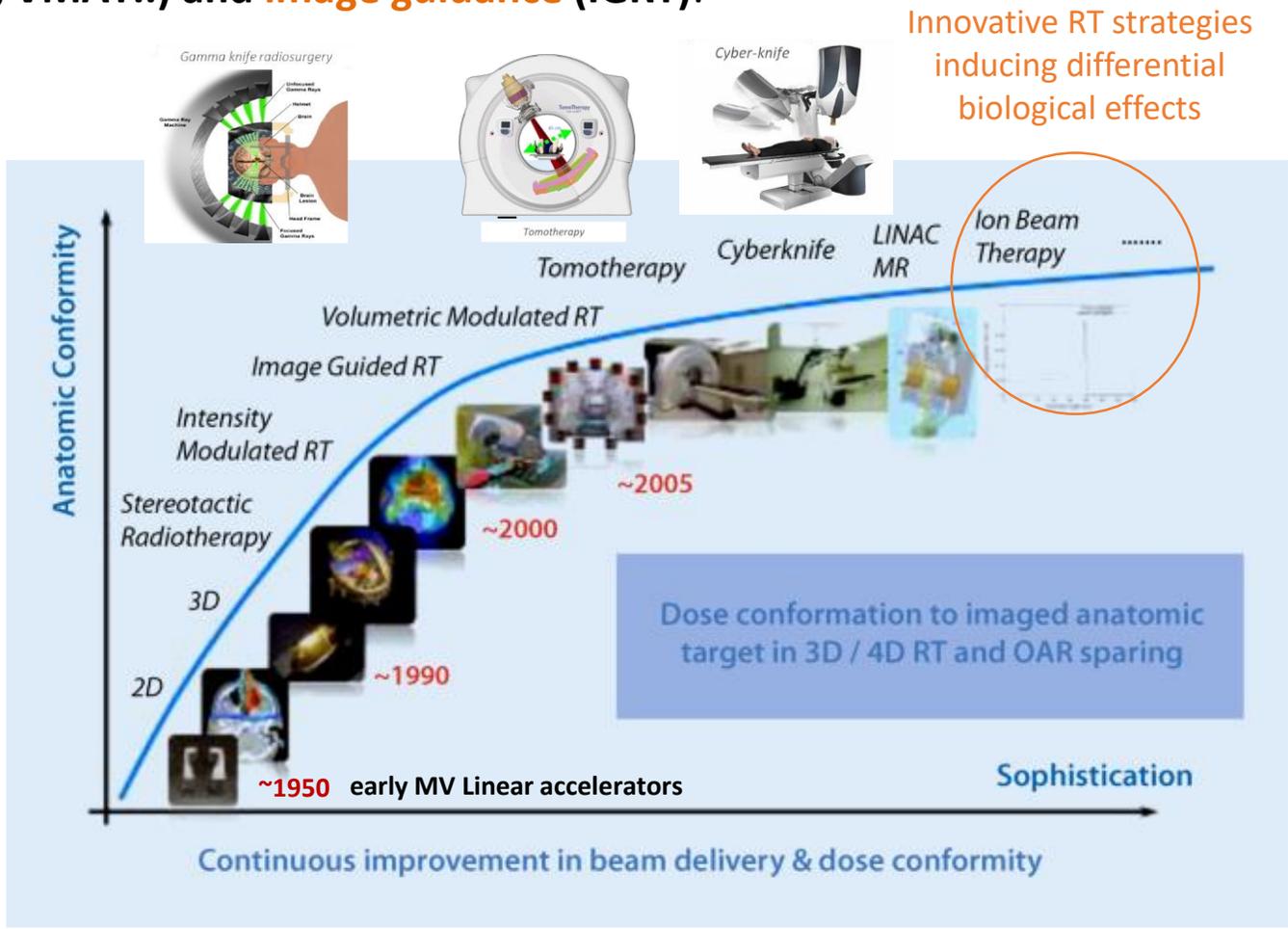
➤ **X-rays EBRT** (~95% of all RT treatments) improved the dose conformation to the tumor through advanced techniques of **radiation intensity modulation** (IMRT, VMAT..) and **image guidance** (IGRT):



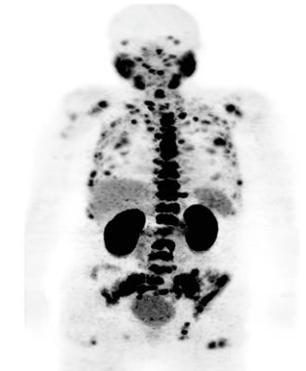
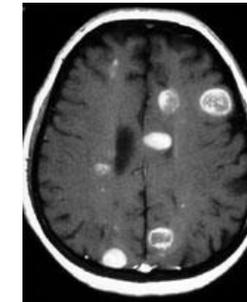
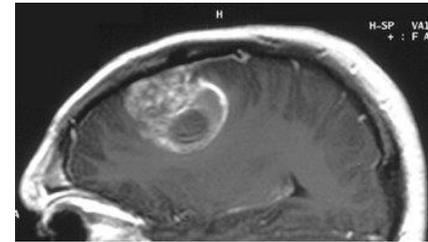
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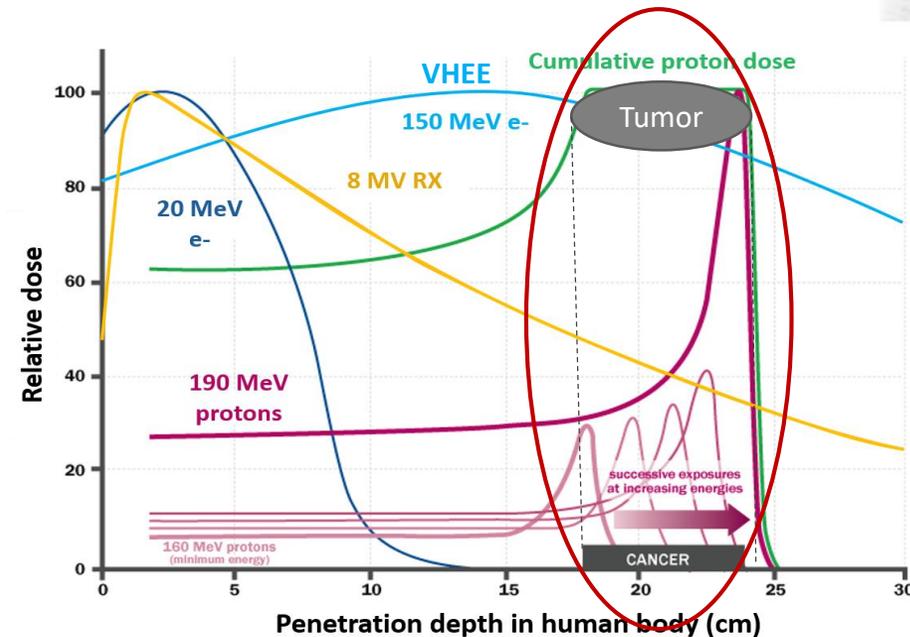


- The **toxicity to healthy tissue** still limits the dose delivered and the curative use of RT :
 - In particular for very **radioresistant, bulky and diffuse cancers** (e.g. glioblastoma...), and for **non-localized tumors** (multiple metastasis)



- **How to improve the treatment?**
 - Induce a more efficient tumoral irradiation
 - **High-LET particles:** hadrontherapy (p, α , ^{12}C , ions)

- **Protons**  < 200 MeV
- **Carbon ions**  < 4800 MeV (400 MeV/n)



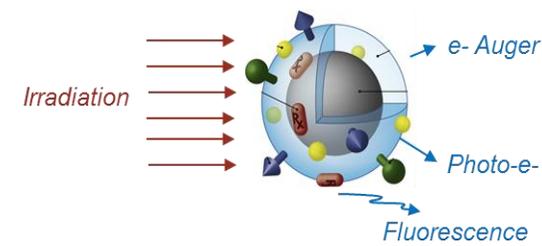
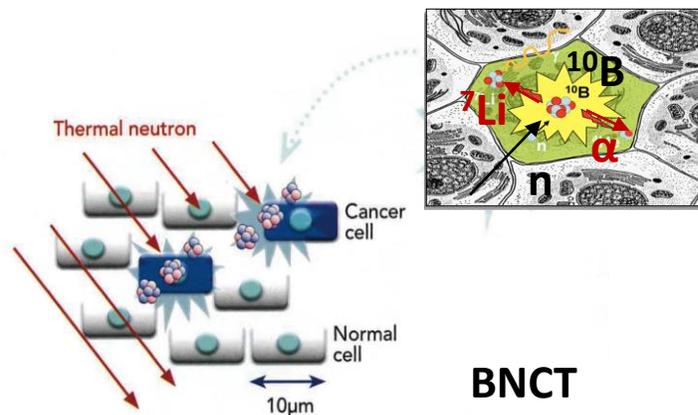
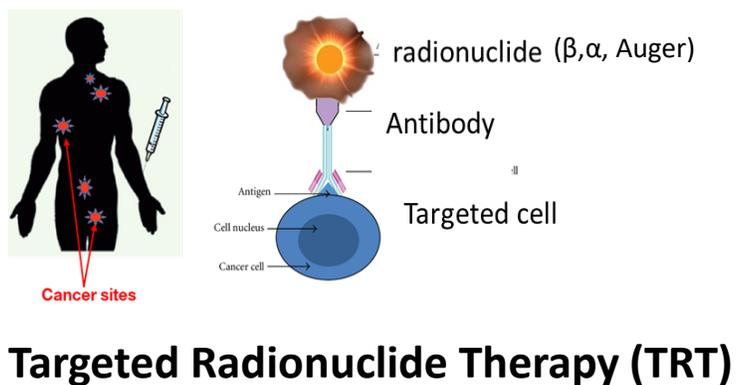
Limitations and other therapeutic strategies

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	α -TRT	BNCT	NP
Radionuclide/particle	^{223}Ra , ^{225}Ac , $^{212/213}\text{Bi}$, ^{211}At , ^{212}Pb ...	$^{10}\text{B}/^{11}\text{B}$	e- (PE, Auger)
Energies α (et ^7Li) or e-	5-9 MeV	0.8-1.7 MeV	0-100 keV
Range α (and ^7Li) or e-	40 –100 μm (<i>few cells</i>)	5 –9 μm (<i><cell</i>)	0-100 μm
LET (<i>keV/μm</i>)	60 – 100	≥ 200	0.5-20

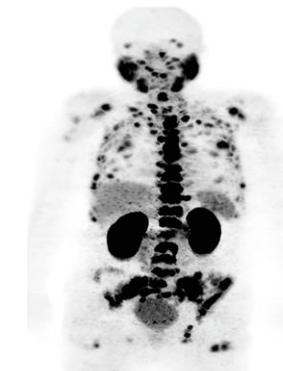
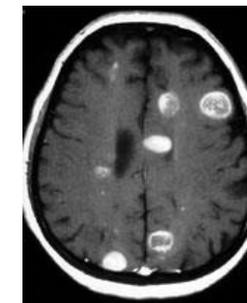
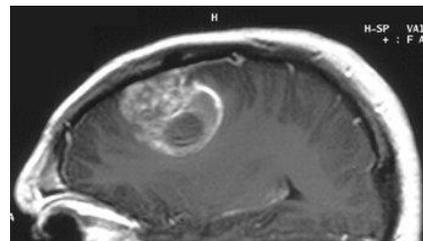
- **How to improve the treatment?**

- Induce a more efficient tumoral irradiation
 - **High-LET particles:** hadrontherapy (p , α , ^{12}C , ions)
 - **Targeted radiotherapies** (using molecular targeting or sensitizers)+**high-LET:** radionuclide therapy (TRT), BNCT, nanoparticles...



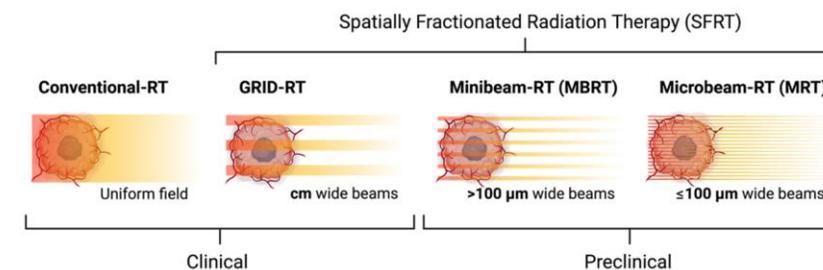
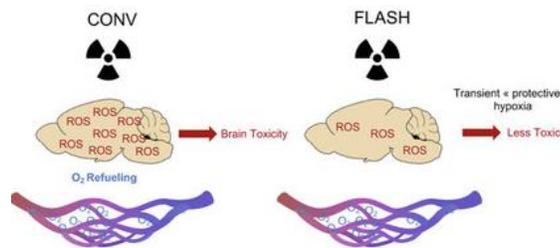
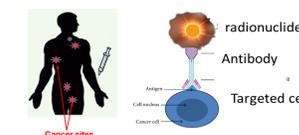
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➤ How to improve the treatment?

- Induce a more efficient tumoral irradiation
 - **High-LET particles:** hadrontherapy (p, α, ¹²C, ions)
 - **Targeted radiotherapies** (using molecular targeting or sensitizers)+**high-LET:** radionuclide therapy (TRT), BNCT, nanoparticles...
- Preserve the healthy tissues:
 - **Improve ballistics** with different particle/energy/molecular targeting: **hadrontherapy, VHEE, TRT (α /Auger)**
 - **Dose delivery mode:** spatial fractionation of dose (**SFRT**) (beam size < mm), Ultra-high dose-rate (UHDR, "**FLASH**" effect)



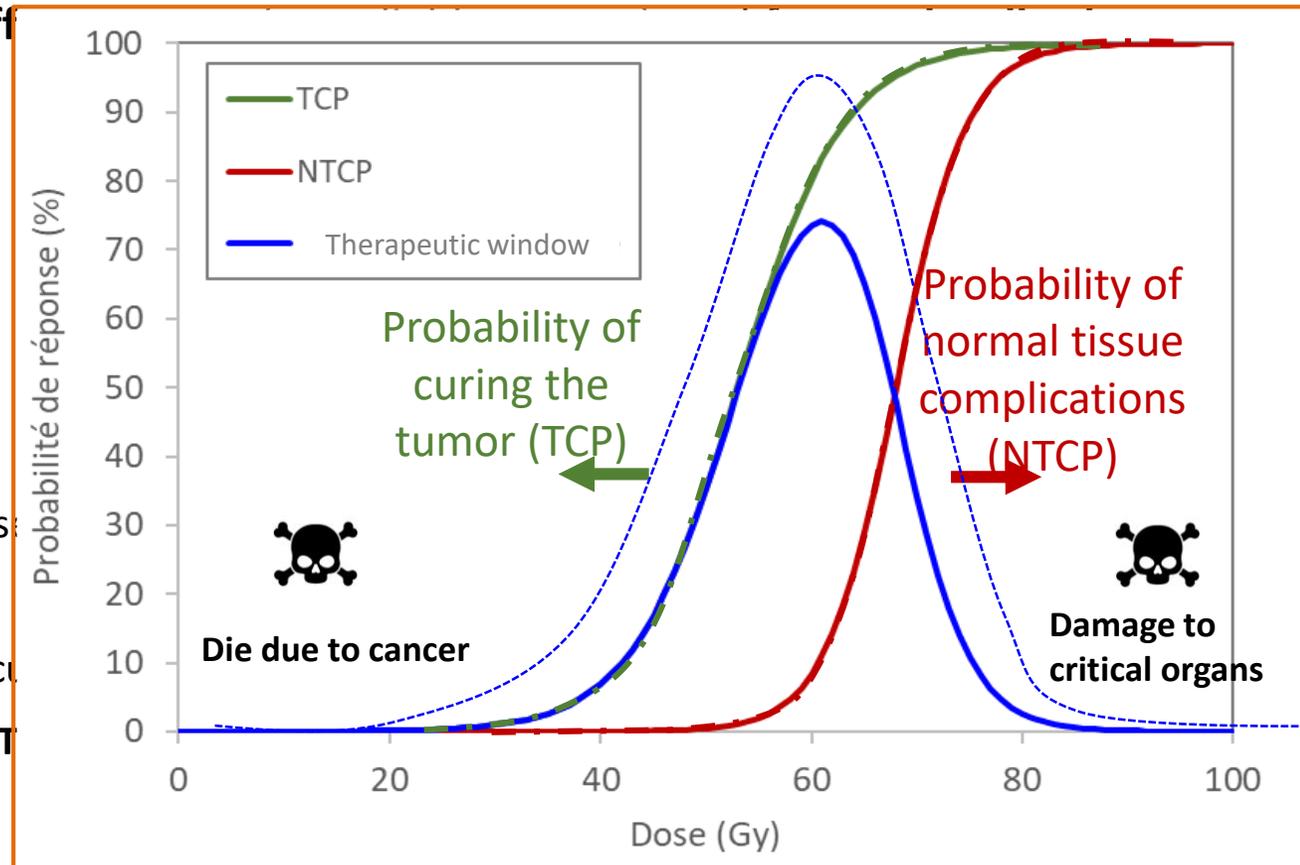
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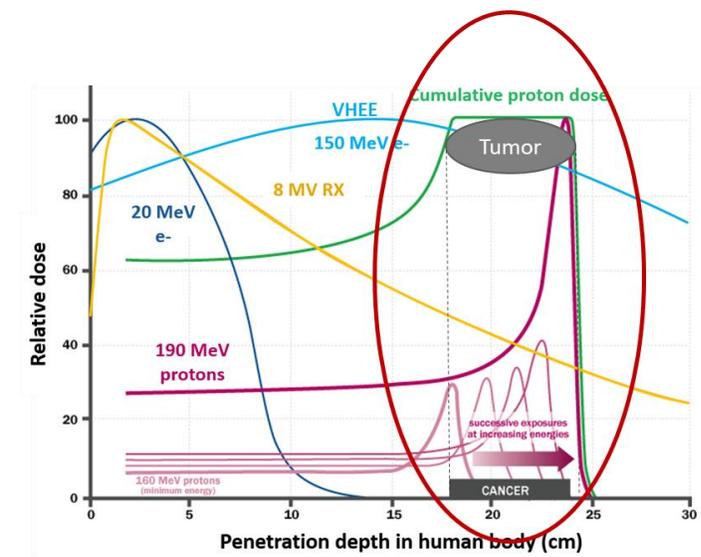
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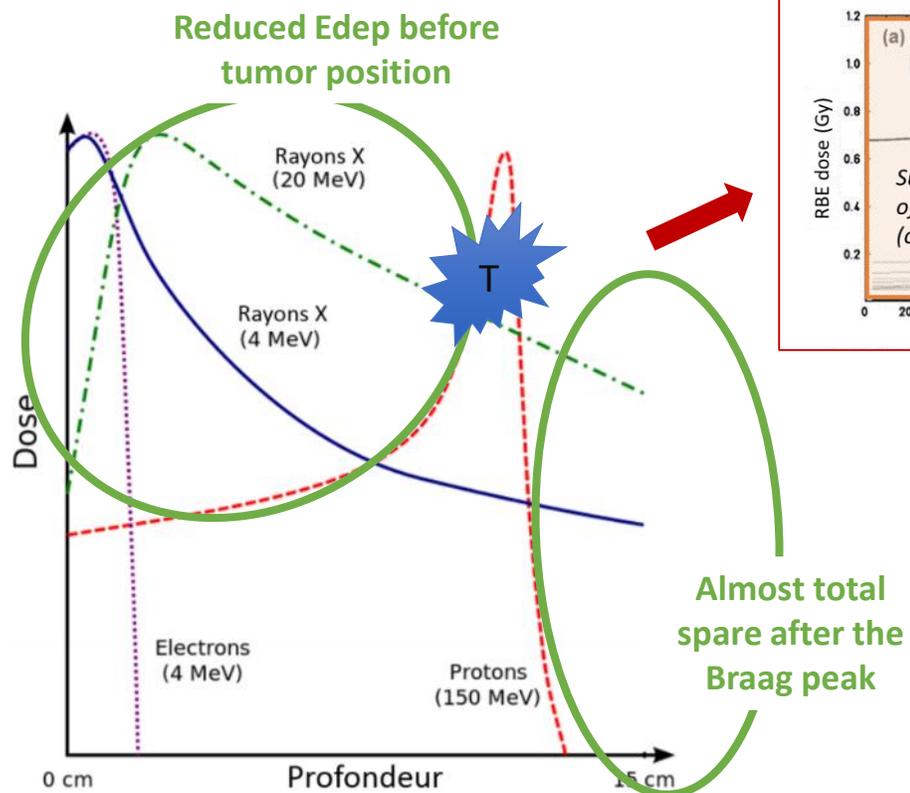
➔ Play on physical parameters to induce a different biological effect

Hadrontherapy

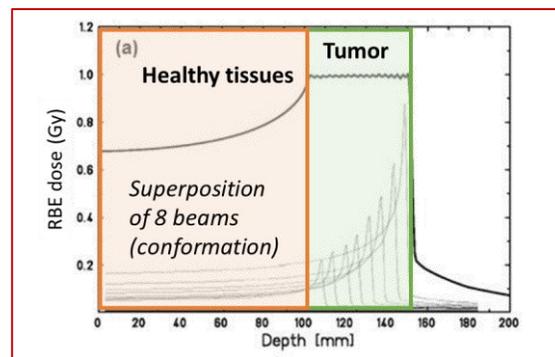
Protons, He, Carbon or heavier ions



Hadrontherapy: Ballistic advantage over photons

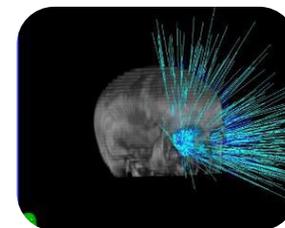
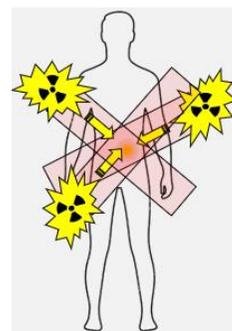


Source: Robin Fabbro thesis

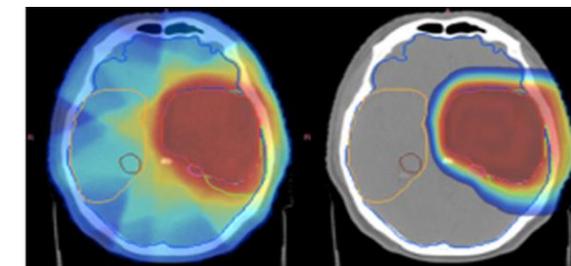


Beam energy modulation to reach the tumor depth and full coverage

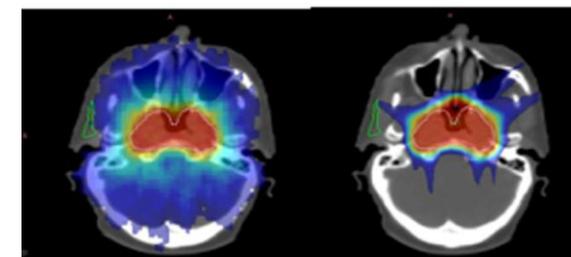
Protons needs **less beam incidences** than X-rays to reach dose conformity = **less irradiated normal tissues**



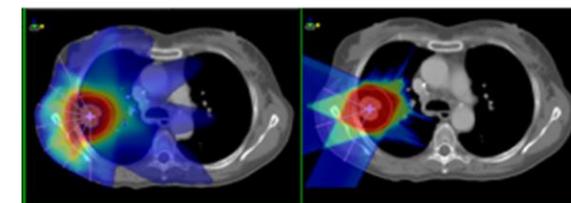
X-rays
(VMAT/IMRT) **Protons**
(PPBS)



C
S



H
N



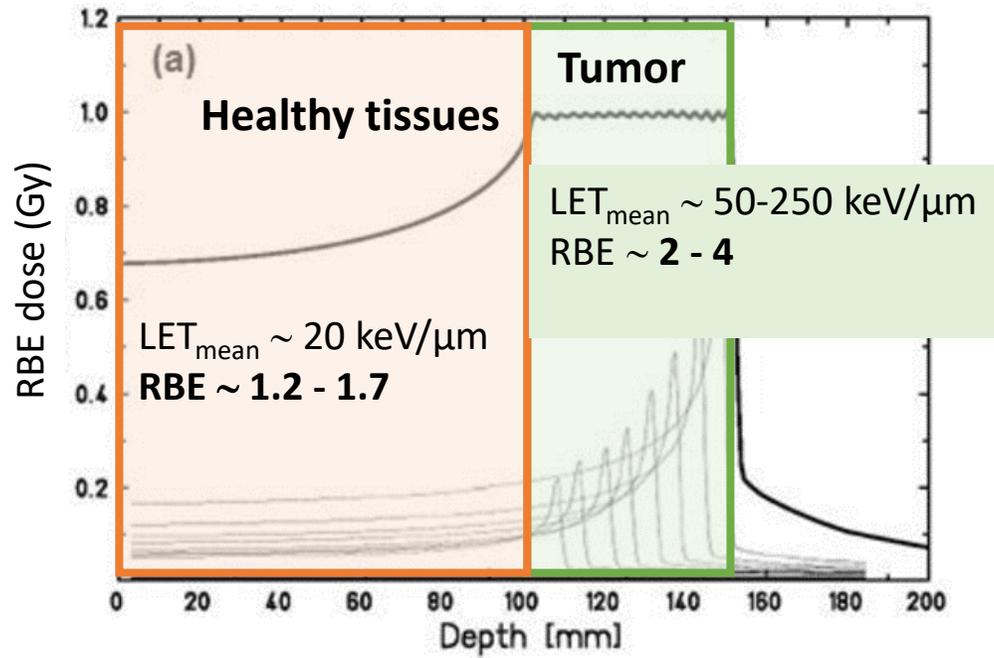
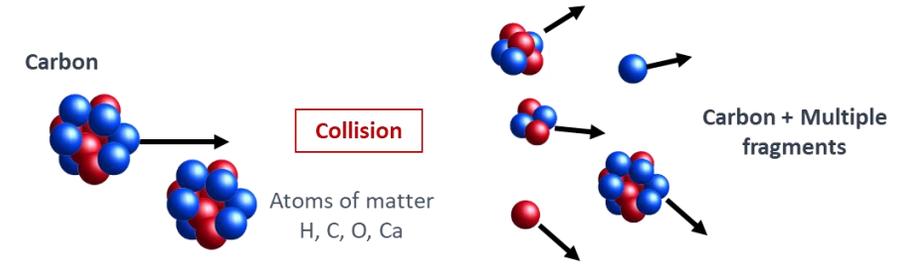
L
C
U
G

➔ Take advantage of the spatially limited energy deposit before tumor and max at the end of the range (Bragg peak).

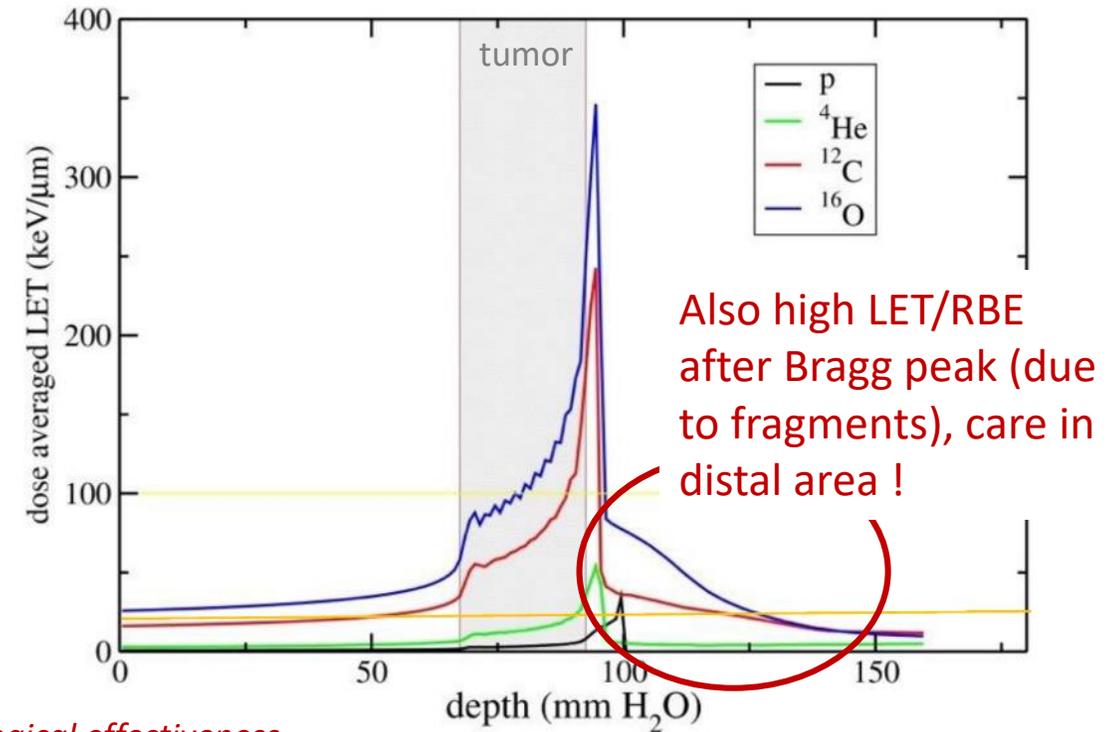
From Durante et al. 2019, Applied nuclear physics at the new high-energy particle accelerator facilities.

Carbon ion therapy (or heavier ions)

- Ballistic advantage over photons
- Differentiated RBE in tumor vs healthy cells



LET changes with depth

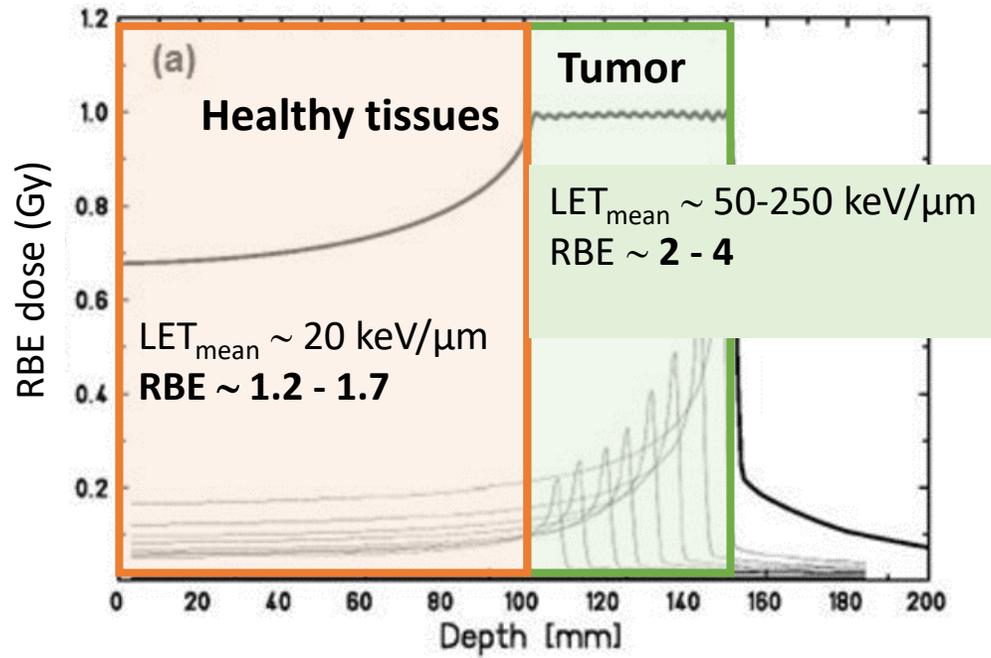


Complications ↗ Tumor control ↗ ↗

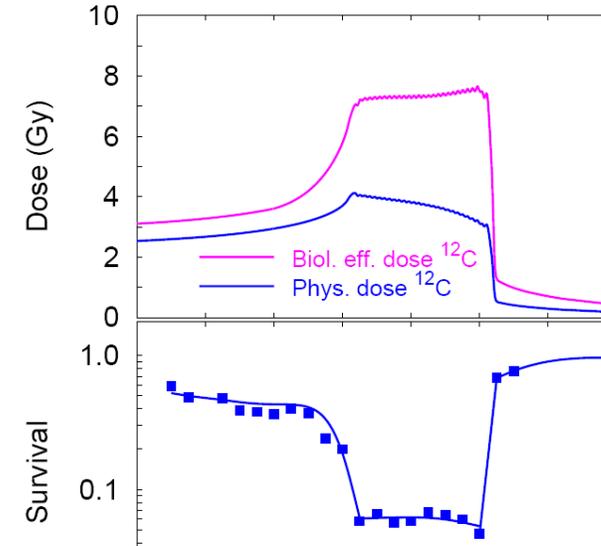
*RBE = relative biological effectiveness

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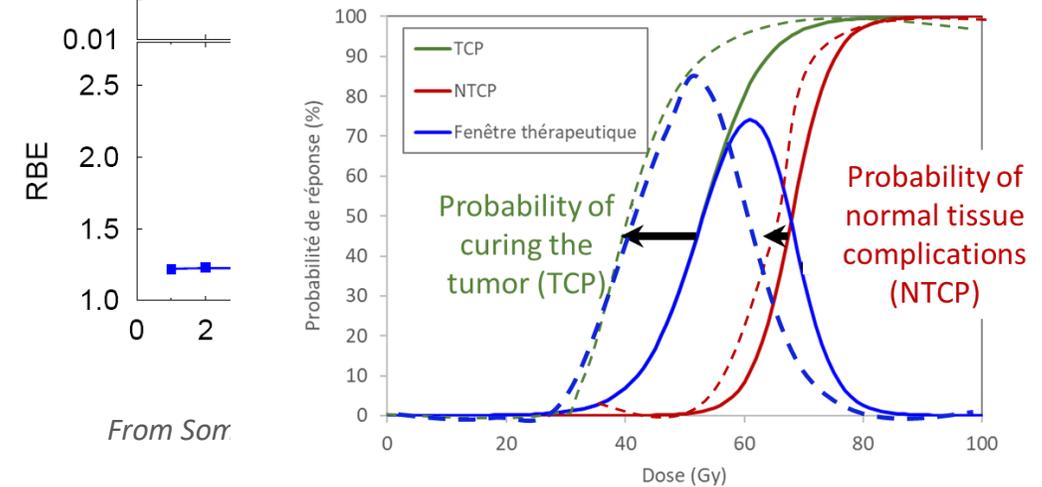
- Ballistic advantage over photons
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Complications ↗ Tumor control ↗ ↗



In the treatment planing systems, need to consider the RBE* variation with depth of ion beams



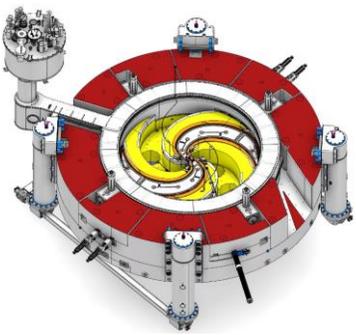
From Sorr

*RBE = relative biological effectiveness Toxicity increased in all tissues, but more in the tumor region

Hadrontherapy: accelerators and dose delivery techniques

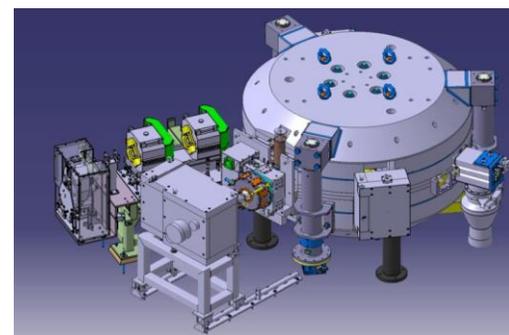
➤ Production of ion beams:

Cyclotrons (p...)



ex. C400 IBA, prototype for carbons at Cyclhad, Caen (2028..)

synchro-cyclotron (p)



Ex. S2C2 IBA (installed at CAL, Nice)

synchrotron (p, He, C, ...)



ex. CNAO, Italy

➤ Beam lines:

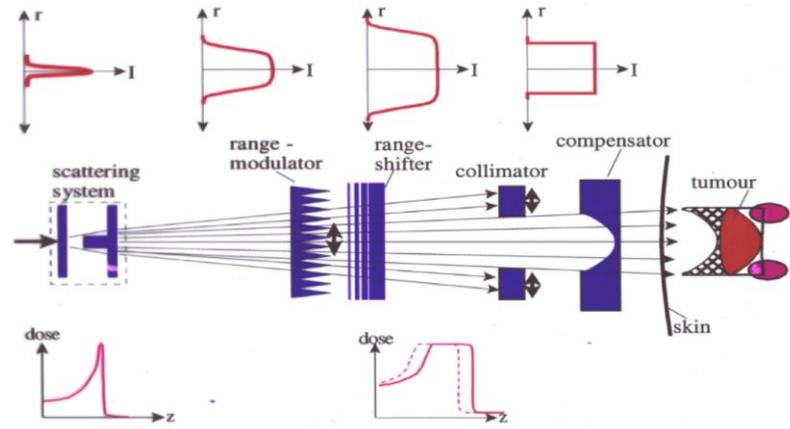


Ex. hadrontherapy center of Heidelberg (DE) with 2 fixed and one gantry beamline

➤ See Gabriel Gaubert presentation on CYCLHAD

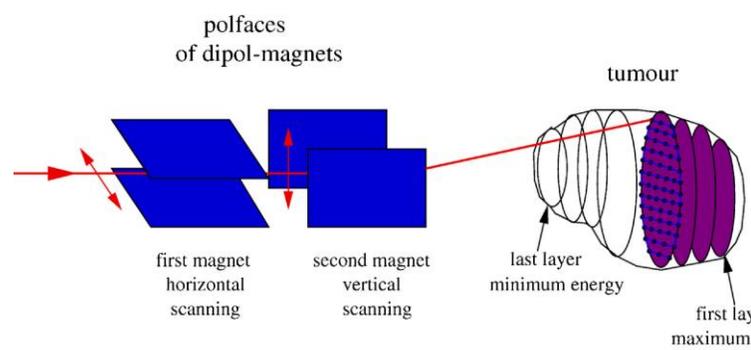
➤ Beam delivery:

Passive beam delivery



- (+) Whole target irradiated in once (no beam parameter change).
- (-) 2nd dose (neutron) production. Unwanted dose in proximal part

Active: pencil beam scanning



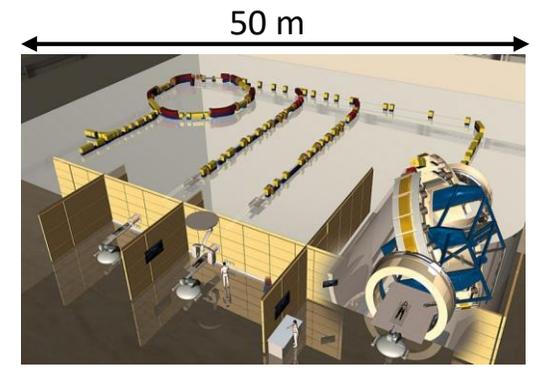
- (+) no passive elements. High precision in dose conformation. Less activation and 2nd neutron dose.

O. Jäkel et al, Z Med Phys 2022

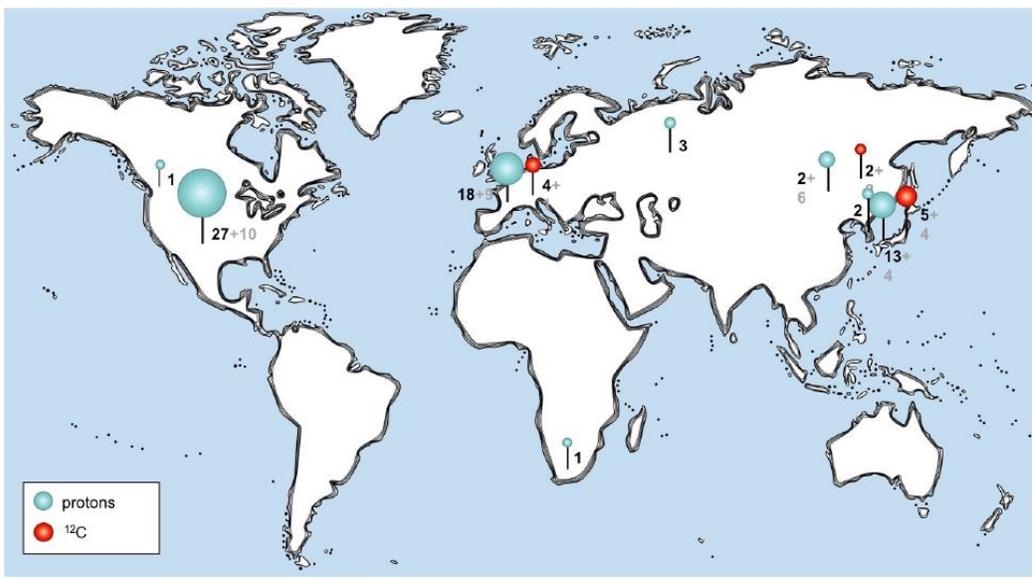
Hadrontherapy: clinical centers

➤ Hadrontherapy centers:

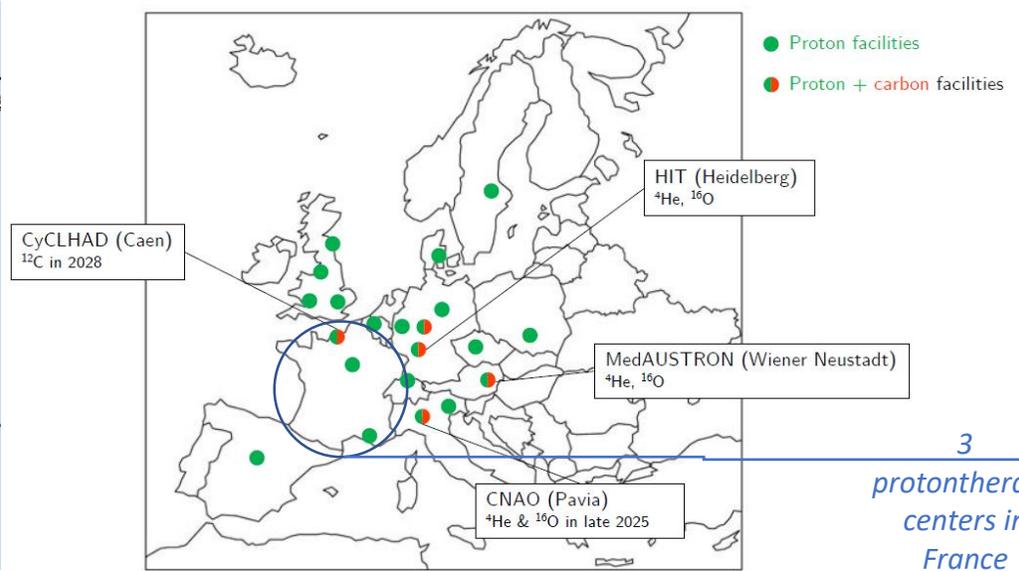
- **Significant development** thanks to turnkey industrial solutions
- ~350 000 patients treated with protons, 50 000 with ^{12}C ions worldwide
- **Main indications:** ophtalmogical, intracranial and pediatric treatments
- However **cost** (>60 M€ (p) vs ~1M€ X-rays LINAC) and **size** (needs dedicated building) **limits access**



Ex. hadrontherapy center of Heidelberg (DE)



Hadrontherapy cancer facilities in the world (~125 operational facilities in 2023, according to ENLIGHT)



Operational hadrontherapy cancer facilities in Europe (~30)

CPO (Orsay, since 1991)

CAL (Nice, since 1991)

Cyclhad (Caen, since 2018)

3
protontherapy
centers in
France

See Gabriel Gaubert presentation on CYCLHAD

➤ Instrumentation and online quality control of ion beams:

- Beam monitoring systems
- « Online » dose delivery control and ion range verification: prompt gamma imaging, online PET...
- Dosimeter developments and LET measurements (microdetectors)

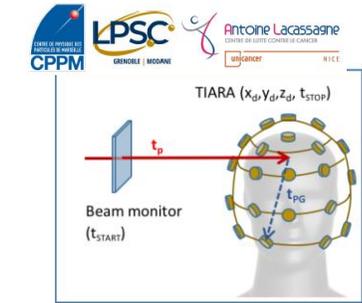


Subotech LPSC



CNAO ARRONAX Laboratoire sprince-Ringuet

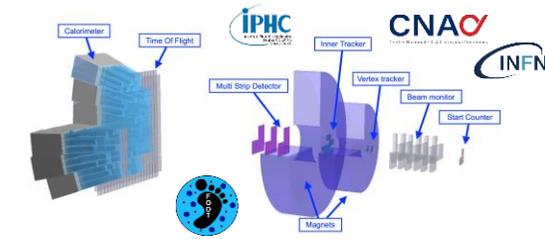
Ex. of diamond (LPSC) and PEPITES (LLR) beam monitor
→ C. Thiebaut pres. on PEPITES



Prompt Gamma Timing Imaging detector for ion range control

➤ Numerical tools, dose and RBE planification systems:

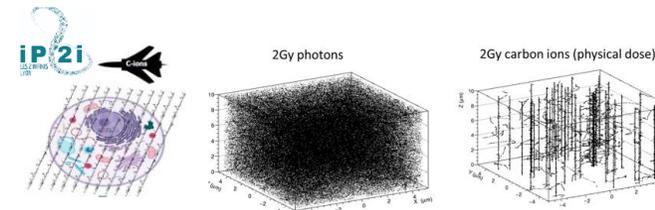
- Fragmentation of ions: uncertainties in cross sections and computation tools → measurements and implementation in TPS
- Multiscale modeling, biophysical models → ion RBE consideration in TPS



FOOT project: measure diff. cross section of ion fragmentation for hadrontherapy

➤ Radiobiology of ions:

- Understand biological mechanism, "hadronbiology"
→ Need for hadronic research platforms (GANIL, CAL, ARRONAX, CNAO... soon **BioALTO**)



Spatial distribution of OH[•] radicals after photon or C-ion irradiation supporting « bombardier furtif » theory

➤ Optimization protocols to enhance therapeutic index:

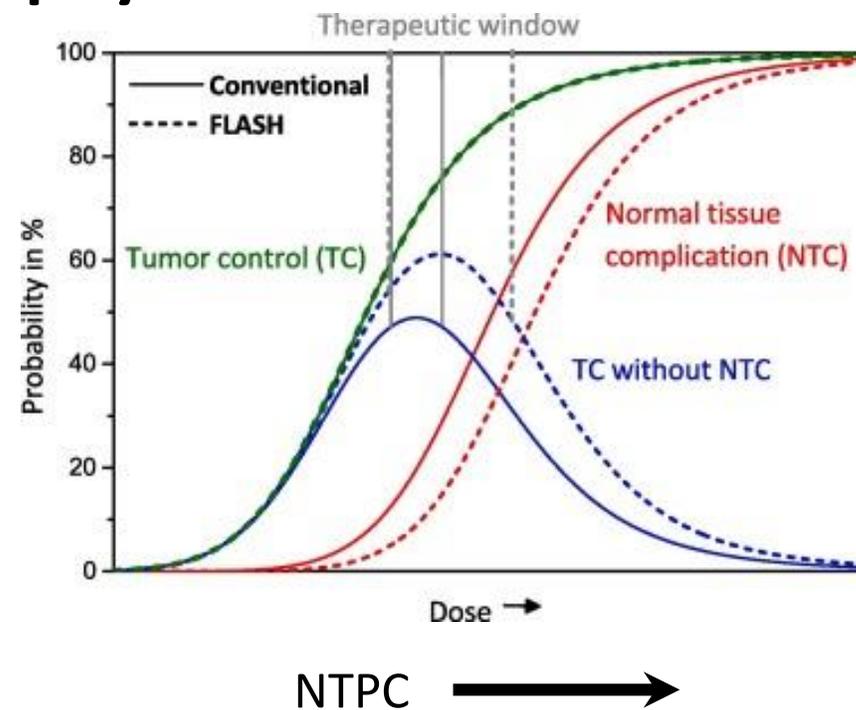
- clinical data analysis (PMRT project) and opening for new treatment indications
→ work with clinicians



BioALTO beamline under installation

Dose delivery mode : FLASH therapy

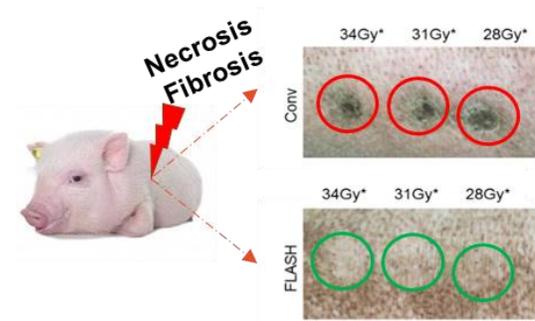
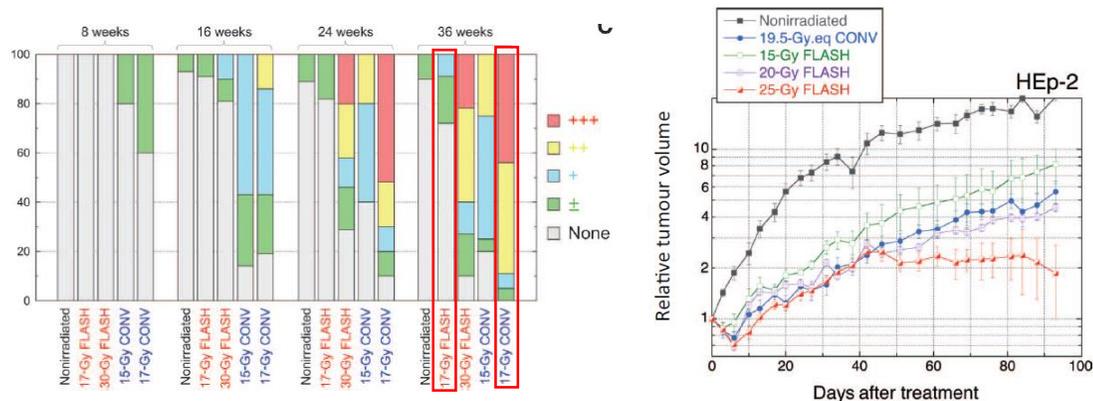
Ultra-high dose rate irradiations:
principle and challenges



UHDR irradiation: « FLASH » therapy

➤ Very-high dose rates (> 40 Gy/s) protect normal tissues:

- Pioneer work of Favaudon *et al.* 2014: observed **lower normal tissue toxicity** (lung fibrosis) using **high-dose rate e- beam (> 40 Gy/s, E~6 MeV, total dose delivered < 100 ms)** with **similar tumor control** to conv. (~0.03 Gy/s).



Vozenin *et al.* 2018
Rohrer-Bley *et al.* 2022

First demonstration of **lung fibrosis reduction (twice more dose)** on mice treated with FLASH compared to CONV irradiation, with **comparable tumor response** (Favaudon *et al.* 2014).

- FLASH-effect confirmed with **e-/γ/p beams** in several *in vivo* experiments. Recently demonstrated with **scattered and PBS proton beam** (Diffenderfer *et al.* 2019).
- **First patient treated** in Lausanne (Bourhis *et al.* 2019).
- **Several clinical trials planned/started** (on electron beam UHDR facilities, < 10 MeV)

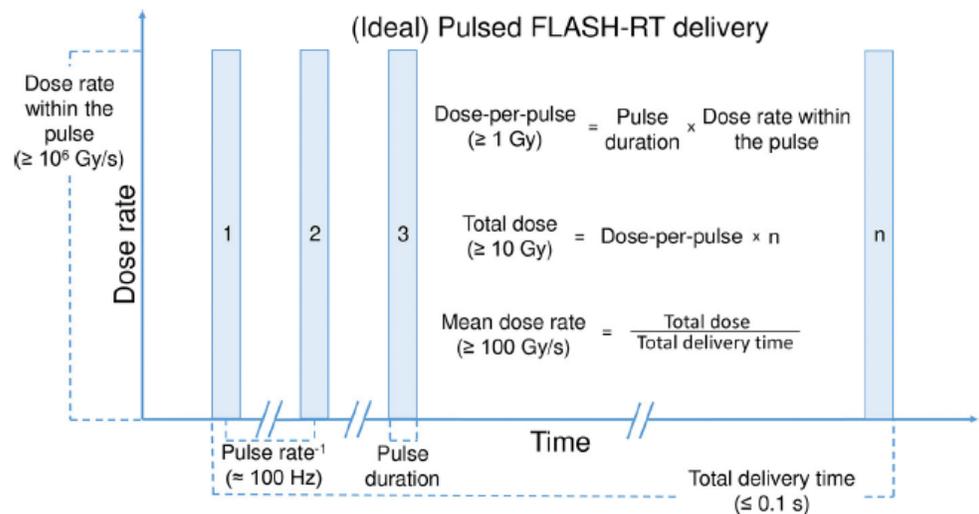


High and fast enthusiasm with FLASH therapy... Sometimes forgetting the basic rules of protection in RT

➔ Some negative results in veterinary trials on cats (Vozenin *et al.*) or dogs (Børresen B. *et al.*, *Front Onc* 2023)

UHDR irradiation: « FLASH » therapy

➤ What physical parameters may be needed to have a “Flash” effect ?

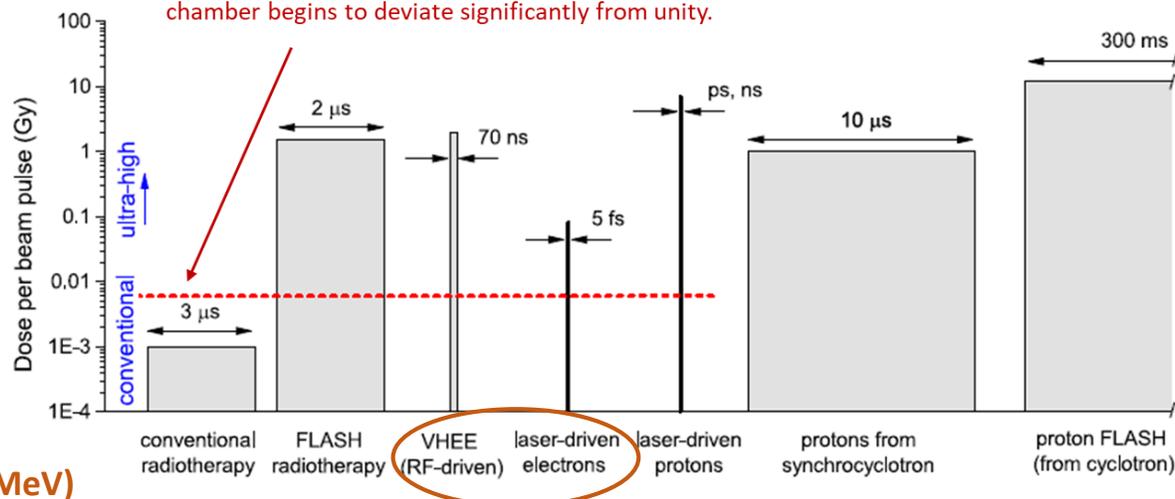


From Wilson et al. (2020), *Frontiers in Oncology*, volume 9:1563.
<https://doi.org/10.3389/fonc.2019.01563>

	FLASH	CONV
• Mean dose rate (\dot{D})	≥ 100 Gy/s	$\sim 0,03$ Gy/s
• Total irradiation time (t)	≤ 100 ms	$> \text{min}$
• Dose per pulse (DPP)	≥ 1 Gy	~ 1 mGy
• Pulse dose rate (\dot{D}_p)	$\geq 10^6$ Gy/s	$\geq 10^3$ Gy/s
• Pulse duration (t_p)	?	~ 1 μs

➤ Which beams: different time-structures

Limit at which the charge collection efficiency of a conventional ionization chamber begins to deviate significantly from unity.



Very-high energy electrons (VHEE, 100-300 MeV)
Good candidates for FLASH RT on deep tumors

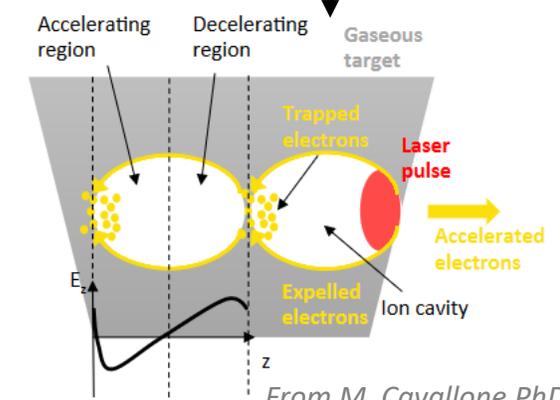
FLASH therapy: challenges and open questions

- **Development of UHDR stable facilities** (with deep beam penetration)
- ➔ **Very-high energy electrons (VHEE, 100-300 MeV)** Good candidates for FLASH RT on deep tumors



PRAE accelerator construction	
Beam parameters	phase 1-2 (3)
Energy, MeV	50-70 (100-140)
Charge (variable), nC	0.00005 - 2
Normalized emittance, μm	0
RF frequency, GHz	0
Repetition rate, Hz	0
Transverse size, mm	0
Bunch length, ps	< 10
Energy spread, %	< 0.2
Bunches per pulse	1

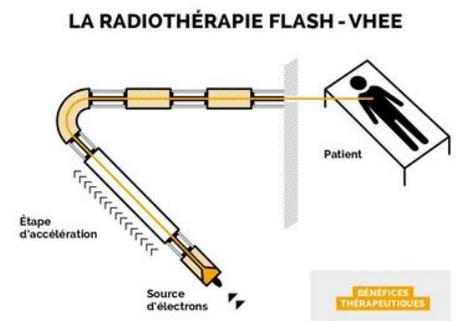
Production in **high-gradient** (~100 MV/m) RF accelerators (ex. CLEAR, CERN) or with **wake-field Laser-Plasma** (~GV/m)



2015: VHEE platform project at IJCLab → stopped 2019



May be the first **FLASH-VHEE clinical treatment facility** in France/world (~2028)



Project of laser-plasma electron source for FLASH preclinical studies at LOA (A. Flacco et al.)

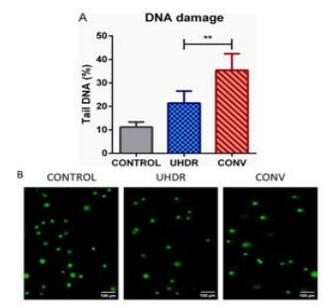
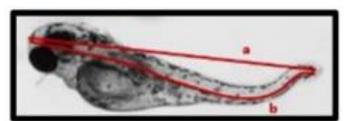
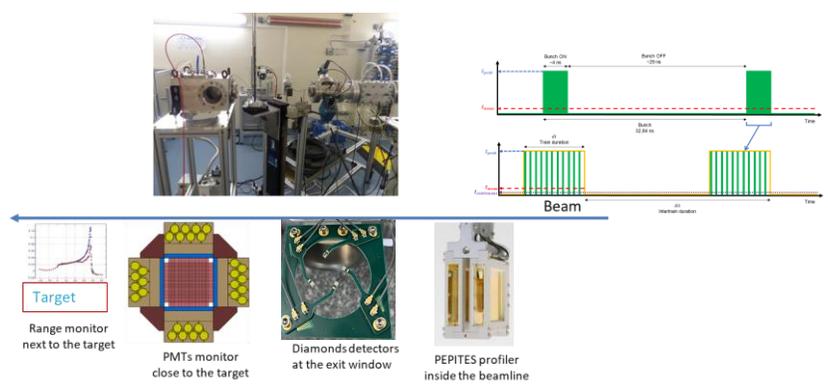


FLASH therapy: challenges and open questions

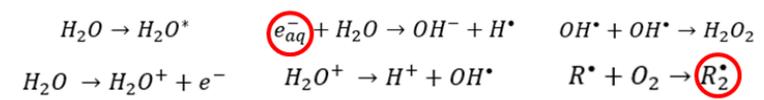
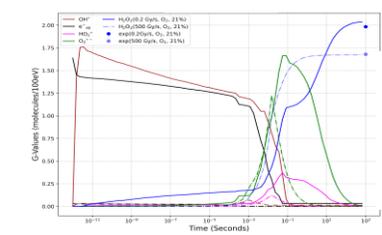
- **Development of UHDR stable facilities** (with deep beam penetration)
 - ➔ **Very-high energy electrons (VHEE, 100-300 MeV)** Good candidates for FLASH RT on deep tumors
- **Limits of physical parameter's impact on FLASH biology:** pulse duration/intensity, mean or instantaneous dose-rate, irradiated volume size ?
- **Chemical and biological mechanisms of FLASH-effect ?** Role of oxygen ? Is it observable *in vitro* ?
 - ➔ **Need for research radiobiology platforms AND dose monitoring** of radiobiology experiments.

➔ **IN2P3 Master project "FLASH"** (2026-2028): several programs at **ARRONAX** (Nantes), **CYRCé** (Strasbourg) and **BioALTO** to characterize **chemical** (ROS production yield) and **biological responses** in **FLASH ion-beams**

Courtesy
L. Maigne



Bogaerts et al, *Radiother Oncol* 2024



Instrumentation developments for UHDR pulsed beams irradiation and monitoring (without charge recombination)

Studies on biological in vivo and in vitro samples ion-FLASH vs CONV responses

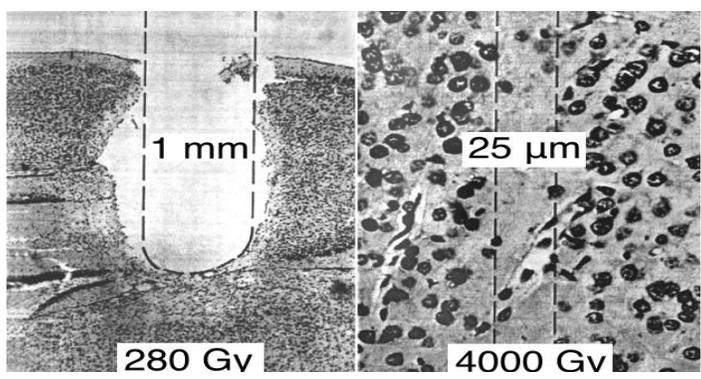
ROS production yield measurements and implementation in OpenGATE

Dose delivery mode : Spatial Fractionation

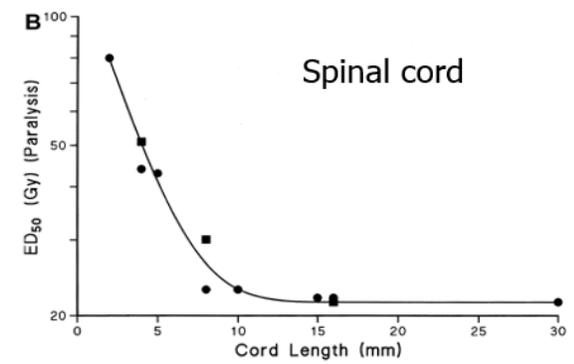
Grid therapy, minibeam (MBRT), microbeam (MRT)

Spatially fractionated RT (SFRT)

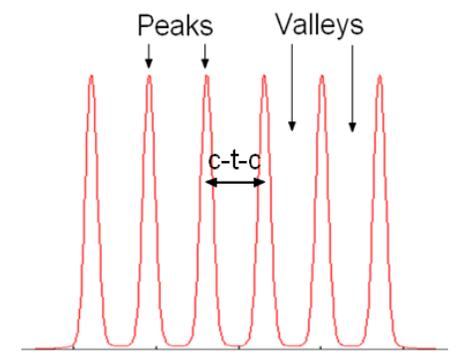
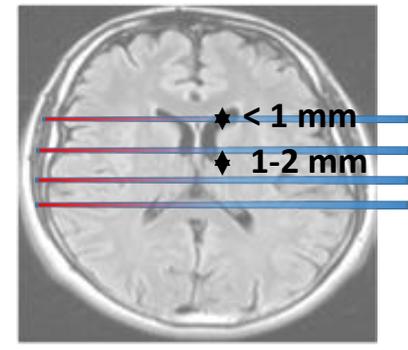
- SFRT can (also) protect normal tissue, with equivalent tumor control efficiency
 - Combines submillimetric beam sizes with spatial fractionation of the dose



Dose-Volume effect (Zeman et al. 1959)



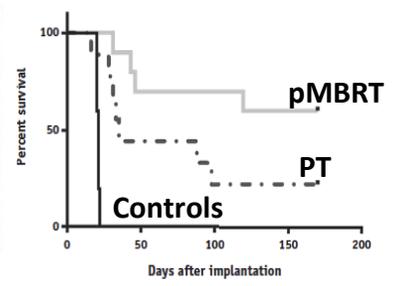
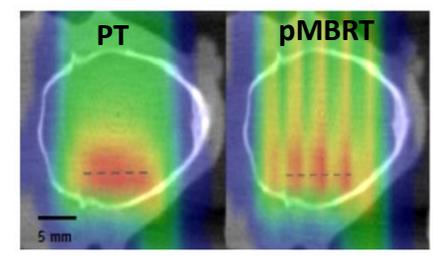
Hopewell et al., Radioth. Oncol. (2000)



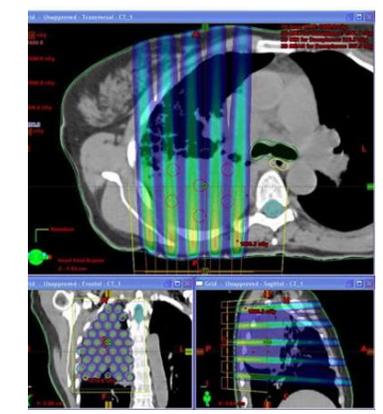
Heterogeneous dose profiles

➔ Dose-volume effect = the smaller the beam size, the higher the tolerance dose in healthy tissues.

- MRT: Beam < 200 μm (synchrotron)
- MBRT: 400-700 μm (accessible compact sources)
- Grid (or Lattice): ~0.5-1 cm (used clinically).



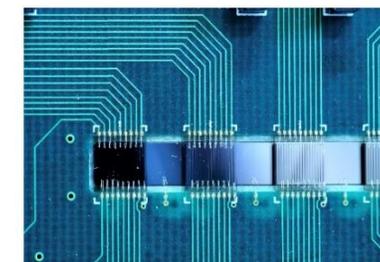
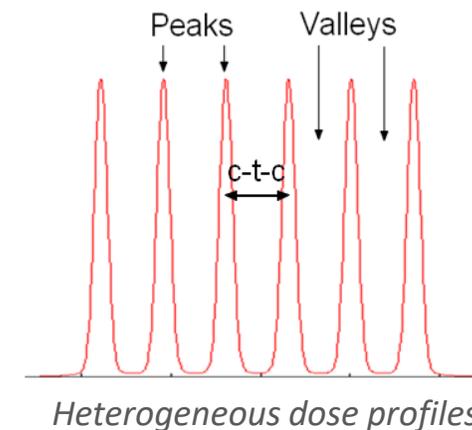
25 Gy Proton MBRT improved rat tumor control (Prezado et al. 2019)



Ex. GRID therapy in lung treatment (Yan et al. 2020.)
Reduce acute skin toxicity

➤ Challenges/developments of SFRT:

- Explore the *terra incognita* of **influence parameters**
 - **SFRT metrics** to use for « equivalent » uniform dose responses ?
 - **Systematic evaluation of tissue/tumor response** according to irradiation parameters (ctc, beam size, PVDR...)
 - ➔ **Need for dedicated radiobiological studies.**
- **Biological processes induced in normal and cancerous cells/tissues ?**
 - **Not well known:** hypothesis of cell migration, hypoxia, immature vasculature...
- **Reliable dosimetry protocols** for very small beam size and potential high-dose rates! (MRT) ➔
- **Need for compact source developments** for clinical development (*RIP ThomX...*).



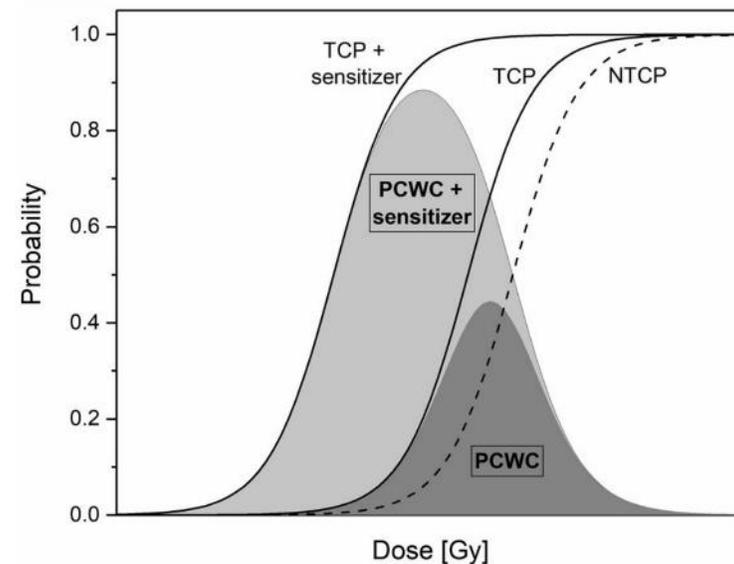
Dedicated Diamond detector (LPSC) for MRT beam monitoring

Targeted RT using short-range particles

Boron Neutron Capture Therapy (BNCT)

Targeted Radionuclide therapy (TRT)

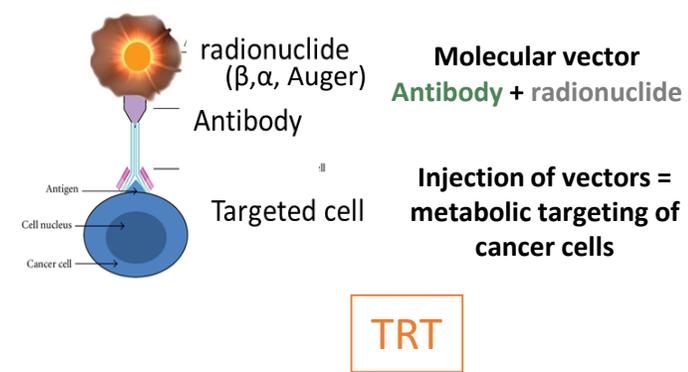
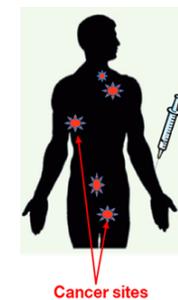
Metallic nanoparticles



Targeted Radionuclide Therapy (TRT)

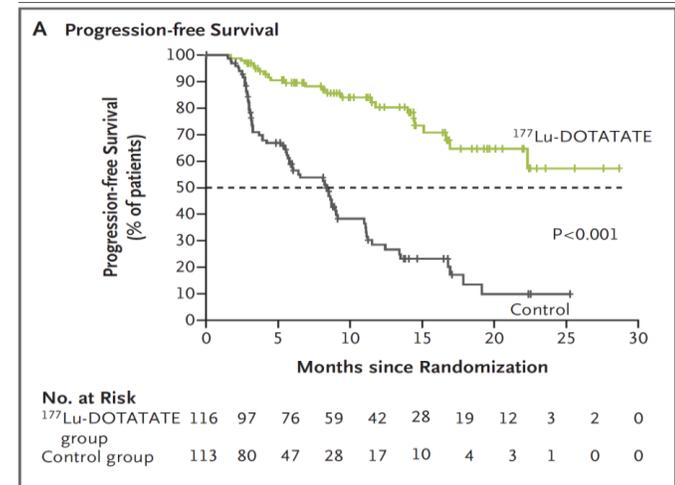
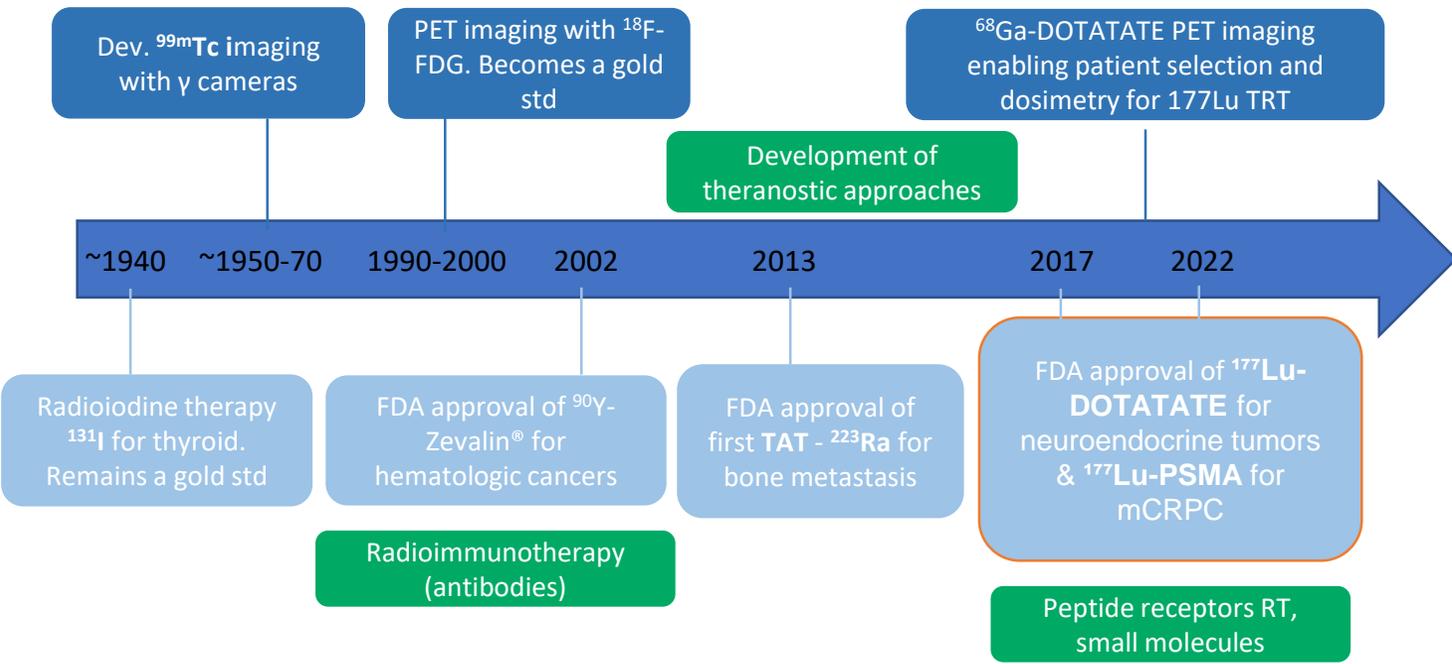
➤ TRT uses unsealed sources for selectively target cancer cells thanks to radiopharmaceuticals (RP)

Rapid evolution of diagnostics and TRT over the past 20 years :



TRT

New era of TRT and theranostics

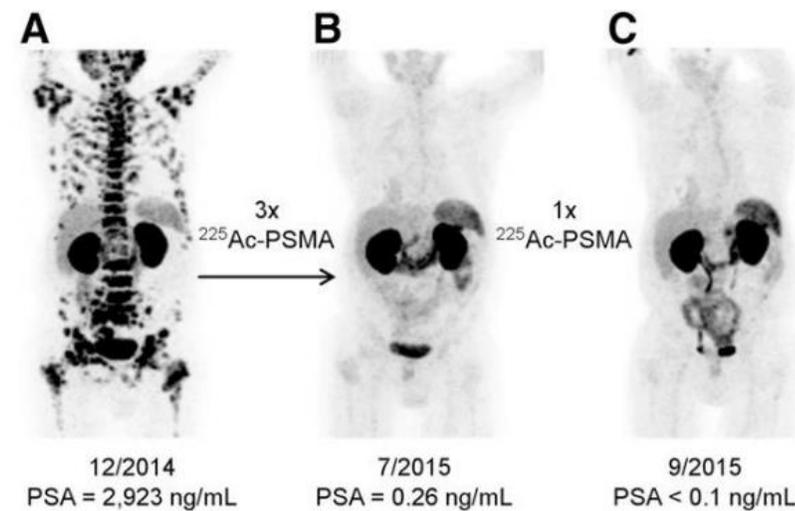


Strosberg et al. Phase 3 Trial of ^{177}Lu -Dotatate for midgut Neuroendocrine tumors, *N. Engl. J. Med.* 376;2, 2017

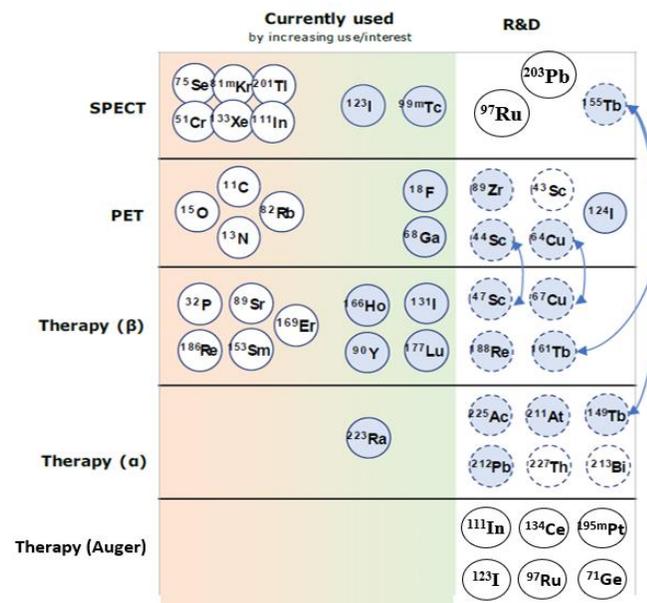
*PET: Positron Emission Tomography ; FDA: Food and Drug Administration
 PSMA: Prostate-Specific Membrane Antigen ; mCRPC: metastatic castration-resistant prostate cancer

Targeted Alpha Therapy (TAT)

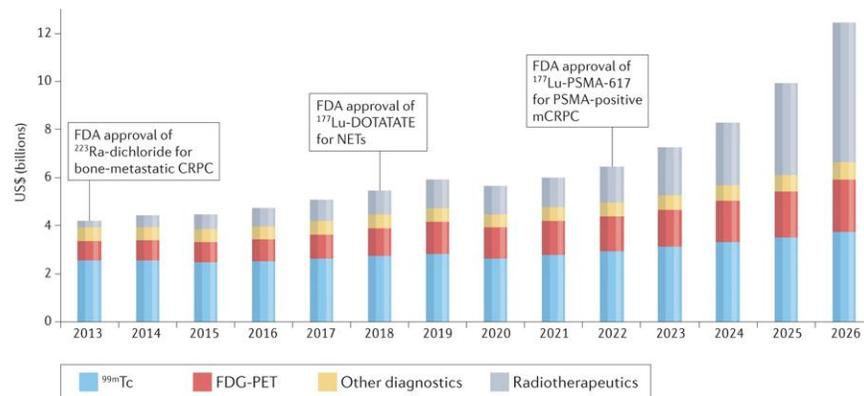
- **Interest in Targeted Alpha Therapy (TAT)** with various emitters (^{225}Ac , ^{211}At , ^{213}Bi , ^{212}Pb ...) and ligands. **~30 clinical trials ongoing**
- **Novel targets & ligand development** to expand TRT applications with theranostic pairs
- **Expansion of TRT to earlier treatment indications**, and proposition of combined β/α /Auger TRT
- ➔ Increasing demand for new isotopes with reliable production routes



Spectacular response of Metastatic Castration-Resistant Prostate Cancer patient using ^{225}Ac -PSMA-617 TAT, Imaging performed with ^{68}Ga -PSMA. From Kratochwill J. Nucl Med, 57(12), 2016



Presentation Ali Ouadi

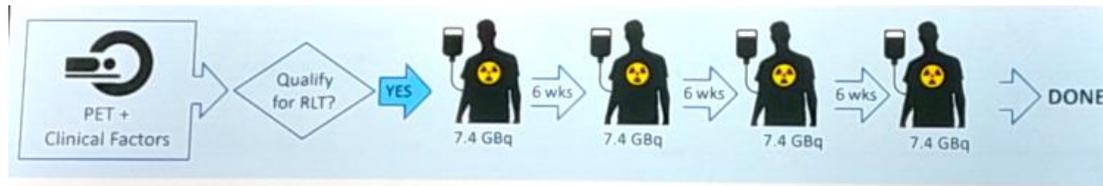


The predicted global nuclear medicine market 2013–2026, from Bodei L, et al... Nat Rev Clin Oncol. 2022 Aug;19(8):534-550.



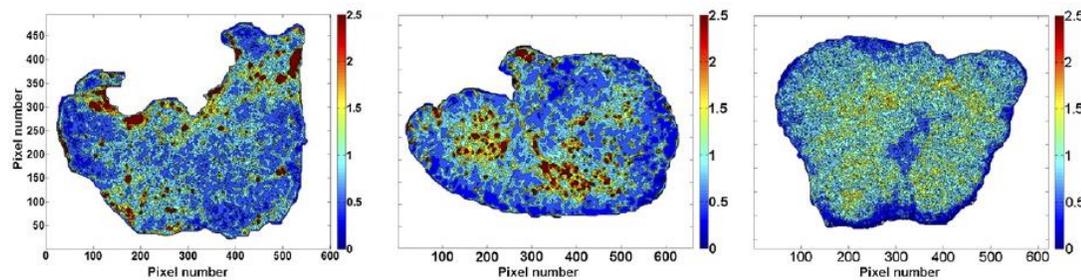
Adapted from Co-ordinated Approach to the Development and Supply of Radionuclides in the EU - N°ENER/D3/2019-231 - Final Report

- Despite effective palliation of tumor growth, current fixed activity is applied = sub-optimal for curative treatment:



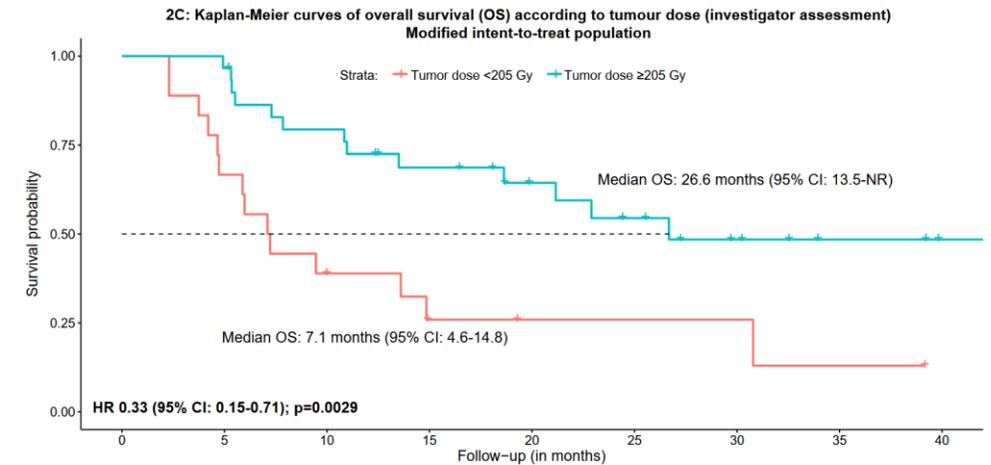
- **Dosimetry may guide personalization** to achieve durable complete response by adapting activity / cycle
 → However not systematically performed due to heavy protocol, additional cost and patient's discomfort

- **Additional difficulties with alpha emitters or high-LET/short range emitters:**



Example of heterogeneous activity distribution in tumor after 7min, 7h, and 21h after injection, via alpha-camera method. From Bäck T & Jacobsson L. *J Nucl Med.* 2010;51(10):1616-23.

- **Demonstration of personalize dosimetry benefit**



Garin et al., SIRT using personalised dosimetry for locally advanced hepatocellular carcinoma (HCC) patients: multicenter randomised phase 2 study (DOSISPHERE-01 trial). *Lancet*, 6(1),2021

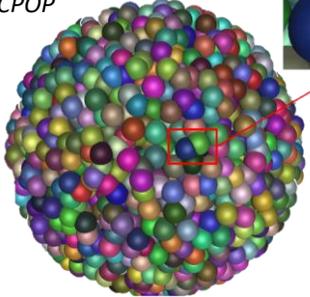
Difficulty to observe clear “dose-effect relationship”.

- **High heterogeneity at cell /tissue scales**
 → *homogeneous hypothesis may lead to errors*
- **High (and variable) RBE**
- **Complex cellular or systemic biological response.**
 → Multiscale modeling can help to quantify impact of such « unknown » heterogeneous distributions.

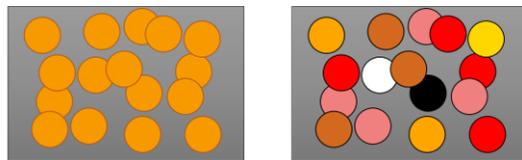
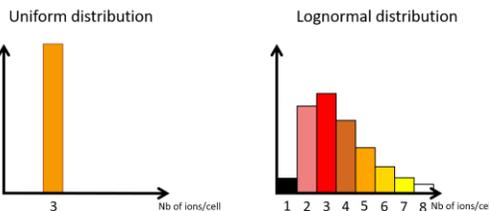
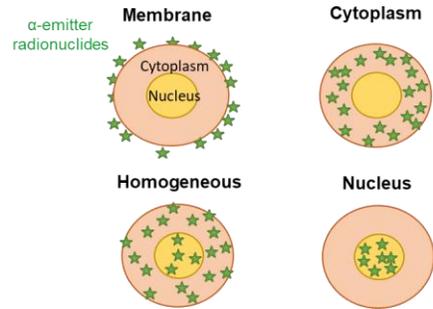
- **Objective: quantify the error in predictions when source microdistribution is unknown**
- Microtumor irradiated with ^{211}At sources (**Geant4**): computation of **mean cell survival (NanOx)** and **tumor control probability (TCP)**

$$TCP = \prod_{i=1}^n (1 - S_i)$$

Microtumor modeled with CPOP



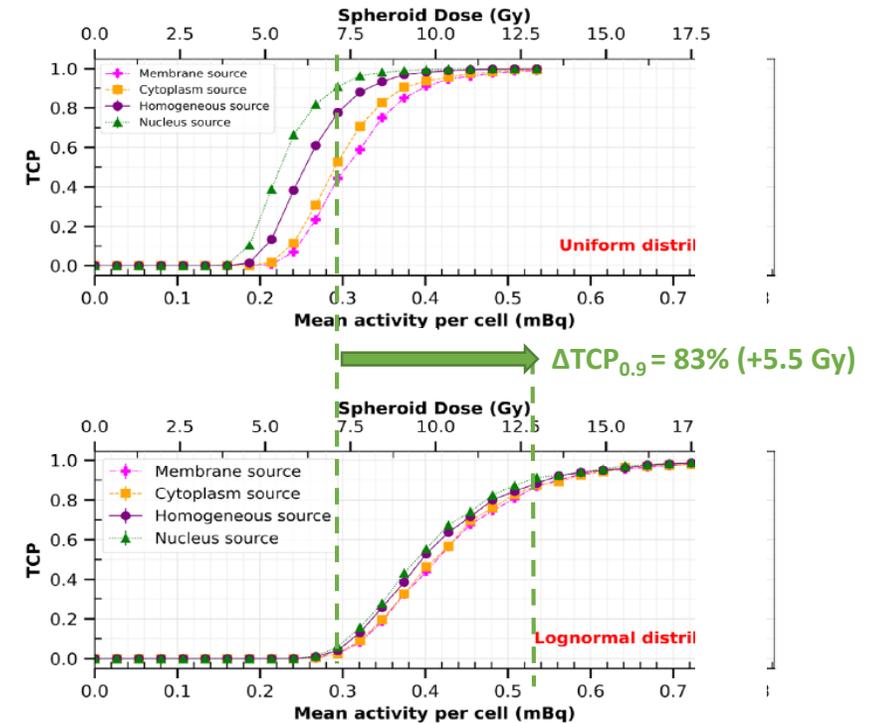
Different intracellular distributions



Different intratumoral distributions

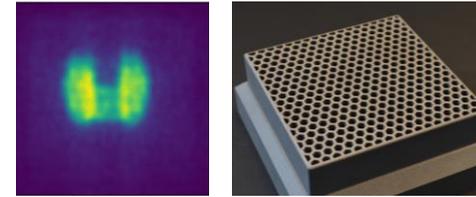
The lognormal distribution, which is closer to experimental reality, reduces efficiency by up to 80% compared to the generally assumed uniform distribution.

Tumor control probability (TCP) as a function of cell internalization and intratumoral distribution of ^{211}At sources

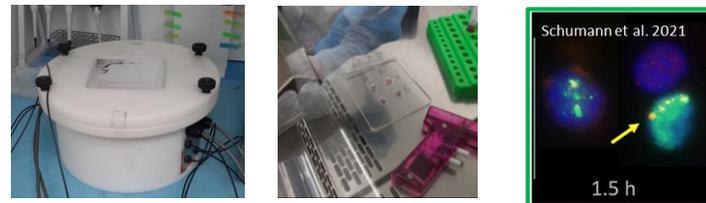


➤ TAT personalize (bio)dosimetry requires:

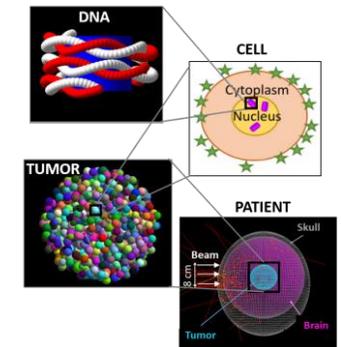
- **Theranostic radionuclide pairs** with alpha emitters
- **Gamma camera adapted to high-energy** (> 300 keV)
- **Dosimetry protocols** based on PET/SPECT quantifications
- **Multiscale modeling tools** to account for heterogeneities in bio-dose prediction and quantify uncertainties
- **Dedicated controlled radiobiological experiments** (*in vitro* / *in vivo*) to characterize complex TAT biological effects



Ex. of Thidos gamma camera for dose monitoring during TRT treatment (IJCLab)



Ex. of Si-based detector dedicated to the online control of TRT dosimetry (GANIL)

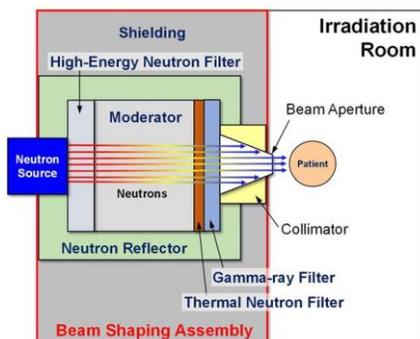


- Identify the **relevant metrics** to characterize TAT efficacy (beyond absorbed dose)

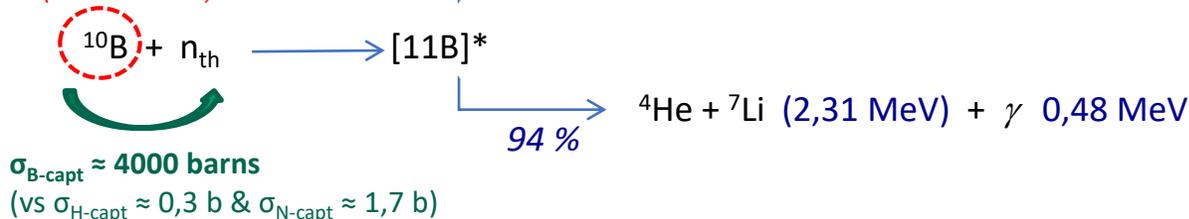
→ Master Project
“Targeted Therapies”

Boron Neutron Capture Therapy (BNCT)

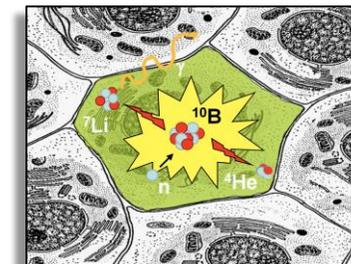
- **BNCT Principle:** combine external **epithermal neutron irradiation** with injected **^{10}B -based compound** to maximize neutron capture cross section at tumor location → **$^{10}\text{B}(n,^7\text{Li})\alpha$**



Enriched boron isotope, delivered in cancerous cells (BPA or BSH)



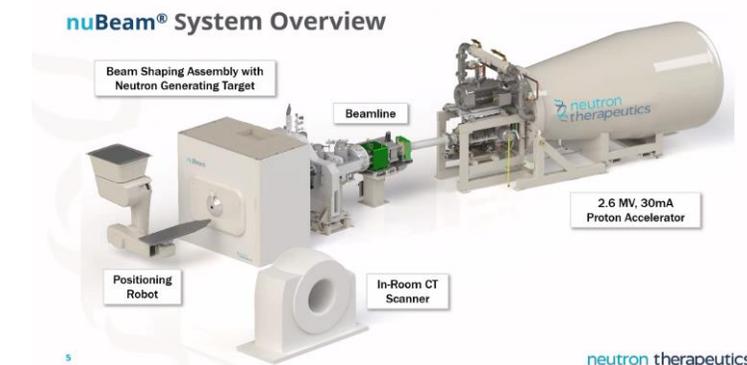
Max range ~5-9µm;
LET > 200 keV/µm



- **Several clinical trials** (*Barth et al. 2012, Shen S et al. 2024*): promising results for high grade glioblastoma and recurrent Head and Neck cancers. Historically delivered in nuclear reactors

- **Accelerator-based BNCT:** new era for clinical trials as compact accel neutron sources (CANS) allow **performing BNCT in hospital.**

- About **26 new AB-BNCT** facilities world-wide, 9 in Japan (*IAEA**). Clinical trial started in Finland 2025, BNCT accepted in clinical routine for recurrent H&N cancers in Japan.
- Companies proposing integrated systems (*e.g. neutron therapeutics, TAE life science...*)



NuBeam® system (ex. installed in Finland, Japan, UK...)

*IAEA report 2023 “advances in boron neutron capture therapy”; <https://nucleus.iaea.org/sites/accelerators/Pages/default.aspx>

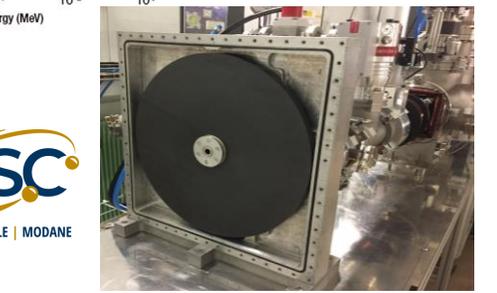
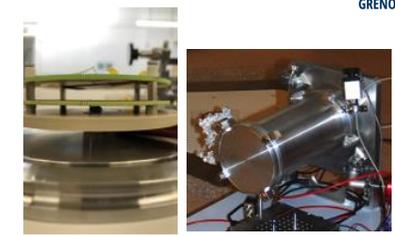
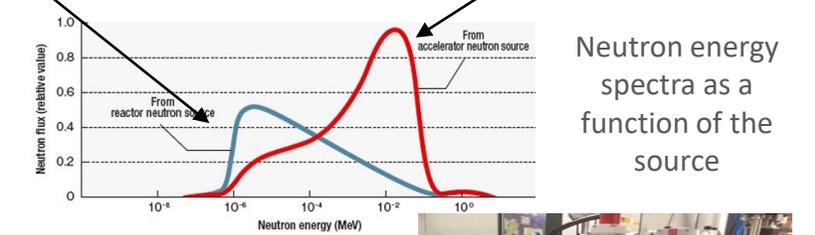
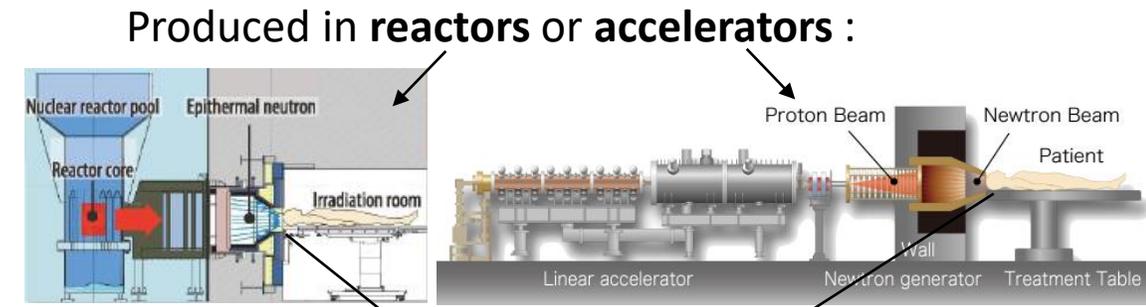
➤ **AB-BNCT**: improved patient care and beam spectra for treating deeper tumors, **in hospital**

➤ **IAEA recommendations** for neutron beam quality:

	Epithermal Flux Φ_{epi} $0.5eV < E_n < 10keV$ (n/cm ² /s)	Fast Neutron Contamination $D\Phi_f/\Phi_{epi}$ (Gy/cm ² /n)	Thermal Neutron Contamination $\Phi_{thermal}/\Phi_{epi}$	Gamma Contamination D_γ/Φ_{epi} (Gy/cm ² /n)	Beam Collimation J/ Φ
IAEA Reference Value	$\geq 1 \times 10^9$	$\leq 7 \times 10^{-13}$	$\leq 5\%$	$\leq 2 \times 10^{-13}$	≥ 0.7

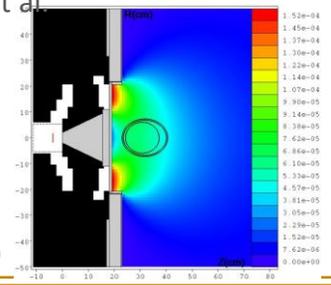
➤ **Some AB-BNCT challenges:**

- **Production targets:** possible reactions ${}^7\text{Li}(p,n){}^7\text{Be}$, ${}^9\text{Be}(p,n){}^9\text{B}$, ${}^9\text{Be}(d,n){}^{10}\text{B}$, ${}^{13}\text{C}(d,n){}^{14}\text{N}$
High power (30-75 kW) degrades targets. → **Design optimal targets.**
- **Online monitoring:** need for real time monitoring (target aging = neutron flux \searrow) and delivered dose → **Develop n & γ (480 keV) detectors.**
- **Lack of standardization** : complexify treatment comparisons.
→ **Neutron field spectral and fluence characterization** with adapted detectors.
- **Beam shaping assembly:**
Find optimal moderation to maximize penetration in tissue with high-enough intensity.



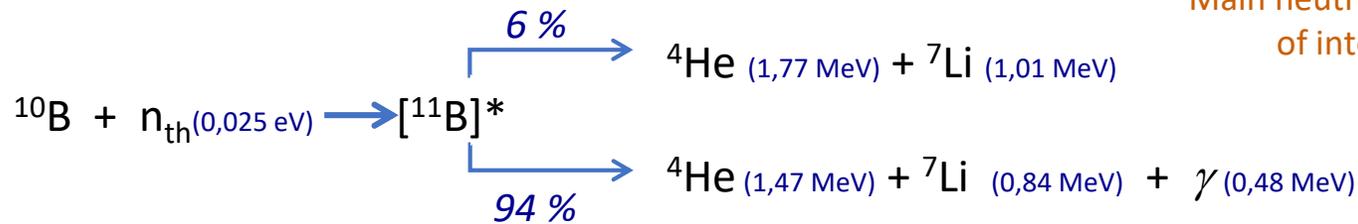
Gaz detectors for field monitoring (left) and for neutron spectrometry

Design a rotating target on a graphite wheel + ${}^9\text{Be}$ (or ${}^{13}\text{C}$) deposit
D. Santos et al.

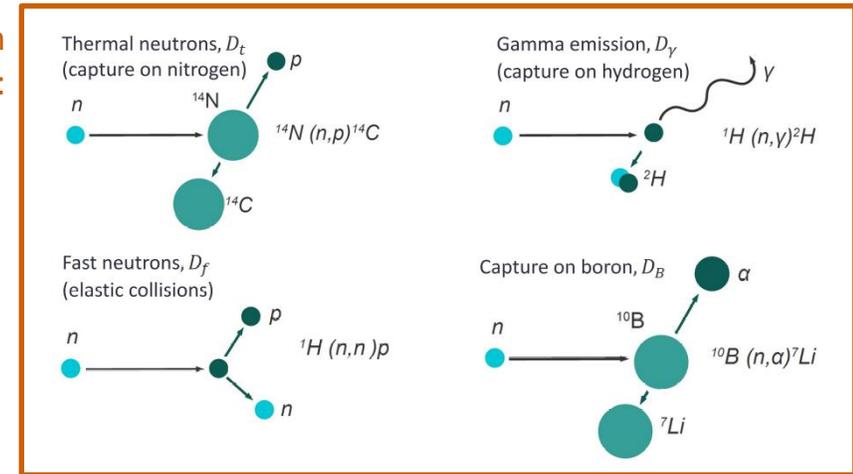


BSA design to optimize treatment depth in BNCT –Chabod et al.)

- **BNCT dosimetry:** complex cumulation of several components: **neutron thermalization, neutron capture in normal tissue and gamma** (from source and capture) + the **desire boron dose** → **Monte Carlo based TPS**

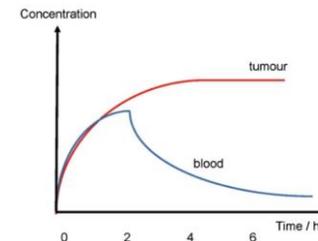


Main neutron interaction of interest in BNCT:



- **Biological dose:** based on boron concentration measurement in blood and cumulation of **weighted** components by **fix RBE** (or CBE) factors.

$$D_W = w_f D_f + w_t D_t + w_\gamma D_\gamma + w_B D_B$$

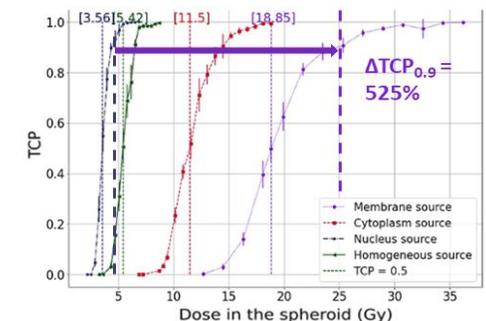


Minimum required tumor/tissue uptake ratio = 3.5

Insufficient: high variation in RBE according to cell line, neutron spectra, particle type and dose, in addition to **high dose heterogeneity** due to compound biodistribution and very low-range/high RBE of He/Li ions.

➔ Similar dosimetric issues that in targeted alpha therapy for the Boron dose
➔ multiscale modeling with biophysical model

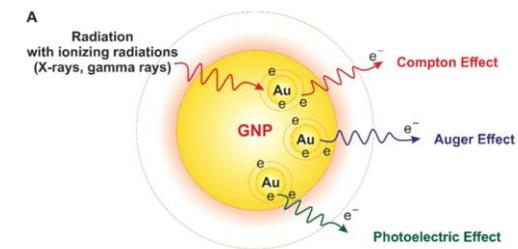
BNCT estimation : TCP as a function of cell internalization of ^{10}B



Targeted therapies: nanoparticles (NP)

➤ Metallic / Oxide NP can enhance radiosensitization of RT:

- First showed by Hainfeld *et al.* in 2004: GNP + RX
- Confirmed in numerous studies with different NP/beams
- 2 clinical trials in France: AGuIX® (Gd), NBTXR3® (Hf oxide)



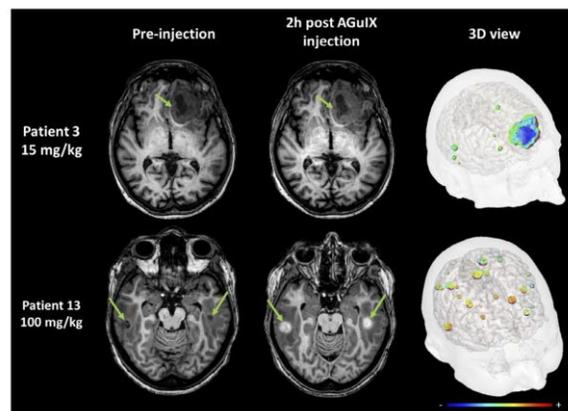
Borran *et al.*, 2018.
Rad. Phys. Chem.

Clinical Trial > Radiother Oncol. 2021 Jul;160:159-165. doi: 10.1016/j.radonc.2021.04.021. Epub 2021 May 5.

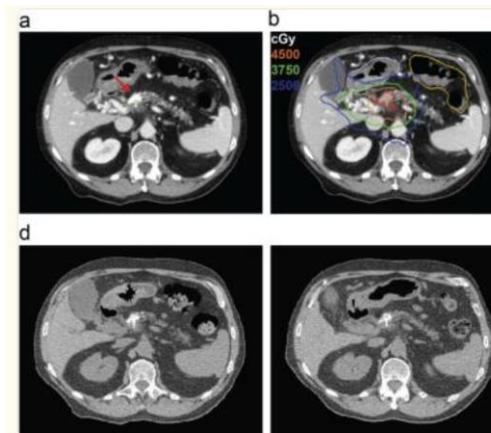
Theranostic AGuIX nanoparticles as radiosensitizer: A phase I, dose-escalation study in patients with multiple brain metastases (NANO-RAD trial)

Camille Verry¹, Sandrine Dufort², Julie Villa³, Marylaure Gavard⁴, Carole Iriart⁵, Sylvie Grand⁵, Julie Charles⁶, Benoit Chovelon⁷, Jean-Luc Cracowski⁸, Jean-Louis Quesada⁸, Christophe Mendoza⁹, Lucie Sancey⁹, Audrey Lehmann¹⁰, Florence Jover³, Jean-Yves Giraud³, François Lux⁹, Yannick Crémillieux¹¹, Stephen McMahon¹², Petrus J Pauwels¹³, Daniel Cagney¹⁴, Ross Berbeco¹⁴, Ayal Alizer¹⁴, Eric Deutsch¹⁵, Markus Loeffler², Géraldine Le Duc², Olivier Tillement⁹, Jacques Balosso³

Affiliations + expand
PMID: 33961915 DOI: 10.1016/j.radonc.2021.04.021
Free article



Verry C. *et al.*, *R&O*, 2021



Bagley F.B. *et al.*, *Clin Transl Radiat Oncol*, 2021
Pancreatic adenocarcinoma

Clinical Trial > Lancet Oncol. 2019 Aug;20(8):1148-1159. doi: 10.1016/S1473-0245(19)30326-2. Epub 2019 Jul 8.

NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2-3, randomised, controlled trial

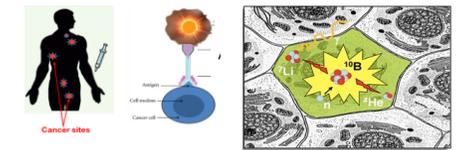
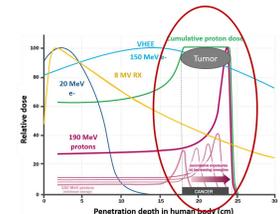
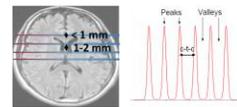
Sylvie Bonvalot¹, Piotr L Rutkowski², Juliette Thariat³, Sébastien Carrère⁴, Anne Ducassou⁵, Marie-Pierre Suryach⁶, Peter Agoston⁷, Angela Hong⁸, Augustin Mervoyer⁹, Marco Rastrelli¹⁰, Victor Moreno¹¹, Rubi K Li¹², Béatrice Tiangco¹³, Antonio Casado Herraiz¹⁴, Alessandro Gronchi¹⁵, László Mangel¹⁶, Teresa Sy-Ortin¹⁷, Peter Hohenberger¹⁸, Thierry de Baère¹⁹, Axel Le Cesne²⁰, Sylvie Helfire²¹, Esmá Saada-Bouzi²², Aneta Borkowska²³, Rodica Anghel²⁴, Ann Co²⁵, Michael Gebhart²⁶, Guy Kantor²⁷, Angel Montero²⁸, Herbert H Leong²⁹, Ramona Vergis³⁰, Lore Lapeire³¹, Sorin Dima³², Gabriel Kacso³³, Lyn Austen³⁴, Laurence Mousseau-Zabotto³⁵, Vincent Servois³⁶, Eva Wardelmann³⁷, Philippe Terrier³⁸, Alexander J Lazar³⁹, Judith V M G Bovée⁴⁰, Cécile Le Pêcheux⁴¹, Zsuzsanna Papp⁴²

➤ High complexity to optimize NP-based treatments

- Radiosensitization is cell-line and NP-type dependent: need for standardization
- Treatment efficacy may depend on tumor targeting and cell-uptake
- Macroscopic dose-enhancement cannot explain alone observed biological effects

➤ Several strategies to increase differential effect in Radiation Therapy:

- Playing on **particle type/energy**: hadrontherapy, VHEE, targeted therapy with high-LET particles...
- Playing on **dose-delivery mode** : FLASH therapy, SFRT
- Combining **radiosensitizer** or using a **molecular targeting**: radionuclide therapy, BNCT, nanoparticles-enhanced RT



➤ Many research projects:

- **Instrumentation** for **dose delivery monitoring** and **irradiation platforms**
- **Developments** in **multiscale modeling**
- **Radiobiological studies** to understand underlying mechanisms and optimize treatments parameters

➔ Need for multidisciplinary field of research with biologist, chemists, physicists and clinicians

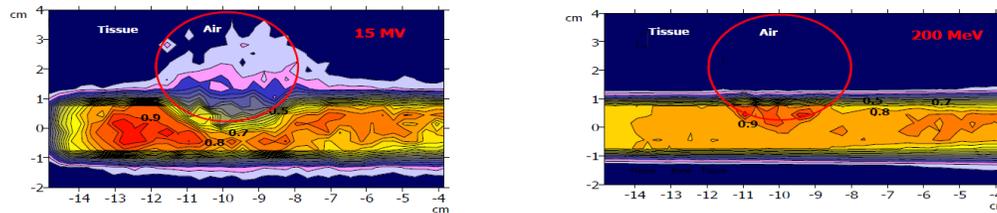


Thank you for your attention !

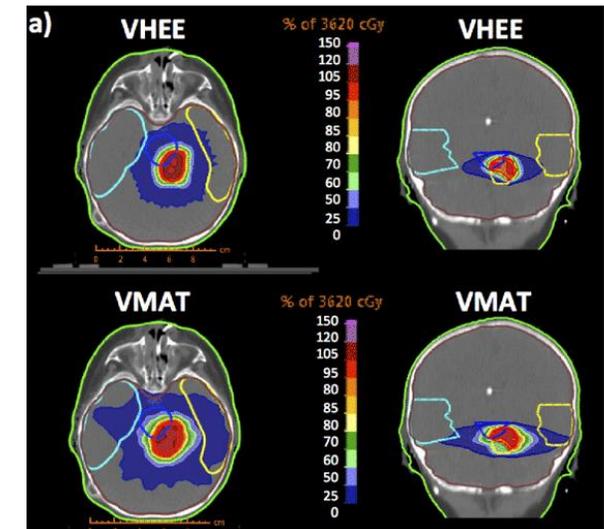
rachel.delorme@lpsc.in2p3.fr

➤ Advantages vs MV photons

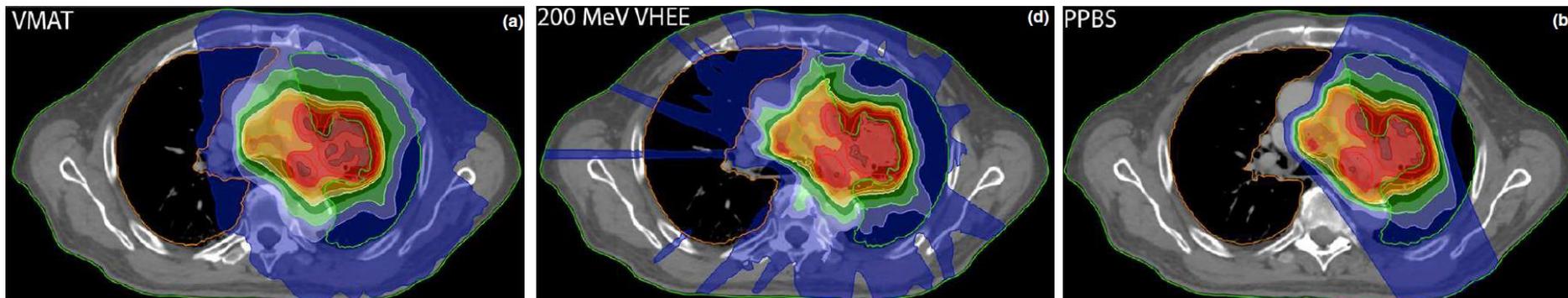
- ✓ **Clinical case comparisons:** compared to VMAT gold std
→ Better protection of Organs at Risk (OAR)
- ✓ Flatter depth dose profile: **deep tumors**
- ✓ **Relative insensitivity to heterogeneities**
- ✓ Magnetic collimation
- ✓ **Might be advantageous vs protons** for Head & Neck



Papiezy, DesRosiers et al. 2002



Brain tumour dose maps for 100 MeV VHEE and 6 MV volumetric modulated arc photon therapy (VMAT) Bazalova-Carter, 2015 (Stanford)



Clinical case VHEE compared to VMAT → Better protection of OAR (prostate, Lung, brain, H&N...) Schuler et al. 2017