Radiothérapie externe du futur

Point de vue d'un physicien médical

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Radiothérapie externe du futur : machines et calcul de dose

Plan :

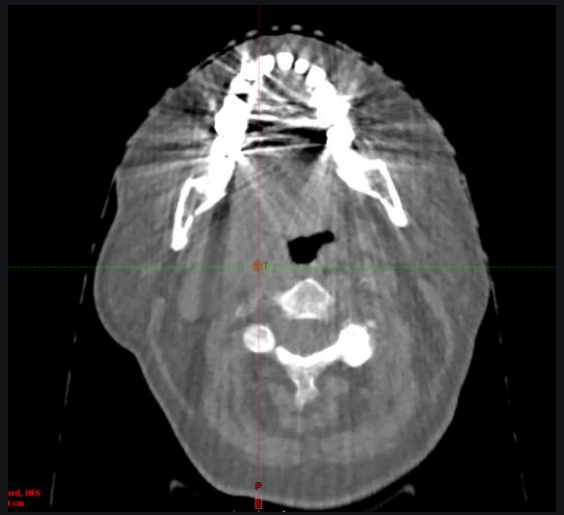
- machines actuelles et doses « actuelles »
- limites des doses « actuelles », incertitudes
- machines innovantes et doses « innovantes »
  - Seminars unconventional radiotherapy techniques
- niveau d'évidence
- considérations médico-économiques

D’où je parle

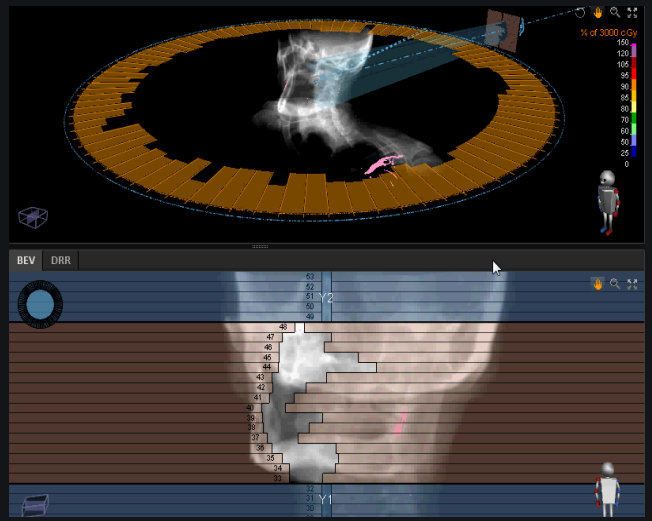
Accélérateurs linéaires 6 MV

Machines actuelles : radiobiologie

La seule règle quantitative utilisée en clinique est le modèle linéaire quadratique

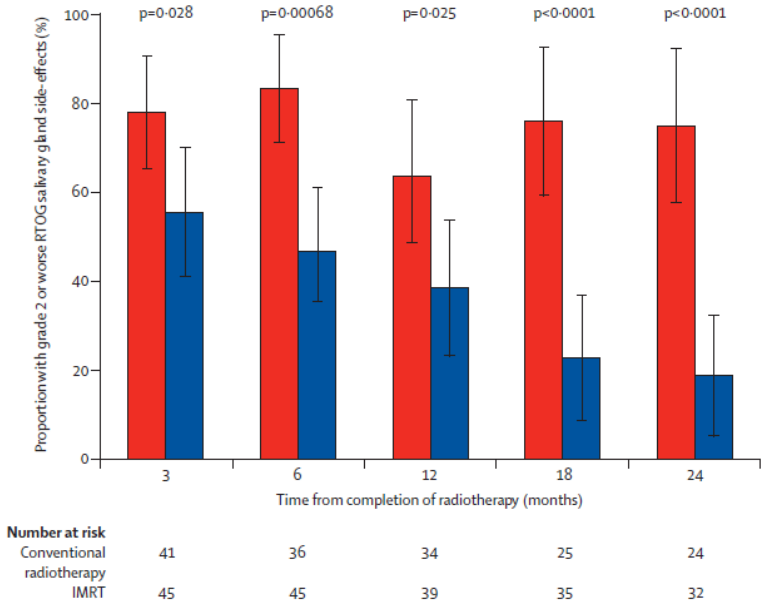


CT ou CBCT avant chaque séance



VMAT

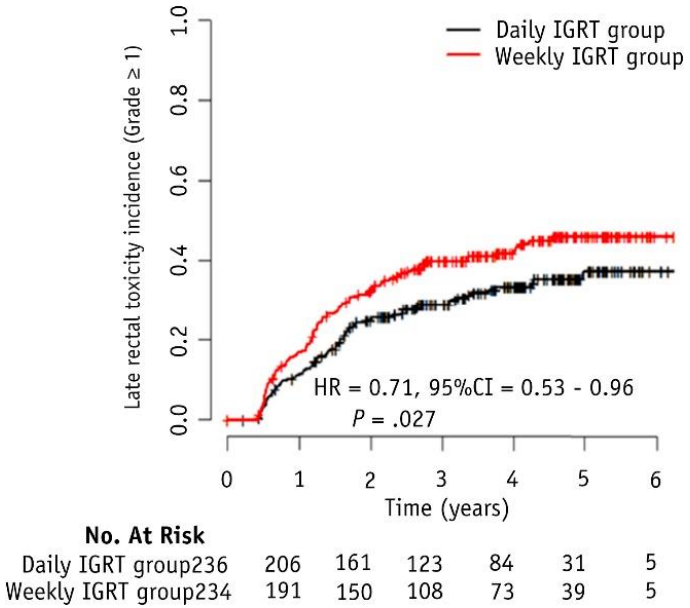
Machines actuelles : IMRT/VMAT



Effet différentiel > 50%

📖 Nutting, C. M. *et al.* Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): A phase 3 multicentre randomised controlled trial. *Lancet Oncol.* (2011).

Machines actuelles : IGRT



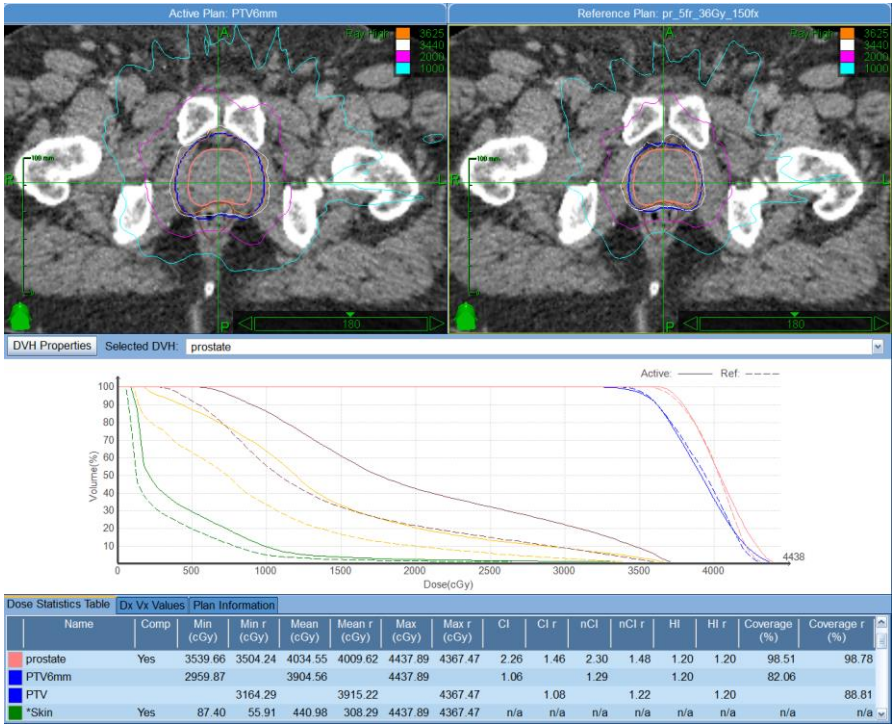
No. At Risk						
Daily IGRT group236	206	161	123	84	31	5
Weekly IGRT group234	191	150	108	73	39	5

Effet différentiel > 25%

📖 de Crevoisier, R. *et al.* Daily Versus Weekly Prostate Cancer Image Guided Radiation Therapy: Phase 3 Multicenter Randomized Trial. *Int. J. Radiat. Oncol. Biol. Phys.* (2018).

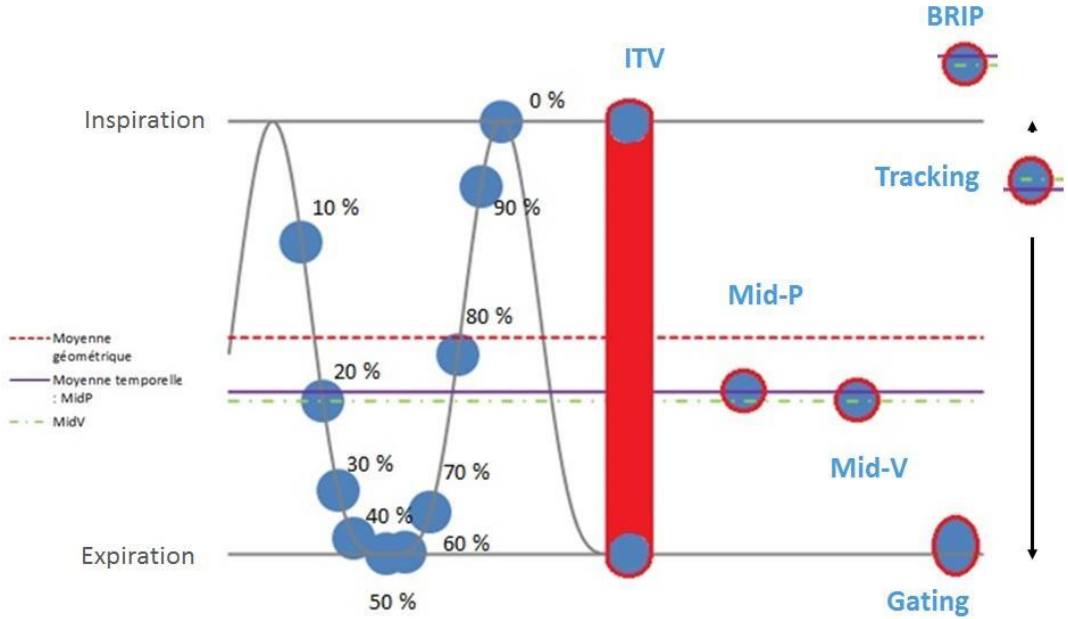
Machines actuelles : IGRT

marge PTV = 6 mm vs 3 mm



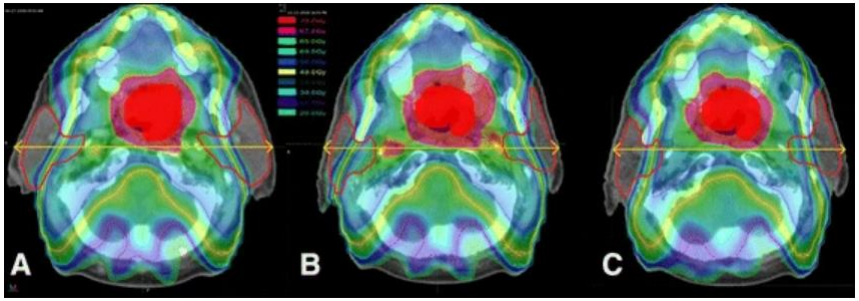
Name	Comp	Min (cGy)	Min r (cGy)	Mean (cGy)	Mean r (cGy)	Max (cGy)	Max r (cGy)	CI	CI r	nCI	nCI r	HI	HI r	Coverage (%)	Coverage r (%)
prostate	Yes	3539.66	3504.24	4034.55	4009.62	4437.89	4367.47	2.26	1.46	2.30	1.48	1.20	1.20	98.51	98.78
PTV6mm		2959.87		3904.56		4437.89		1.06		1.29		1.20		82.06	
PTV			3164.29		3915.22		4367.47		1.08		1.22		1.20		88.81
*Skin	Yes	87.40	55.91	440.98	308.29	4437.89	4367.47	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

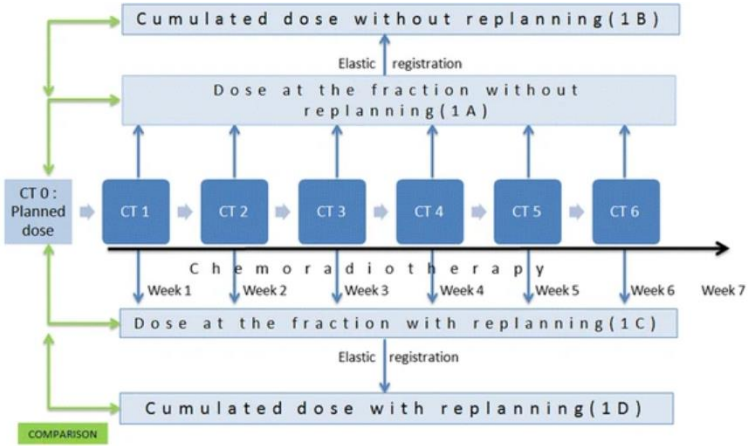
Machines actuelles : mouvements respiratoires



📖 Rapport SFPM n°38 Gestion des mouvements internes en radiothérapie externe : dispositifs et mise en œuvre pour le traitement des patients

Machines actuelles : RT adaptative



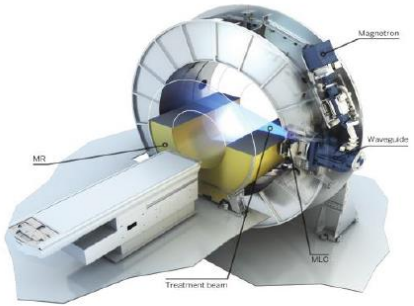


📖 Castelli, J., et al. (2015). Impact of head and neck cancer adaptive radiotherapy to spare the parotid glands and decrease the risk of xerostomia. *Radiation Oncology*

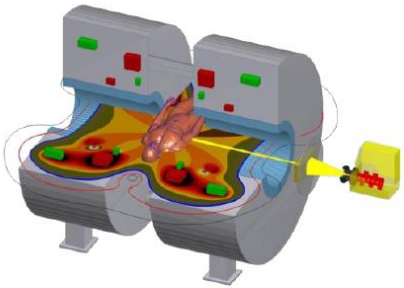
📖 Castelli, J., et al, (2023). Weekly Adaptive Radiotherapy vs Standard Intensity-Modulated Radiotherapy for Improving Salivary Function in Patients With Head and Neck Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncology*

Machines actuelles : RT adaptative, MR-linac

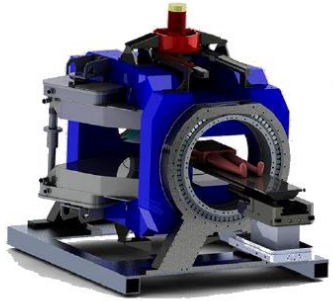
Elekta

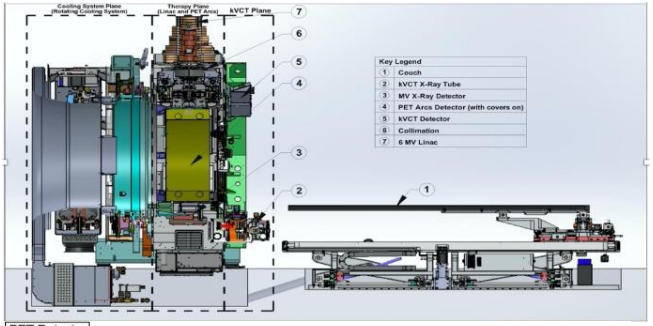


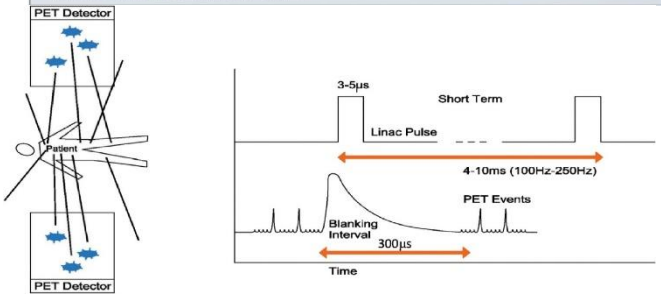
Australia



Alberta

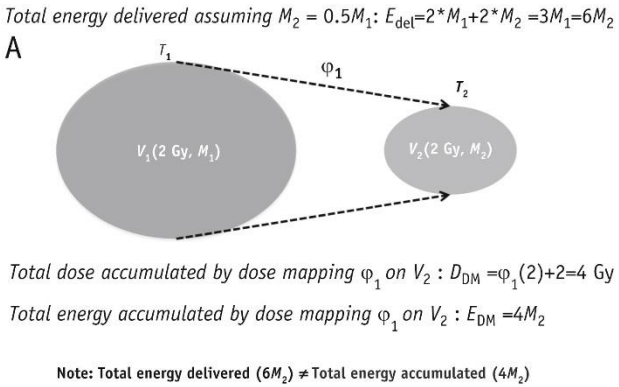


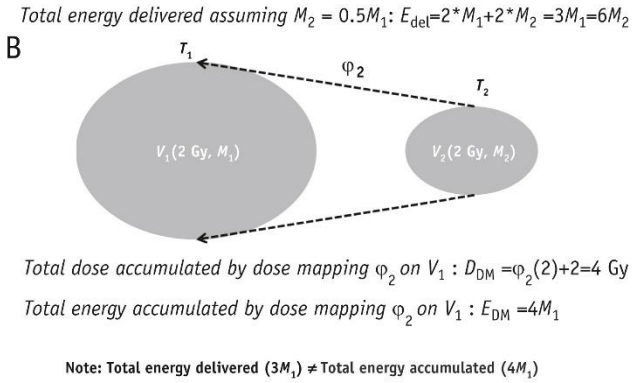




📖 Oderinde, O. M. *et al.* The technical design and concept of a PET/CT linac for biology-guided radiotherapy. *Clin. Transl. Radiat. Oncol.* (2021).

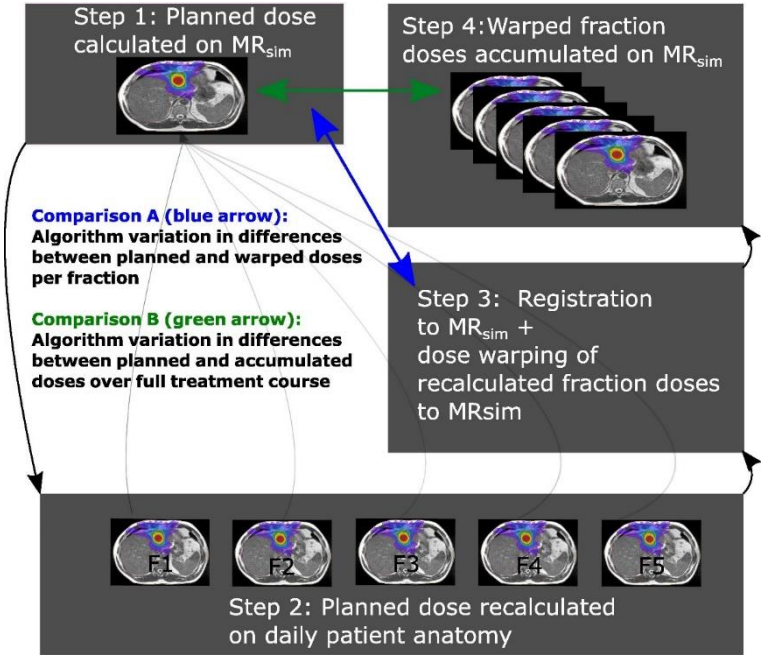
Cumul de dose

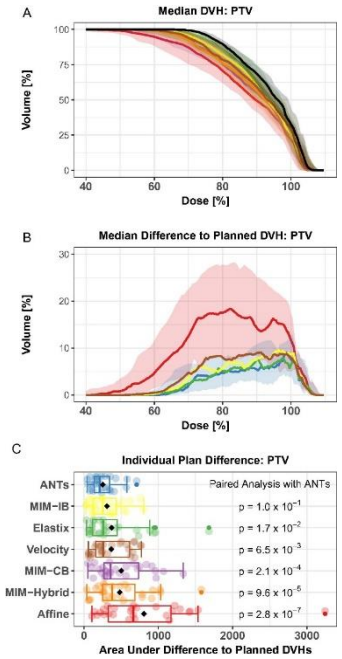




📖 Zhong, H. & Chetty, I. J. Caution Must Be Exercised When Performing Deformable Dose Accumulation for Tumors Undergoing Mass Changes During Fractionated Radiation Therapy. *Int. J. Radiat. Oncol. Biol. Phys.*

Incertitudes ++ sur le cumul de dose

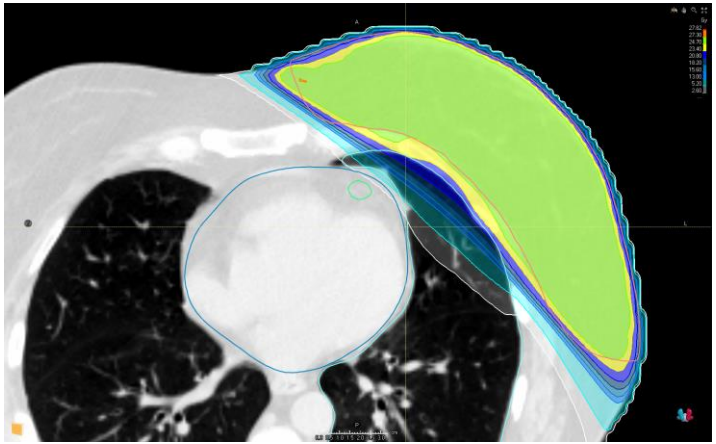




📖 Wahlstedt, I. *et al.* Interfractional dose accumulation for MR-guided liver SBRT: Variation among algorithms is highly patient- and fraction-dependent. *Radiother. Oncol.* (2023).

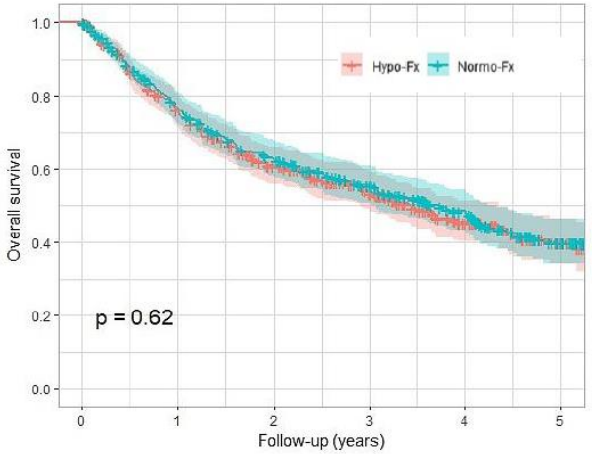
Machines actuelles : hypofractionnement

Prostate : PACE-B



Sein : Fast-Forward

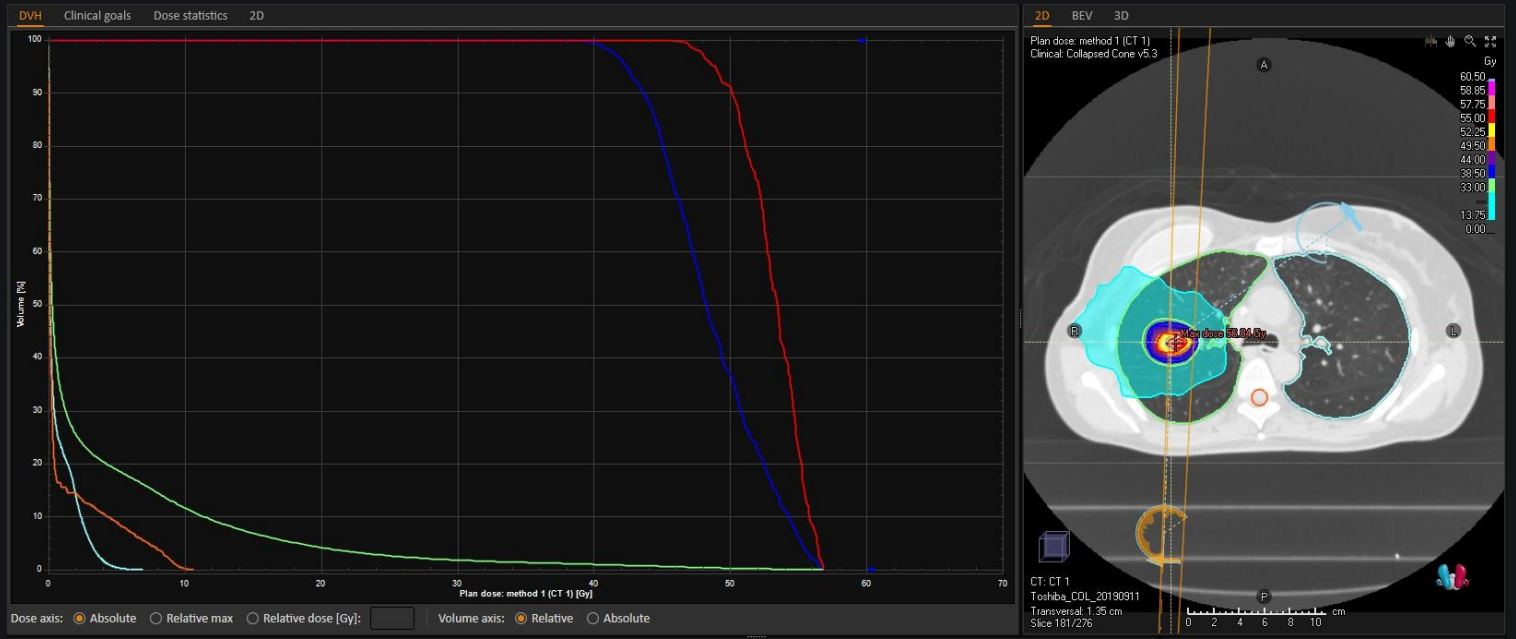
Machines actuelles : hypofractionnement



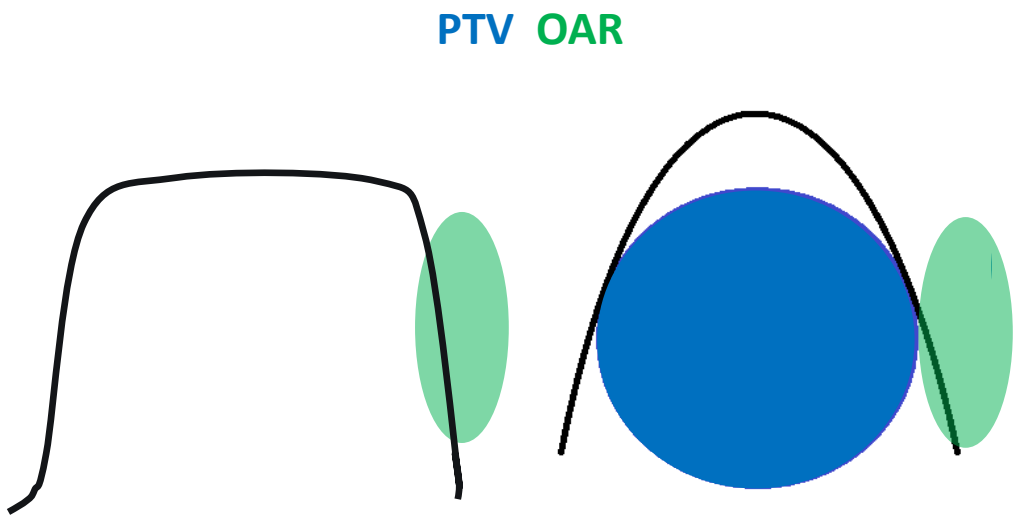
ORL : HYPNO 35 vs 20 séances

Machines actuelles : stéréotaxie

Ex : 3 x 18 Gy



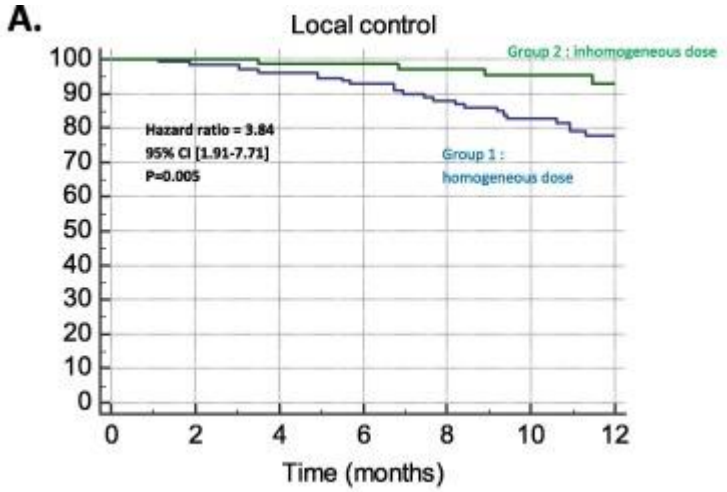
Machines actuelles : stéréotaxie



« isodose de couverture »

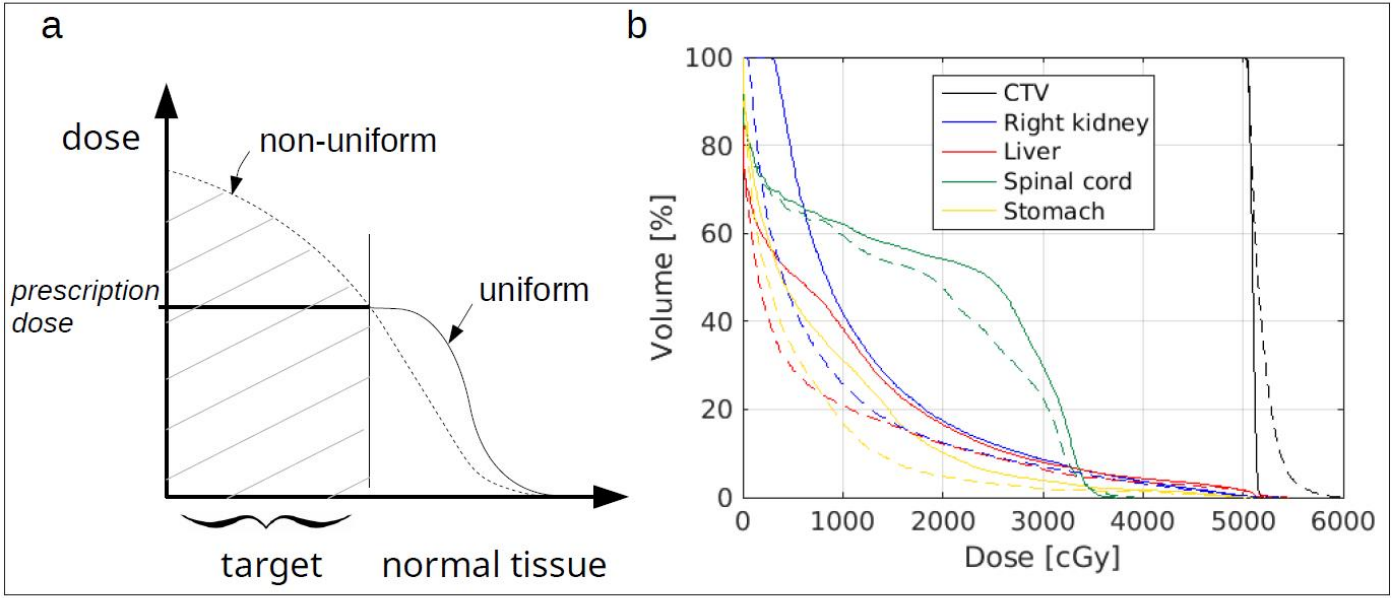
Machines actuelles : stéréotaxie

Est-ce la dose périphérique qui caractérise le contrôle local ?



📖 F. Lucia *et al.*, “Inhomogeneous tumor dose distribution provides better local control than homogeneous distribution in stereotactic radiotherapy for brain metastases,” *Radiother. Oncol.*, 2019.

Machines actuelles : stéréotaxie



📖 The Price of Target Dose Uniformity Craft, D. et al.(2016). *IJROBP*

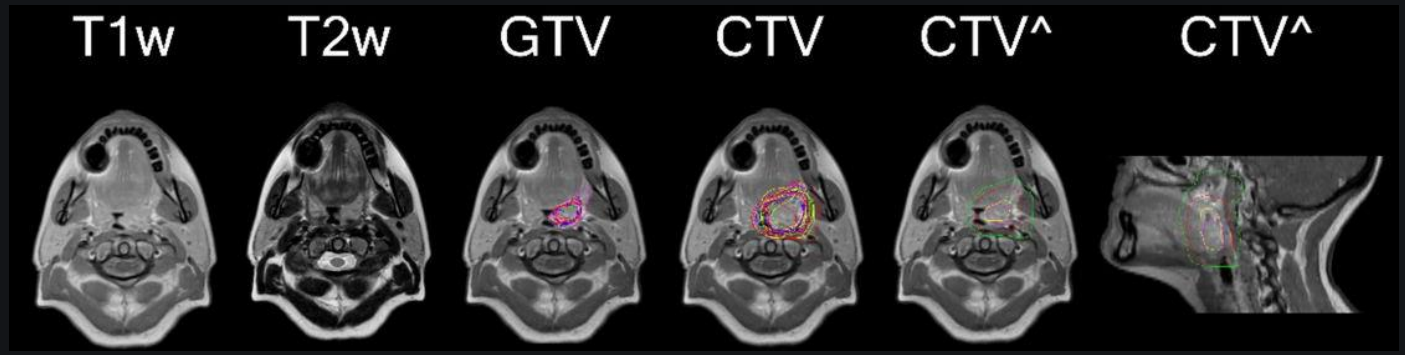
Limites des doses « actuelles », incertitudes

- Même dose pour tous les patients (même avec la radiothérapie adaptative) selon la pathologie
- Dose homogène vs dose inhomogène pour la stéréotaxie
- Pas de modélisation de l’effet volume
- Radiobiologie fruste
- Progrès significatifs envers les toxicités, modérés sur le contrôle

Limites des doses « actuelles », incertitudes

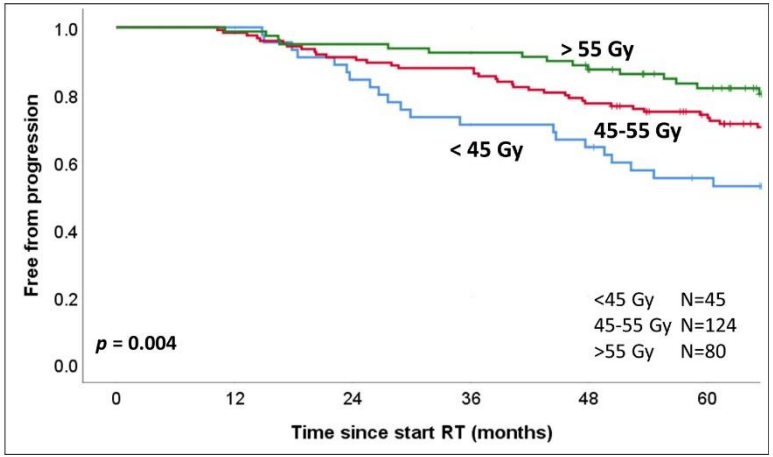
- Incertitudes : volume cible : GTV et CTV

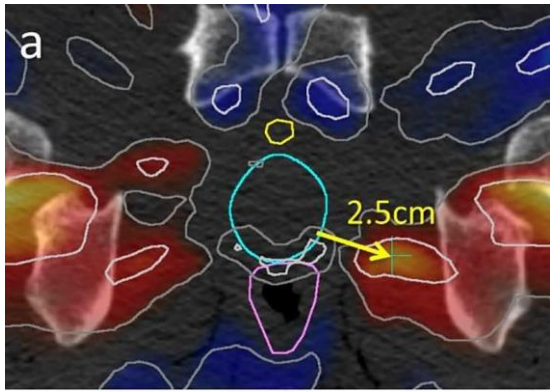
  variabilité inter-opérateur



📖 Cardenas, C. E. *et al.* Comprehensive Quantitative Evaluation of Variability in Magnetic Resonance-Guided Delineation of Oropharyngeal Gross Tumor Volumes and High-Risk Clinical Target Volumes: An R-IDEAL Stage 0 Prospective Study. *IJROBP. 2022*

Limites des doses « actuelles », incertitudes





📖 Witte, M., et al, Association between incidental dose outside the prostate and tumor control after modern image-guided radiotherapy. *Phys. Imaging Radiat. Oncol.* (2021).

Limites des doses « actuelles », incertitudes

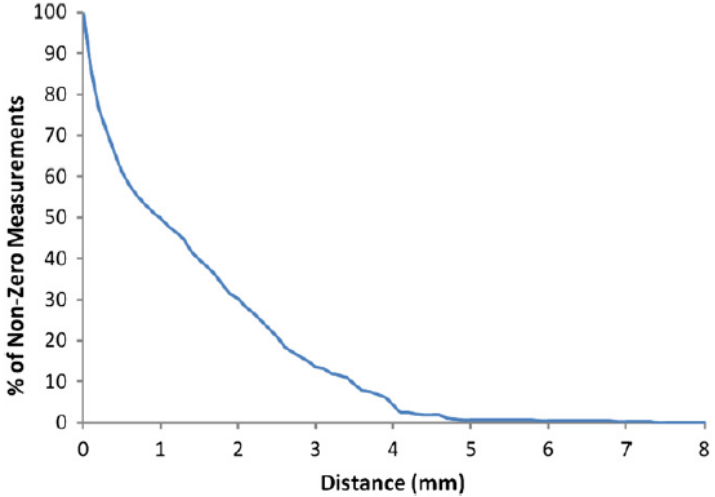
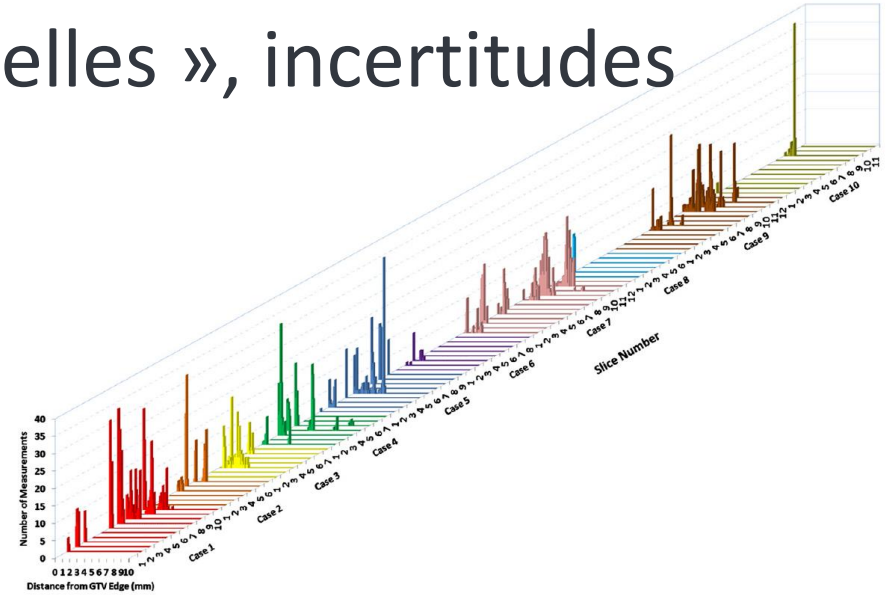
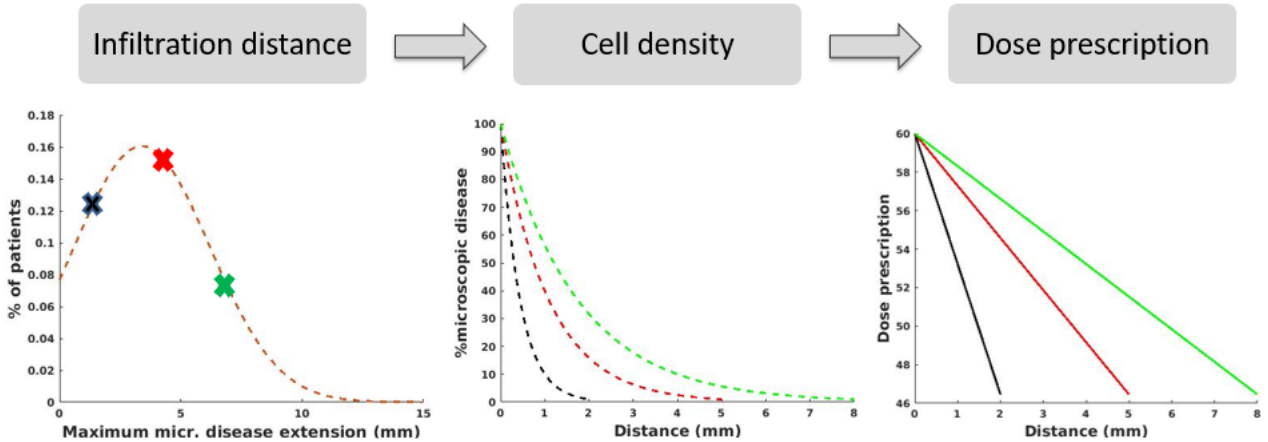


Fig. 8. Graph showing the percentage of nonzero measurements against distance from the gross tumor volume.



📖 Campbell, S. *et al.* Evaluation of microscopic disease in oral tongue cancer using whole-mount histopathologic techniques: Implications for the management of head-and-neck cancers. *IJROBP* (2012).

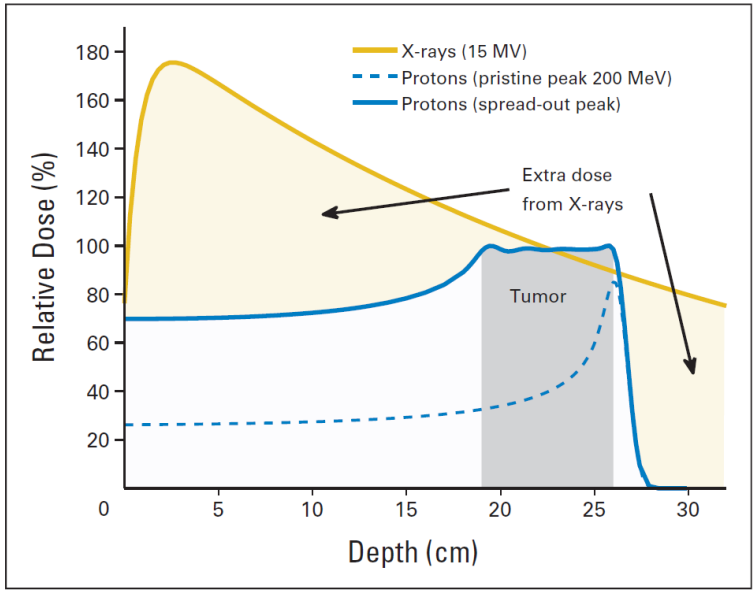
variable dose prescription according to cell density



Avec la permission d'Edmond Sterpin

Machines innovantes

Protonthérapie



📖 Mitin, T., et al. (2014). Promise and Pitfalls of Heavy-Particle Therapy. *Journal of Clinical Oncology*

Machines innovantes

Protonthérapie

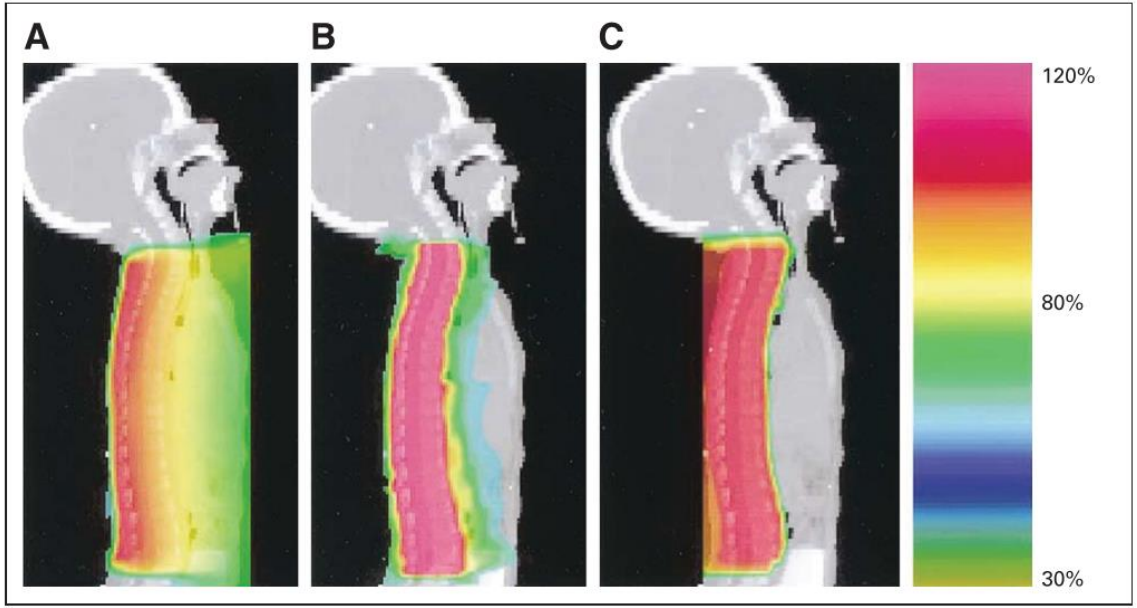


Fig 2. Isodose distribution in the sagittal projection along the spinal column for (A) x-rays, (B) intensity-modulated radiation therapy, and (C) protons.

Machines innovantes

Protonthérapie

Cochrane Library

Cochrane Database of Systematic Reviews

Protons versus photons for the treatment of chordoma (Review)

El Sayed I, Trifiletti DM, Lehrer EJ, Showalter TN, Dutta SW

Main results

We included six observational studies with 187 adult participants. We judged all studies to be at high risk of bias. Four studies were included in meta-analysis.

We are uncertain if proton compared to photon therapy worsens or has no effect on local control (hazard ratio (HR) 5.34, 95% confidence interval (CI) 0.66 to 43.43; 2 observational studies, 39 participants; very low-certainty evidence).

Machines innovantes

Carbon ion therapy

“ Only 5% of all of the CIRT trials reviewed here are phase III comparative randomized trials, and none of these involve OS as an endpoint. Only 1 randomized trial involves prostate cancer, which is the most common cancer disease in the Western world, and very few randomized trials have been initiated in the past 3 years.”

📖 Malouff, T. D., Mahajan, A., Krishnan, S., Beltran, C., Seneviratne, D. S., & Trifiletti, D. M. (2020). Carbon Ion Therapy: A Modern Review of an Emerging Technology. In *Frontiers in Oncology*

Doses innovantes

Highlights

- Improvement of therapeutic ratio by novel unconventional radiotherapy approaches.
- Immunomodulation using high-dose spatially fractionated radiotherapy.
- Boosting radiation anti-tumor effects by adding an immune-mediated cell killing.

Doses innovantes

FLASH 40 Gy/s vs 0.1 Gy/s en routine clinique

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Pencil beam scanning proton FLASH maintains tumor control while normal tissue damage is reduced in a mouse model

Brita Singers Sørensen [a,b,*], Mateusz Krzysztof Sitarz [a], Christina Ankjærgaard [c], Jacob G. Johansen [a], Claus E. Andersen [c], Eleni Kanouta [a], Cai Grau [a], Per Poulsen [a,d]

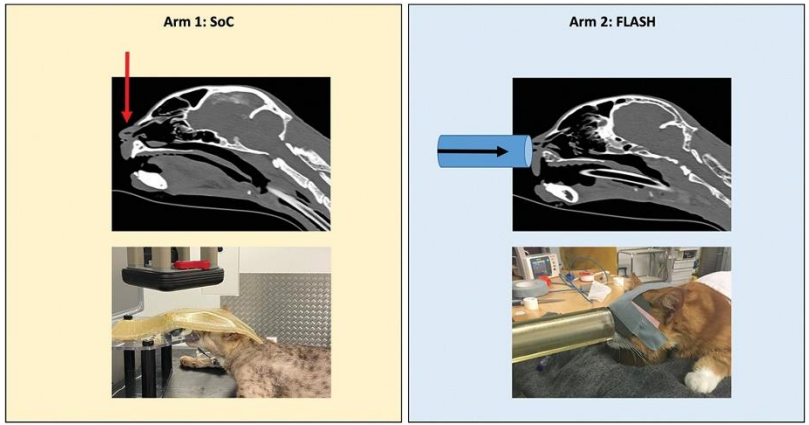
[a] Danish Centre for Particle Therapy, Aarhus University Hospital; [b] Department of Experimental Clinical Oncology, Aarhus University Hospital; [c] DTU Health Tech, Roskilde; and [d] Department of Oncology, Aarhus University Hospital, Denmark

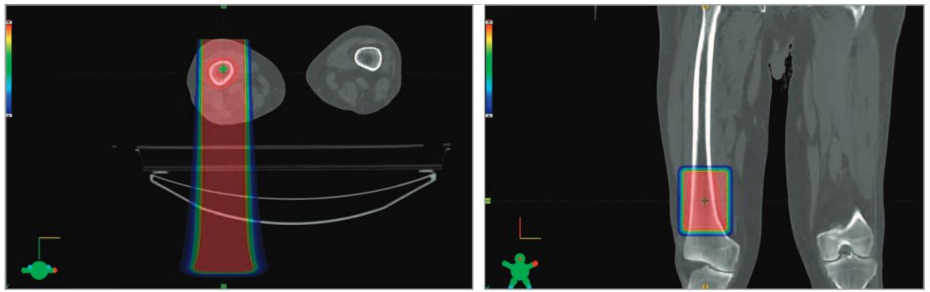
« dose modifying factor for acute skin toxicity, was found to be 1.50 »

« for late tissue damage, (..) dose modifying factor is 1.14 »

Doses innovantes

FLASH 40 Gy/s



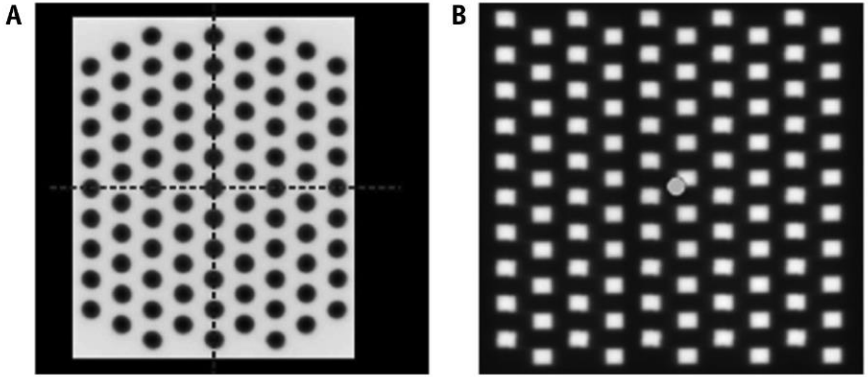


📖 Bley, C. R., et al, (2022). Dose- And Volume-Limiting Late Toxicity of FLASH Radiotherapy in Cats with Squamous Cell Carcinoma of the Nasal Planum and in Mini Pigs. *Clinical Cancer Research*

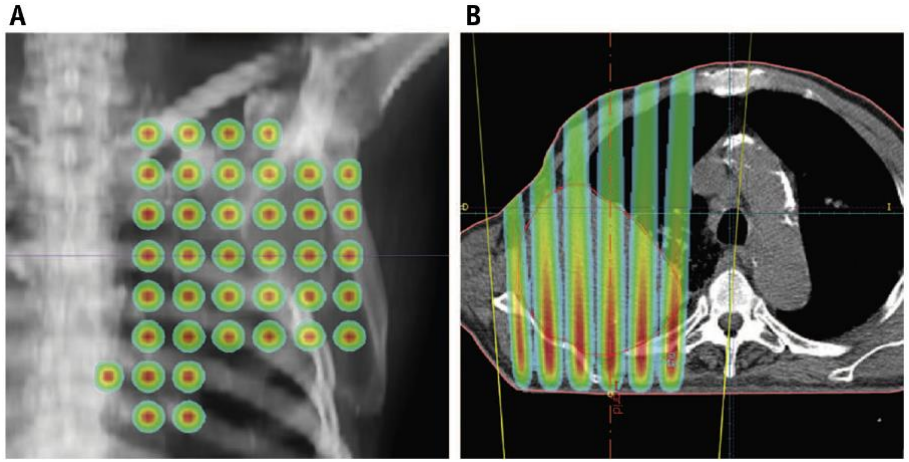
📖 Mascia, A. E., et al, (2023). Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases: The FAST-01 Nonrandomized Trial. *JAMA Oncology*

Doses innovantes

GRID-Therapy

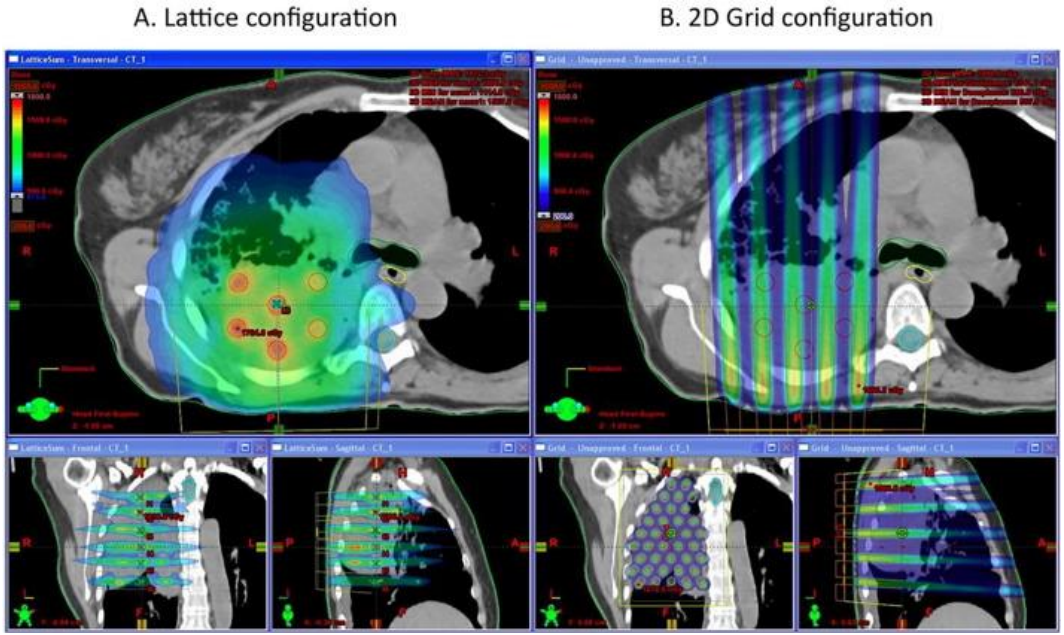


📖 Billena, C., & Khan, A. J. (2019). A Current Review of Spatial Fractionation: Back to the Future? In *International Journal of Radiation Oncology Biology Physics*



Doses innovantes

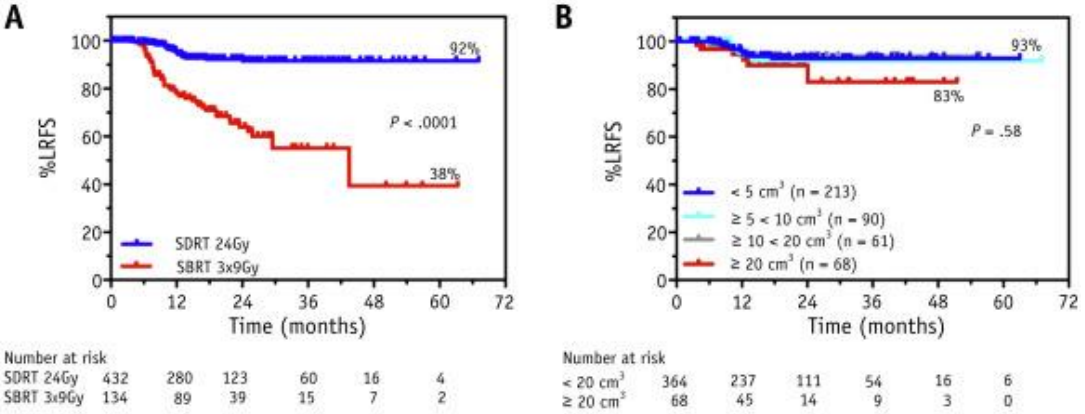
LATTICE



📖Yan, W., et al,(2020). Spatially fractionated radiation therapy: History, present and the future. In *Clinical and Translational Radiation Oncology*

Doses innovantes

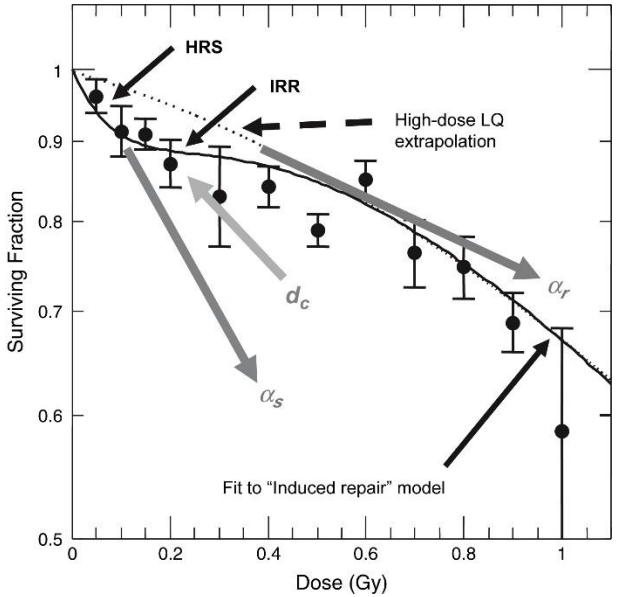
SINGLE DOSE



📖 Greco, C., et al. (2019). Phenotype-Oriented Ablation of Oligometastatic Cancer with Single Dose Radiation Therapy. *International Journal of Radiation Oncology Biology Physics*

Doses innovantes

LOW DOSE

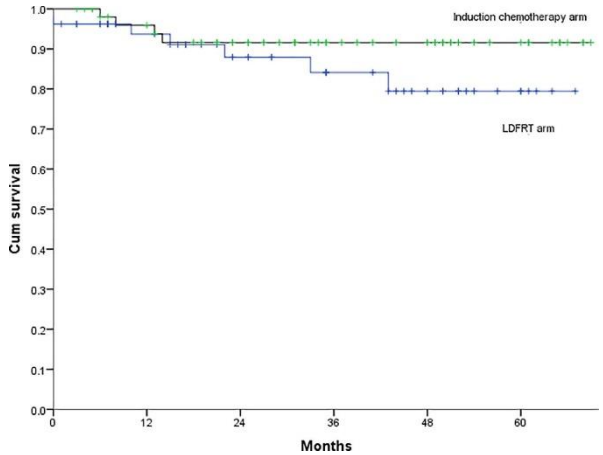


📖 Marples, B., & Collis, S. J. (2008). Low-Dose Hyper-Radiosensitivity: Past, Present, and Future. *International Journal of Radiation Oncology*Biology*Physics*,

Doses innovantes

LOW DOSE FRACTIONATED RADIOTHERAPY

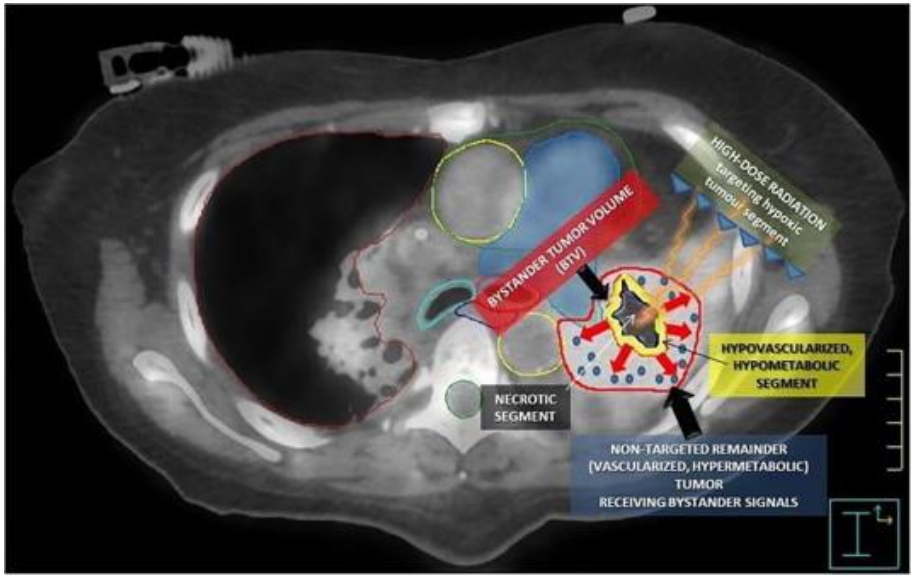
📖 Al-Rajhi, N. M., et al, (2021). Low-dose fractionated radiation with induction docetaxel and cisplatin followed by concurrent cisplatin and radiation therapy in locally advanced nasopharyngeal cancer: A randomized phase II–III trial. *Hematology/ Oncology and Stem Cell Therapy*,



Locoregional-free survival. *Note.* LDFRT = low-dose fractionated radiotherapy

Doses innovantes

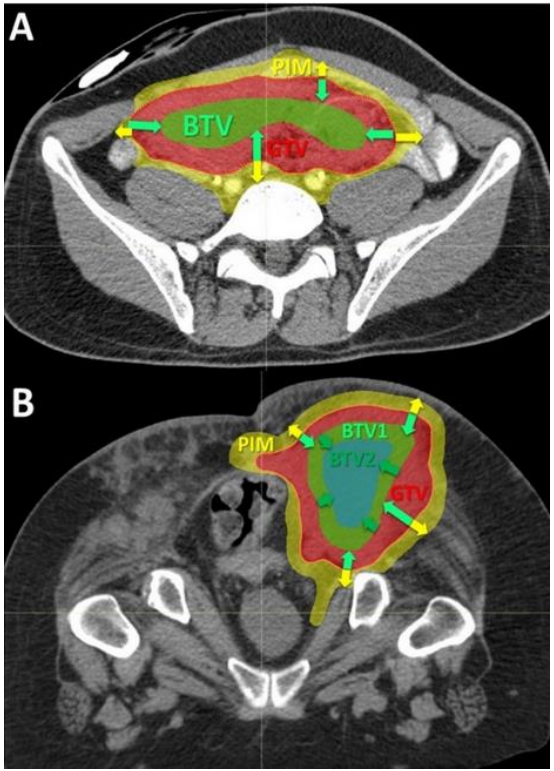
PATHY PArtial Tumor irradiation targeting HYpoxic segment



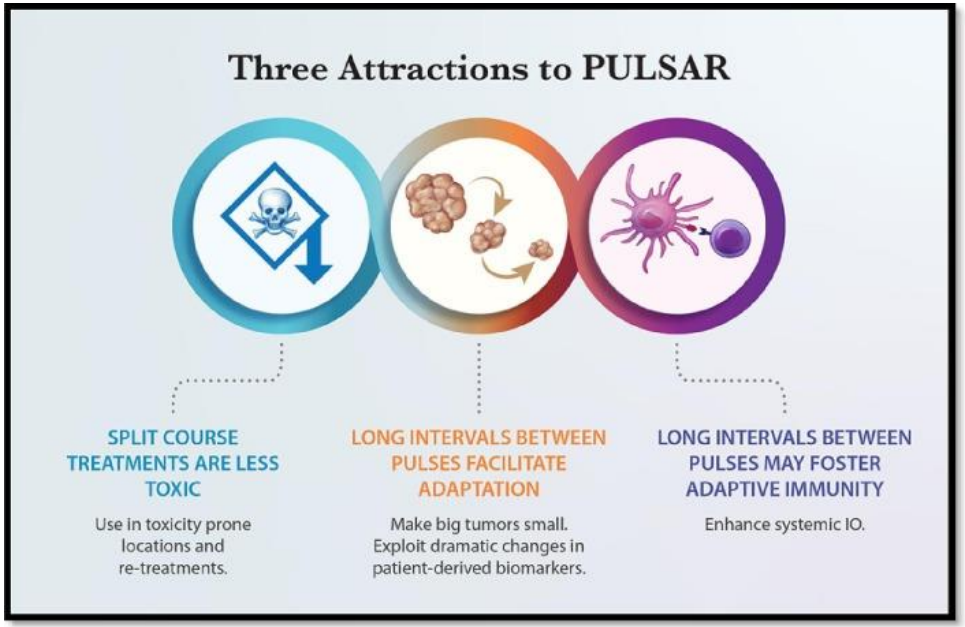
Doses innovantes

PATHY

📖 Tubin, S., Fossati, P., Carlino, A., Martino, G., Gora, J., Stock, M., & Hug, E. (2022). Novel Carbon Ion and Proton Partial Irradiation of Recurrent Unresectable Bulky Tumors (Particle-PATHY): Early Indication of Effectiveness and Safety. *Cancers*,



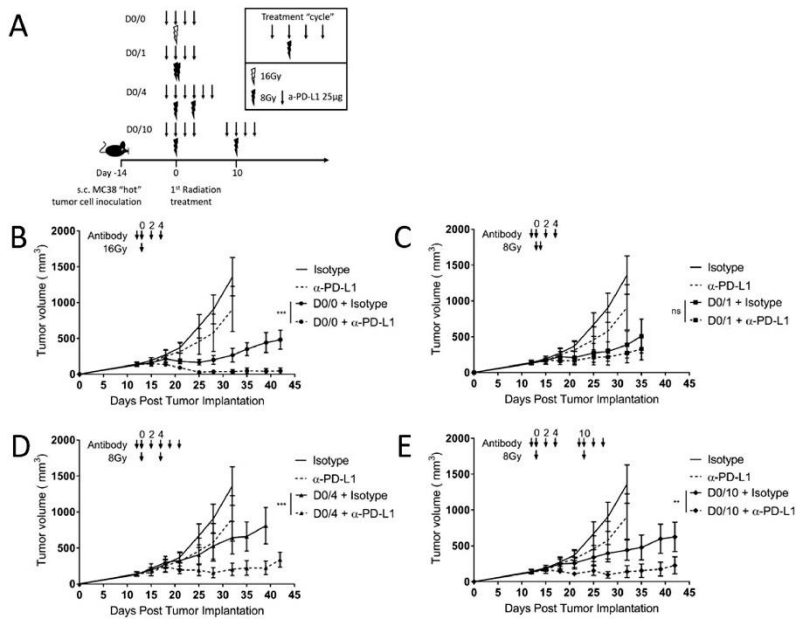
Doses innovantes



Personalized, Ultra-fractionated, Stereotactic, Adaptive Radiotherapy

Doses innovantes

PULSAR

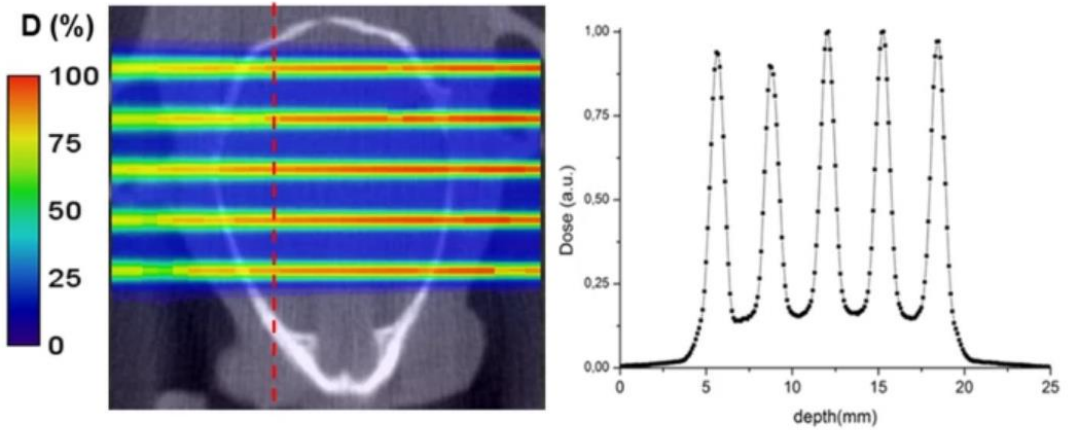


📖 Moore, C. et al,(2021). Personalized Ultrafractionated Stereotactic Adaptive Radiotherapy (PULSAR) in Preclinical Models Enhances Single-Agent Immune Checkpoint Blockade. *International Journal of Radiation Oncology Biology Physics*,

Doses innovantes

MINIBEAMS

Figure 1

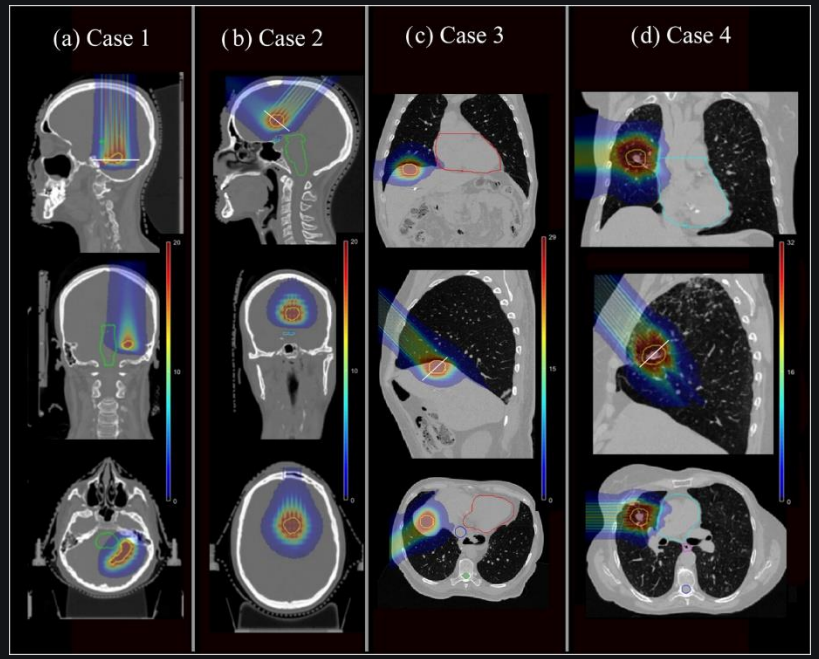


Dosimetry. Left: 2D dose map in the rat head (coronal view). The red line marks the approximate position of the center of the tumor. Right: Corresponding lateral dose profile at the tumor position.

📖 Prezado, Y., et al. (2018). Proton minibeam radiation therapy widens the therapeutic index for high-grade gliomas. *Scientific Reports*

Doses innovantes

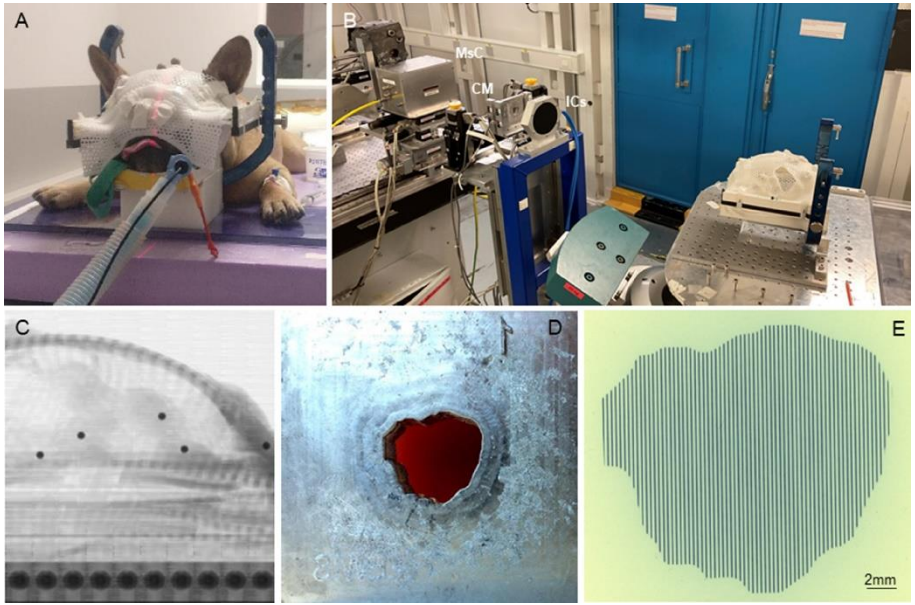
MINIBEAMS



📖Ortiz, et al. (2023). Proton minibeam radiation therapy for treating metastases: A treatment plan study. *Medical Physics*

Doses innovantes

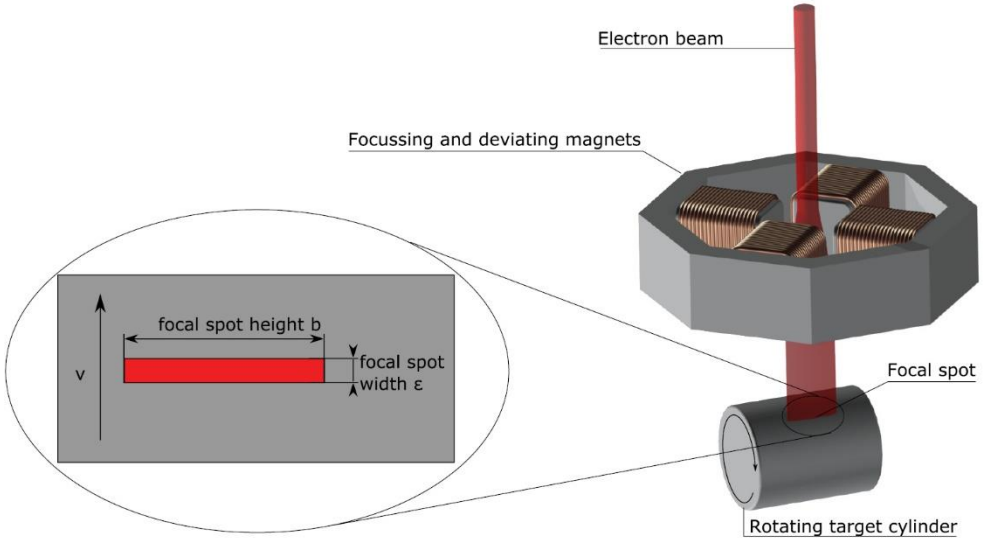
MICROBEAMS



📖 Adam, J. F. et al,(2022). Toward Neuro-Oncologic Clinical Trials of High-Dose-Rate Synchrotron Microbeam Radiation Therapy: First Treatment of a Spontaneous Canine Brain Tumor. *International Journal of Radiation Oncology Biology Physics*,

Doses innovantes

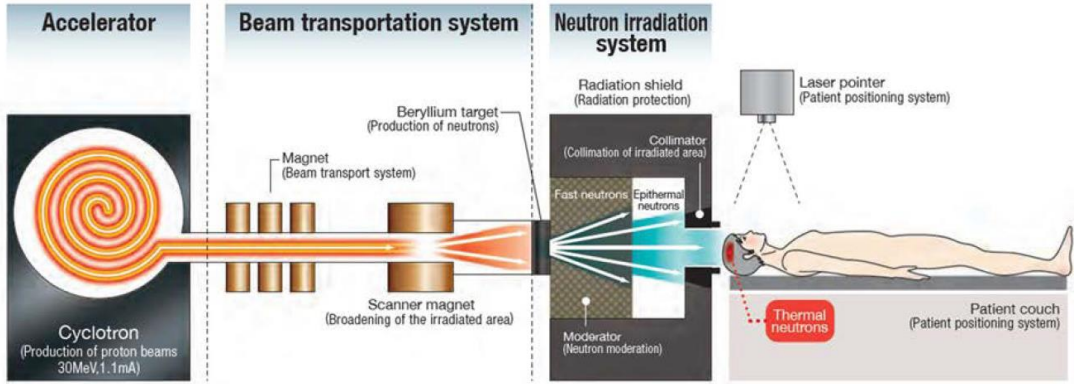
MICROBEAMS

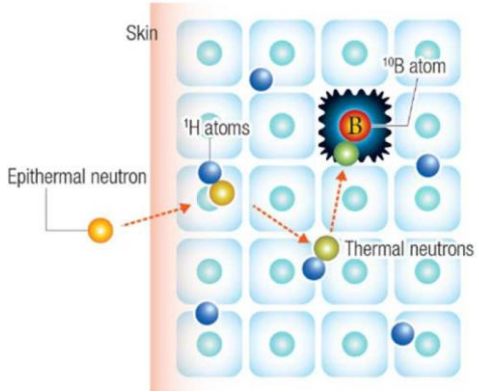


📖 Bartzsch, S., & Oelfke, U. (2017). Line focus x-ray tubes - A new concept to produce high brilliance x-rays. *Physics in Medicine and Biology*

Machines innovantes

BNCT : boron neutron capture therapy

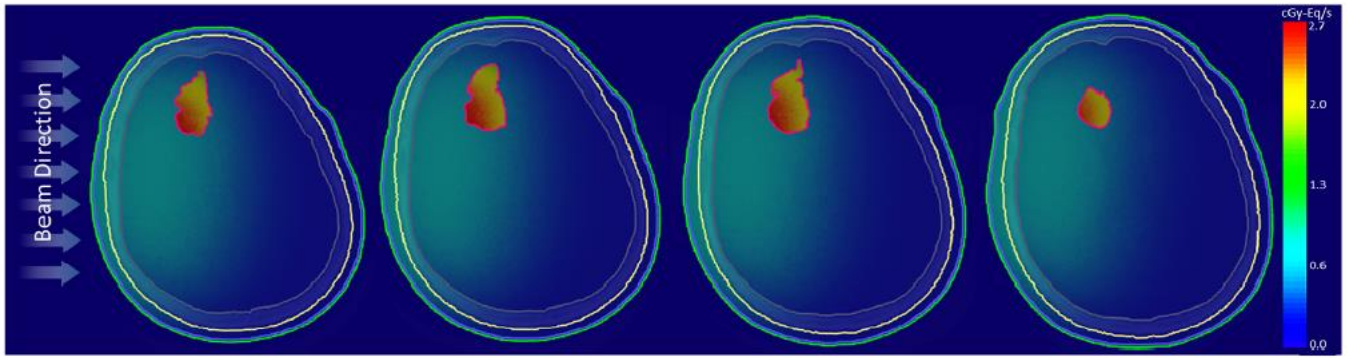




📖 IAEA. (2023). *ADVANCES IN BORON NEUTRON CAPTURE THERAPY*.

Machines innovantes

BNCT

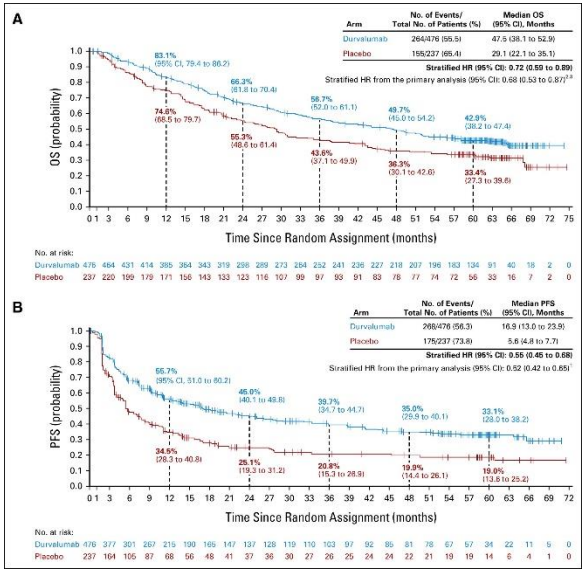


(a)

📖 Teng, Y. C., Chen, J., Zhong, W. B., & Liu, Y. H. (2023). Correcting for the heterogeneous boron distribution in a tumor for BNCT dose calculation. *Scientific Reports*

Considérations médico-économiques

- Peu/pas de soutien de l'industrie
- Niveau de preuve élevé requis pour le remboursement
- Positionnement des nouvelles techniques



📖 Spigel, D. R. *et al.* Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *J. Clin. Oncol.* (2022).

Conclusions

- Liste non exhaustive des pistes explorées (VHEE, nanoparticules …)
- Les effets radiobiologiques et sur le système immunitaire des traitements de routine sont mal connus
- La radiobiologie des techniques innovantes devrait passer par une meilleure radiobiologie de la routine
- Les techniques innovantes doivent avoir le même niveau de précision et de conformité aux cibles que la routine actuelle
- Les techniques innovantes devraient permettre de tenir compte de l'hétérogénéité tumorale et des incertitudes de prise en compte de la maladie microscopique
- La question du cumul des doses doit être résolue

Merci de votre attention

- https://www.youtube.com/watch?v=L4DBZLIUjUg&list=PL5IOhHd3LZtmmS4D7Zm4140ZRWnBGUMeS&index=2
- https://www.estro.org/Congresses/ESTRO-2023/1515/closingdebate--flashiloveyou-butweonlyhave14hourst