Basic Clinical Radiobiology

Particles in Radiotherapy

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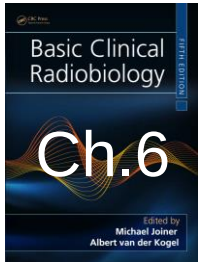
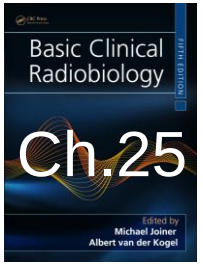




Acknowledgements

- Slides adapted from Dr. Michael Joiner

Learning Objectives

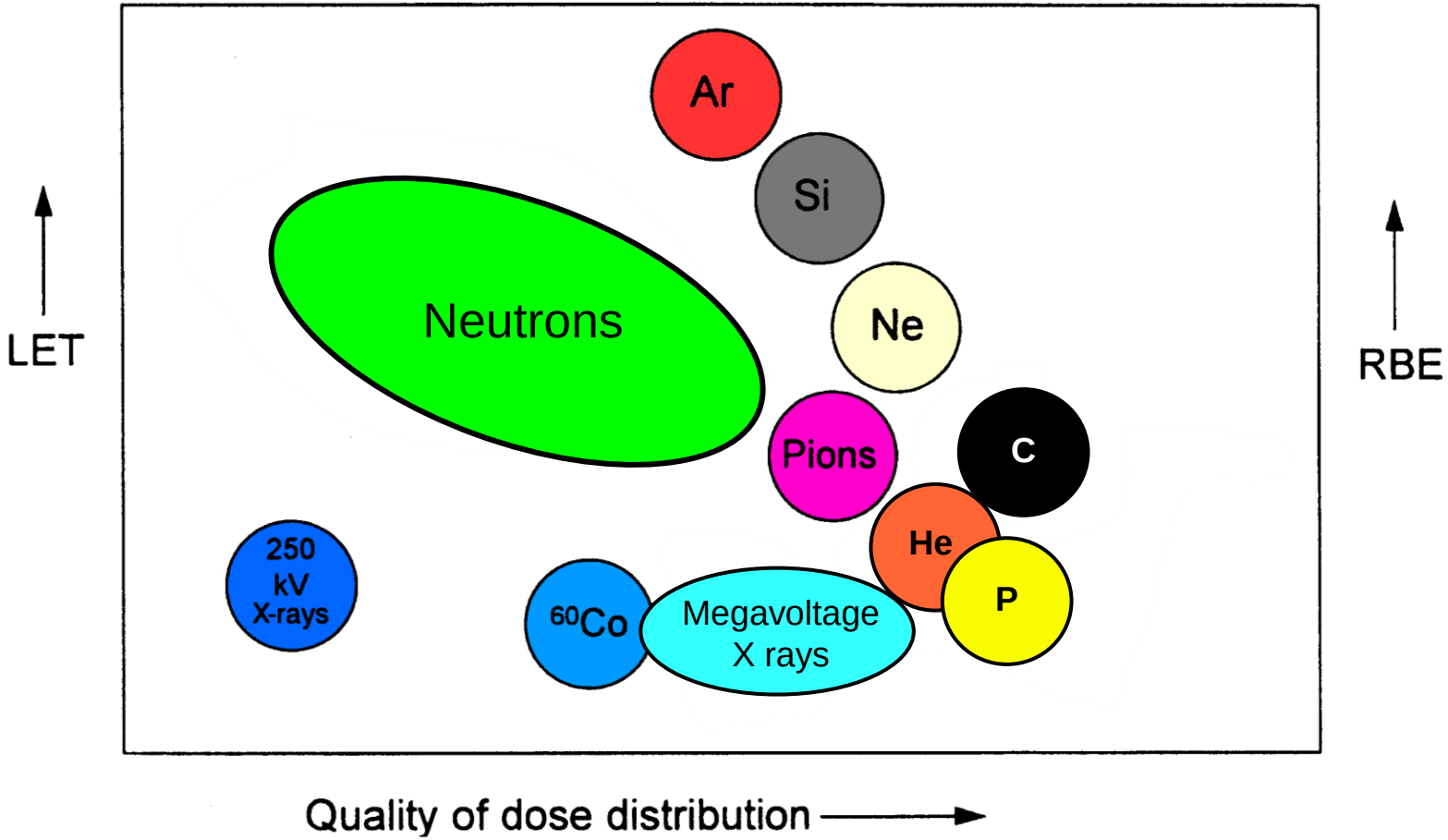
- Define particle therapy
- Understand physical benefits of particle therapy
- Understand radiobiological benefits (and challenges) of particle therapy
- Describe and give examples of clinical uses of particle therapy

Particle Therapy (Hadron Therapy)

- Hadron
  - Any type of subatomic particle made up of quarks and subject to the strong force (two types of hadrons: baryons and mesons)
  - Protons and neutrons are hadrons
  - Hadron or particle therapy refers to radiotherapy using: protons, light-ions or heavy-ions (*and fast neutrons*)
- Light vs Heavy-ions
  - Atomic number is the number of protons in the nucleus of an atom
  - Atomic mass is the number of protons + neutrons
  - Light ions: $z < 6$, heavy ions: $z >= 6$
    - Helium is a light ions
    - Carbon is a heavy ion

Particle Therapy

- Both physical and radiobiological benefits to particle therapy (protons, carbon-ions) compared with conventional (photon) treatment
  - Physical: less dose deposition proximal and distal to the tumor, less scattering
    - Bragg Peak
  - Biological: Higher LET and RBE
    - Impact on both tumor and normal tissues


LET
RBE
Ar
Si
Neutrons
Ne
Pions
C
He
P
250 kV X-rays
60Co
Megavoltage X rays
Quality of dose distribution

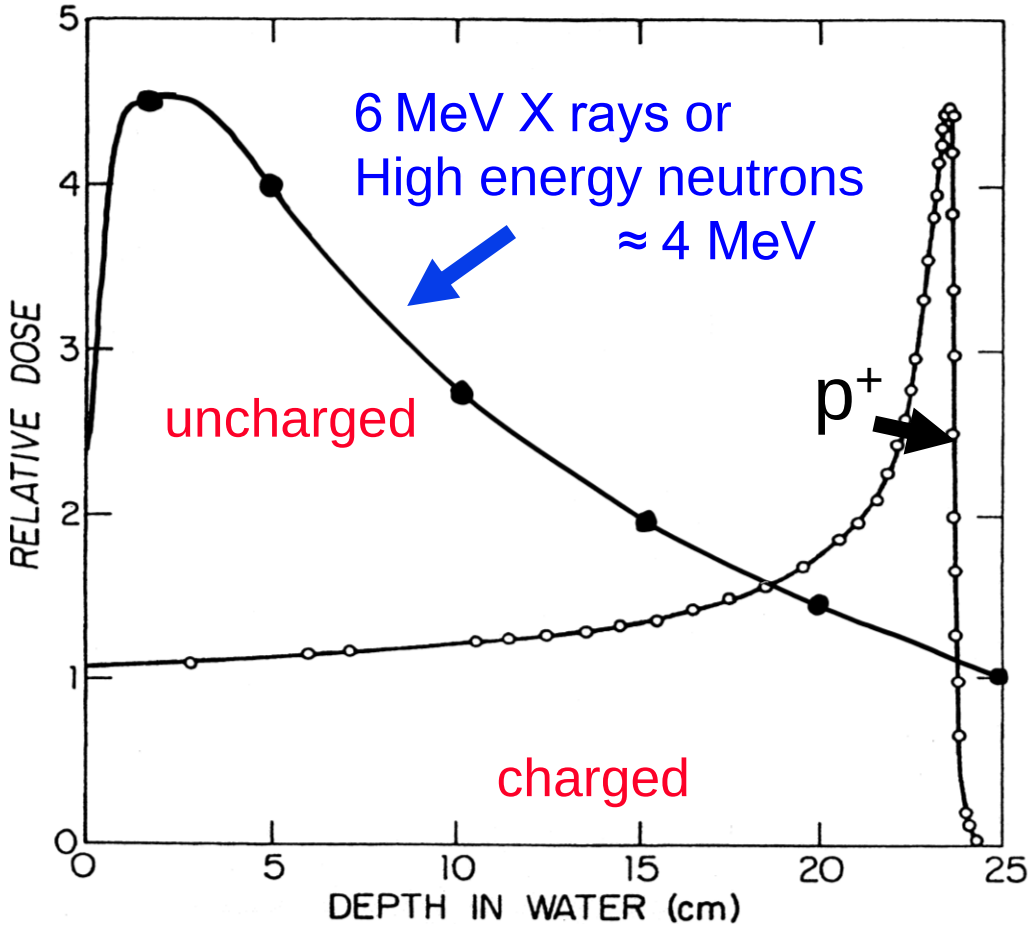
Physical
basis for particle therapy

Uncharged	Charged	
X rays γ rays	e^- p^+ He^{2+}	Low LET
Neutrons	C^{6+} Ne^{10+} Si^{14+} Ar^{18+}	High LET

Physical Benefits of Particle Therapy

- Bragg Peak
- Increasing particle mass -> less influence of scattering and straggling
- Increasing particle mass -> nuclear fragmentations which contributes to dose beyond the Bragg Peak

Bragg Peak


6 MeV X rays or
High energy neutrons
≈ 4 MeV
uncharged
p+
charged
RELATIVE DOSE
DEPTH IN WATER (cm)
0
1
2
3
4
5
0
5
10
15
20
25

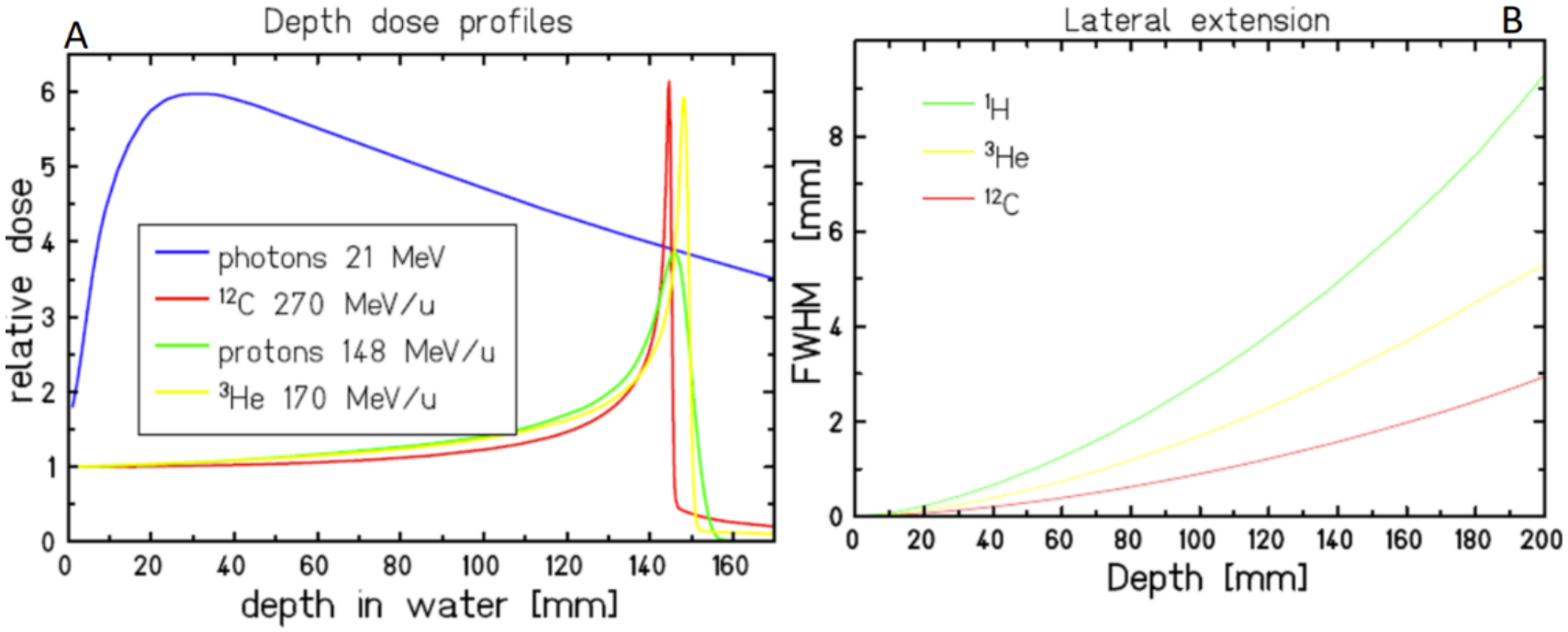
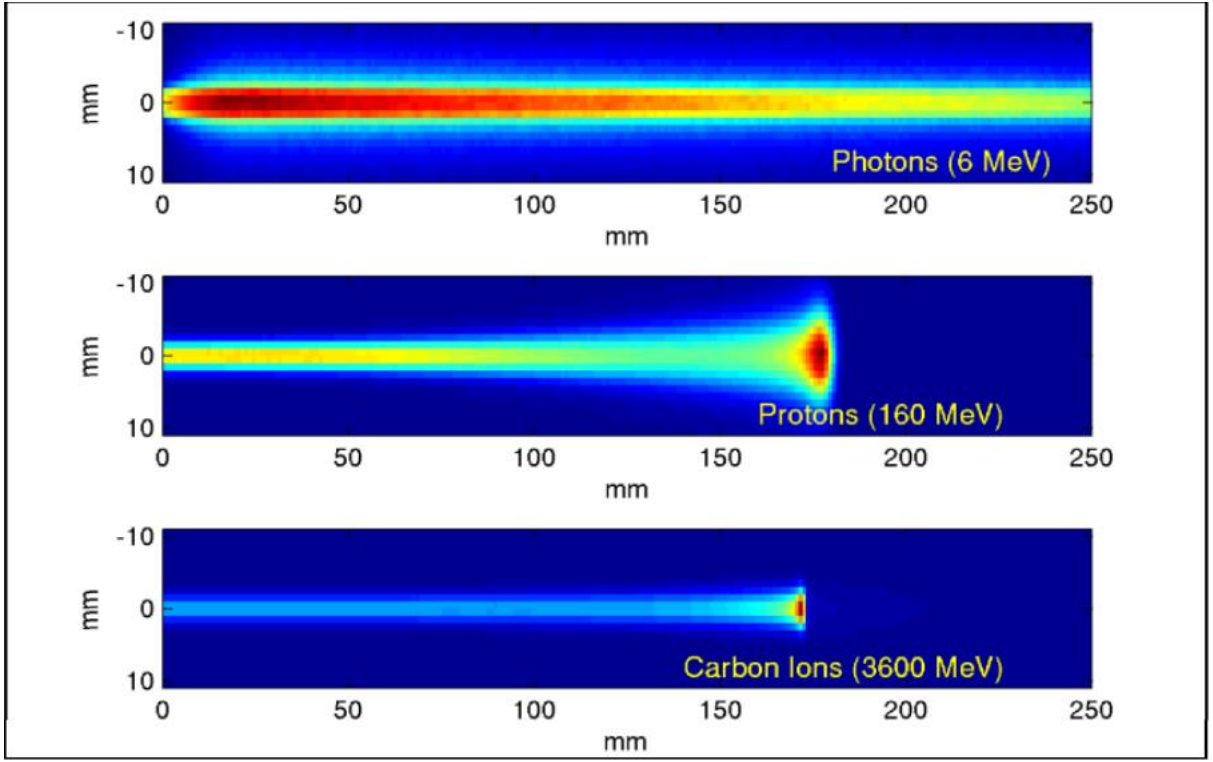


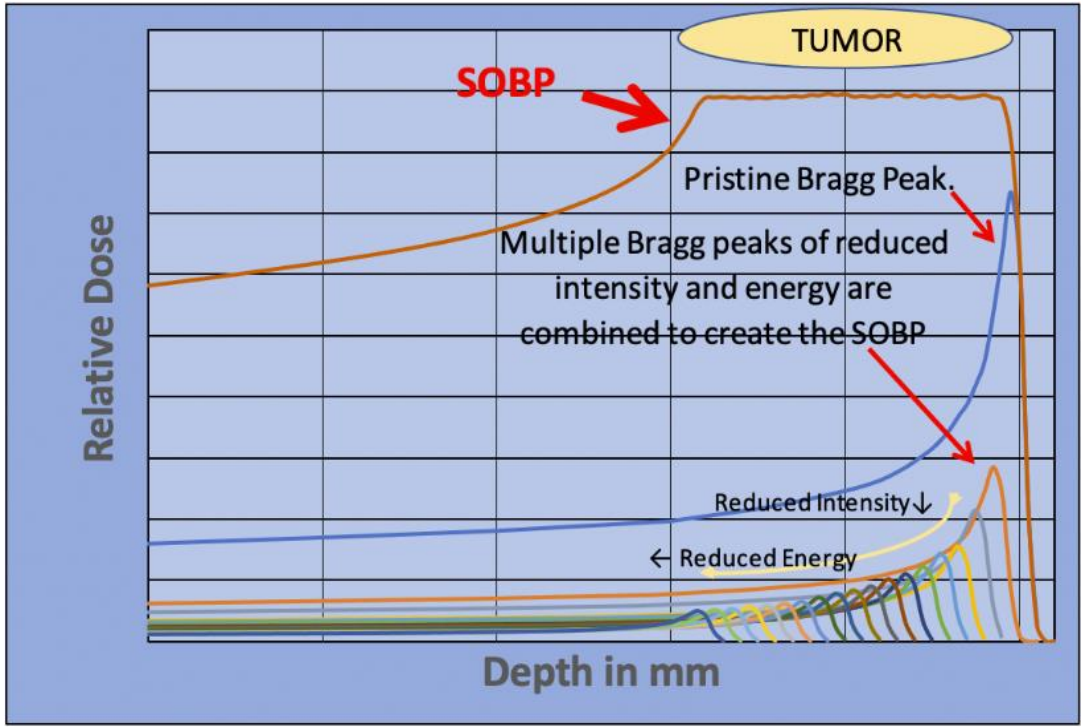
Figure 1. Physical properties of carbon ions in comparison to X-rays, protons, and helium ions. (**A**). Depth-dose distributions showing the Bragg peak for all ions at the same range, and the reduced straggling of heavier ions. (**B**). Lateral scattering is reduced by increasing the ion mass.

cancers
Review
Carbon Ion Radiobiology
Walter Tinganelli [1] and Marco Durante [1,2,*]



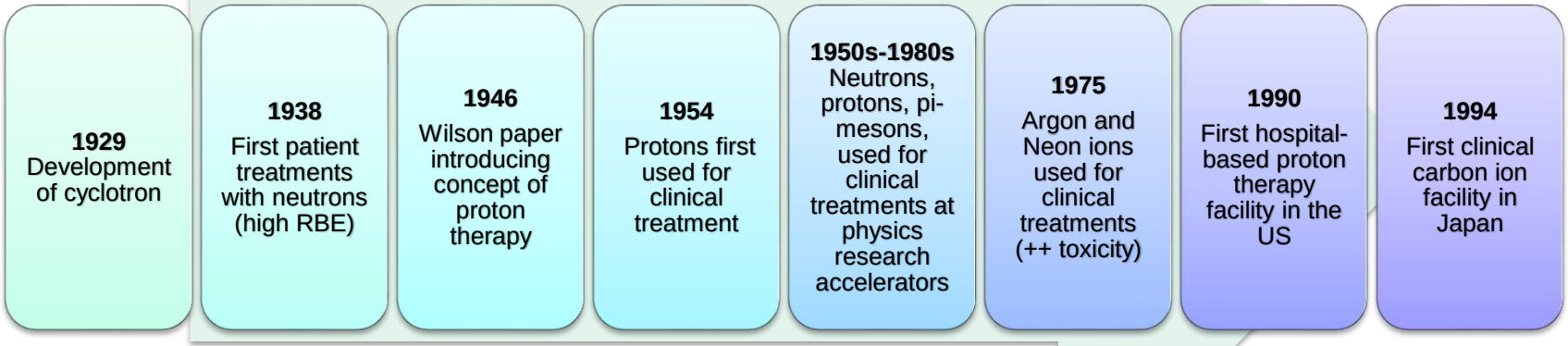
Kraft, History of Heavy ion therapy at GSI

Spread-out Bragg Peak



https://www.oncolink.org/healthcare-professionals/oncolink-university/proton-therapy-professional-education/oncolink-proton-education-modules/the-physics-of-proton-therapy

Brief History of Hadron Therapy



Degiovanni A, Amaldi U. History of hadron therapy accelerators. Phys Med. 2015 Jun;31(4):322-32. doi: 10.1016/j.ejmp.2015.03.002. Epub 2015 Mar 23. PMID: 25812487
Wilson R.R. Radiological use of fast protons. Radiology. 1946;47(5):487–491. doi: 10.1148/47.5.487.

Biological

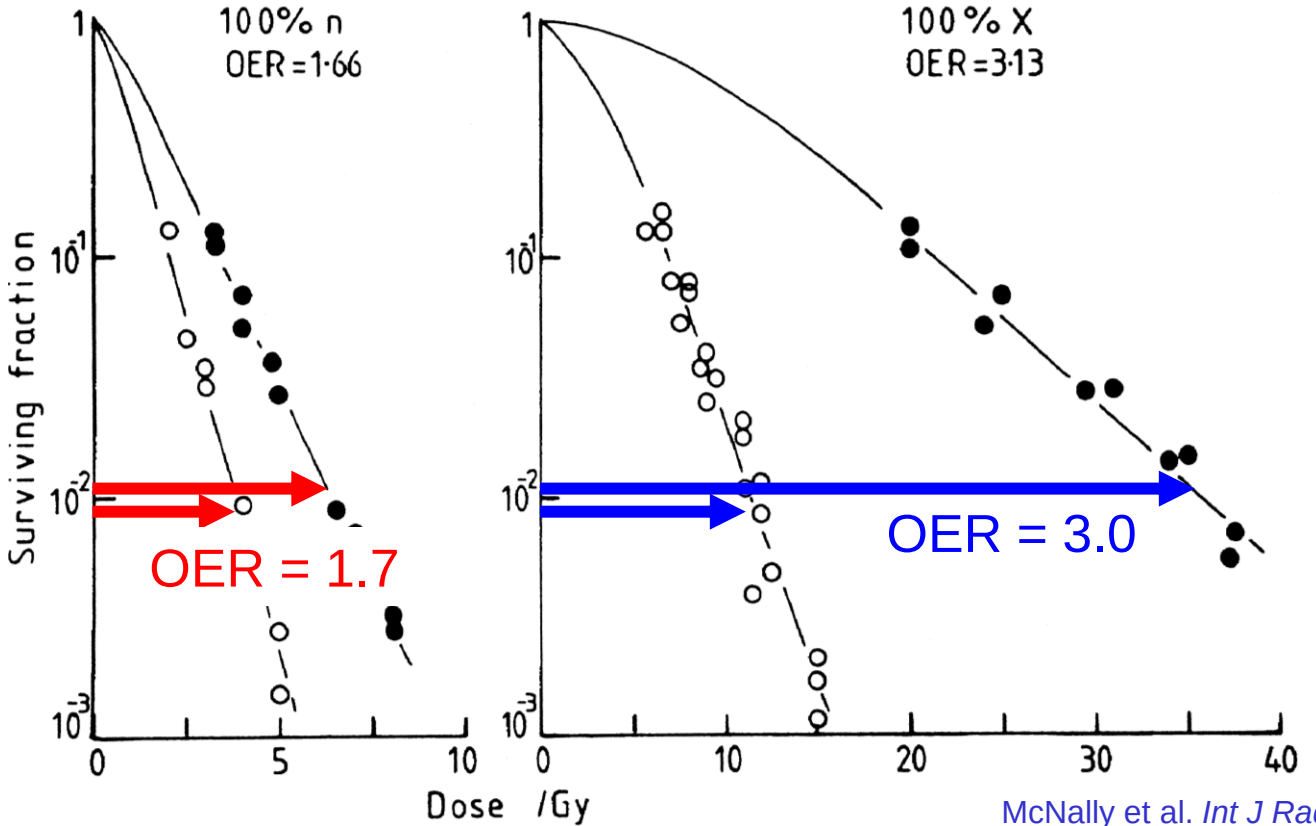
basis for *high-LET* therapy

(*e.g.* carbon ions, neutrons)

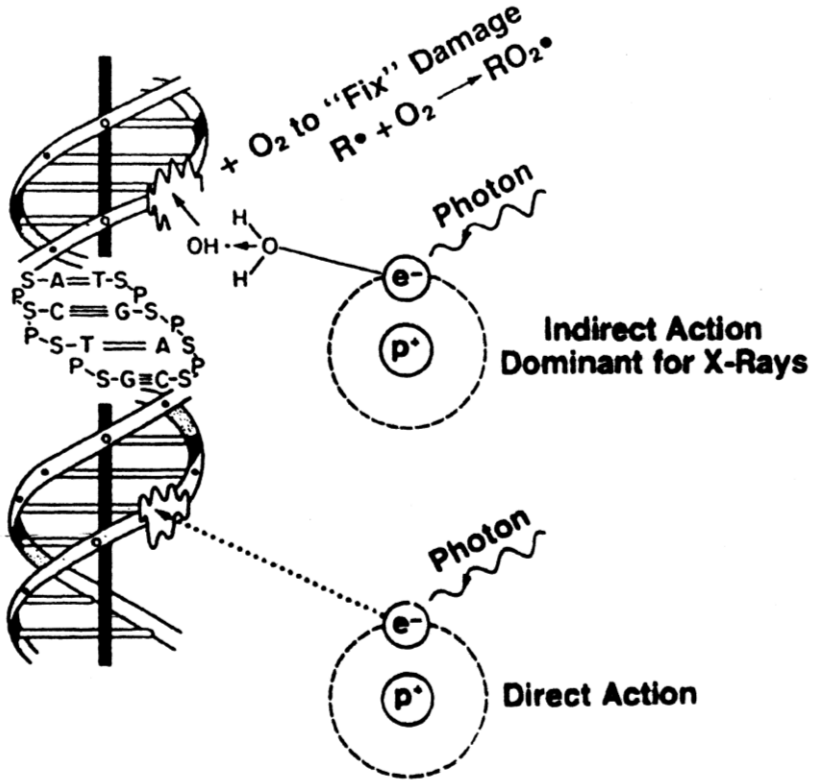
Biological Benefits of High LET Radiotherapy

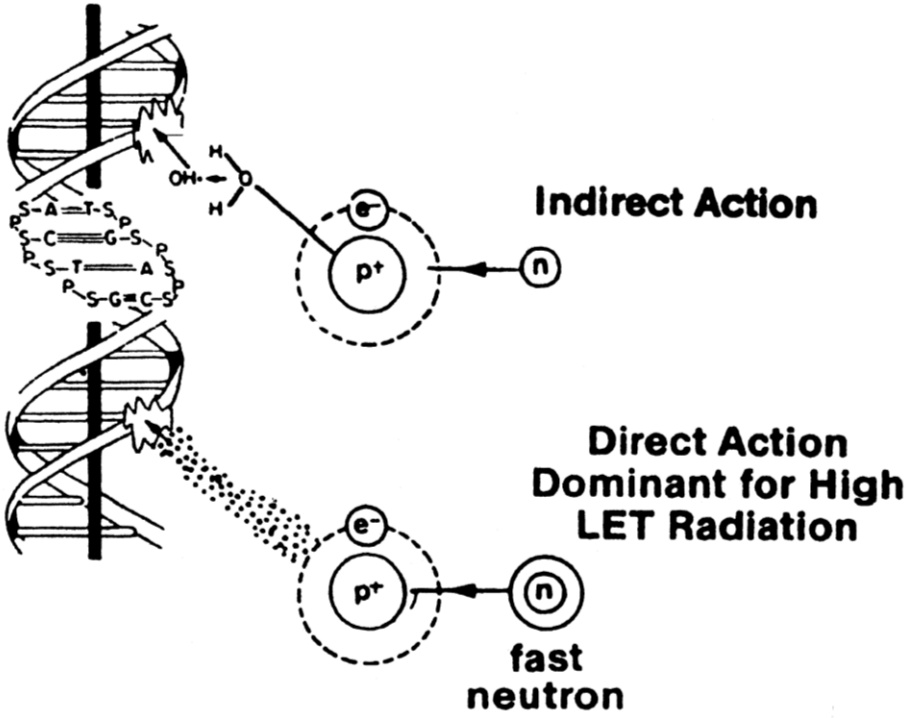
- Decreased influence of oxygen
- Decreased influence of cell cycle position
- Decreased range of radiation response of different cell types

Reduced effect of oxygen

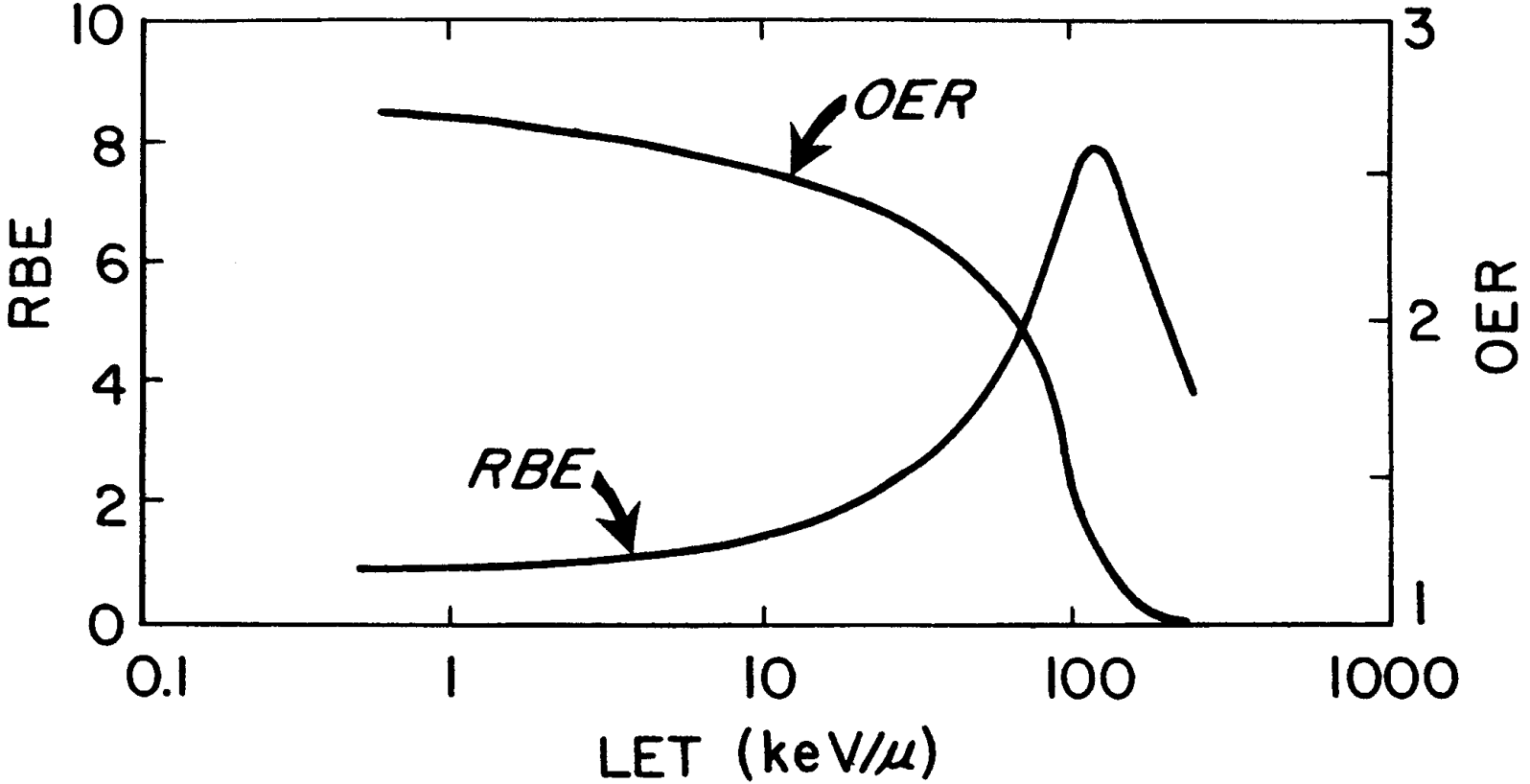


McNally et al. *Int J Radiat Biol* 1985;48:847


+ O2 to "Fix" Damage
R• + O2 → RO2•
Photon
Indirect Action
Dominant for X-Rays
Photon
Direct Action


Indirect Action
Direct Action
Dominant for High
LET Radiation
fast
neutron

Variation of RBE and OER with LET



Reduced Range of Radiation Response

- Range of radiation response of different cell types is reduced with high-LET radiation (neutrons) compared with X-rays
  - In-vitro response of 20 human cell lines to photon and neutron irradiation
  - Same median cell survival for 2 Gy (photons) and 0.68 Gy (neutrons)
  - Average RBE = 2 Gy /0.68 Gy = 2.94

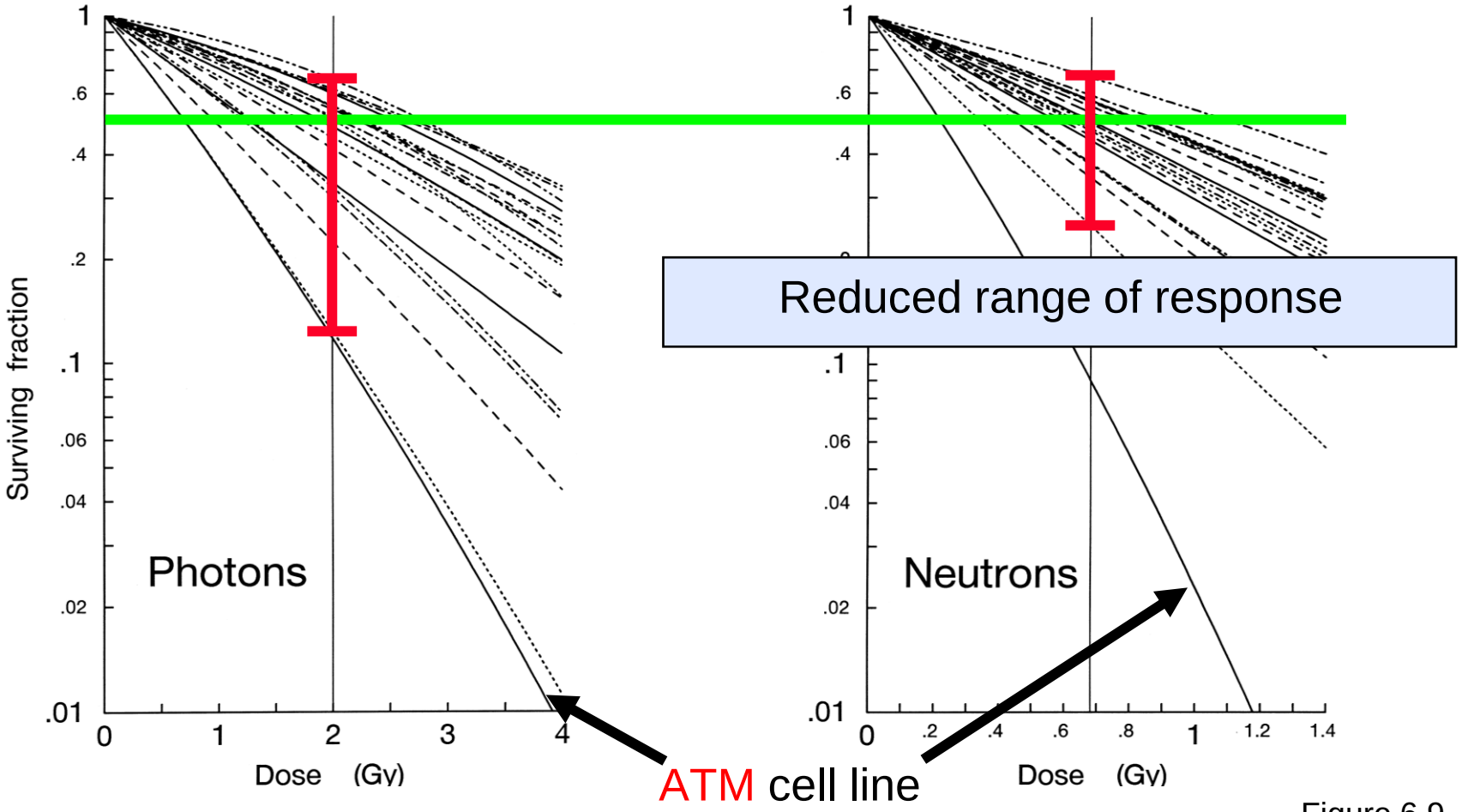
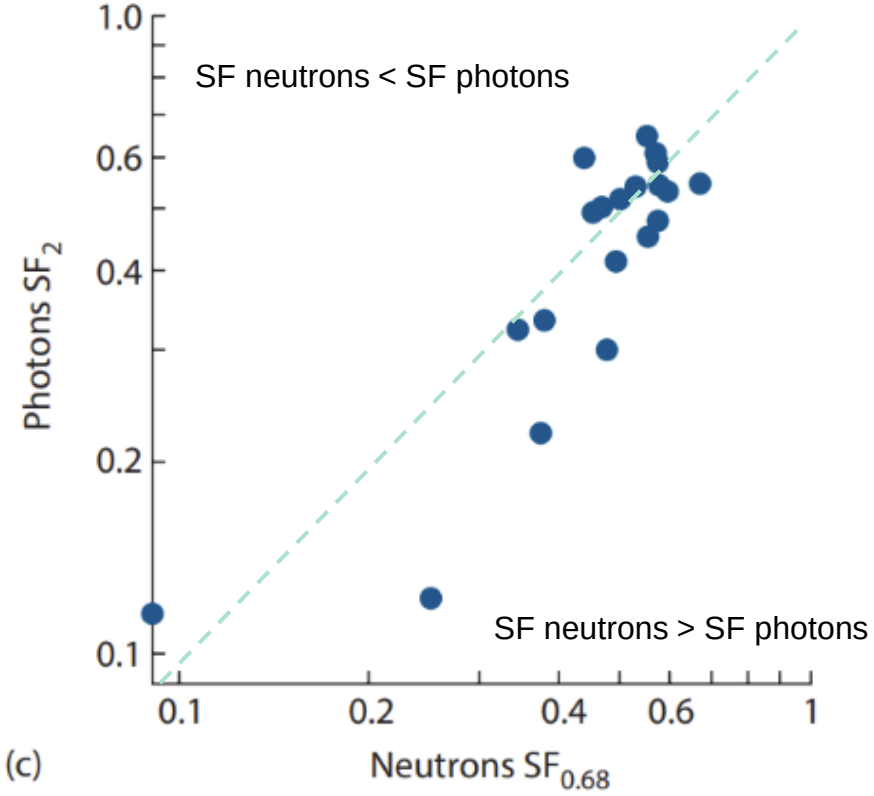

Surviving fraction
1
.6
.4
.2
.1
.06
.04
.02
.01
0
1
2
3
4
Dose (Gy)
Photons
Neutrons
.2
.4
.6
.8
1
1.2
1.4
Reduced range of response
ATM cell line

Figure 6.9



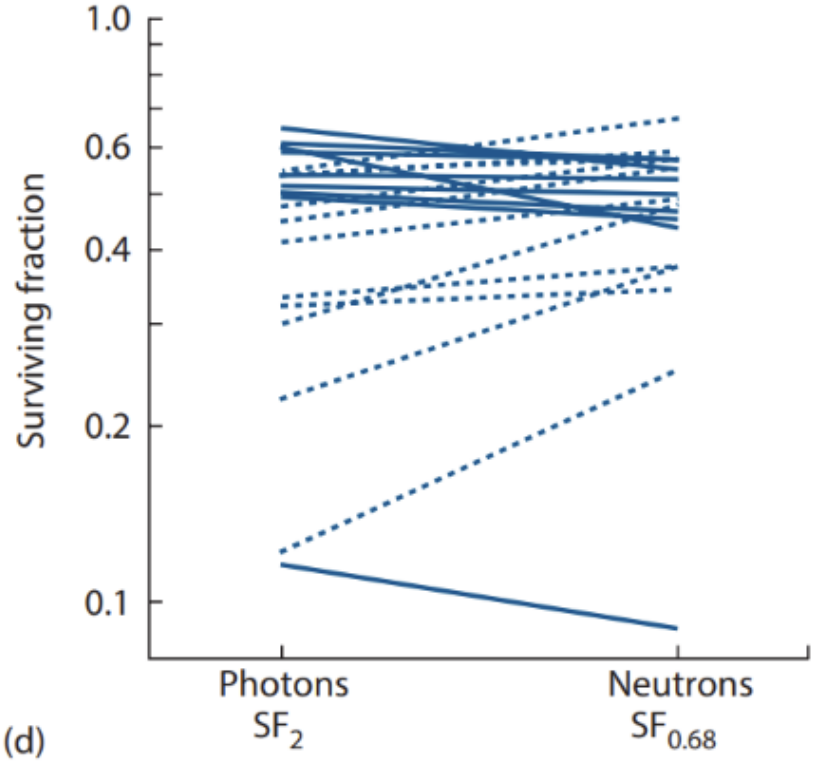


Figure 6.9 Response of 20 human tumour cell lines to (a) 4 MVp photons, or (b) p(62.5)-Be neutrons. The vertical lines show the photon (2 Gy) and neutron (0.68 Gy) doses that give the same *median* cell survival; the average RBE is therefore 2/0.68 = 2.94. (c) The range of cell survival at the reference neutron dose of 0.68 Gy ($SF_{0.68}$) is less than the range of cell survival at a photon dose of 2 Gy (SF_2). In 9/20 of the cell lines neutrons gave lower cell survival than photons at these doses (d).

Benefit of High LET Radiation

- Benefit of high LET radiation in clinical setting may therefore depend on the relative radiosensitivity of the tumour and surrounding normal tissue

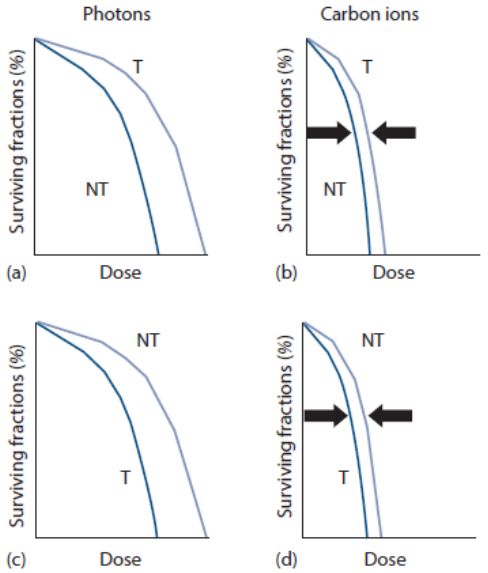
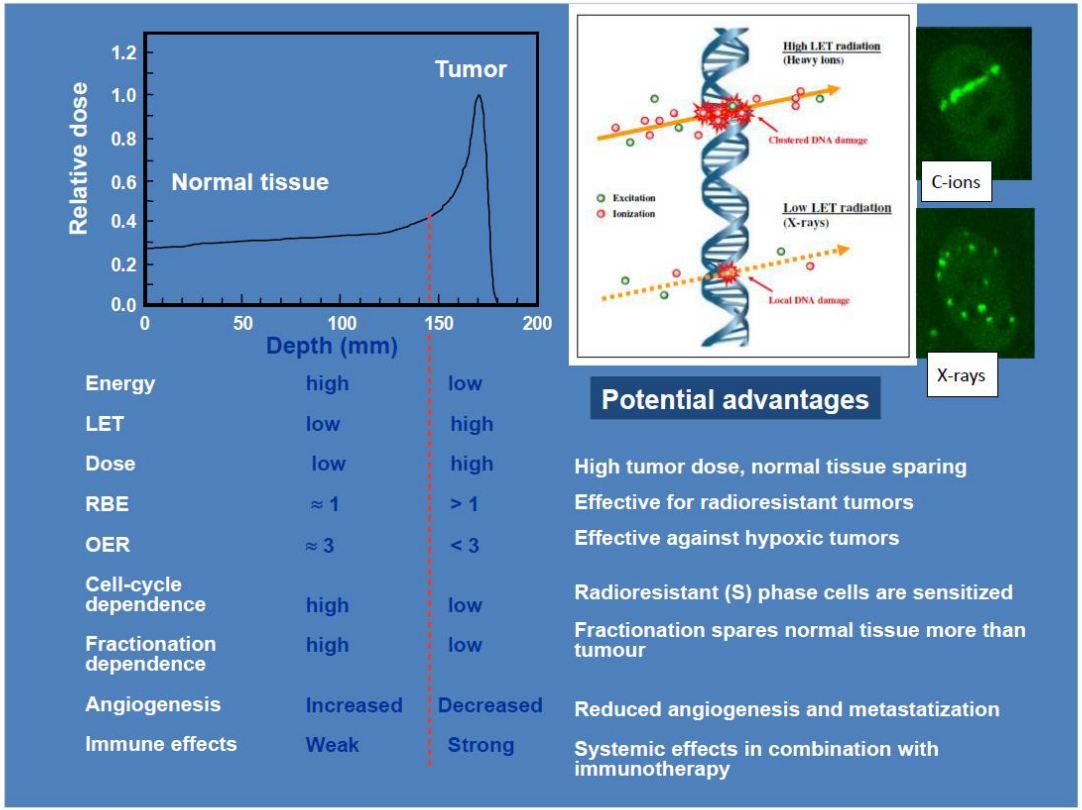


Figure 25.3 The differential biological effect. For tumours (T) more radioresistant to photons than normal tissue (NT) (a), the use of carbon ions could be beneficial by decreasing the unfavourable difference in radiosensitivity between tumour and normal tissue (b). For tumours more radiosensitive to photons than normal tissue (c), the use of carbon ions could be detrimental by decreasing the favourable difference in radiosensitivity between normal tissue and tumour (d).



cancers
Review
Carbon Ion Radiobiology
Walter Tinganelli [1] and Marco Durante [1,2,*]

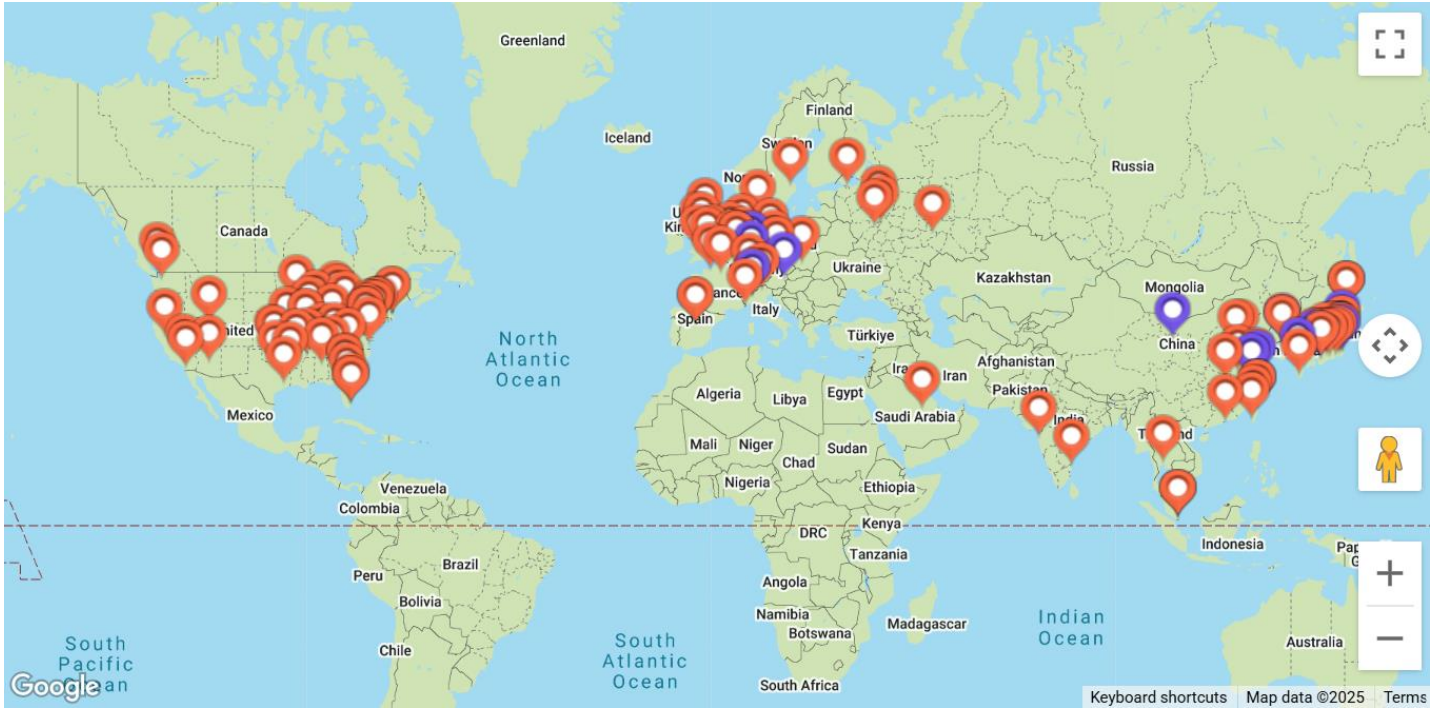
Figure 2. Summary of the physical and radiobiological properties of heavy ions along the Bragg curve. The figures on top right show a sketch of the quality of DNA damage and the corresponding γH2AX foci distribution with carbon ions and X-rays. Adapted from [12].

Biological bases for high-LET particle therapy (*e.g.* carbon ions, neutrons)

- Reduced range of response
- Reduced influence of oxygen
- Reduced influence of cell cycle

CLINICAL APPLICATIONS OF PARTICLE THERAPY

Current Clinical Use of Particle Therapy

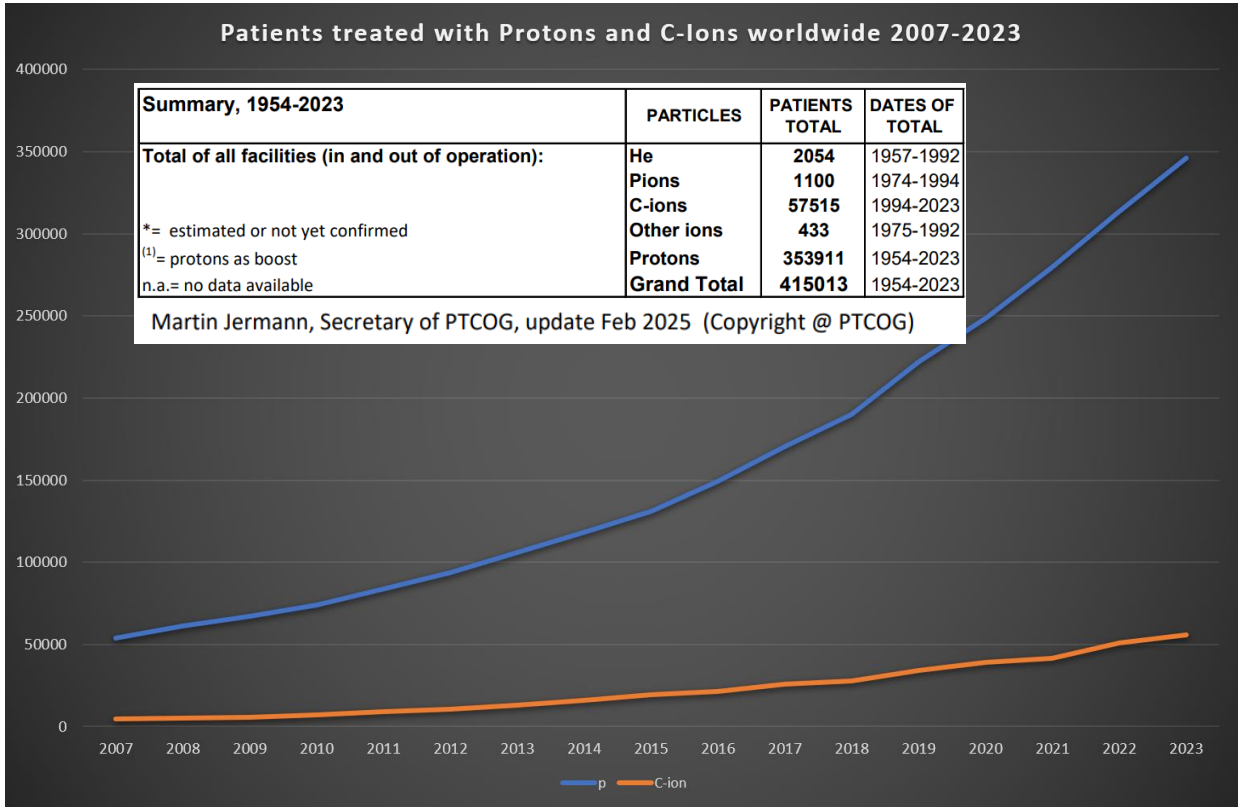


114 Proton therapy centres

16 Carbon ion centres

https://www.ptcog.site/index.php/facilities-world-map

Current Clinical use of Particle Therapy



Summary, 1954-2023	PARTICLES	PATIENTS TOTAL	DATES OF TOTAL
Total of all facilities (in and out of operation):	He	2054	1957-1992
	Pions	1100	1974-1994
	C-ions	57515	1994-2023
*= estimated or not yet confirmed	Other ions	433	1975-1992
(1)= protons as boost	Protons	353911	1954-2023
n.a.= no data available	Grand Total	415013	1954-2023

Martin Jermann, Secretary of PTCOG, update Feb 2025 (Copyright @ PTCOG)

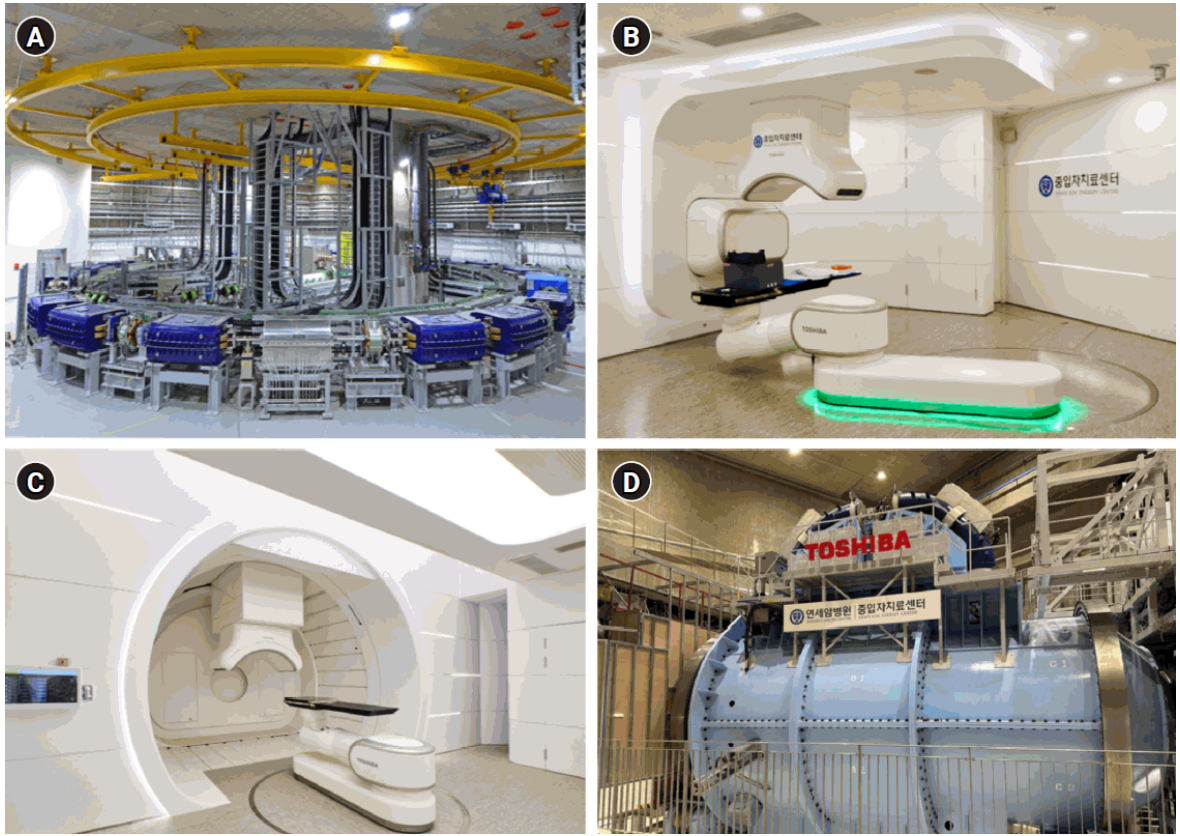
In Canada (2017):
>100,000 courses of radiation therapy

In Canada (2020):
48 radiation treatment facilities in Canada.

Data from CPQR

Why don't we treat all patients using Particle therapy

- Clinical evidence for proton and carbon-ion therapy is still developing
- Proton and carbon ion therapy is significantly more expensive
- Requires large, highly specialized equipment
- There is limited availability



Yonsei Carbon ion facility in Korea

Han MC et al. The first Korean carbon-ion radiation therapy facility: current status of the Heavy-ion Therapy Center at the Yonsei Cancer Center. Radiat Oncol J. 2024 Dec;42(4):295-307. doi: 10.3857/roj.2024.00206. Epub 2024 Dec 20. PMID: 39748530; PMCID: PMC11701461.

- 9 m in length
- Rotational radius 6.3 m
- Weight: 200 tons

PROTON THERAPY

GENERAL
Benign or malignant tumors or hematologic malignancies in children aged 21 years and younger treated with curative intent and occasionally palliative intent treatment of childhood tumors when at least one of the three criteria noted above under "indications for coverage" apply
Benign or malignant tumors or hematologic malignancies in the adolescent/young adult (AYA) population aged 22 years to 39 years treated with curative intent when at least one of the three criteria noted above under "indications for coverage" apply
Patients with genetic syndromes making total volume of radiation minimization crucial, such as but not limited to NF-1 patients, deleterious ATM mutations, Li-Fraumeni, retinoblastoma patients, and patients with known or suspected genetic mutations. In addition, patients with other genetic mutations who are at increased risk of developing second cancers at or near the same body location such as but not limited to BRCA 1/2, Lynch syndrome, etc.
Medically inoperable patients with a diagnosis of cancer typically treated with surgery where dose escalation is required due to the inability to receive surgery
Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)
Primary malignant or benign bone tumors
CENTRAL NERVOUS SYSTEM
Ocular tumors, including intraocular melanomas
Tumors that approach or are located at the base of skull, including but not limited to: • Chordoma • Chondrosarcomas • Other histologies arising in this site
Malignant and benign primary CNS tumors excluding IDH wild-type GBM, that are treated with curative intent and with potential for long term prognosis
Primary spine or spinal cord tumors or metastatic tumors to the spine or spinal cord where organ at risk tolerance may be exceeded with photon treatments
Primary and metastatic tumors requiring craniospinal irradiation
HEAD AND NECK
Cancers of the nasopharynx, nasal cavity, paranasal sinuses and other accessory sinuses
Advanced stage and unresectable head and neck cancers
THORACIC
Primary cancers of the esophagus
Primary tumors of the mediastinum, including thymic tumors, mediastinal tumors, mediastinal lymphomas and thoracic sarcomas
Malignant pleural mesothelioma
ABDOMINAL
Hepatocellular cancer and intra-hepatic biliary cancers
Non-metastatic retroperitoneal sarcomas
PELVIC
Advanced and unresectable pelvic tumors with significant pelvic and/or peri-aortic nodal disease
Patient with a single kidney or transplanted pelvic kidney with treatment of an adjacent target volume and in whom maximal avoidance of the organ is critical

ASTRO (American) Guidelines

INDICATIONS AND LIMITATIONS OF COVERAGE AND/OR MEDICAL NECESSITY

Indications for Coverage

PBT is considered reasonable in instances where sparing the surrounding normal tissue is of added clinical benefit to the patient and cannot be adequately achieved with photon-based radiation therapy. Examples of such an advantage include, but are not limited to:

1. The target volume is near one or more critical structures and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s), which would portend a higher risk of toxicity.

2. A proton-based technique would decrease the probability of clinically meaningful normal tissue toxicity by lowering an integral dose-based metric and/or organ at risk dose volume constraint associated with toxicity.

3. The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/ASTROPBTModelPolicy.pdf

Patient Selection for Proton Therapy

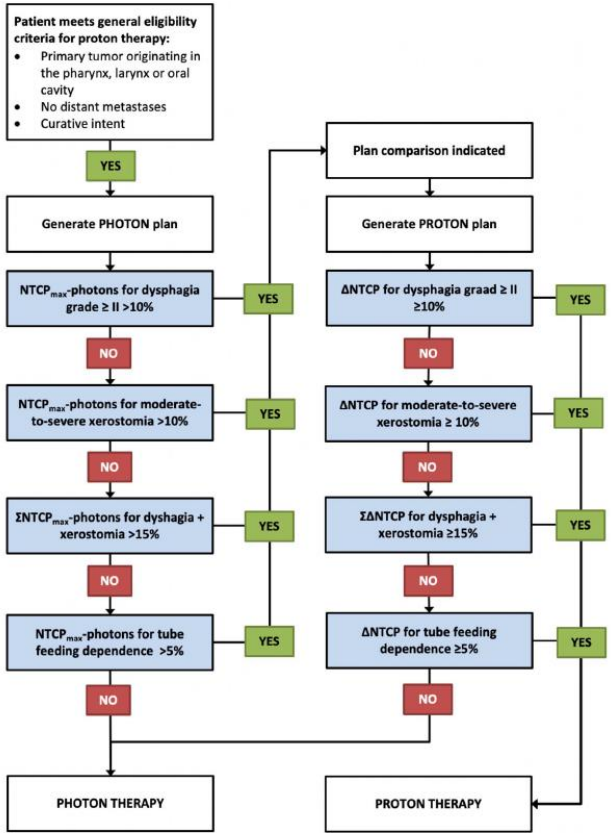
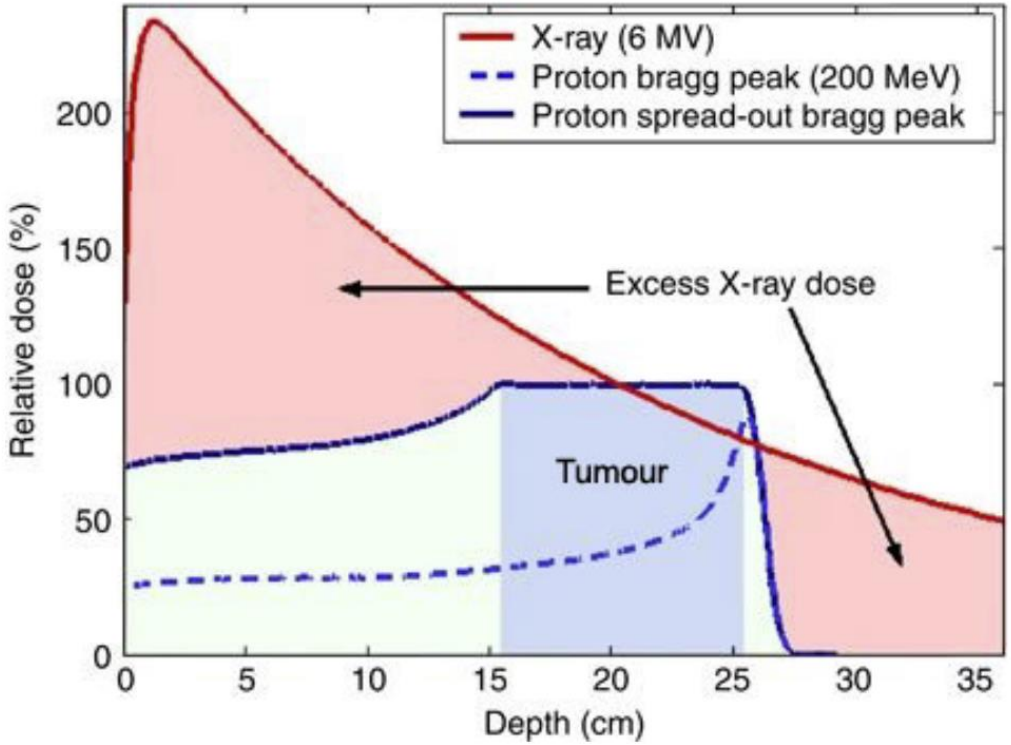
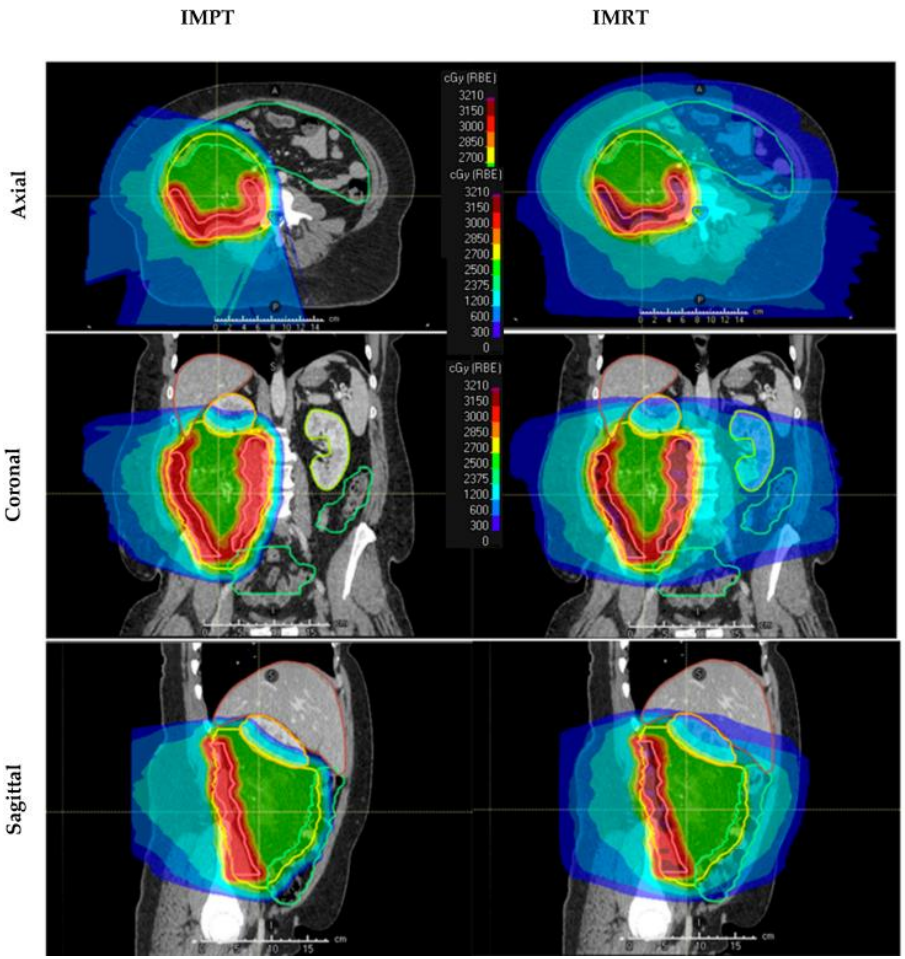


Figure. Flowchart for selecting patients for a plan comparison and PT, respectively. For each toxicity endpoint, the maximum ΔNTCP ($\Delta NTCP_{max}$) has to be calculated first by the following equation: $\Delta NTCP_{max} = [NTCP - PHOTONS] - [NTCP_{min} - PROTONS]$, in which, $NTCP_{min} - PROTONS$ is the NTCP value, assuming that with protons, the dose to all DVH parameters in the model can be reduced to zero. Abbreviations: DVH, dose-volume histogram; NTCP, Normal Tissue Complication Probability; PT, proton therapy.

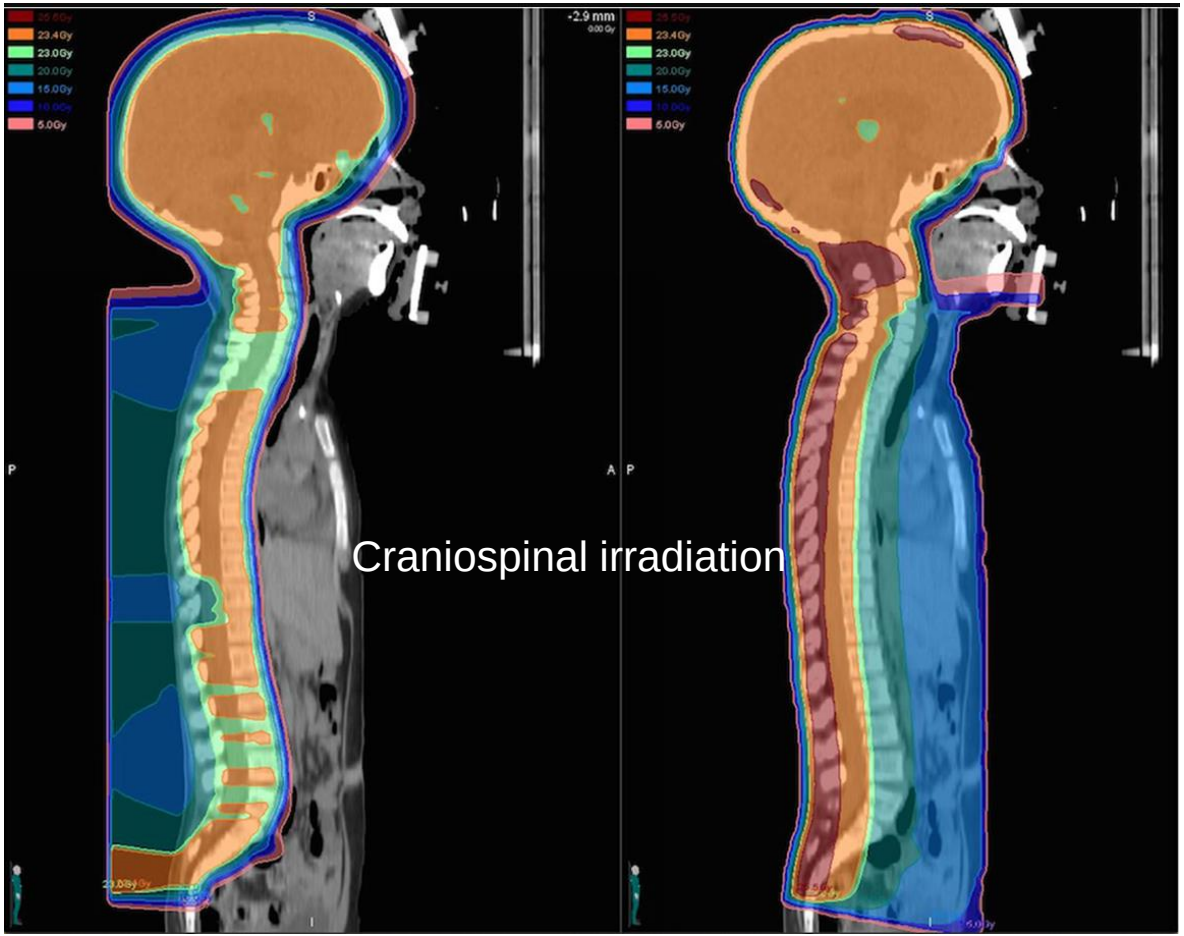
Langendijk JA, Hoebers FJP, de Jong MA, Doornaert P, Terhaard CHJ, Steenbakkers RJHM, Hamming-Vrieze O, van de Kamer JB, Verbakel WFAR, Keskin-Cambay F, Reitsma JB, van der Schaaf A, Boersma LJ, Schuit E. **National Protocol for Model-Based Selection for Proton Therapy in Head and Neck Cancer**. Int J Part Ther. 2021 Jun 25;8(1):354-365. doi: 10.14338/IJPT-20-00089.1. PMID: 34285961; PMCID: PMC8270079.



https://www.ebme.co.uk/articles/clinical-engineering/proton-beam-therapy



Gogineni E et a **Comparative In Silico Analysis of Ultra-Hypofractionated Intensity-Modulated Photon Radiotherapy (IMRT) Versus Intensity-Modulated Proton Therapy (IMPT) in the Pre-Operative Treatment of Retroperitoneal Sarcoma**. Cancers (Basel). 2023 Jul 4;15(13):3482. doi: 10.3390/cancers15133482. PMID: 37444592; PMCID: PMC10341304



Eaton BR et al. **Secondary Malignancy Risk Following Proton Radiation Therapy**. Front Oncol. 2015 Nov 26;5:261. doi: 10.3389/fonc.2015.00261. PMID: 26636040; PMCID: PMC4659915.

Clinical Benefits of Proton Therapy

- Reduction in normal tissue volume/doses
- Reduction in associated side-effects
- Cost-effectiveness with respect to long-term management of toxicity

Clinical Proton Treatment Planning: RBE = 1.1

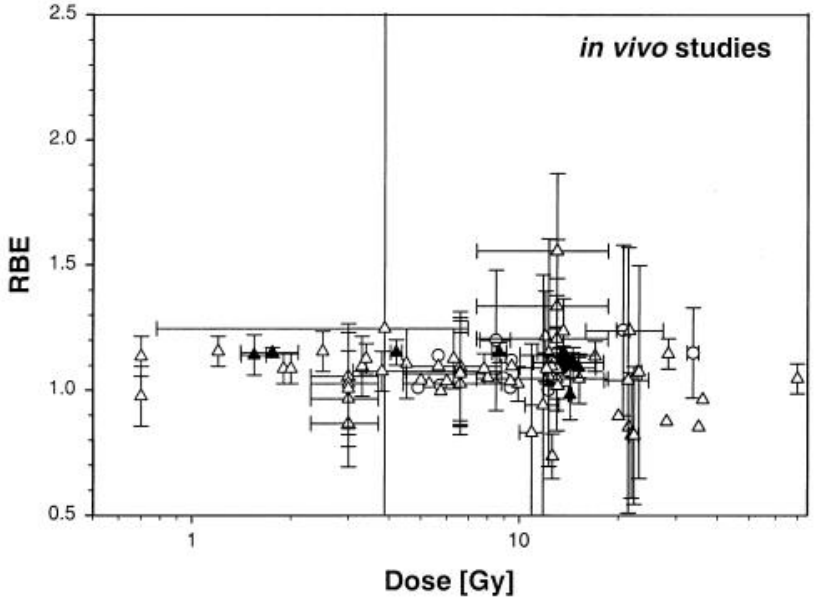


Fig. 2. Experimental proton RBE values (relative to ^{60}Co) as a function of dose/fraction measured *in vivo* in the center of a SOBP. Closed symbols show RBE values for jejunal crypt cells, open symbols stand for RBEs for all other tissues. Circles represent RBEs for <100-MeV beams and triangles for >100-MeV beams.

Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS, Suit HD. **Relative biological effectiveness (RBE) values for proton beam therapy**. Int J Radiat Oncol Biol Phys. 2002 Jun 1;53(2):407-21. doi: 10.1016/s0360-3016(02)02754-2. PMID: 12023146.

cancers
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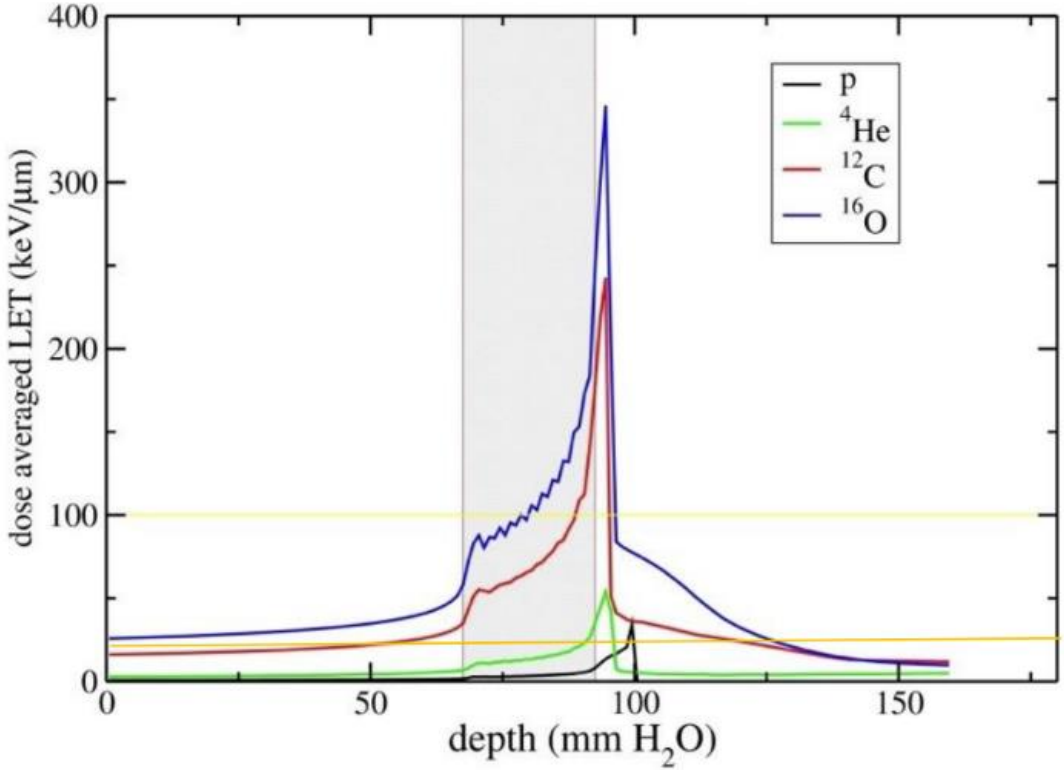

Figure 3. LET versus depth in tissue for a single SOBP of p, He, C, and O providing a uniform physical dose (2 Gy). The grey area represents the tumor region, a 2.5 × 2.5 × 2.5 cm^3 volume centered at 8 cm in water. The yellow and orange lines are 100 and 20 keV/µm level, respectively. Figure from [15], distributed under Creative Commons CC-BY.

Protons are low LET Radiation …

Haas-Kogan D, Indelicato D, Paganetti H, Esiashvili N, Mahajan A, Yock T, Flampouri S, MacDonald S, Fouladi M, Stephen K, Kalapurakal J, Terezakis S, Kooy H, Grosshans D, Makrigiorgos M, Mishra K, Poussaint TY, Cohen K, Fitzgerald T, Gondi V, Liu A, Michalski J, Mirkovic D, Mohan R, Perkins S, Wong K, Vikram B, Buchsbaum J, Kun L. ***National Cancer Institute Workshop on Proton Therapy for Children: Considerations Regarding Brainstem Injury***. Int J Radiat Oncol Biol Phys. 2018 May 1;101(1):152-168. doi: 10.1016/j.ijrobp.2018.01.013. PMID: 29619963; PMCID: PMC5903576.

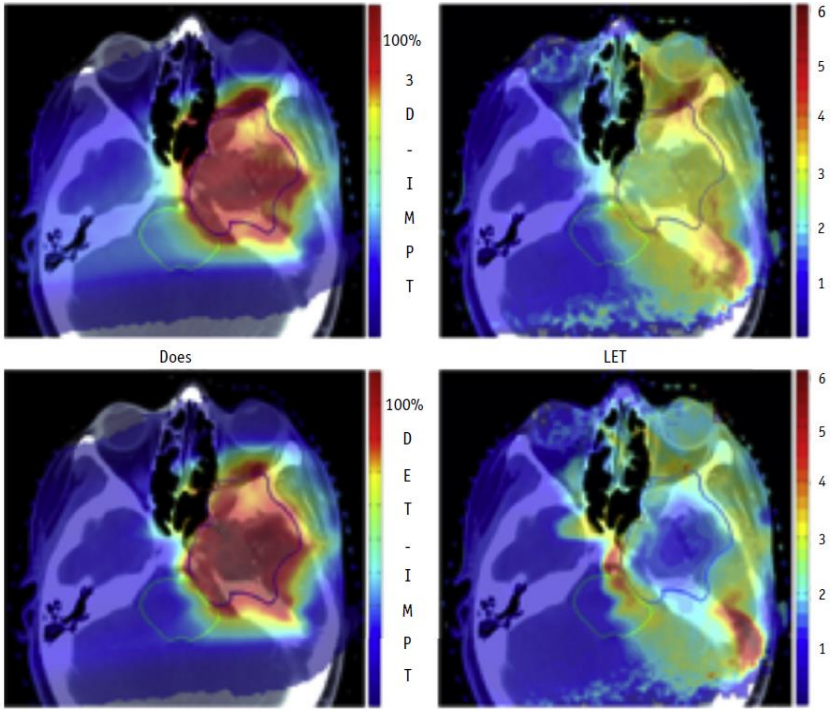

Fig. 1. Two intensity modulated proton therapy plans that display clinically equivalent dose distributions but different linear energy transfer distributions (chordoma: dose in percentage of prescribed dose; gross tumor volume line in blue; right column shows the mean dose-averaged linear energy transfer distributions in keV/µm). Adapted from reference (58).

CARBON-ION THERAPY

Clinical Evidence for Carbon-ion therapy

Table 2
Strength of evidence.

Strong evidence	Conflicting evidence	Weak evidence
Chondrosarcoma	Liver	Oesophagus
Chordoma	Pancreas	Paediatric cancers
Nasopharynx	Central nervous system	Small-cell lung
Non-small-cell lung	Uterine cervix	Osteosarcoma
Oral cavity		Kidney
Prostate		
Rectum		
Salivary gland		

- 78 primary studies
- Looked at clinical outcomes (survival, local control) and toxicity
- Categorized data based on strength of evidence

Light E, Bridge P. Clinical indications for carbon-ion radiotherapy in the UK: A critical review. Radiography (Lond). 2024 Mar;30(2):425-430. doi: 10.1016/j.radi.2023.12.014. Epub 2024 Jan 9. PMID: 38199158.

Carbon-ion Radiotherapy: Clinical Examples

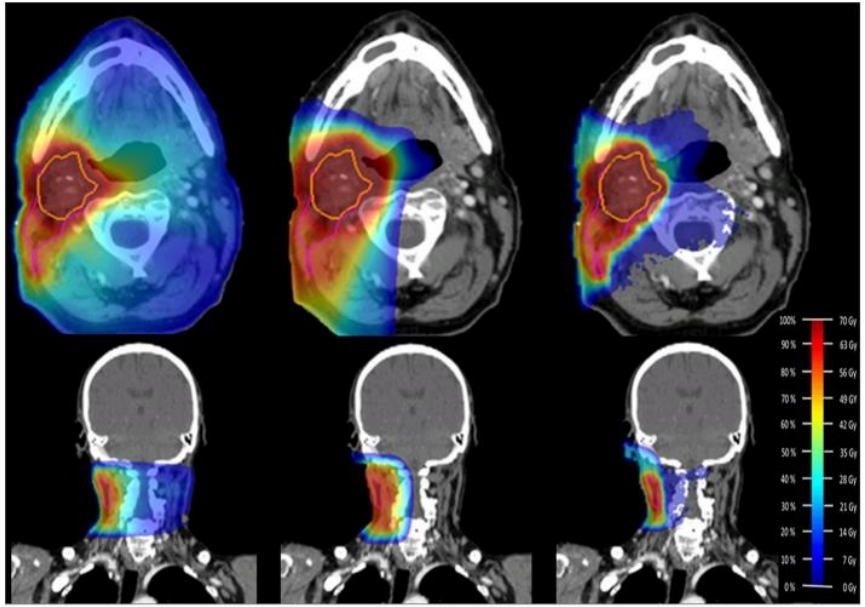

Fig. 1. A set of re-irradiation treatment plans for a patient with a nodal recurrence of oropharynx carcinoma of the right tonsillar fossa, $rcT_0N_{2a}M_0$. In the VMAT (left column), IMPT (middle column) and IMIT (right column) plans, the CTV_{54Gy} (pink) and high-dose CTV_{70Gy} (orange). The dose-range is presented from high (red) to low (blue).

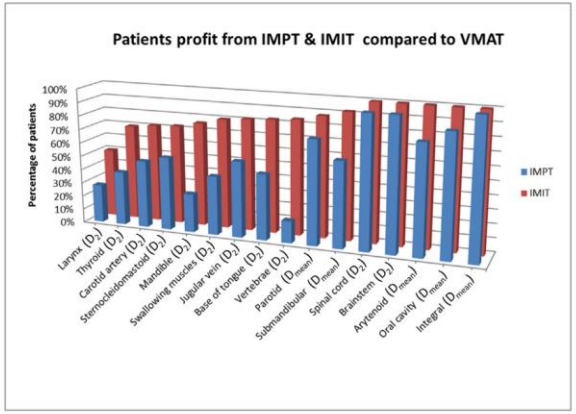

Fig. 3. Percentage of patients receiving lower dose to the organs at risk when applying IMPT and/or IMIT compared to VMAT. The maximum dose received by 2% of that specific structure (D_2) and the mean dose (D_{mean}) both in Gy(E) are given.

Eekers DBP, Roelofs E, Jelen U, Kirk M, Granzier M, Ammazzalorso F, Ahn PH, Janssens GORJ, Hoebers FJP, Friedmann T, Solberg T, Walsh S, Troost EGC, Kaanders JHAM, Lambin P. **Benefit of particle therapy in re-irradiation of head and neck patients. Results of a multicentric in silico ROCOCO trial**. Radiother Oncol. 2016 Dec;121(3):387-394. doi: 10.1016/j.radonc.2016.08.020. Epub 2016 Sep 14. PMID: 27639891.

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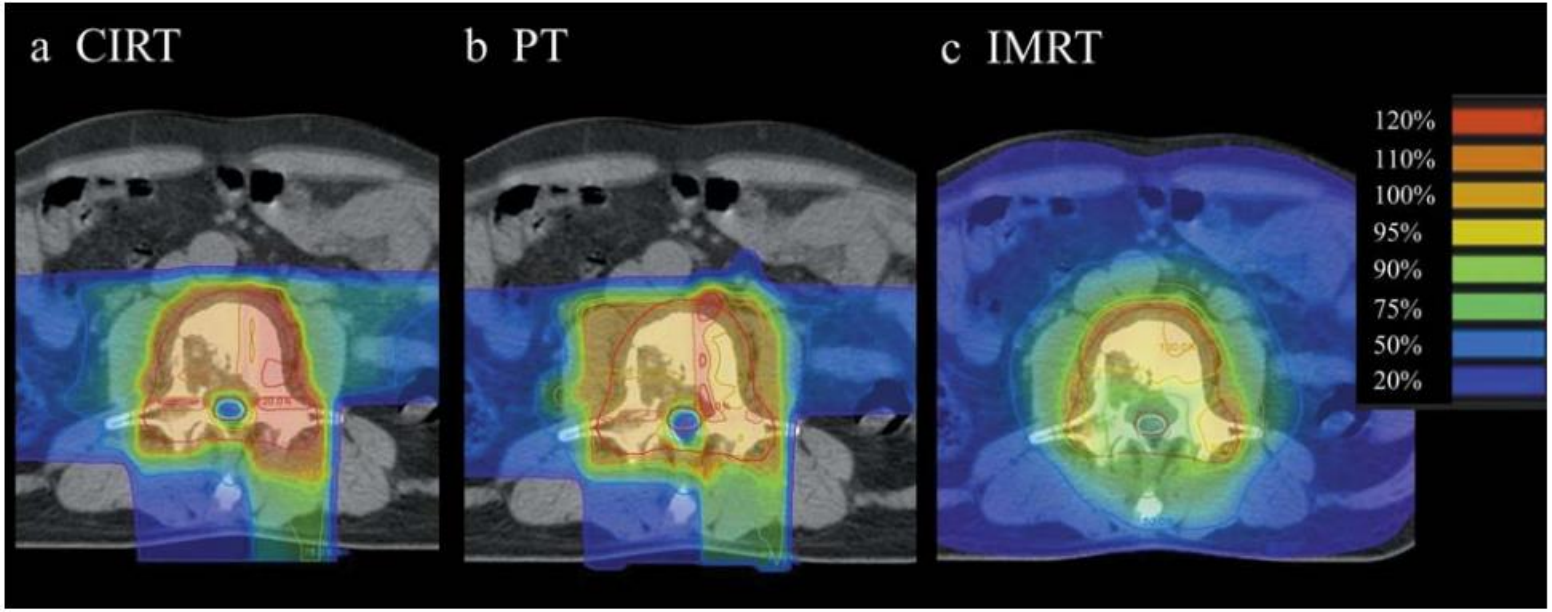


Figure 4. *Dose distribution of a representative case with tumor encircling the whole circumference of the spinal cord. a: carbon ion radiotherapy (CIRT), b: proton therapy (PT), c: intensity-modulated radiotherapy (IMRT).*

Matsumoto K, Nakamura K, Shioyama Y, Sasaki T, Ohga S, Yamaguchi T, Yoshitake T, Asai K, Kakiuchi G, Honda H. Treatment Planning Comparison for Carbon Ion Radiotherapy, Proton Therapy and Intensity-modulated Radiotherapy for Spinal Sarcoma. Anticancer Res. 2015 Jul;35(7):4083-9. PMID: 26124359.

Treatment Planning for Carbon Ion Radiotherapy

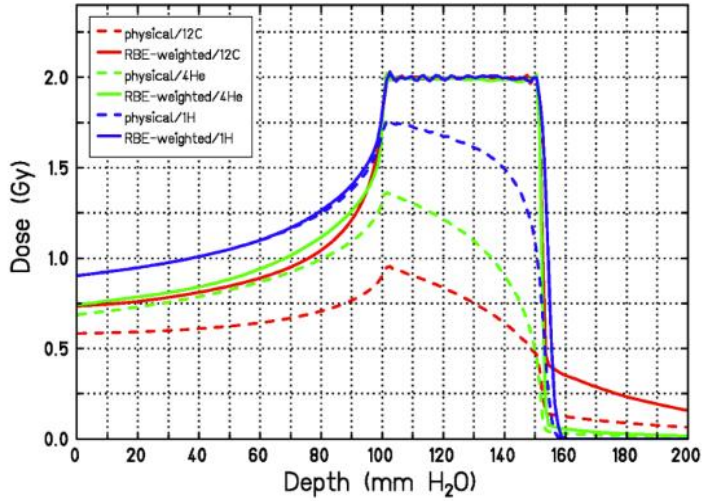


Figure 7. Physical (dashed lines) and RBE-weighted dose (solid lines) for a single 5-cm SOBP using protons, He- or C-ions. The physical dose shape is calculated with LEM-IV to achieve the same RBE-weighted dose in the target region for all ions. Figure modified from [78].

cancers

Review

Carbon Ion Radiobiology

Walter Tinganelli [1] and Marco Durante [1,2,*]

- Treatment planning must convert physical dose to RBE-weighted dose
- Different models are used for this calculation
- Can make comparison of clinical data difficult

Summary: Particle Therapy

- **Physical advantages of Particle Therapy**
  - Bragg peak
  - Adjustable Bragg peak depth
  - Sharp beam edges (small penumbra)
- **Biological advantages of high LET Radiation**
  - low OER, reduced cell-cycle effect, less repair of tumor cells; high-LET benefits partially maintained even after spreading out the Bragg peak

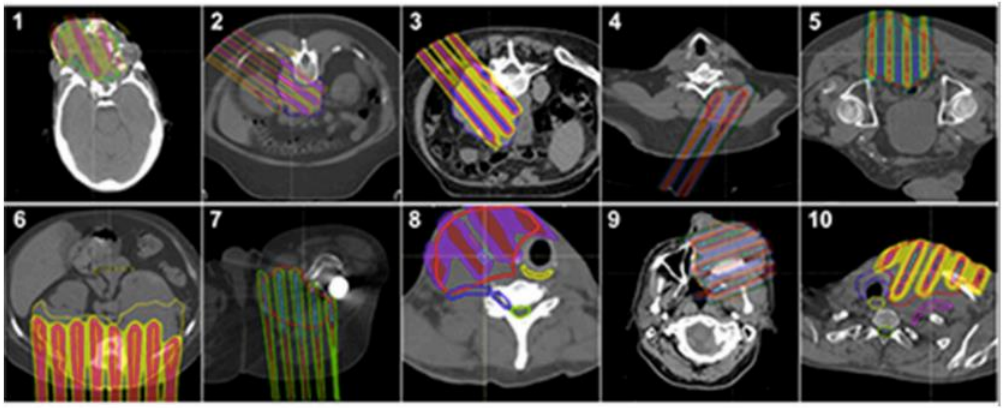
Exciting Applications of Particle Therapy

Proton Flash Therapy:
FAST-01 clinical trial

Mascia AE, Daugherty EC, Zhang Y, Lee E, Xiao Z, Sertorio M, Woo J, Backus LR, McDonald JM, McCann C, Russell K, Levine L, Sharma RA, Khuntia D, Bradley JD, Simone CB 2nd, Perentesis JP, Breneman JC. **Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases**: The FAST-01 Nonrandomized Trial. JAMA Oncol. 2023 Jan 1;9(1):62-69. doi: 10.1001/jamaoncol.2022.5843. Erratum in: JAMA Oncol. 2023 May 1;9(5):728. doi: 10.1001/jamaoncol.2023.0218. PMID: 36273324; PMCID: PMC9589460.

Spatially fractionated radiotherapy

Figure 3. Patient treatment plans. Axial treatment plans of contoured GTV and the dose distribution.



Mohiuddin M, Lynch C, Gao M, Hartsell W. Early clinical results of proton spatially fractionated GRID radiation therapy (SFGRT). Br J Radiol. 2020 Mar;93(1107):20190572. doi: 10.1259/bjr.20190572. Epub 2019 Nov 7. PMID: 31651185; PMCID: PMC7066961