Částicová radioterapie – trendy, výzvy, stav



Jiří Kubeš

PTC Czech

Radioterapie

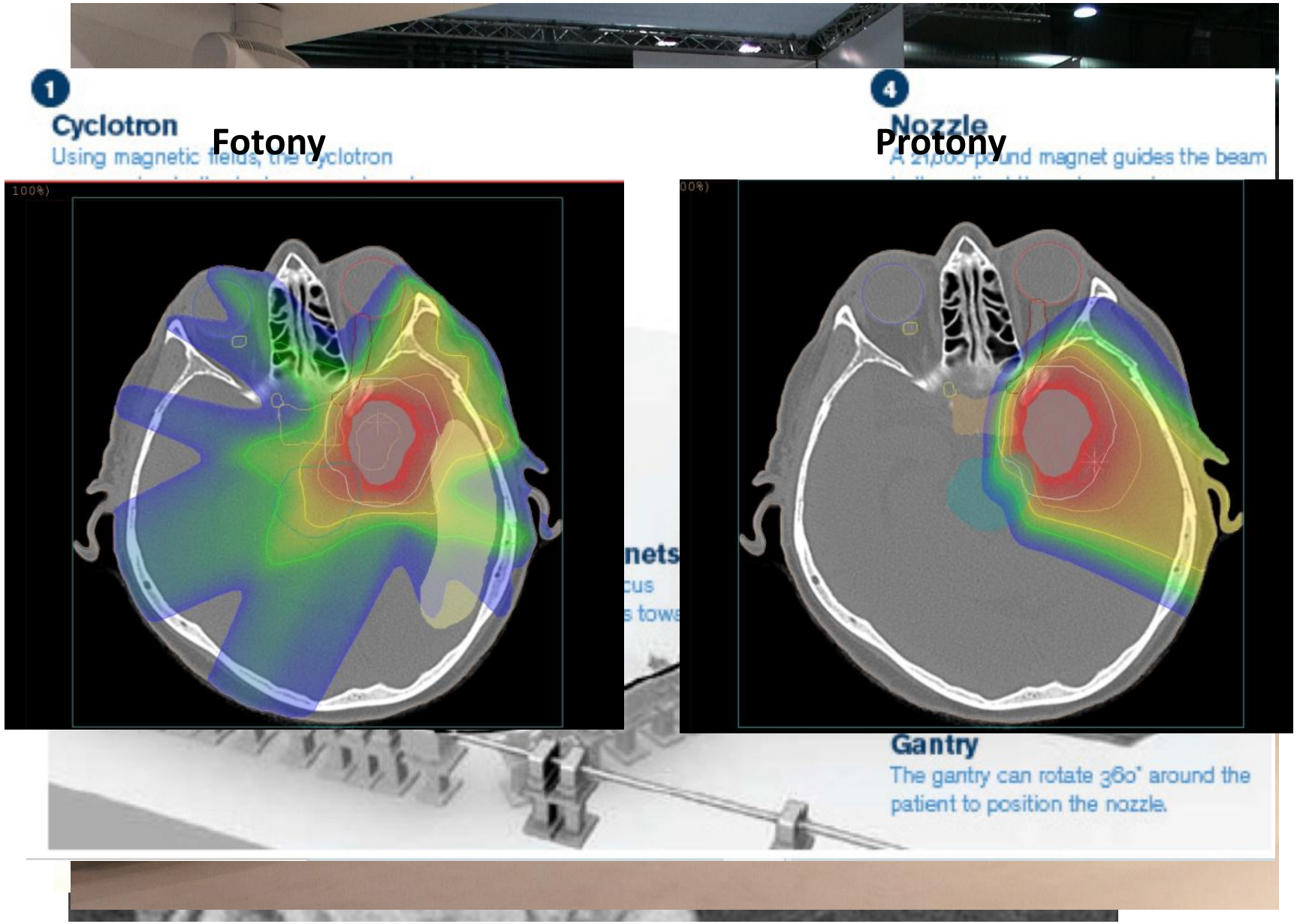
- Léčba nádorových onemocnění ionizujícím zářením
- Majoritně (97%) fotonové ionizující záření
- Homogenní ozáření nádorového ložiska co nejvyšší dávkou za přijatelných rizik nežádoucích efektů

- Východisko: Nádor je geneticky mutovaná tkáň, nad kterou ztratil imunitní systém kontrolu

Radioterapie

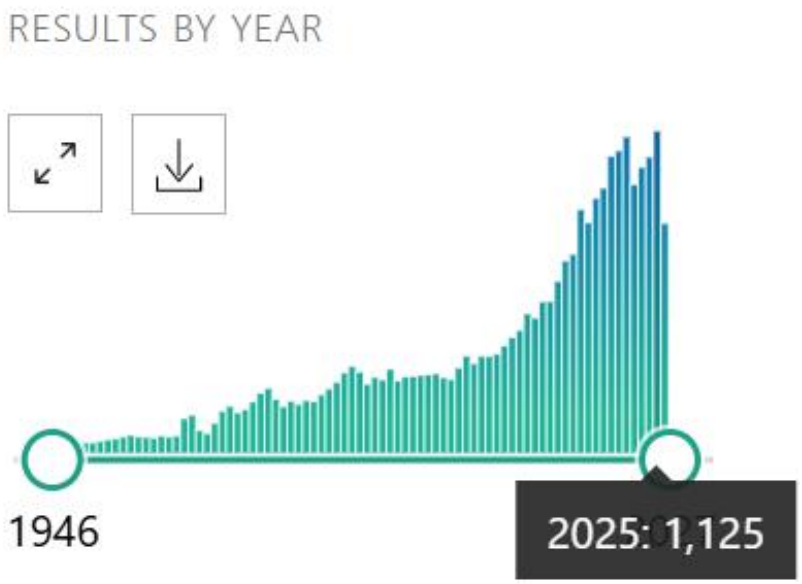
Fotonová radioterapie (od 1896)

Protonová radioterapie (od 1954)



Radioterapie a imunitní systém

Radiotherapy and immune system
Pubmed 2024



Vztah mezi nádorem a imunitním systémem

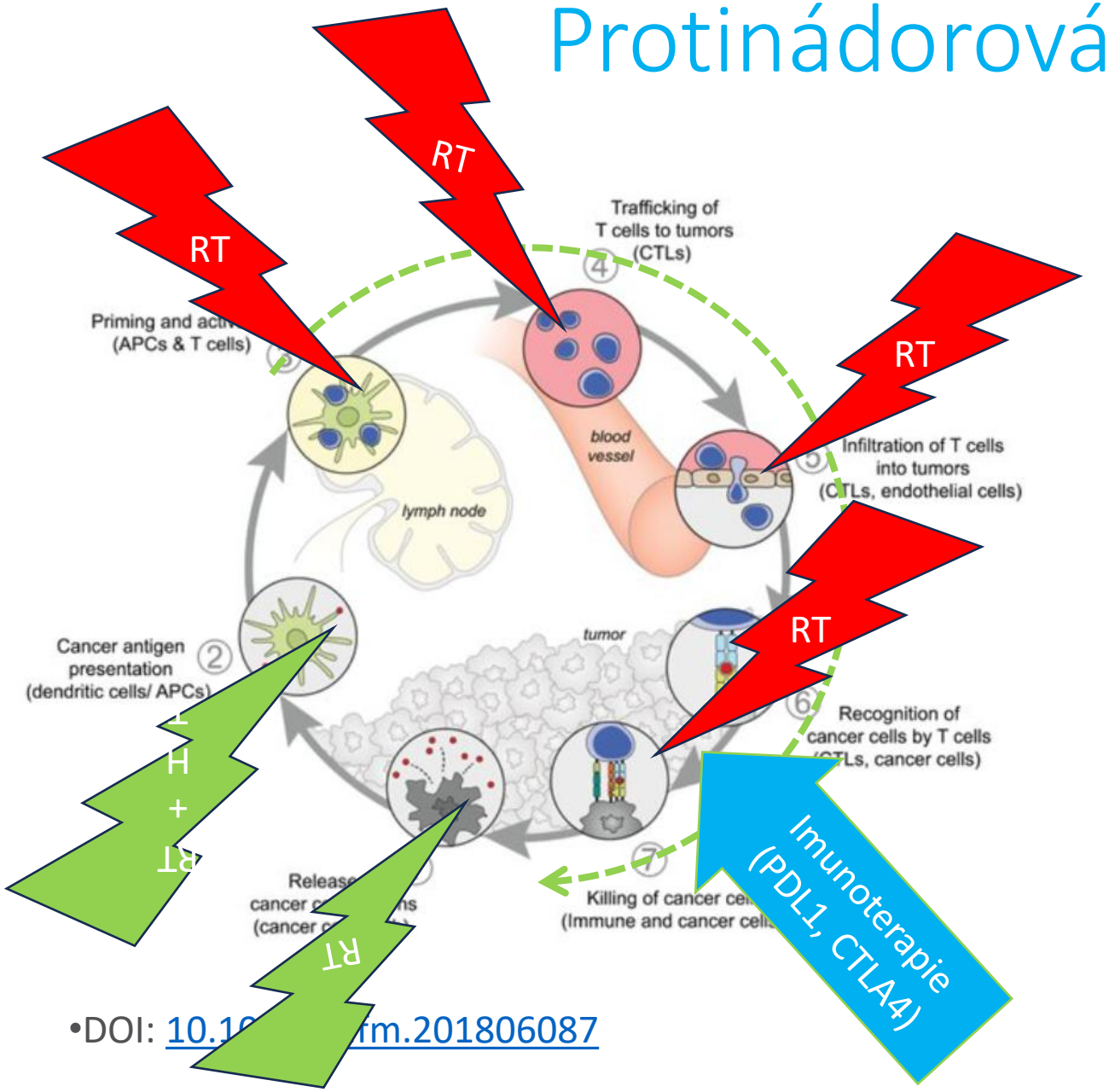
Kvalitativní – jak nádor uniká dohledu imunitního systému

- „maskováním“ – např. absence exprese MHC I (nádor není viditelný pro buňky imunitního systému – CD8 T lymfocyty, NK buňky)

- Aktivní suprese – exprese PDL1, CTLA4 – nádor je viditelný pro T lymfocyty, ale inaktivují se PDL1 i CTLA4)

Kvantitativní – jaký je poměr nádorových a imunitních buněk

Protinádorová imunita



•DOI: 10.1 rm.201806087

1963

QUALITATIVE AND QUANTITATIVE REACTIONS OF LYMPHOCYTES TO X RAYS*

Robert Schrek

Tumor Research Laboratory, Research Service and Surgical Service, Veterans Administration Hospital, Hines, Ill.

The reactions of the lymphocyte to X rays appear to be unique. It is only the nondividing cell that is killed by small doses of X rays. I shall show later that a dose as small as 10 r produces a perceptible effect on the lymphocyte. This nondividing cell is approximately as sensitive as a cell in mitosis.

On the other hand, there are no unique phenomena in science. If we understood the reactions of lymphocytes to X rays, we should probably understand to a considerable extent the radiosensitivity of dividing cells, and vice versa. In view of the relative ease of studying lymphocytes both qualitatively and quantitatively, I believe that the biochemical and physiologic mechanisms of radiosensitivity will first be understood in lymphocytes. In this paper, I present some data that must be explained in any theory of radiosensitivity.

1978

Lymphology 11 (1978) 238–242

The Influence of Therapeutic Irradiation on Blood and Peripheral Lymph Lymphocytes

H.E. Heier

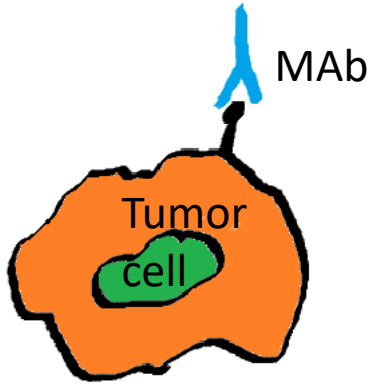
From the Norwegian Radium Hospital, Laboratory for Hematology and Lymphology, Oslo 3, Norway

Protinádorová imunita

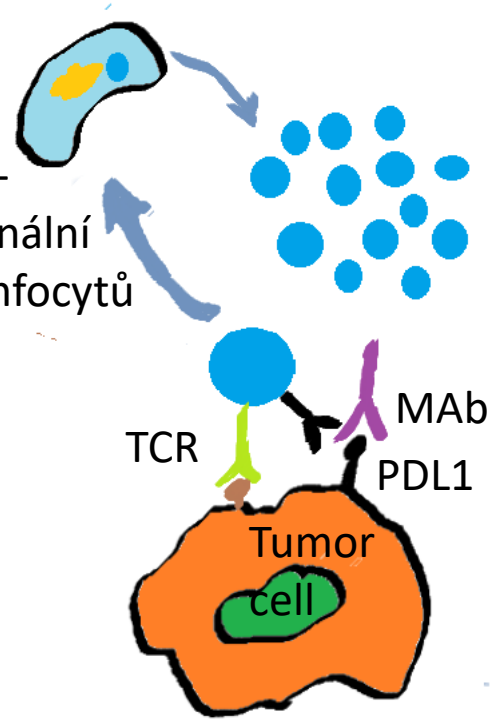
- Renesance myšlenky - existence nástroje pro reaktivaci imunity

Monoklonální protilátky proti receptorům
- Obvykle zablokování funkce receptoru (anti-Her2, anti-VEGF a podobně)
- Nebo ukáže nádorovou buňku imunitní buňce

1 -> 1



Lymph node – aktivace a klonální expanze T-lymfocytů



Expanze tumor specifických T lymfocytů

1 -> 10^3-10^4

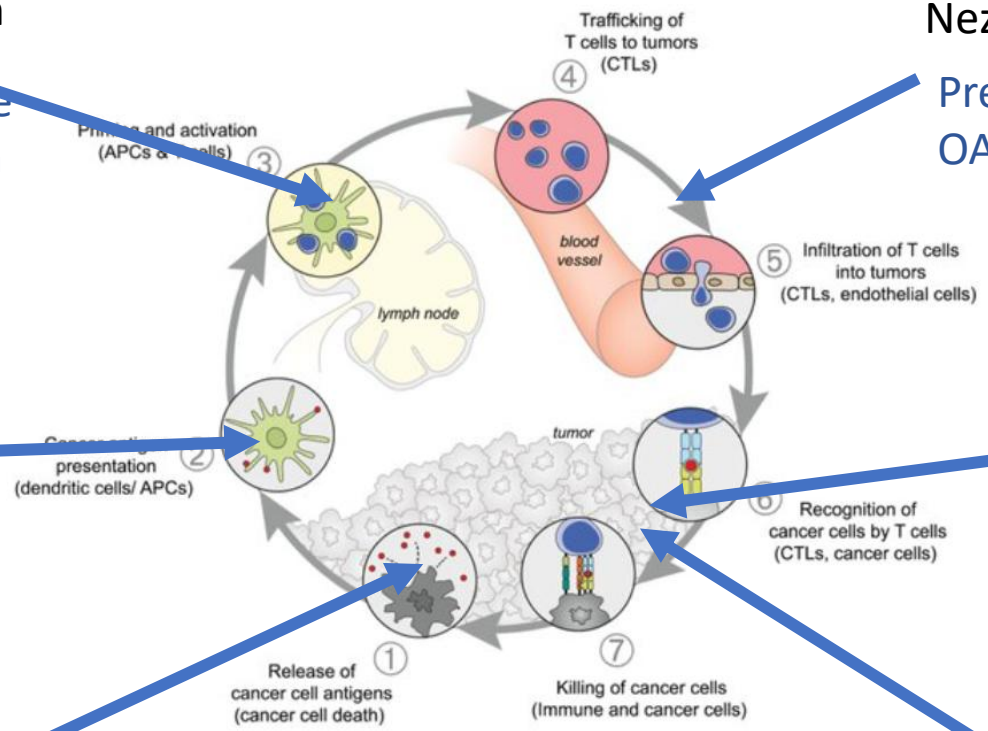
Trendy v částicové RT – souhra s imunitním systémem

Umožnit aktivaci protinádorové imunity v nádoru/ drénujících mízních uzlinách

Vynechání uzlinových oblastí – redukce objemů, ostrá hranice mezi nádorem a uzlinovou oblastí – ostrý spád dávky

Potencovat aktivaci protinádorové imunity v drénujících mízních uzlinách

Kombinace radioterapie a hypertermie



Nezpůsobit depleci lymfocytů!

Prevence/mitigace RIL (nové OAR, hypofrakcionace, FLASH)

Aktivace imunitního systému v nádorovém mikroprostředí

GRID, Lattice, Microbeams, PATHY

Umožnit aktivitu lymfocytů v nádorovém mikroprostředí

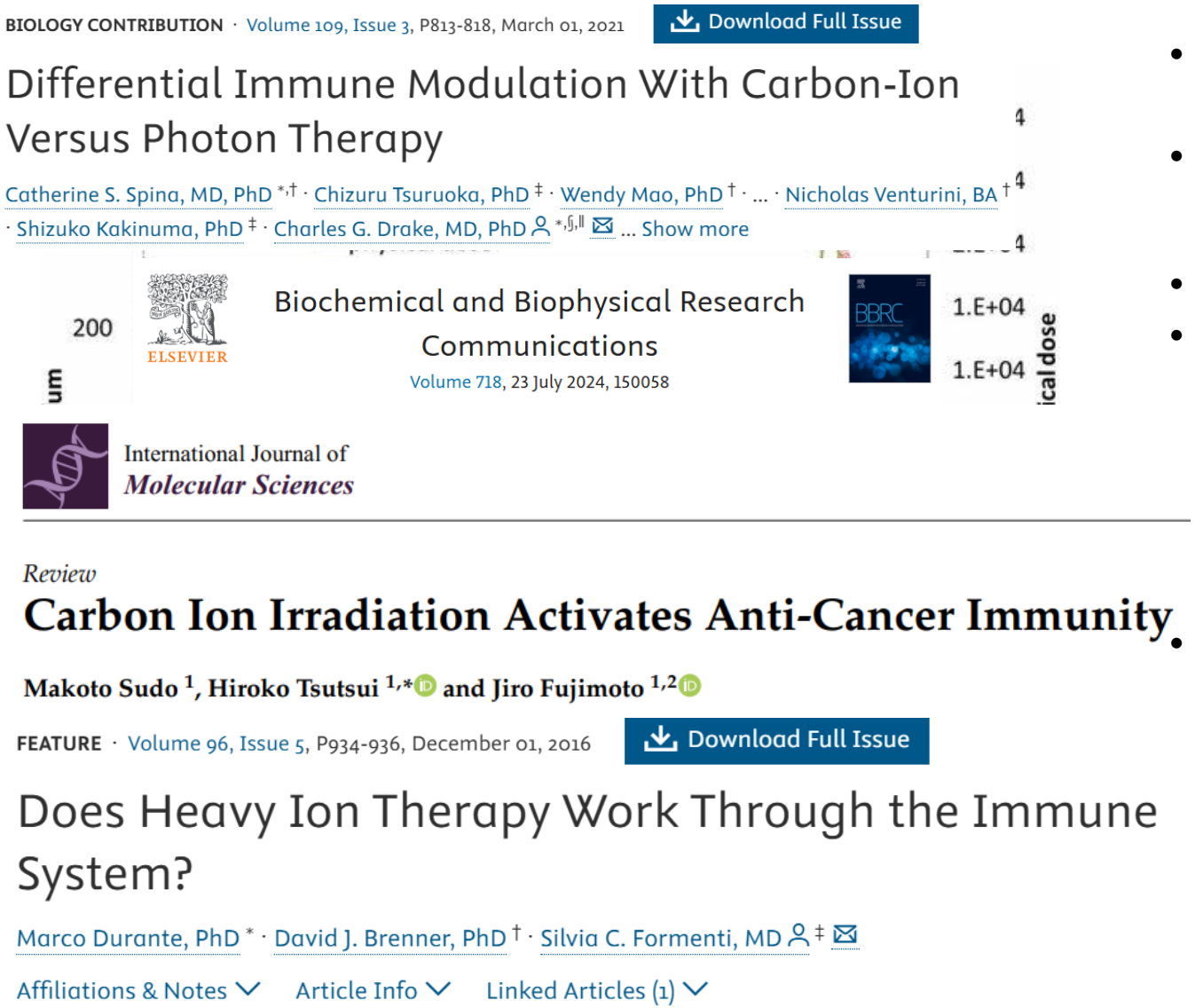
Check point inhibitory (anti PDL1, anti CTLA4….)

- zlepšit poměr nádorových buněk vs imunitních buněk
- zvýšit počet antigenních fragmentů stimulujících imunitu

Dávková eskalace, Vyšší RBE – Protony + Ionty – He, C; LET optimalizace

•DOI: 10.1002/adfm.20180608

Lokální destrukce nádoru – heavy ions



BIOLOGY CONTRIBUTION · Volume 109, Issue 3, P813-818, March 01, 2021 Download Full Issue

Differential Immune Modulation With Carbon-Ion Versus Photon Therapy

Catherine S. Spina, MD, PhD *,† · Chizuru Tsuruoka, PhD ‡ · Wendy Mao, PhD † · ... · Nicholas Venturini, BA † · Shizuko Kakinuma, PhD ‡ · Charles G. Drake, MD, PhD *,§,‖ ... Show more

200 um

ELSEVIER

Biochemical and Biophysical Research Communications

Volume 718, 23 July 2024, 150058

BBRC

1.E+04 1.E+04 ical dose

International Journal of *Molecular Sciences*

Review

Carbon Ion Irradiation Activates Anti-Cancer Immunity

Makoto Sudo [1], Hiroko Tsutsui [1,*] and Jiro Fujimoto [1,2]

FEATURE · Volume 96, Issue 5, P934-936, December 01, 2016 Download Full Issue

Does Heavy Ion Therapy Work Through the Immune System?

Marco Durante, PhD * · David J. Brenner, PhD † · Silvia C. Formenti, MD ‡

Affiliations & Notes Article Info Linked Articles (1)

- Menší laterální polostín
- Lepší poměr pík/plató

- LET až 250 keV/µm
- Vyšší RBE – překonání radioresistence

Jiná interakce s imunitním systémem

- Komplexní děj, včetně vyšší antigenní stimulace

Heavy ions – nedosažitelný cíl?

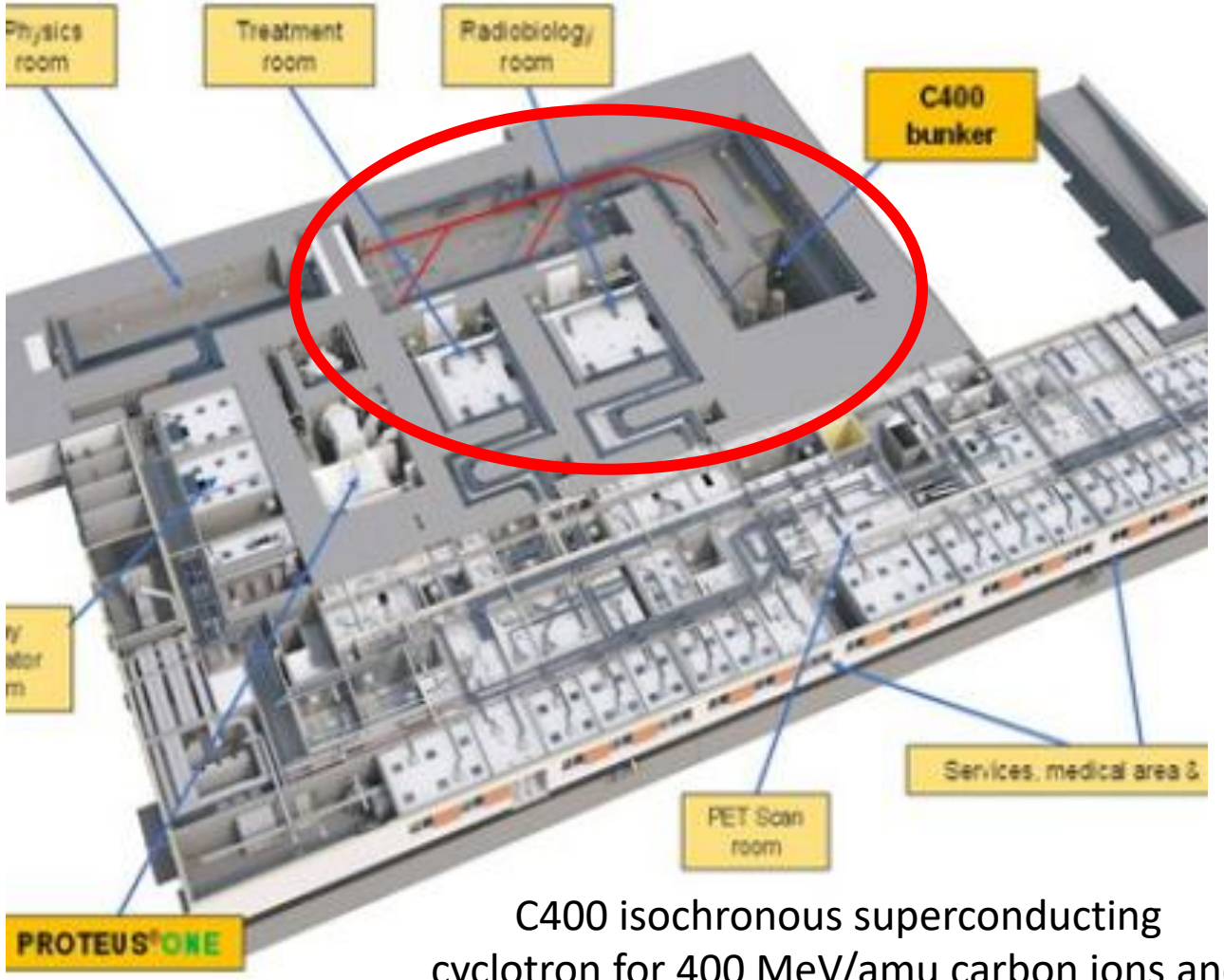


Synchrotron – MedAustron, Austria

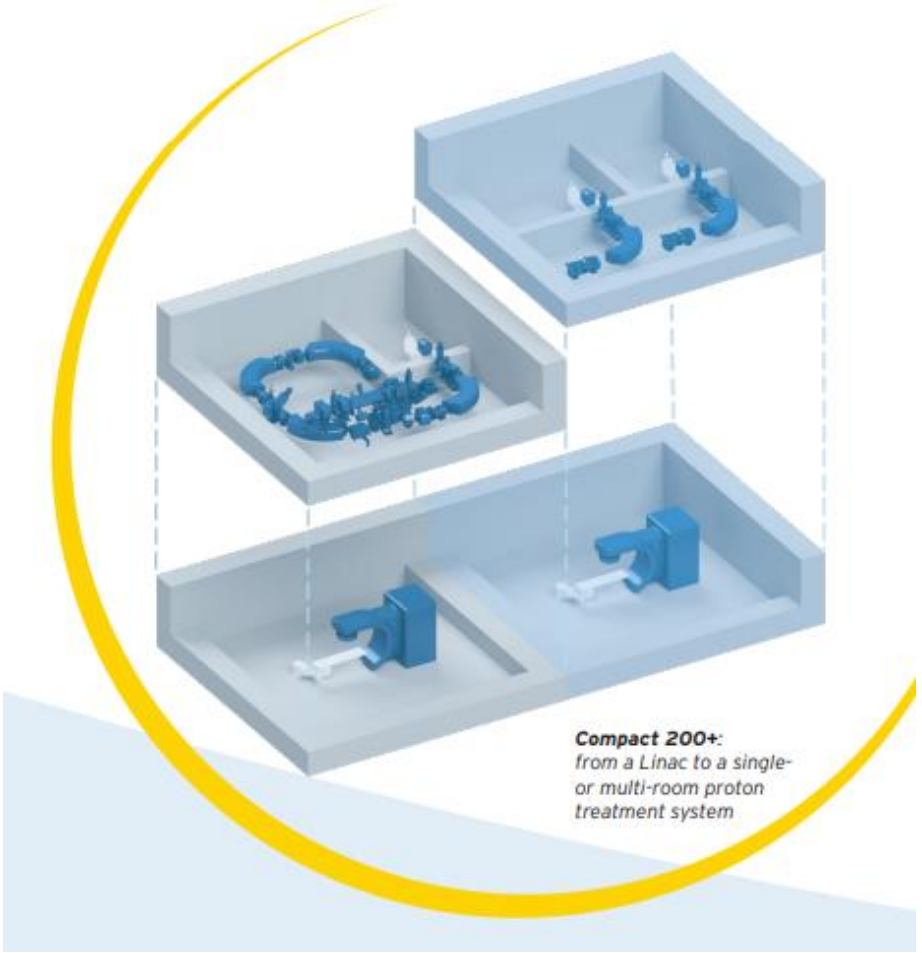


MB Massat — **From Bullet to Canon?** Exploring the Promise of Heavy Particle Ion Therapy. **Appl Radiat Oncol. 2021;(1):46-48**. March 30, 2021.

Nové systémy pro těžší částice



C400 isochronous superconducting cyclotron for 400 MeV/amu carbon ions and 260 MeV protons. Průměr 6,3 m. *(IBA)*

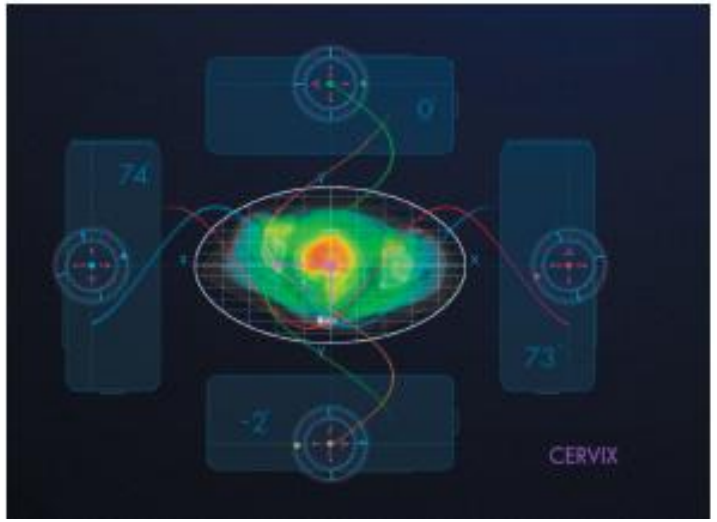


Compact 200+ - Kompaktní synchrotronový systém *(Medaustron)*

Kombinace částicové RT a hypertermie



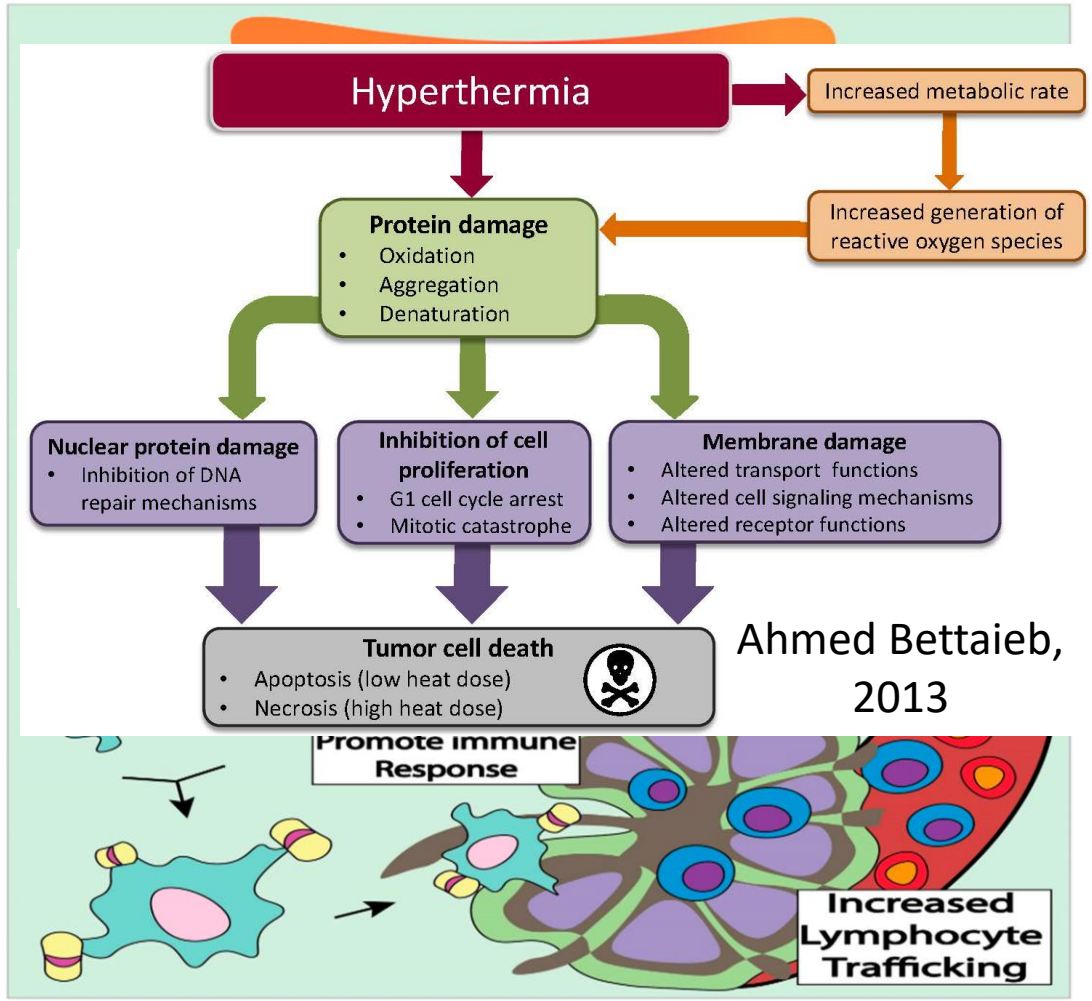
Multi-beam systémy s isofází v GTV (Alba)



Pokročilé plánovací systémy (Alba)

Efekty hypertermie

- Přímé poškození nádorových buněk
- Inhibice reparace DNA v nádoru
- Potenciace protinádorové imunitní reakce



Ahmed Bettaieb, 2013

Mahmood J. Cancers **2018**, *10*(12), 469

Kombinace částicové RT a hypertermie

- Zvyšuje počet usmrcených nádorových buněk
- Zvyšuje počet nádorových antigenů

} Inhibice reparace DNA

- Stimuluje imunitní reakci v spádových uzlinách

Ag + Hsp + DC v mízních uzlinách – aktivace T-lymfocytů

- Lze při ní šetřit/neozářit nepostižené spádové uzliny

Ostrý pokles gradientu při částicové RT

Concurrent Hyperthermia With Pencil Beam Scanning Proton Therapy: Largest Institutional Experience to Date

J.K. Molitoris,[1] J.W. Snider, III,[2] A. Koroulakis,[3] C. DeCesaris,[3] O.M. Siddiqui,[3] E.S. Kowalski,[3] D. Rodrigues,[4] E.M. Nichols,[5] and Z. Vujaskovic[6]; *[1]Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD, [2]University of Alabama Birmingham School of Medicine, Birmingham, AL, [3]Department of Radiation Oncology, University of Maryland Medical Center, Baltimore, MD, [4]University of Maryland School of Medicine, Baltimore, MD, [5]Maryland Proton Treatment Center, Baltimore, MD, [6]University of Maryland, Baltimore, MD*

International Journal of Hyperthermia

http://informahealthcare.com/hth
ISSN: 0265-6736 (print), 1464-5157 (electronic)

Int J Hyperthermia, 2014; 30(7): 524–530
© 2014 Informa UK Ltd. DOI: 10.3109/02656736.2014.963703

informa healthcare

RESEARCH ARTICLE

Could hyperthermia with proton therapy mimic carbon ion therapy? Exploring a thermo-radiobiological rationale

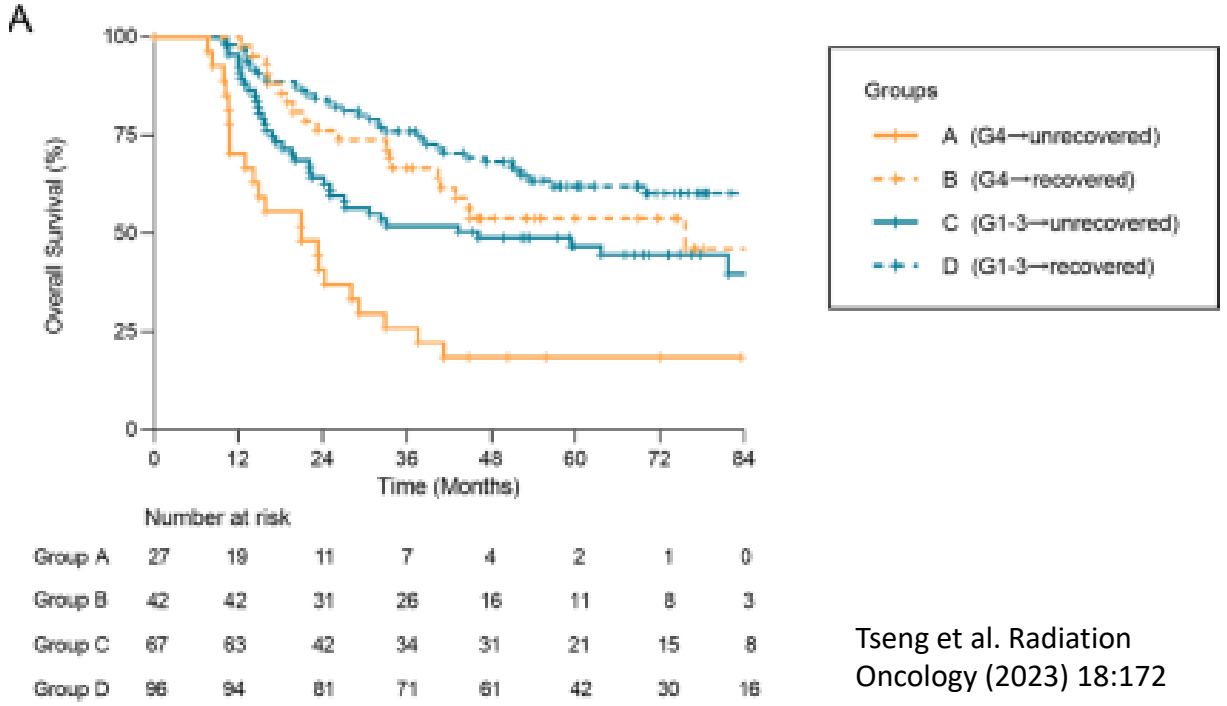
Niloy R. Datta[1], Emsad Puric[1], Ralf Schneider[2], Damien C. Weber[2,3], Susanne Rogers[1], & Stephan Bodis[4,5]

[1]Centre for Radiation Oncology, KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland, [2]Centre for Proton Therapy, Paul Scherrer Institut, Villigen, Switzerland, [3]Department of Radiation Oncology, University of Zürich, Switzerland, [4]Centre for Radiation Oncology, KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland, and [5]Department of Radiation Oncology, University Hospital Zurich, Switzerland

Lymfopenie indukovaná radioterapií – výskyt, význam

Metaanalýzy hodnotící RIL po fotonové radioterapii		
	Frekvence výskytu RIL G3-4	**Hazard ratio pro úmrtí (metaanalýzy)**
Mozkové nádory	**21-35%**	**1,63**
Nádory ORL oblasti	**73—88%**	**2,94**
Karcinom jícnu	**24-45%**	**1,50**
Karcinom plic	**64%**	**1,59**
Nádory jater	**87%**	
Karcinom pankreatu	**27-45%**	**2,33**
Čípek děložní	**53-61%**	**2,67**

Lymphocyte recovery from RIL in locally advanced esophageal squamous cell cancer : correlation with prognosis….



Tseng et al. Radiation Oncology (2023) 18:172

Lymfopenie indukovaná radiací je klinicky běžnou situací a negativně ovlivňuje celkové přežití

Na jakých dozimetrických parametrech radioterapie závisí RIL?

- Integrální dávka/Mean body dose/Objem PTV – čím vyšší, tím větší riziko lymfopenie
- Dávka na orgány s vysokým výskytem lymfocytů – Slezina, Thymus, lymfatické uzliny
- Dávka na cirkulující krev
- Dávka na orgány s vysokým objemem cirkulující krve – srdce, plíce, velké cévy
- Dávka na kostní dřeň
- Lokalita radioterapie – epigastrium/mozek horší než pánev
- Frakcionace radioterapie – normofrakcionace je horší než akcelerace
- Rychlost dodání dávky – delší doba je horší

Yang L et al Cancer Biomark. 2022;34(1):149-159; Reddy AV et al., Radiat Oncol. 2021 Dec 24;16(1):242; Ladbury CJ et al., Int J Radiat Oncol Biol Phys. 2019 Oct 1;105(2):346-355; Chen D et al., Radiother Oncol. 2020 Sep;150:114-120; Zhao Q et al., Technol Cancer Res Treat. 2022 Jan-Dec;21:15330338221112287;

Lymfopenie indukovaná radioterapií

Radiotherapy &Oncology

Částicová radioterapie

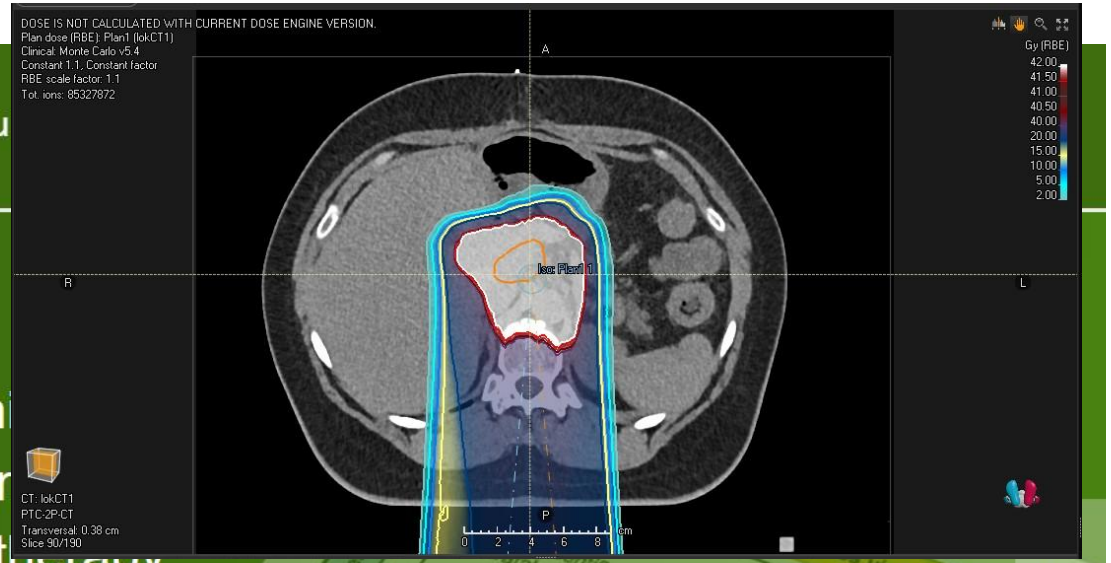
SYSTEMATIC REVIEW | VOLUME 177, P81-94, DECEMBER 01, 2022

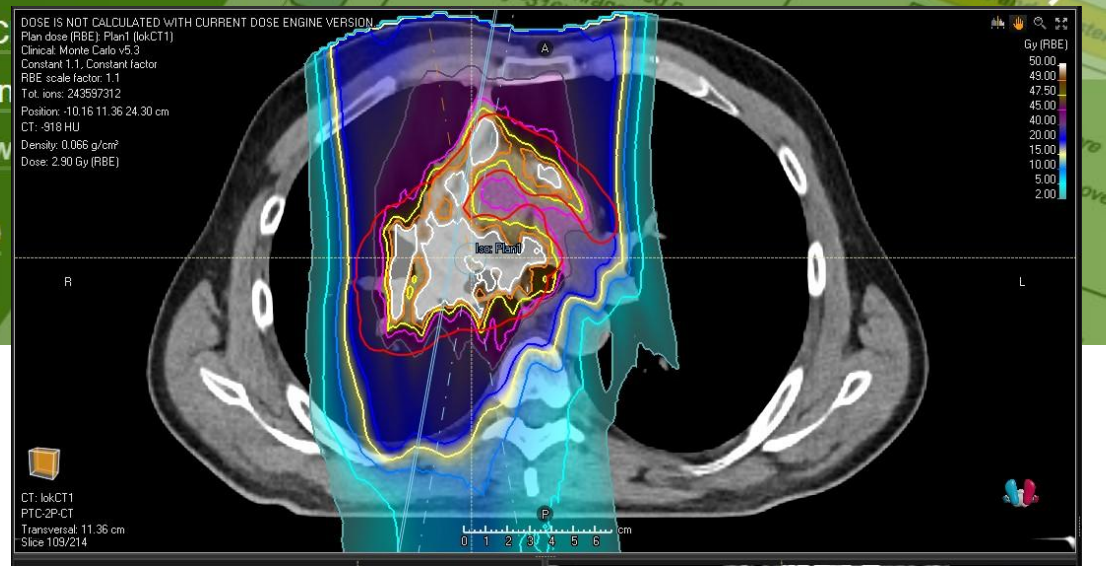
Lymphocyte sparing normal tissue effects in the clin
A systematic review of dose constraint consideration
radiation-related lymphopenia in the era of immunotherapy

Alec M. Block • Rituraj Upadhyay • James S. Welsh • Matthew M. Harkenrider • Sun
Cheng En Hsieh • Satyajit Pradhan • William Small Jr • Abhishek A. Solanki • Show

Published: November 02, 2022 • DOI: https://doi.org/10.1016/j.radonc.2022.10.019

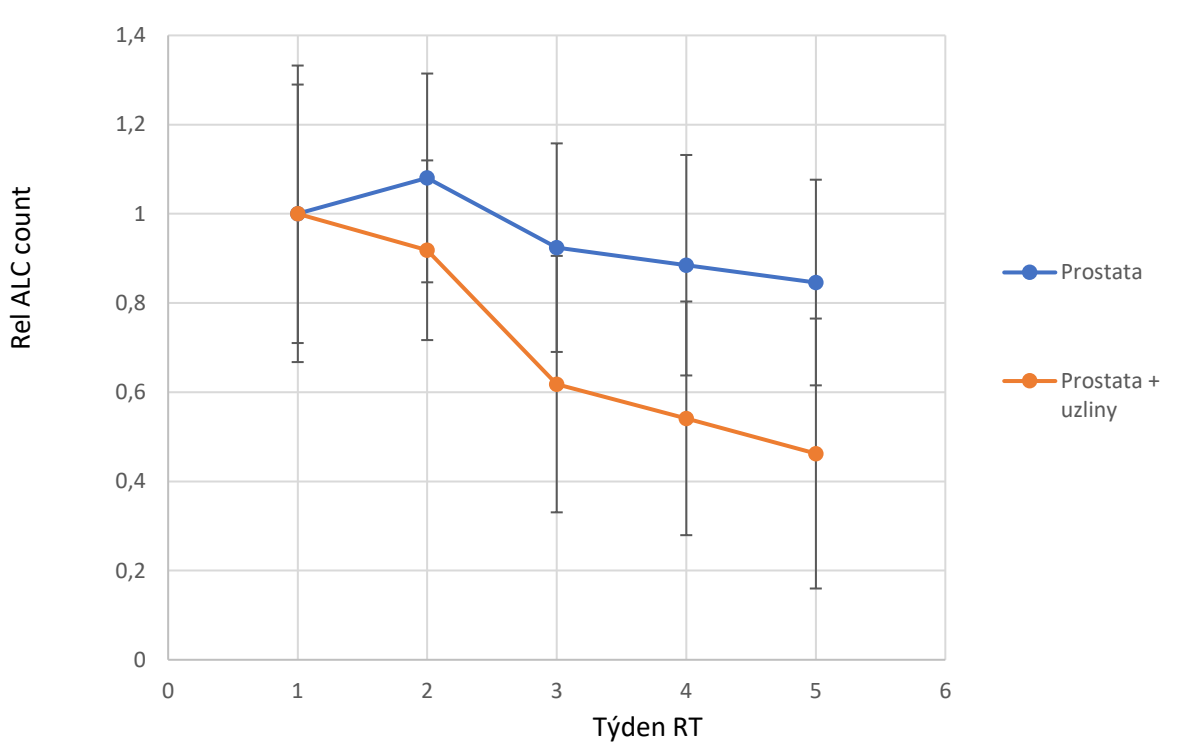
- Nízká integrální dávka
- Možnost neozářit uzliny
- Možnost neozářit velké cévy
- Rychlost dodání dávky
- Trendy k akceleraci/hypofrakcionaci/Flash





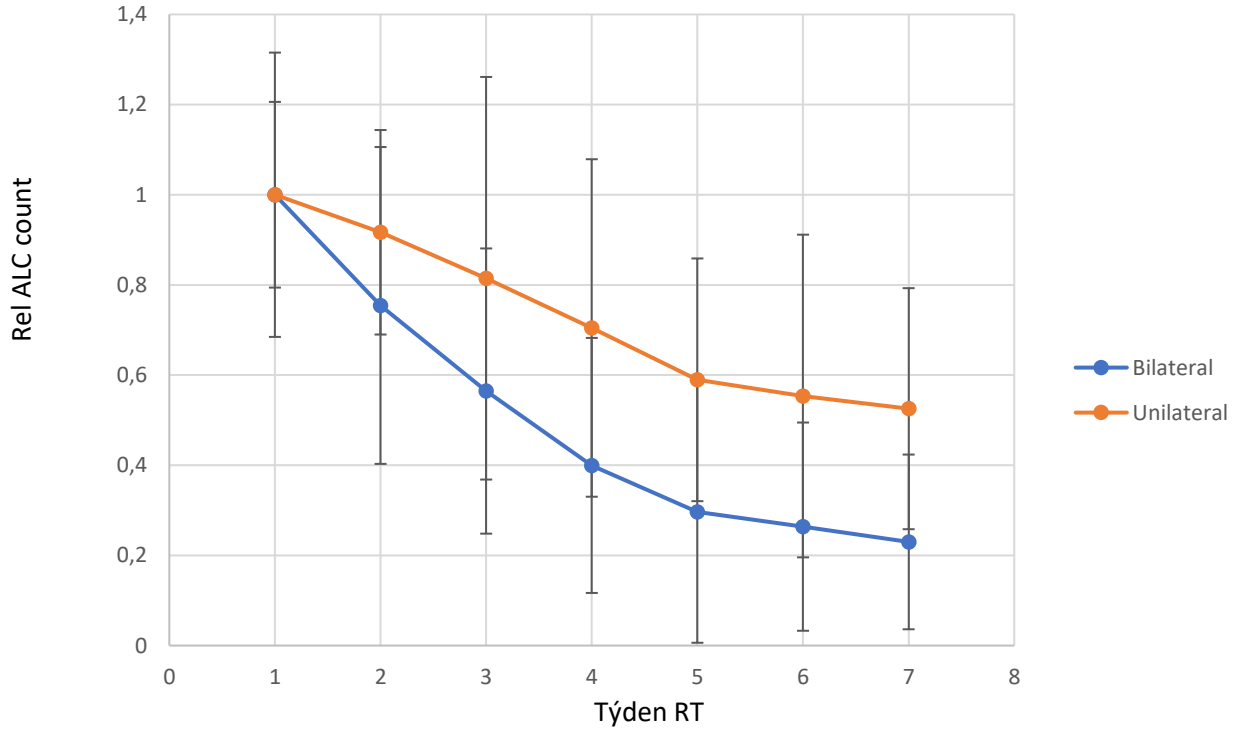
Stejné lokality/různé ozářené objemy

Prostata+uzliny vers. Prostata - ALC vers. týden RT



Iso 2 Gy	2420/8089

H&N Unilateral vers H&N Bilateral - **ALC** / týden RT



Iso 2 Gy	1803/3297

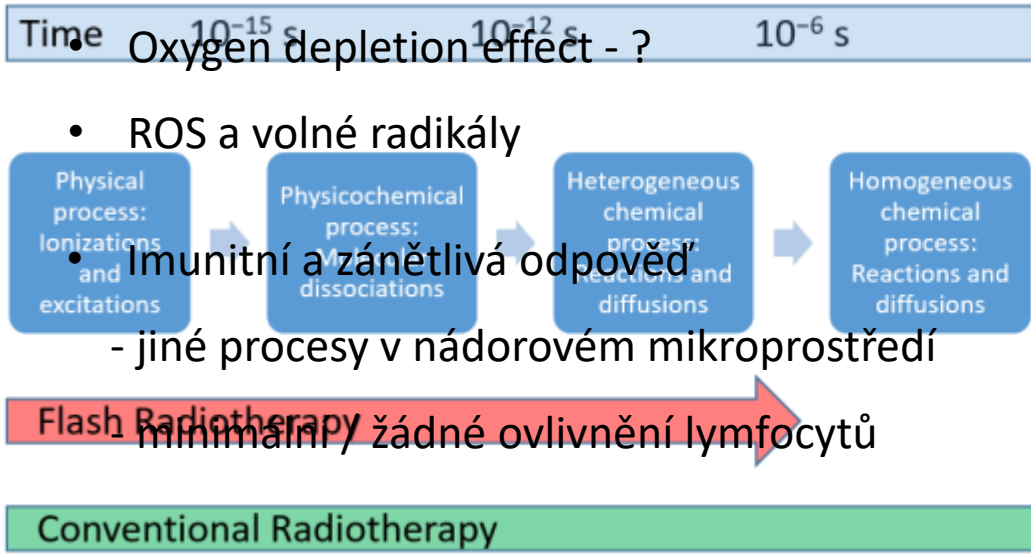
PTC Czech – nepublikovaná data

33(1)
•Clinical Oncology

FLASH radioterapie

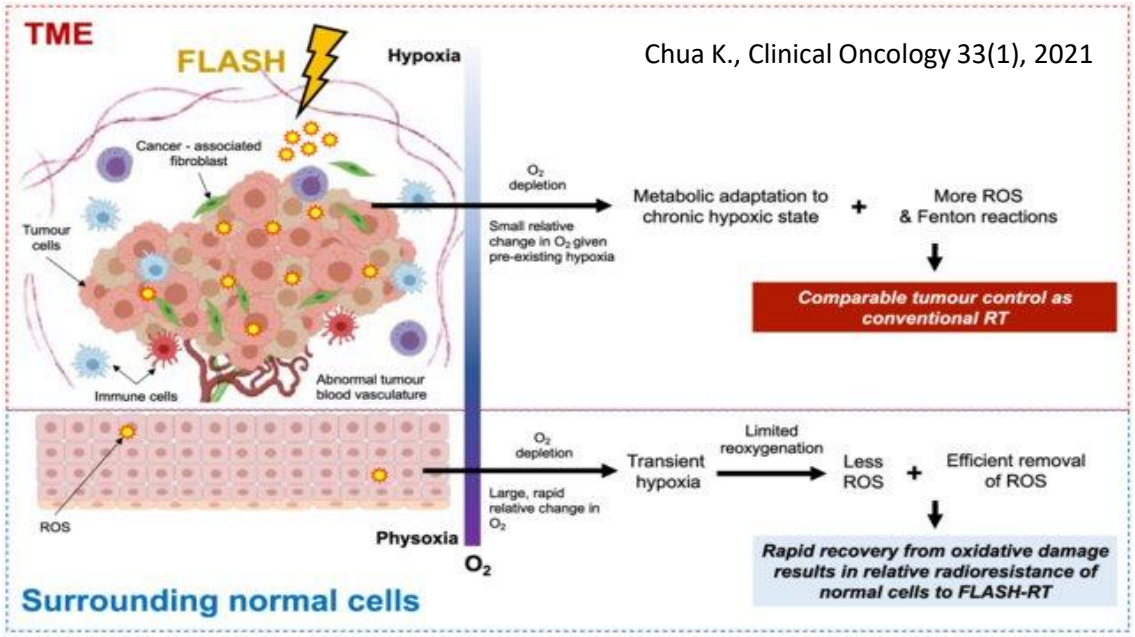
- FLASH RT = Dose rate > 40 Gy/s
- Zatím preklinická data, minimum klinických dat
- Stejný efekt na tumor, menší na zdravé tkáně

Mechanismy účinku FLASH RT – není zcela jasný

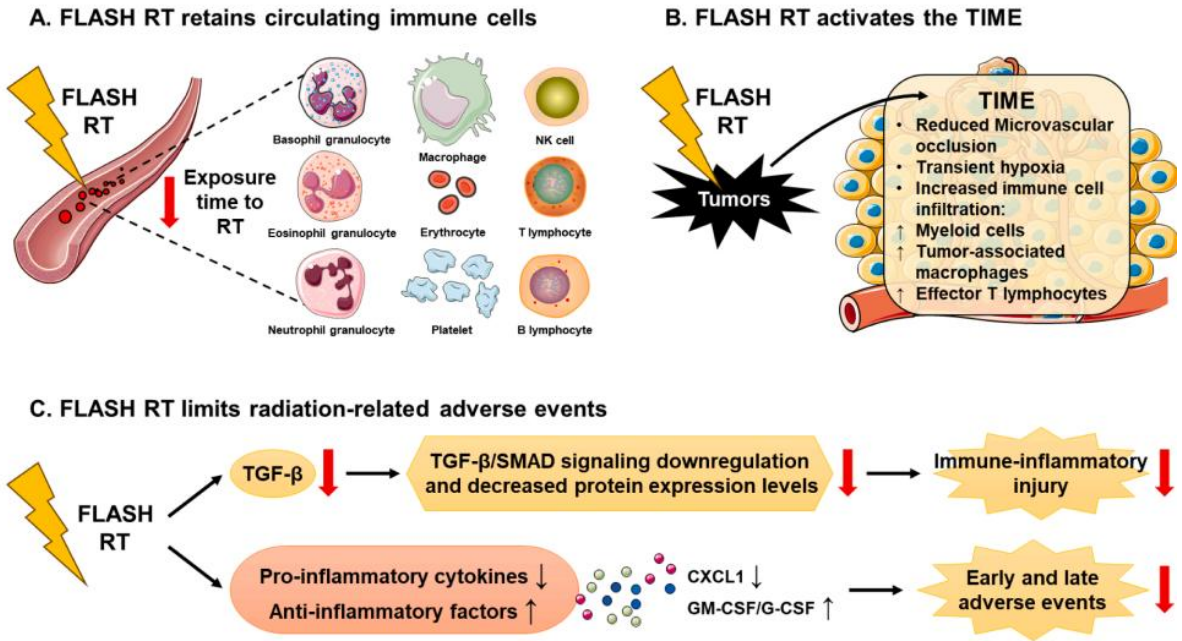


- Oxygen depletion effect - ?
- ROS a volné radikály
- Imunitní a zánětlivá odpověď

  - jiné procesy v nádorovém mikroprostředí
  - minimální / žádné ovlivnění lymfocytů



Chua K., Clinical Oncology 33(1), 2021



Wang Yu, Translational Oncology 51, 2025

Technologie pro FLASH/úskalí

Elektrony

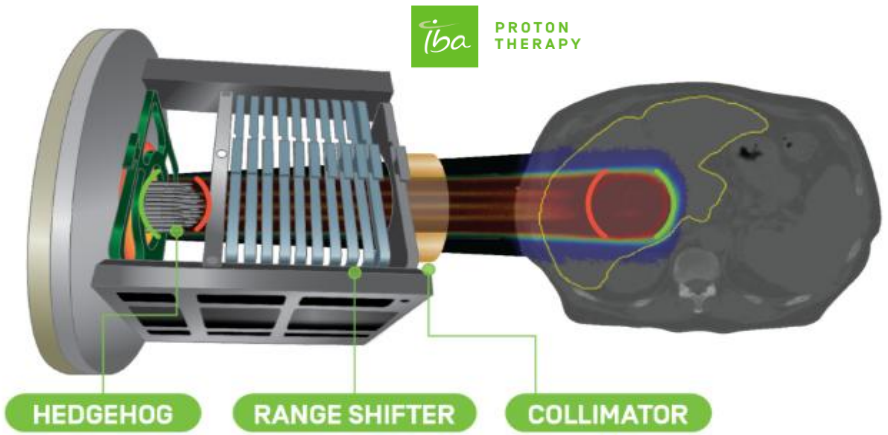
Fotony

Protony

Těžší ionty



Částicová radioterapie je technologicky připravena pro FLASH!

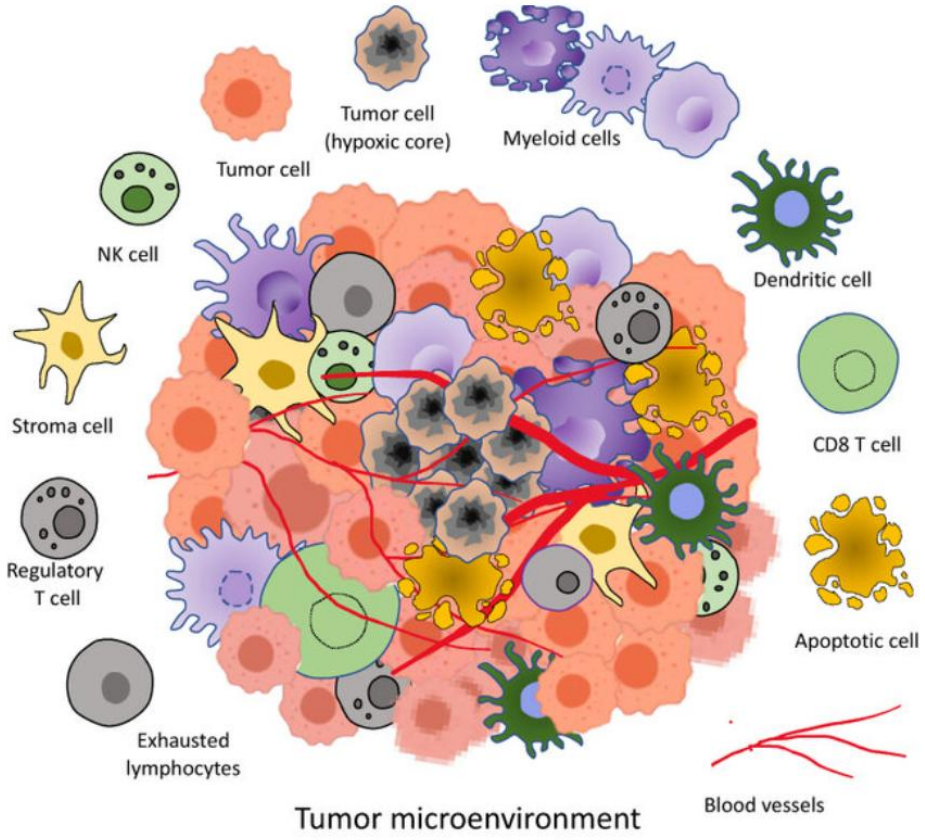


<u>Úskalí</u>

- Dosimetrie
- Rychlost vs přesnost
- Nemožnost korekce
- Klinická data
- Nejasnost mechanismu

Nádorové mikroprostředí

- Směs nádorových, podpůrných a imunitních buněk
- Významně ovlivňuje vývoj nádoru



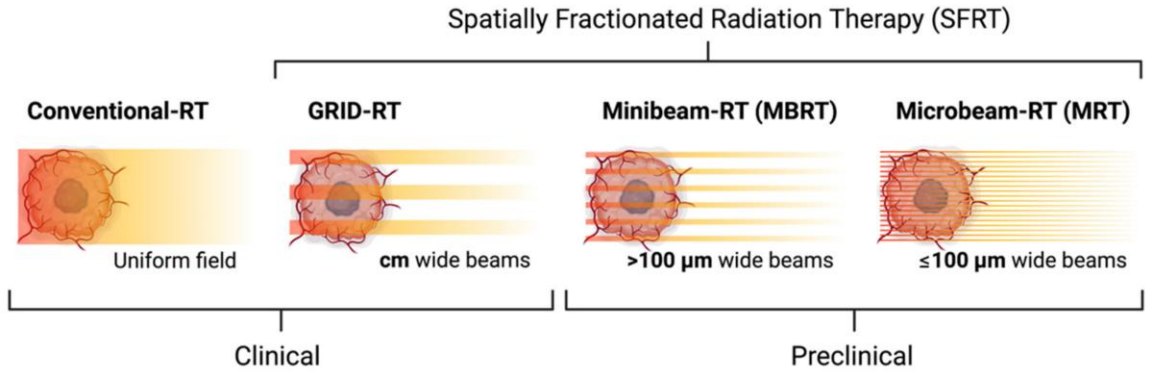
- Je přístup „kill them all“ správný?
- Partial tumor irradiation

•Khaled Allemailem International Journal of Nanomedicine 18:5531-5559

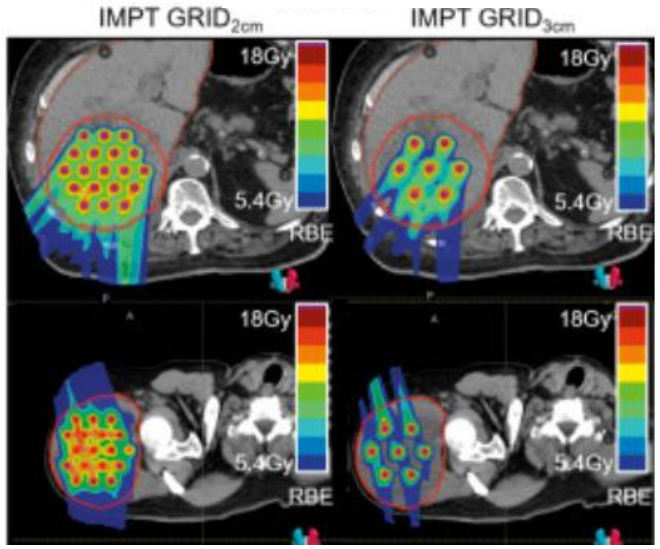
SFRT – Spatially Fractionated Radiation Therapy

Zachovat část nádorového mikroprostředí bez vlivu ionizujícího záření

- Menší toxicita
- **<u>Aktivace imunitního systému</u>**

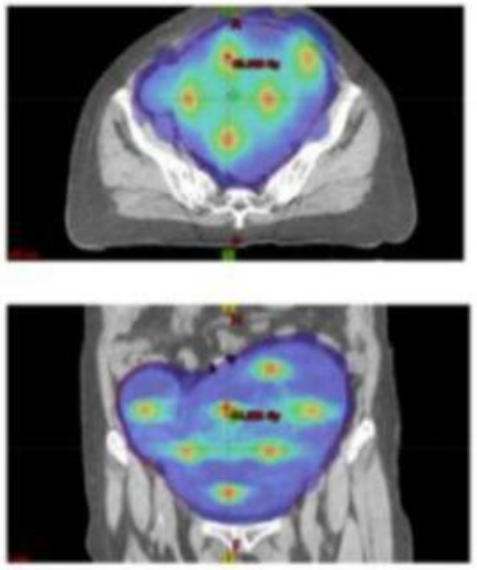


GRID RT



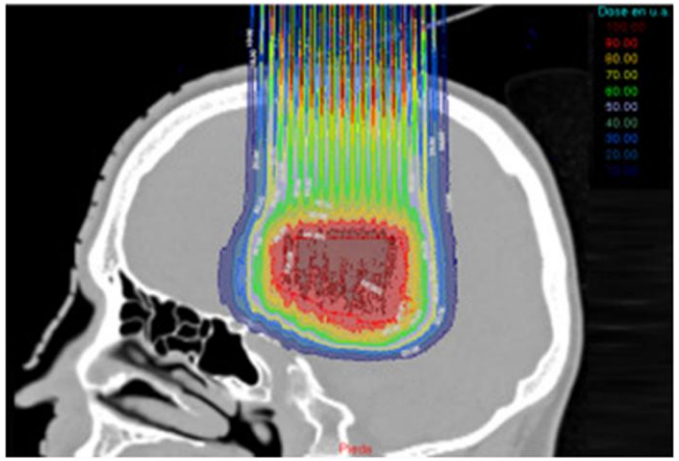
Halthore A., IJPT 9(3)

Lattice RT



Iori F, Clin Transl Radiat Oncol. 2022 Dec 20;39:100569

MINI/MICRO beams



Prezado Y Expert Reviews in Molecular Medicine 24, e3, 1–12

Spatially fractionated GRID radiation potentiates immune-mediated tumor control

Rebecca A Bekker [1,4], Nina Obertopp [2,4], Gage Redler [3], José Penagaricano [3], Jimmy J Caudell [3], Kosj Yamoah [3], Shari Pilon-Thomas [2], Eduardo G Moros [3], Heiko Enderling [5,6,✉]

Radiat Oncol. 2024 Sep 13;19(1):121.

Heterogeneous intratumor irradiation: a new partner for immunotherapy

Paul Bergeron[a], Fabien Milliat[b], Eric Deutsch[a], and Michele Mondini[a]

Oncoimmunology. 2024 Dec 31;13(1):2434280

Role of Spatially Fractionated Radiotherapy (LATTICE) Treatment in Inoperable Bulky Soft-Tissue Sarcomas

Katarina Majercakova [1,*], Natalia Tejedor Aguilar [2], Josep Isern Verdum [1], Helena Vivancos Bargalló [2], Antonio Vila Capel [1], Miriam Mancera Soto [2], Guillermo Gómez de Segura Melcón [2], Jady Vivian Rojas Cordero [1], José Antonio González-López [3], Silvia Bagué Rosell [4], Diana Hernandez Jover [5], Saba Rabi Mitre [1], Ana Peiró Ibañez [6], Ana Sebio [7] and Gemma Sancho-Pardo [1]

Cancers (Basel). 2025 Feb 13;17(4):624

Spatially fractionated radiotherapy (Lattice SFRT) in the palliative treatment of locally advanced bulky unresectable head and neck cancer

Peng Xu, Shuo Wang, Jie Zhou, Ke Yuan, Xianliang Wang, Lintao Li, Jinyi Lang, Shun Lu*

Department of Radiation Oncology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, Chengdu, China

Clin Transl Radiat Oncol. 2024 Jul 30;48:100830

Kombinace s imunoterapií

From Photon Beam to Accelerated Particle Beam: Antimetastasis Effect of Combining Radiotherapy With Immunotherapy

Liqiu Ma [1,2*]

Frontiers in Public Health, 2022

Particle radiotherapy in the era of radioimmunotherapy

Zihan Zhou [a 1] ✉, Bingjie Guan [a 1] ✉, Huang Xia [a] ✉, Rong Zheng [a b c] ✉, Benhua Xu [a b c] ✉

Cancer Letters, 2023

Immunological Effects of Proton Radiotherapy: New Opportunities and Challenges in Cancer Therapy

Anhang Zhang[1,2,3] | Liyuan Fan[4] | Qi Liu[1,2,3] | Xiaoxin Zuo[1,2,3] | Jian Zhu[1,2,3]

Cancer Innovation, 2024

- Nutná podmínka konceptu !
- Check-point inhibitory
- Sekvence

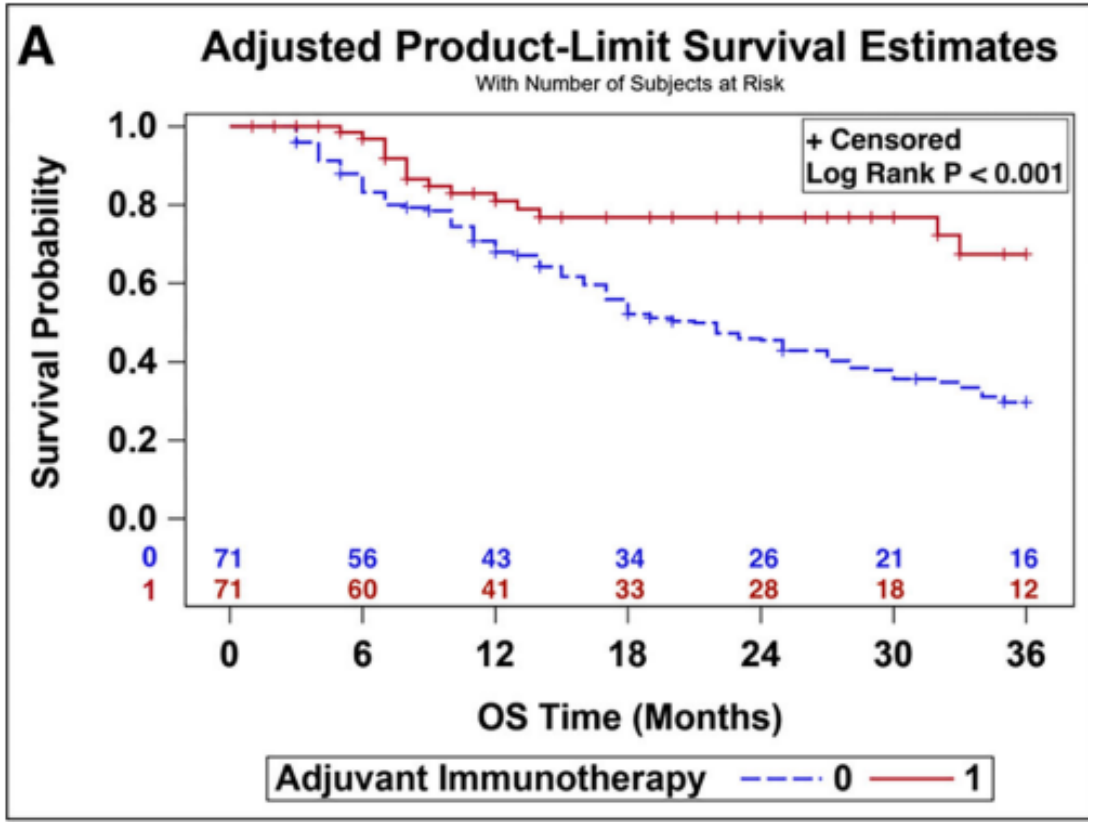
  - před, současně nebo po ?

Kombinace s imunoterapií

Survival outcomes and toxicity of adjuvant immunotherapy after definitive concurrent chemotherapy with proton beam radiation therapy for patients with inoperable locally advanced non-small cell lung carcinoma

Kelsey L. Corrigan, MD, MPH[1,*], **Ting Xu, PhD**[1,2,*,a], **Yuki Sasaki, MD**[1], **Ruitao Lin, PhD**[2],

Materials and Methods: We analyzed 377 patients with LA-NSCLC who were prospectively treated with CPBT with or without adjuvant IO from 2009–2021. Optimal variable ratio propensity score matching (PSM) matched CPBT with CPBT+IO patients. Survival was estimated with the Kaplan-Meier method and compared with log-rank tests. Multivariable Cox proportional hazards regression evaluated the effect of IO on disease outcomes.



Conclusion: This study, one of the first to investigate CPBT followed by IO for inoperable LA-NSCLC, showed that IO conferred survival benefits with no increased rates of toxicity.

Radiother Oncol. 2024 April ; 193: 11012

Dostupnost

- Částicová radioterapie – celosvětově 1-3% pacientů

Group 1
Based on the medical necessity requirements and published clinical data that meets the selection criteria above, disease sites that frequently support the use of PBT include the following:

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

ASTRO Model Policies

2026

PROTON BEAM THERAPY (PBT)
This Model Policy* addresses coverage for Proton Beam Therapy.

HEAD AND NECK
Cancers of the nasopharynx, nasal cavity, paranasal sinuses and other accessory sinuses
Advanced stage and unresectable head and neck cancers
Oropharyngeal 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

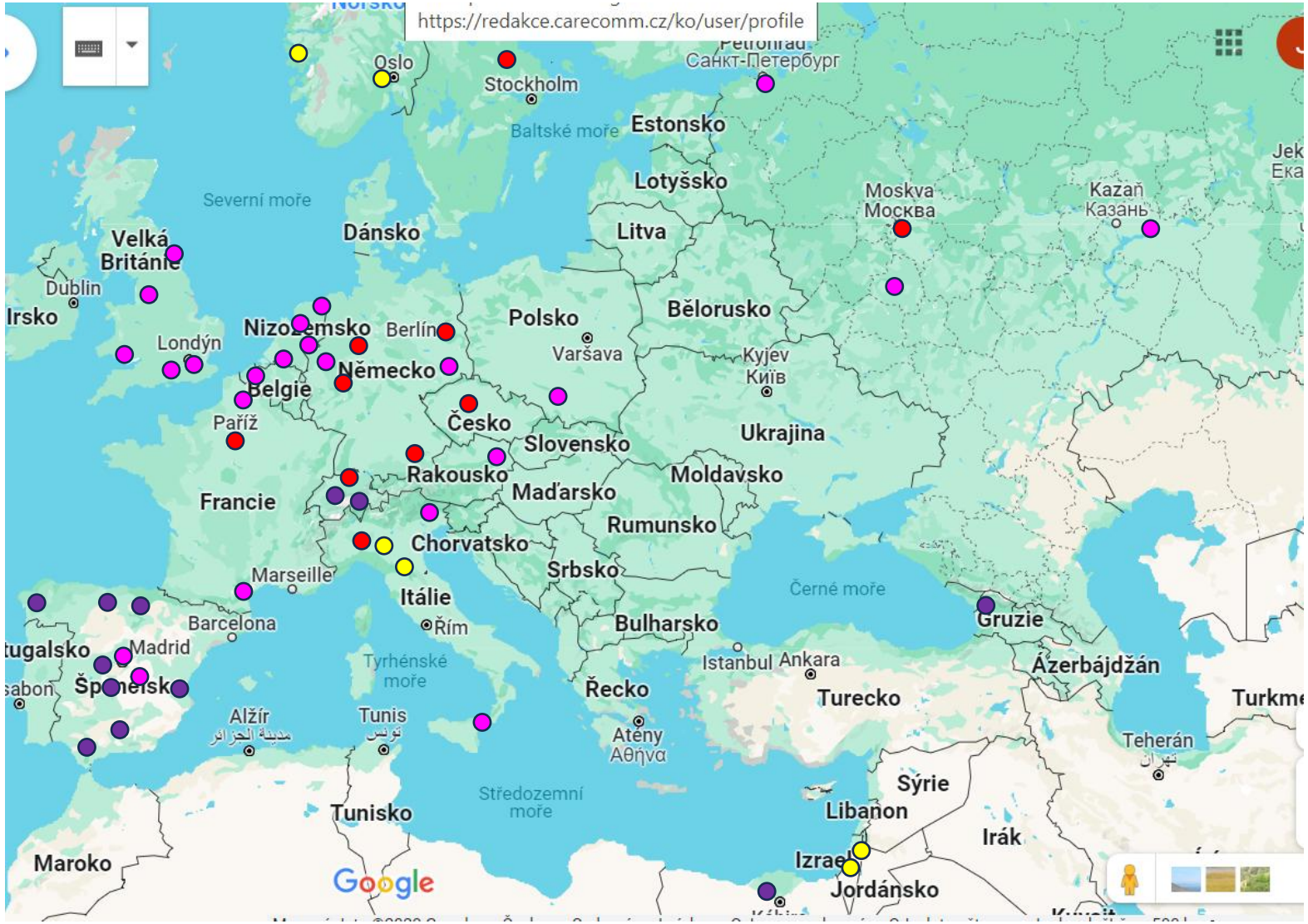
ABDOMINAL
Hepatocellular cancer and intra-hepatic biliary cancers
Non-metastatic retroperitoneal sarcomas

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

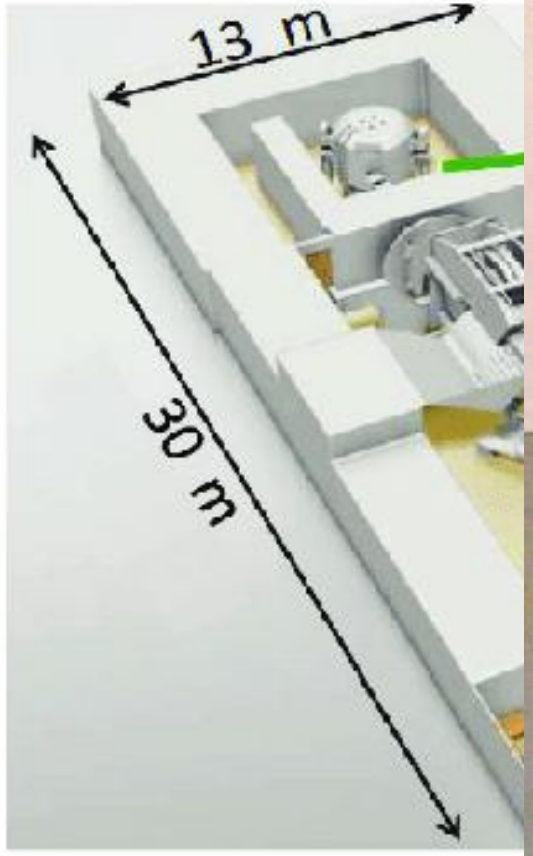
Protony ve světě



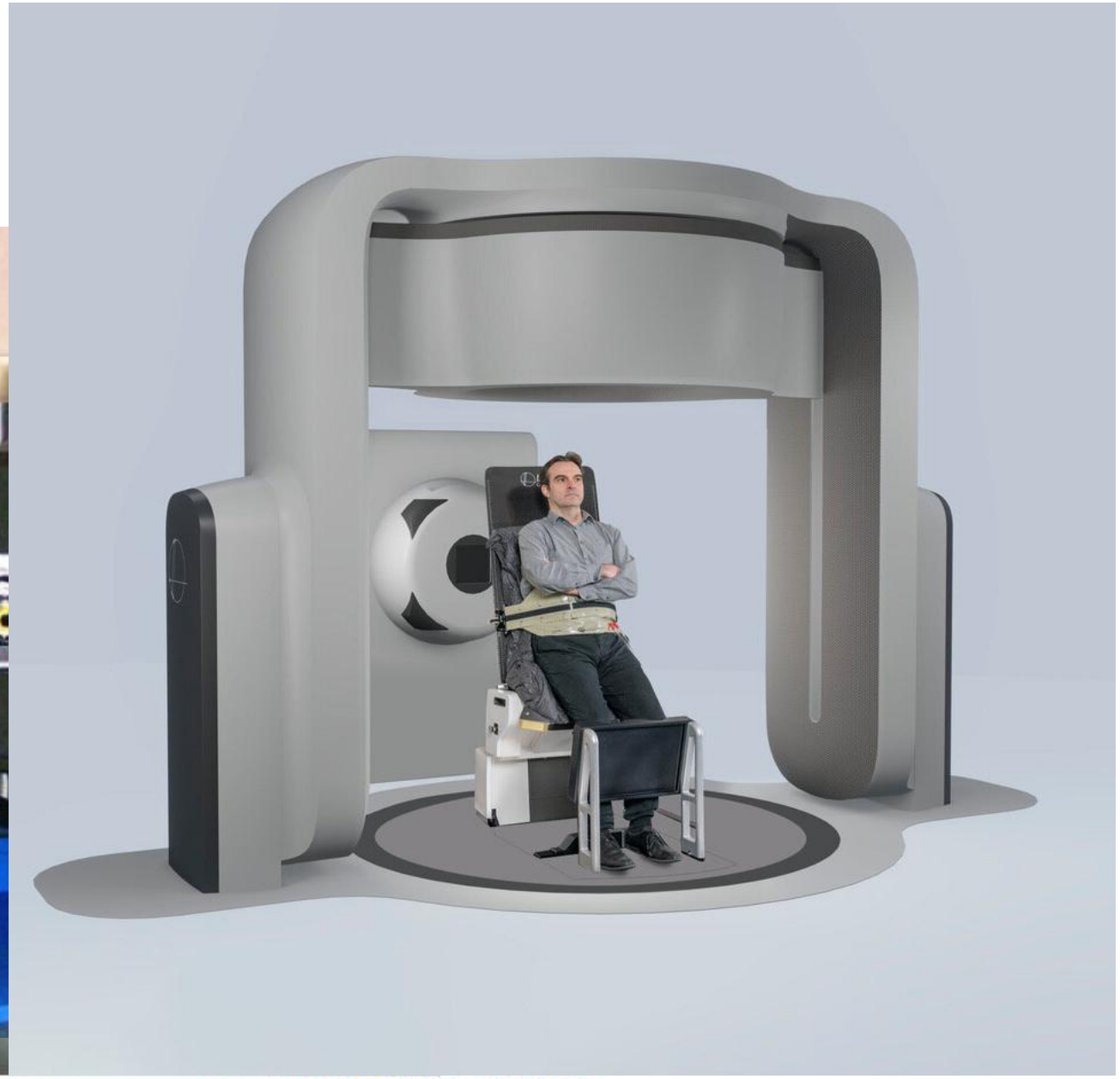
Protony ve světě



Dostupnost







Kompaktní řešení - IBA

Zmenšování technologie

Up-right RT

PTC Czech

- Centrum poskytující
  - diagnostiku
  - terapii (pRT, CHT, HORT)
  - dispenzarizaci
- Personálně dobře a stabilně zajištěné
- S důrazem na rychlost poskytnutí péče a pohodlí pacienta
- Integrované v systému zdravotní péče



Review

Radiation dose constraints for organs at risk in neuro-oncology; the European Particle Therapy Network consensus

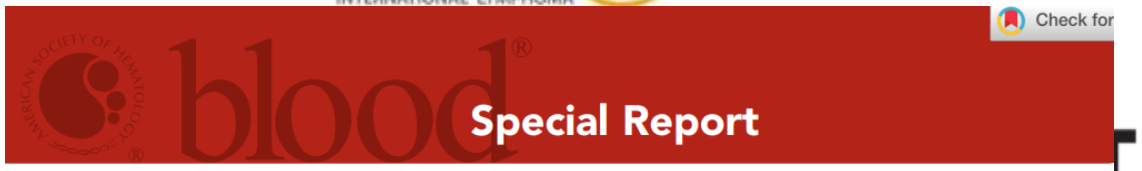




REVIEW

Proton Beam Therapy for Pancreatic Tumors: A Consensus Statement from the Particle Therapy Cooperative Group Gastrointestinal Subcommittee





Proton therapy for adults with mediastinal lymphomas: the International Lymphoma Radiation Oncology Group guidelines

Bouthaina Shbib Dabaja,[1] Bradford S. Hoppe,[2] John P. Plastaras,[3] Wayne Newhauser,[4] Katerina Rosolova,[5,6] Stella Flampouri,[2] Radhe Mohan,[7] N. George Mikhaeel,[8] Youlia Kirova,[9] Lena Specht,[10] and Joachim Yahalom[11]

THE LANCET
Oncology

Management of vertebral radiotherapy dose in paediatric patients with cancer: consensus recommendations from the SIOPE radiotherapy working group

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journal homepage: www.thegreenjournal.com



Ultrahypofractionated Proton Radiation Therapy in the Treatment of Low and Intermediate-Risk Prostate Cancer-5-Year Outcomes

Georgios Ntentas [d,f,g], Vladimír Vondráček [a,b], Barbora Ondrová [a], Jana Marková [c],
Alice Sýkorová [l], Juraj Ďuraš [m], Jan Kořen [o,p], Matěj Navrátil [a], Michaela Vařejková [q,r],
Tomáš Doležal [q], Jana Prausová [a], on behalf of the Czech Hodgkin Lymphoma Study Group

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Kubeš J. et al. Int J Radiat Oncol Biol Phys. 2021 Jul 15;110(4):1090-1097.

Temporal dynamics of lymphocytes in prostate cancer patients treated with proton therapy

frontiers | Frontiers in Oncology

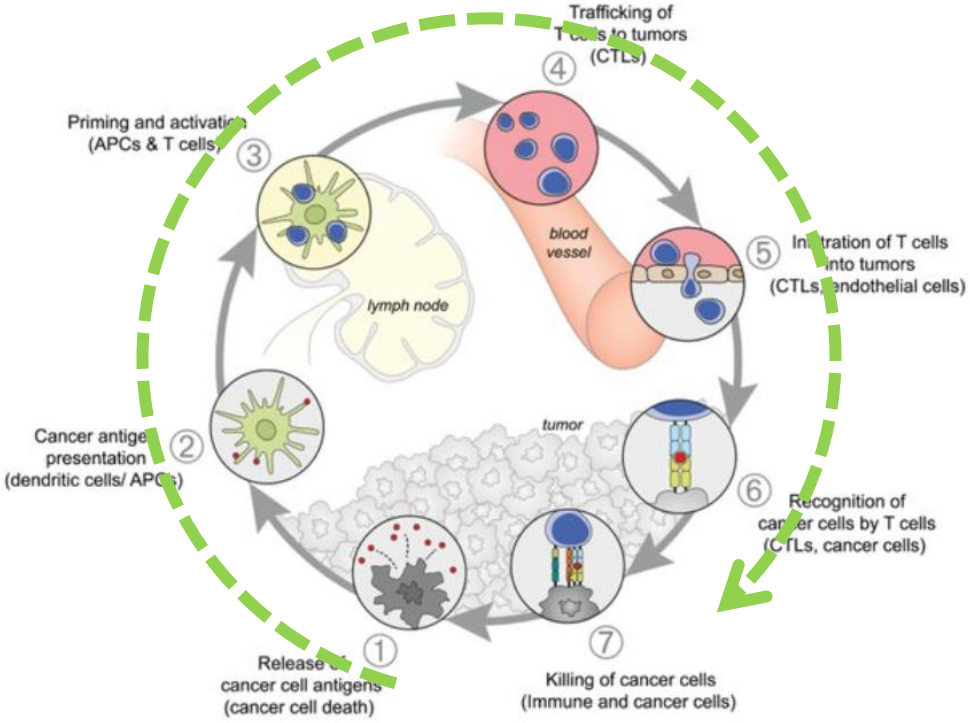
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Al-Hamami SS et al., Front Oncol. 2025 Apr 16;15:1470876.

Závěr

- Interakce mezi nádorem a imunitním systémem je v centru pozornosti
- Je nutné nejen zničit nádor, je zároveň zachovat funkční imunitní systém (lymfocyty, uzliny, mikroprostředí)
- Je nutné správně kombinovat tyto postupy s moderní imunoterapií

- Částicová radioterapie má předpoklady pro splnění výše uvedeného
  - Heavy ions
  - hypofrakcionace…..FLASH
  - nová definice cílových objemů
  - LymphoTEC
  - GRID, Microbeams
  - kombinace s hypertermií
  - kombinace s imunoterapií





Poděkování

Lékařský a fyzikální tým PTC



Děkuji za pozornost