Opportunities for Personalized Multi-Modality ~~Radiation Therapy~~ Cancer Care

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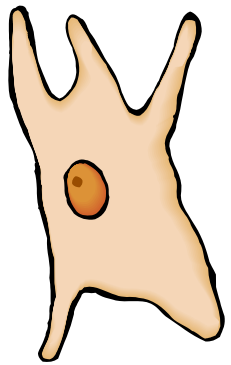

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Date and Time: Sunday July 12 from 1-3 PM (Eastern)
Location: Virtual

Disclaimer

- Co-investigator on a Research Collaboration Agreement with RaySearch Inc.
- Have a long-stranding and unapologetic bias towards biological modeling for outcome assessment and treatment individualization and a more recent bias towards multi-modality patient care

BGRT: Biologically guided radiation therapy—The future is fast approaching!

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School of Health Sciences, Purdue University, 550 Stadium Mall Drive, West Lafayette, Indiana 47907-2051

X. Allen Li[a)]
Department of Radiation Oncology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226

RD Stewart , XA Li, BGRT: Biologically Guided Radiation Therapy-The Future Is Fast Approaching! Med Phys. 2007 Oct;34(10):3739-51. PMID: 17985619 DOI: 10.1118/1.2779861

Learning Objectives

- Understand some of the strengths and weaknesses of low and high linear energy transfer (LET) treatment options – past, present and future
- Gain an appreciation for how low and high LET treatments might be exploited to individualize and advance patient care
- Understand some of the drivers of patient care with palliative and curative intent in Radiation Oncology
- Provoke discussion and ***debate*** on forward-looking strategies to more fully exploit Radiation Oncology treatment modalities in combination with other Oncology care options

Local Tumor Control – Low and High LET Treatments

- **Low LET MV x-rays are the dominate treatment modality and will remain so for the foreseeable future**
  - Number of treatment facilities translates to rapid advances in auxiliary technologies for image guidance and motion management
- **Low LET protons and high LET carbon reduce dose to normal tissue while delivering the same or better tumor control because of their finite range in tissue**
  - Image guidance, motion management and intensity modulation lags several years behind what's available in MV x-ray facilities. Patient QA and other concerns also arise because high LET radiations are more damaging to electronics than low LET radiations.

Comparison of MV x-ray and proton therapy plans

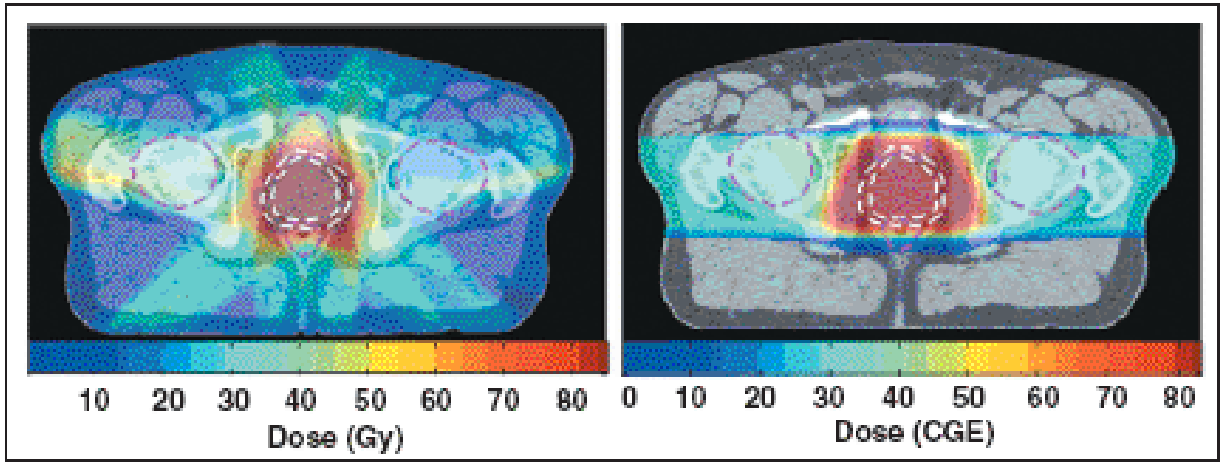


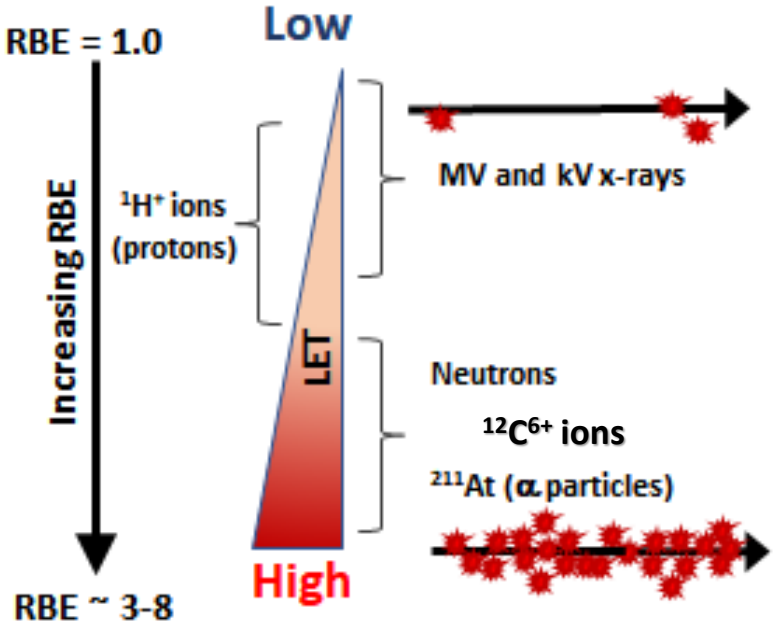
Figure 1: Protons vs Photons—Photon IMRT plan (left) and proton plan (right) to 79.2 GyE. CGE = cobalt gray equivalent; IMRT = intensity-modulated radiation therapy. Adapted, with permission, from Trofimov et al.[11]

Trofimov A, Nguyen PL, Coen JJ, Doppke KP, Schneider RJ, Adams JA, Bortfeld TR, Zietman AL, Delaney TF, Shipley WU. Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: a treatment planning comparison. ***Int J Radiat Oncol Biol Phys.*** **69(2), 444-453 (2007).**

Biological Effects of low and high LET Radiations

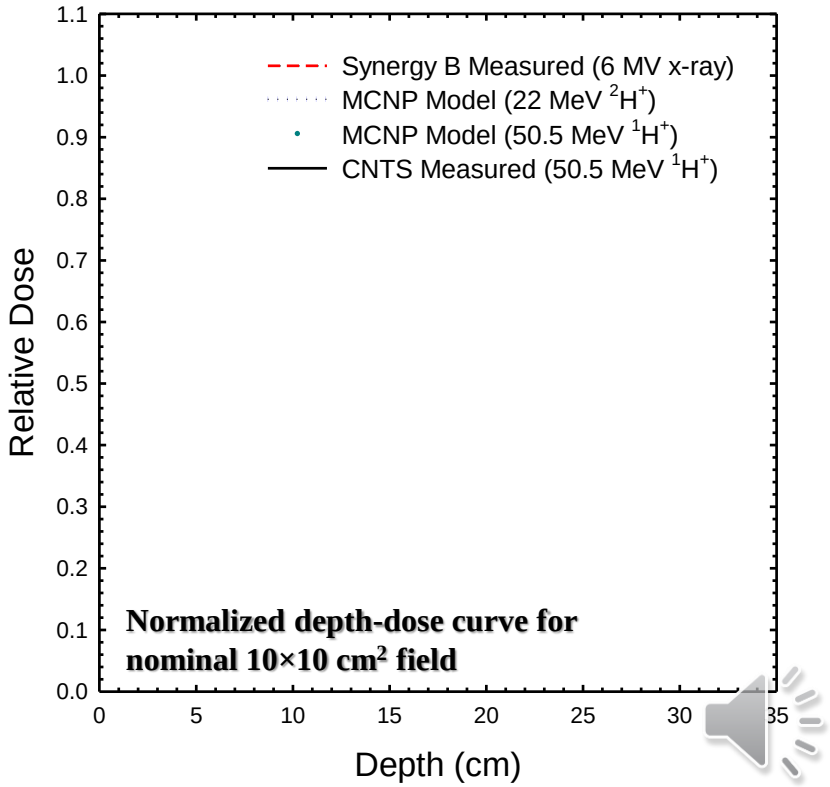
- At the cellular and sub-cellular levels, high LET radiation are far more damaging than low LET radiations
- **Relative biological effectiveness** (RBE) for Z > 1 ions (and fast neutrons) can reach 3-8 for some tumor targets compared to ~ 1.1 for protons

RBE is the dose of a low LET radiation divided by the dose of a high LET radiation that produces the same biological effect



Fast neutron therapy – past and present

- **Fast neutrons**, a form of high LET radiation with an **RBE comparable to carbon ions**, have depth-dose profiles similar to 6 MV x-rays
  - Initial clinical trials at UW used 22 MeV $^{2}H^{+}$ ions to produce neutrons. Depth-dose profile similar to ^{60}Co (less skin sparing, sharper drop-off in dose)
- Failure of high LET fast neutron therapy in clinical trials conducted in the late 70's and early 80's primarily an engineering and technology failure
  - **In ability to adequately spare normal tissue without sacrificing tumor coverage and dose**



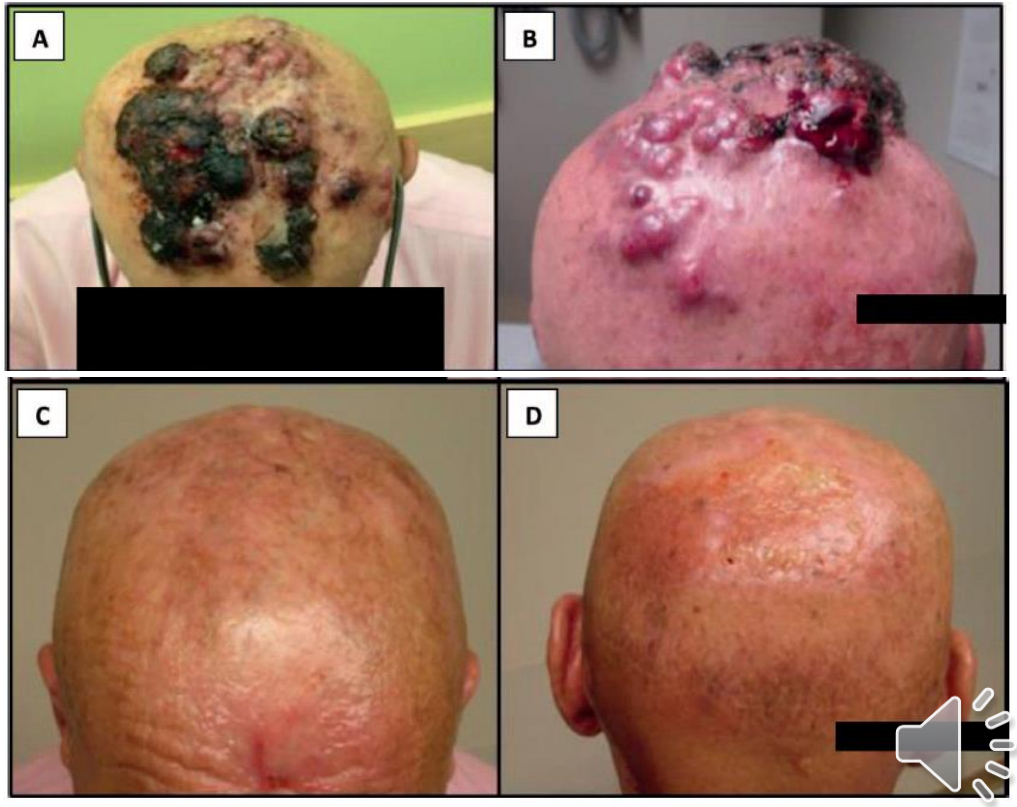
Example – the Advantage of High LET Radiation

High LET radiations are effective at over-coming multiple mechanisms of radiation resistance, *including tumor hypoxia*.

Panels A and B: A 78-year-old man with Merkel Cell carcinoma of the scalp. The tumor had previously progressed through multiple courses of low LET radiation (~ 91 Gy) and immunotherapy.

Panel C and D: the cancer responded rapidly and completely responded after treatment with high LET fast neutrons at UW, (~ 18.4 Gy). Effective neutron RBE > 5.

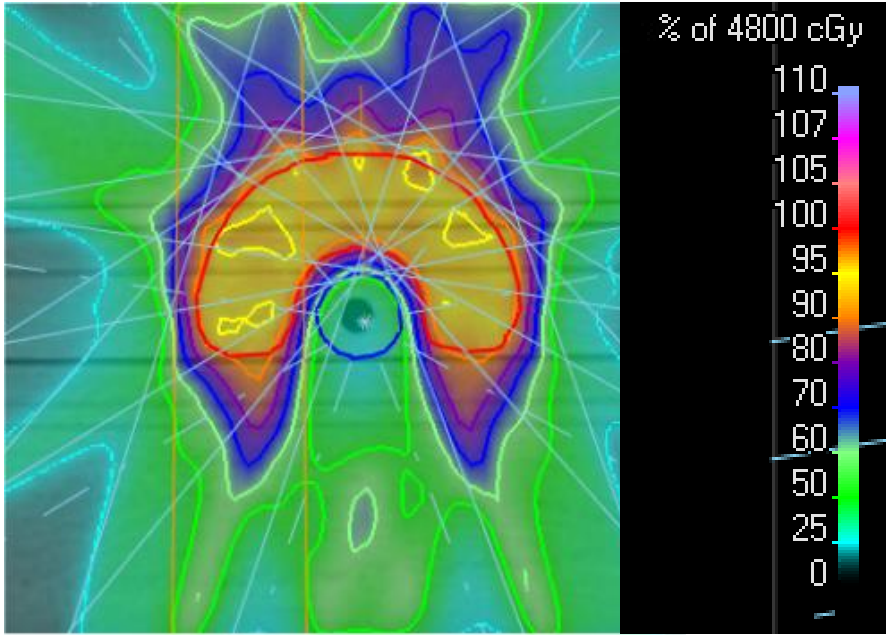
The patient's tumor eventually recurred, but was newly responsive to immunotherapy. He is cancer-free after 5 years.



Macomber M W, Tarabadkar E S, Mayr N A, Laramore G E, Bhatia S, Tseng Y D, Liao J, Arbuckle T, Nghiem P, Parvathaneni U 2017 Neutron Radiation Therapy for Treatment of Refractory Merkel Cell Carcinoma. Int. J. Part. Ther. 3(4) 485-491.

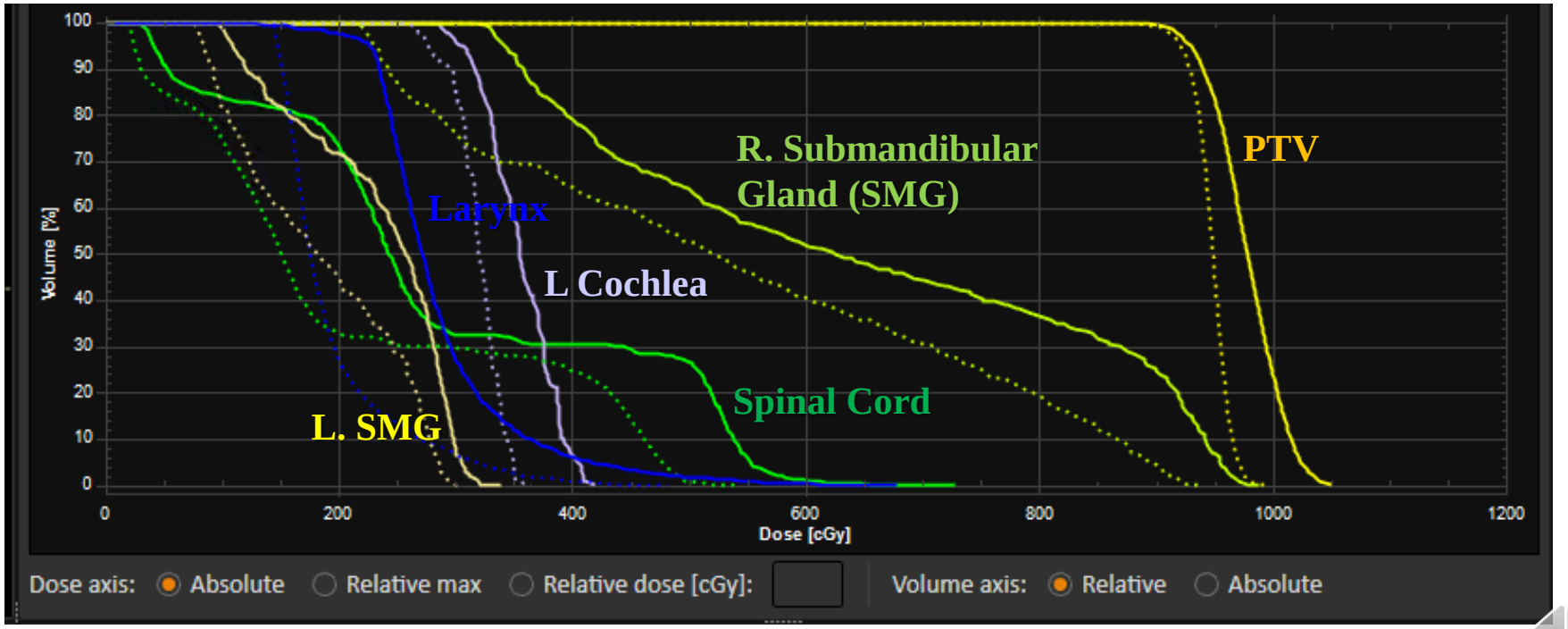
Future - Intensity Modulated Neutron Therapy (IMNT)

- **Engineering and technical advances in fast neutron therapy still lag behind MV x-rays**
  - Lack of image guidance (e.g., CBCT) and motion management are main challenges
  - In past, have been limited to 3D conformal treatments
- **IMRT is a feasible neutron treatment modality with the UW Clinical Neutron Therapy System (CNTS)**
  - Has significant potential to reduce normal tissue toxicity (*improve the therapeutic ratio*)



TG-119 C-Shaped IMNT Plan

DVH of 3DCRT and IMNT Plans for right parotid

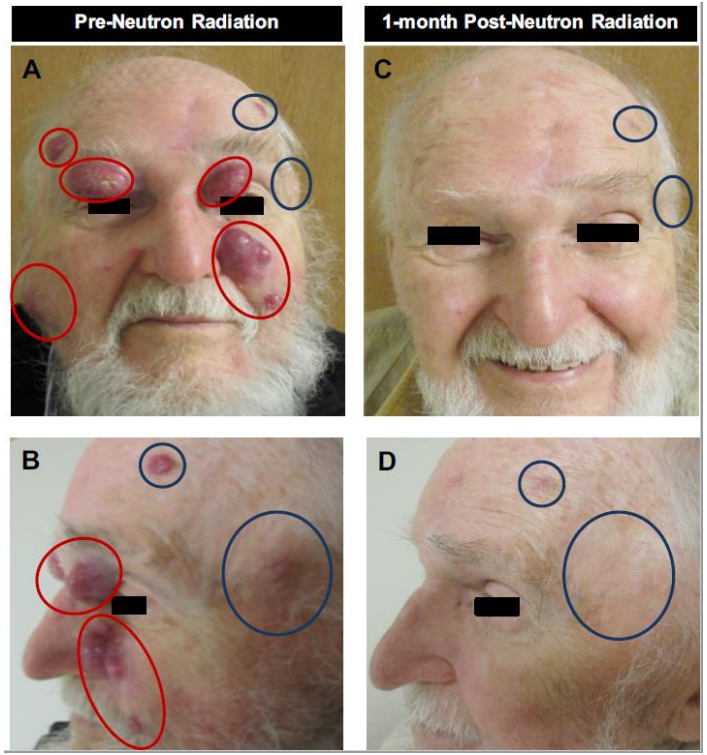


3D CRT: solid lines **IMNT: dotted lines**

Big idea #1 for multi-modality cancer care

- MV x-rays have superior technologies for image guidance and motion management than protons, high LET neutrons and other Z > 1 ions
  - Have inability to overcome mechanisms of intrinsic radiation resistance and tumor hypoxia
- High LET carbon ions and fast neutrons have a unique ability to overcome multiple mechanisms of radiation resistance, including the effects of tumor hypoxia
  - Normal tissue toxicity and lack of advance image guidance and motion management hamper the clinical usefulness of high LET external beam radiation therapy (also, current lack of facilities within the U.S.)
- ***Idea*: target (*radiation resistant*) gross disease with high LET radiation and tight margins. Treatment sub-clinical disease with image-guided MV x-rays**
  - High LET radiation overcomes regions of tissue resistant to low LET MV x-rays
  - MV x-rays target sub-clinical disease (*little or no hypoxia, lower tumor cell burden*) to minimize damage to dose-limiting normal tissue

Radiation-Induced Abscopal Effects



- Patient with progressive merkel cell carcinoma with multiple tumors on the face
- Progressed while on pembrolizumab (anti-PD1 immunotherapy)
- Surgery and two rounds of palliative MV x-rays
- Five most symptomatic lesions (circled in red) were treated with 2 × 3 Gy neutron with fractions separated by one week while continuing on pembrolizumab

- One month later (right panels), treated lesions exhibited a complete response. An additional 4 lesions outside the treated areas (blue circles) also had a complete response, suggesting an ***adaptive, anti-tumor immune response***.
- Anti-tumor activity induced by high LET treatment ***but not the low LET treatment***.

Schaub SK, Stewart RD, Sandison GA, Arbuckle T, Liao JJ, Laramore GE, Zeng J, Rengan R, Tseng Y, Mayr NA, Bhatia S, Nghiem PT, Parvathaneni U. *Does neutron radiation therapy potentiate an immune response to merkel cell carcinoma*? *International Journal of Particle Therapy*. **5**(1) 183-195 (2018). https://doi.org/10.14338/IJPT-18-00012.1

Big idea #2 for multi-modality cancer care

- For patient with metastatic disease, radiation therapy is often used with palliative intent and as a **last line of defense** after first-line immunotherapy and chemotherapy treatments
- **Might it be advantageous to use immunotherapy in combination with radiation therapy as a first-line treatment (*curative intent*) for patients with metastatic disease?**
  - Seems quite possible that the doses needed to trigger adaptive, anti-tumor activity are well below the tolerance dose for dose-limiting normal tissues
  - Could also target one or a few lesions with radiation rather than all lesions
- **Also, might it be advantageous to use high LET radiations to stimulate anti-tumor immune responses rather than a low LET (**MV x-ray or proton**) radiation treatment?**

Conclusions

- It is worth thinking about the “big picture” strengths and weaknesses of individual treatment modalities. Then, look for opportunities to offset the weaknesses of one treatment modality with the strength of another treatment modality.
- Gains from individualized multi-modality treatment approaches may be huge!

Thank you!